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THE NEURAL BASIS OF BRAIN-STIMULATION REWARD

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1. Introduction

1.1 GENERAL INTRODUCTION

Electrical stimulation of certain regions of the brain is rewarding in that animals (Olds and Milner, 1954) and man (Heath, 1964) will learn a task to obtain the stimulation (for review, see Milner, 1970). Animals will run as fast in a maze or will cross as highly electrified a shock grid to reach rewarding intracranial stimulation as will hungry animals to reach food (Olds, 1956c, 1961). Thirsty rats with some electrode placements choose to self-stimulate rather than to press a lever for water except under extreme water deprivation (Falk, 1961). Food-deprived rats with lateral hypothalamic electrode placements choose brain stimulation rather than food (Routtenberg and Lindy, 1965). Similarly, a hungry human subject disregarded a tray of food when permitted to self-stimulate (Bishop *et al.*, 1963). These experiments, together with the observation that non-contingent intracranial stimulation (e.g. stimulation set to recur regularly) is not capable of eliciting these types of behaviour (Olds and Olds, 1965), show that intracranial electrical stimulation can act as a reward.

The reward produced by the electrical stimulation is sometimes very similar to that produced by a natural reward, e.g. food for a hungry animal. Just as the food-deprived animal will bar-press faster for food reward, so the food-deprived animal will bar-press faster to obtain lateral hypothalamic stimulation (Hoebel, 1969). Similarly, an overfed animal will reject food, and will also work to avoid lateral hypothalamic stimulation (Hoebel, 1969). In these ways it is demonstrated that the lateral hypothalamic stimulation can act as a morsel of food, i.e. as a food reward. In this sense, electrical stimulation is capable of exciting food-reward pathways.

Brain-stimulation reward can therefore be used to study pathways involved in feeding. As food-deprivation does not affect self-stimulation rates at many reward sites (Hoebel, 1969), reward at many sites must be related to other types of behaviour. One example is drinking. In general, electrical stimulation could probably excite any reward pathway, and produce reward appropriate for almost any type of behaviour.

A study of the neural basis of intracranial self-stimulation may clarify the nature of brain-stimulation reward. It may be further useful in several ways. Firstly, it may indicate brain regions concerned with natural reward. For example, the control of eating probably occurs

by adjustment of the reward value of food, and this reward control system can be tapped and analysed with electrical stimulation (Hoebel, 1969). Similarly, reward and punishment are closely related to emotional behaviour, and the neural basis of emotional behaviour can be analysed with brain-stimulation reward. Secondly, it may clarify the basis of abnormal human emotional behaviour some types of which Stein (1971) has suggested are due to malfunction of the reward system. Thirdly, it may clarify the relief from intractable pain produced by stimulation of some rhinencephalic reward sites in man (Brady, 1961; Heath, 1964). Fourthly, the hypothalamus and limbic structures contain potent reward sites, and analysis of the neural basis of reward may clarify the function of these regions of the brain. Fifthly, reward is often an important factor in learning, and analysis of brain-stimulation reward may clarify the neural basis of learning.

1.2 ANALYSIS OF THE NEURAL BASIS OF BRAIN-STIMULATION REWARD

The neural basis of brain-stimulation reward can be analysed by determining which parts of the brain support brain-stimulation reward, which parts if lesioned or damaged affect brain-stimulation reward, where fibres course to from self-stimulation sites with the use of fibre-degeneration methods, and which neurones are active during brain-stimulation reward. Pharmacological methods can also be used to analyse the neurotransmission involved in brain-stimulation reward.

1.2.1 *Brain-stimulation reward sites*

Work before 1965 has been summarized by Olds and Olds (1965). One group of sites extends along the medial forebrain bundle (MFB) from the region of the diagonal band of Broca to the ventral tegmental area of Tsai, which is just lateral to the interpeduncular nucleus in the midbrain. Olds *et al.* (1971) have reported that for the hypothalamus self-stimulation can be obtained near the MFB, while feeding or drinking is produced by stimulation more dorsolaterally. A second group of sites is in the rhinencephalon. In the rat, rhinencephalic self-stimulation has been reported for parts of the septal nuclei (Olds *et al.*, 1960); nucleus accumbens septi (Routtenberg and Huang, 1968); amygdala (Wurtz and Olds, 1963; Valenstein and Valenstein, 1964; Hodos, 1965); hippocampus (Ursin *et al.*, 1966; Milgram, 1969); entorhinal, retrosplenial, and cingulate juxtallocortex (Stein and Ray, 1959; Brady and Conrad, 1960); and the caudate nucleus (Olds, 1960).

Major differences between MFB and rhinencephalic self-stimulation have been summarized by Olds and Olds (1965). MFB self-stimulation occurs at much higher rates than rhinencephalic self-stimulation—under similar conditions rates may be 10,000 vs 500 responses/h. This does not necessarily mean that MFB stimulation is more rewarding than rhinencephalic stimulation, because response rate is not necessarily a good measure of reward indicated by preference. For example, Hodos and Valenstein (1962) found that although rats preferred medium intensity septal stimulation to low intensity hypothalamic stimulation, the rate of bar-pressing was lower for the septal stimulation. One factor which contributes to the high MFB self-stimulation rates is arousal which the stimulation produces in addition to its rewarding effect (see section 4). Rhinencephalic self-stimulation may show "satiation" and stop for the day after several thousand bar-presses, while MFB animals continue until exhausted (although MFB animals requiring priming may show some decline in rate—Kent and Grossman, 1969). MFB reward is accompanied by hyperactivity, whereas at least during

intracranial stimulation, rhinencephalic rewarding stimulation is accompanied by hypoactivity. Pain or anxiety relief in man is obtained from stimulation of some rhinencephalic reward sites, and no relief is obtained from some MFB sites (Brady, 1961, but see Ervin *et al.*, 1969). This situation may also occur in the rat, in which rewarding rhinencephalic (septal) stimulation suppresses the aversive effects of tegmental stimulation (Routtenberg and Olds, 1963), but rewarding MFB stimulation augments the behavioural response to the aversive stimulation (Olds and Olds, 1962; Stein, 1965). It must be noted though that hypothalamic stimulation can attenuate the aversive properties of peripheral shock (e.g. Cox and Valenstein, 1965). Clarification is provided by Mayer and Lieberskind (1974), who found a close relation between sites at which stimulation produced analgesia and reward sites in the rat. Finally, the eating, drinking, or sexual activity which may be produced by stimulation of MFB reward sites is stimulus-bound (for review see Valenstein *et al.*, 1969), while feeding produced by simulation of some hippocampal reward sites occurs for 3–40 s after a 1 s period of stimulation, and may be regarded as a rebound phenomenon (e.g. Milgram, 1969).

Self-stimulation may also occur outside these areas. Cooper and Taylor (1967) found self-stimulation in the thalamic reticular system, and also in the central grey of the midbrain, where it developed over several days. Routtenberg and Malsbury (1969) found self-stimulation of certain brain-stem sites, in particular in or near the substantia nigra, brachium conjunctivum, and rubro-spinal tract, in addition to the ventral tegmental area of Tsai, but not of the reticular formation (where stimulation is neutral or aversive), or of the tegmental reticular nucleus. This system does not appear to be closely related to Olds's (1962) MFB system. In the monkey a group of self-stimulation sites is situated just dorsal to the MFB, near the medial edge of the internal capsule (Routtenberg *et al.*, 1971). In an attempt to determine whether the catecholamine-containing fibre pathways (Ungerstedt, 1971) are related to brain-stimulation reward, Crow *et al.* (1972) found that electrodes near the locus coeruleus in the pons supported self-stimulation. Electrodes near the substantia nigra and the interpeduncular nucleus also supported self-stimulation (Crow, 1972). Unfortunately with these, as with all studies of this type, it is not possible to determine which neural structure near the electrode tip must be stimulated to produce reward. Crow *et al.* (1972) note that with the sites near the locus coeruleus the possibility that a fibre pathway associated with the mesencephalic root of the trigeminal nerve is involved in the self-stimulation cannot be excluded. Interesting reports of self-stimulation of the olfactory bulb (Phillips and Mogenson, 1969; Phillips, 1970) have appeared. Much of the neocortex, most of the thalamus, the reticular formation, and the cerebellum are neutral sites (Olds, 1961; Routtenberg and Malsbury, 1969; but see also sections 3.4 and 5.3). Placements near the medial and lateral lemniscus usually yield aversion (Routtenberg and Malsbury, 1969).

Intracranial self-stimulation has been reported for some similar sites of many vertebrates other than the rat. Examples of other species showing self-stimulation are the goldfish (Boyd and Gardner, 1962), pigeon (Goodman and Brown, 1966), rabbit (Bruner, 1966), cat (MFB, Roberts, 1958; Grastayán *et al.*, 1965; caudate, Justesen *et al.*, 1963; anterior nucleus of the thalamus, Grastayán and Angyán, 1967), dog (Stark and Boyd, 1961), dolphin (Lilly and Miller, 1962), monkey (MFB, Brodie *et al.*, 1960; amygdala, caudate, and putamen, Brady, 1960; Brady and Conrad, 1960; thalamus, Lilly, 1960; basal tegmentum, Porter *et al.*, 1959; reticular formation, Brady, 1960), and man (MFB, amygdala, septal nuclei, and intralaminar nuclei of the thalamus, Heath and Mickle, 1960; Sem-Jacobsen and Torkildsen, 1960; Bishop *et al.*, 1963; Heath, 1964).

Summary

In many vertebrates self-stimulation occurs along the extent of the MFB and at rhinencephalic or limbic sites. The MFB itself is not necessarily the focal structure and in the monkey self-stimulation is obtained dorsolateral to the MFB. MFB self-stimulation is rapid, shows very little satiation, is accompanied by hyperactivity, and occurs at sites from which eating and drinking are sometimes elicited (Margules and Olds, 1962; Hoebel, 1969). Rhinencephalic self-stimulation is slow, may show satiation, is accompanied by hypoactivity, and may be associated with "rebound" eating.

1.2.2 *Effects of lesions on self-stimulation*

Valenstein (1966) has discussed the problems of interpreting effects of lesions on self-stimulation—e.g. it is not clear what a difference in rate of self-stimulation after a lesion may mean as rate does not always correlate with preference. Preference may be a good measure of reward, but bar-pressing rate and running speed are both affected by arousal level (see sections 4.4 and 4.6). Further differences between experiments seem to be due to two factors. Firstly, only animals with imperfect bilateral lesions of the lateral hypothalamus survive the operation without special feeding. Thus an experiment which uses only animals which survive the operation may produce results which are not informative about the role of the lateral hypothalamic region. In some cases, effects have been shown by unilateral or multi-stage bilateral lesions, or by careful postoperative care. Secondly, smaller differences between experiments may be due to lesion-testing time differences. For example, some recovery occurs after anterior MFB lesions (Boyd and Gardner, 1967).

(a) *Lesions caudal to self-stimulation sites.* Careful studies by Olds and Olds (1969) and Boyd and Gardner (1967) have shown that lateral or posterior hypothalamic self-stimulation rate is decreased by small lesions in or near the MFB both anterior (in the pre-optic area) and posterior (near the interpeduncular nucleus of the midbrain) to the stimulating electrode. A posterior lesion produces the greater decrease in rate, and in contrast to an anterior lesion there is no partial recovery of rate over the few days following the lesion. In both studies ipsilateral lesions were effective, but contralateral were not. Therefore the organization of the stimulated system is unilateral between the anterior commissure and the ventral tegmental area of Tsai. Boyd and Gardner noted that their only lesion which did reduce self-stimulation rate without a correlated body-weight change was to the mamillothalamic tract. These experiments receive support from the effects of xylocaine, a local anaesthetic, injected into sites anterior and posterior to MFB self-stimulation sites (Stein, 1969), which similarly decrease self-stimulation rates. The importance of regions caudal to MFB self-stimulation sites is further shown in a study by Bergquist (1970), who found in the opossum that ipsilateral lesions posterior to, but not anterior or lateral to, electrodes which produced sexual, aggressive, motivational, or searching behaviour raised the threshold for the elicitation of that behaviour.

With septal self-stimulation, Schiff (1964) showed that lesions of the ventral (or mid) tegmentum blocked self-stimulation although operant bar-pressing rates increased, showing that there was no response or arousal defect. Valenstein and Campbell (1966) failed to show an effect of lateral hypothalamic lesions on self-stimulation, but their study is not conclusive because of the use of large one-stage bilateral lesions.

(b) *Of amygdala.* Kant (1969) increased septal self-stimulation rates by bilateral amygdaloid lesions. Ward (1961) performed a suction ablation of the amygdala, and after 10–20 days implanted the animals with self-stimulation electrodes in the tegmentum near the interpeduncular nucleus. The animals self-stimulated, but no measure of rate change was, of course, possible. (See also section 2.4.)

(c) *Of septum.* Large bilateral lesions of the septum increased the rate of self-timed intracranial lateral hypothalamic stimulation, but decreased the total stimulation time (Lorens, 1966). The voltage–current threshold for lateral hypothalamic self-stimulation was decreased by septal lesions (Keesey and Powley, 1968). Ward (1960) found no effect on rate of basal tegmental self-stimulation when 4 rats were tested 5–10 days after a septal suction-ablation.

(d) *Of hippocampus and fornix.* Lesions of the fornix have not affected lateral hypothalamic (Boyd and Gardner, 1967) or basal tegmental (Ward, 1960) self-stimulation. Asdourian *et al.* (1966) found that lesions in the hippocampus increased septal self-stimulation rate, and Jackson (1968) found that lesions of the ventral hippocampus lower the current levels required to maintain rates of hypothalamic self-stimulation.

(e) *Of cingulate area.* Coons and Fonberg (1963) reported that lateral hypothalamic lesions blocked cingulate self-stimulation but not vice-versa.

Conclusions

Self-stimulation of, or of sites near, the MFB is decreased more by lesions posterior to than lesions anterior to the self-stimulation electrode. The effective lesions are in or near the MFB. A decreased rate or an increased threshold for self-stimulation is produced by the lesions. In contrast, septal lesions decrease the threshold or increase the rate of MFB self-stimulation. Hippocampal lesions increase the rate of septal and hypothalamic self-stimulation. Amygaloid lesions increase septal self-stimulation rate, and do not block tegmental self-stimulation. These experiments suggest that regions caudal to self-stimulation sites may be critical in controlling whether or not self-stimulation occurs; rhinencephalic lesions appear to affect self-stimulation, producing an increased rate of responding. However, the latter conclusion probably requires revision, as anaesthetization of the amygdala and prefrontal cortex does attenuate self-stimulation (sections 2.4 and 3.4). The forebrain areas may thus modulate self-stimulation, but are probably not essential for self-stimulation, which can occur even when large areas of the forebrain, including the frontal cortex, are removed (Huston and Borbely, 1973).

1.2.3 *The role of physiological concomitants of brain-stimulation reward*

Cardiovascular changes produced by brain-stimulation reward have been reported for the rat by Malmo (1961), Meyers *et al.* (1963), and Perez-Cruet *et al.* (1963). Ward and Hester (1969) found that MFB self-stimulation in cats was unimpaired by bilateral surgical removal of the sympathetic chain and bilateral sectioning of the vagus and pelvic splanchnic nerves. Perez-Cruet *et al.* (1965) showed that lateral hypothalamic self-stimulation increased heart rate and blood pressure in dogs. The injection of dibenzyline, an adrenergic blocking agent, eliminated the cardiovascular effects without affecting self-stimulation. The last two experiments are evidence that cardiovascular changes are not of causal importance in self-stimulation. Further evidence against the importance of cardiovascular, endocrine, or other effects which act slowly (in periods of greater than 1 s) is that self-stimulation is very sensitive to the temporal relationship of the instrumental act and the delivered stimulation, e.g.

signalled reinforcement is preferred over non-signalled (Cantor and LoLordo, 1970), and extinction of self-stimulation is dependent on the time of arrival of brain stimulation relative to a bar-press (Gibson *et al.*, 1965).

EEG seizure activity may appear during rhinencephalic self-stimulation (monkey, Porter *et al.*, 1959), but is very rare during posterior hypothalamic or mesencephalic self-stimulation (rat, Bogacz *et al.*, 1965). Reid *et al.* (1964) (rat) reduced seizure activity and increased self-stimulation rate with an anticonvulsant drug. This dissociation is evidence that seizure activity is not of causal importance in self-stimulation.

1.2.4 *Fibre degeneration studies*

By making small lesions at self-stimulation sites and tracing the resulting orthograde fibre degeneration it is possible to draw inferences about the nature of neural systems involved in brain-stimulation reward. Routtenberg (1971) demonstrated that degeneration from rodent prefrontal cortex reward sites occupies the most medial edge of the internal capsule in a course towards the midbrain. It is in this area in the monkey, about 1 mm dorsolateral to the MFB, that Routtenberg *et al.* (1971) obtained good self-stimulation. It may therefore be that fibres coursing caudally from the frontal cortex are involved in brain-stimulation reward. Some further evidence for this relation comes from the observation that degeneration from the monkey self-stimulation sites described above runs to the mediodorsal nucleus of the thalamus, which is connected with the prefrontal cortex, and also probably runs directly to the caudal orbitofrontal cortex (Routtenberg *et al.*, 1971). The problem with this type of study is that there is no assurance that the degenerating fibres actually fired during the self-stimulation. Which neurones fire during self-stimulation depends on the magnitude of the stimulation current, the nature of the spread of the current, and on the properties of the neurones themselves. The lesion at the self-stimulation site may destroy neurones which are not functionally related to the self-stimulation, and no check is possible. A further difficulty is that with the techniques used only orthograde degeneration has been traced, so that inferences may only be drawn about where fibres course to, not where they come from. Further, no evidence on trans-synaptic effects, i.e. on the further connections of reward pathways, can be gained with degeneration techniques. Nevertheless, experiments performed with the technique are useful in providing an indication about reward pathways. The main indication to have come so far from this work is that fibres near the MFB related to the mediodorsal nucleus of the thalamus and the prefrontal cortex are involved in brain-stimulation reward (Routtenberg *et al.*, 1971). This type of work also led to the claims that the brachium conjunctivum is a reward pathway (Routtenberg and Malsbury, 1969), and that there is a close relation between the extrapyramidal system and reward pathways (Huang and Routtenberg, 1971).

1.2.5 *Electrophysiological studies*

(a) *Single-unit studies*

A good method for analysing reward pathways is to apply electrical stimulation which produces reward to a reward site, and to record from neurones in different parts of the brain to determine how the neurones are affected by the stimulation. If a single unit is fired with a short, fixed latency by the stimulus pulses, it is probably directly excited by the stimulation.

This means that its axon must pass under both the recording and stimulating electrodes. A further test, for collision, can be applied to determine whether the direct excitation is antidromic or orthodromic (see below). If a single unit is fired with a longer, variable latency by the stimulus pulses, and collision cannot be demonstrated, the neurone must be trans-synaptically activated by the stimulation. If the firing rate of a neurone is affected by the stimulation yet the action potentials are not in phase with the stimulus pulses, then poly-synaptic activation is likely. Using these methods it is possible to show which neural pathways are activated by the rewarding stimulation, and to trace the effects of the stimulation across synapses through the central nervous system. Provided that the stimulating current is kept at or below the value which was sufficient for self-stimulation, it can be concluded that activated neurones were activated in self-stimulation. The specificity of the activation with respect to reward can be assessed by using animals in which the implanted electrodes do not support self-stimulation. After neural systems activated in self-stimulation have been traced, further tests can be performed to determine their role in brain-stimulation reward (see below).

The experiments in which reward pathways have been traced and analysed are described in the following sections. In a first neural system (section 2), neurones in the amygdala fire during eating, drinking, and reward produced by lateral hypothalamic stimulation. The amygdaloid neurones are probably involved in the eating, drinking, and reward because anaesthetization of the activated amygdaloid neurones inhibits the eating, drinking, and reward. The amygdaloid neurones are probably involved in natural eating and drinking because after bilateral destruction of the amygdala, rats cannot modulate their food and water intake on the basis of previous experience. It may be because the amygdala is normally concerned with switching intake on and off, presumably by learning whether a particular food is rewarding (see section 2.6), that it becomes involved with brain-stimulation reward. In a second neural system (section 3), neurones in the prefrontal cortex fire during self-stimulation of many different brain sites. The activated neurones in the sulcal prefrontal cortex are probably involved in the reward because bilateral anaesthetization of this region attenuates brain-stimulation reward. Interestingly, eating and drinking are not affected, so that the prefrontal neurones are probably involved in reward not related to eating and drinking. In a third neural system (section 4), neurones in the midbrain and pons fire during self-stimulation, and mediate an arousal effect. The arousal effect influences the rate of self-stimulation, and probably accounts at least in part for the priming effect. Neurones in related areas, e.g. the hippocampus and cingulate cortex, are also activated in self-stimulation (section 5), but their role in brain-stimulation reward is unclear. Neurones in the pons and medulla are also activated in and may be involved in self-stimulation (section 5.6). Neurones in the hypothalamus are activated by brain-stimulation reward and by specific natural rewards (sections 5.5). The activation of these neurones may be sufficient for brain stimulation to provide reward. Each of these activated neural systems, and what is known of their function in self-stimulation and rewarded behaviour, is described in the following sections (2–5).

(b) *EEG studies*

Grastayán *et al.* (1965), working with cats, have found that hippocampal theta activity occurs during stimulation of hypothalamic reward sites. Theta EEG frequencies in the cat are 6–8 Hz. They suggest a close relationship between theta and approach-reward, and hippocampal desynchronization and withdrawal-aversion. Grastayán and Ángyán (1967),

investigating self-stimulation of the anterior nucleus of the thalamus in cats, found that hippocampal desynchronization occurring during stimulation was followed by rebound theta activity, the theta again being involved in approach. Working with immobilized rats, Routtenberg (1970) came to a similar conclusion—rewarding stimulation of brain-stem and MFB sites produced hippocampal synchronization, while rewarding subcortical telencephalic stimulation produced hippocampal desynchronization. Both effects were followed by rebound after-effects. He also found that aversive stimulation produced theta but that the theta frequency was higher than with rewarding stimulation. These studies suggest that the hippocampus may be involved in intracranial self-stimulation. Recently, Ball and Gray (1971) have found that rats showed septal self-stimulation irrespective of theta driving or blocking. Two types of septal stimulation were used, which produced driving or blocked hippocampal theta rhythm, with current intensity held constant. This experiment shows that the theta rhythm itself is not important in brain-stimulation reward.

Ball (1967) found that during self-stimulation the magnitude of potentials evoked in the trigeminal nucleus by stimulation of the infra-orbital nerve was decreased. He argued from this that sensory inhibition may play a role in self-stimulation. A possible explanation for the result in terms of arousal changes is given in section 4.

2. The Function of the Amygdala in Brain-stimulation Reward, Eating, and Drinking

2.1 ACTIVATION OF AMYGDALOID NEURONES IN EATING, DRINKING, AND REWARD ELICITED BY ELECTRICAL STIMULATION OF THE BRAIN (see also Rolls, 1972)

Stimulation electrodes were implanted in the lateral hypothalamus of male rats. Electrical stimulation of this region often produces eating or drinking (see Hoebel, 1969). The lateral hypothalamus is very closely concerned with the regulation of food and water intake, and, following bilateral lesions in the hypothalamus, rats never again show glucostatic regulation of food intake, nor osmotic regulation of water intake (Teitelbaum *et al.*, 1969). Electrical stimulation of the lateral hypothalamic region also produces reward (Margules and Olds, 1962; Hoebel, 1969). Because the lateral hypothalamus is so closely connected with eating, drinking, and reward, it represents a good brain site with which to investigate the neural basis of eating, drinking, and reward. Stimulation electrodes were also implanted in the nucleus accumbens septi, chosen as an example of a rhinencephalic self-stimulation site. Stimulation of this site supports slow self-stimulation, does not produce hyperactivity (Rolls and Kelly, 1972), and does not produce stimulus-bound eating or drinking (eating or drinking which occurs during the stimulation). When the electrodes had been tested for eating, drinking, or self-stimulation, the lowest current which would maintain the behaviour elicited was found. Then the animal was anaesthetized and replaced in the stereotaxic instrument, and the activity of single units was recorded extracellularly while pulses at the threshold intensity were applied to the stimulation electrodes. In this way the units activated in the behaviour could be analysed in acute electrophysiological experiments. The alternative technique, of recording single unit activity while the animal is self-stimulating (Ito and Olds, 1971), produces comparable results (see sections 3 and 5), but yields only about one unit for each electrode implanted with the technique used.

2.1.1 *Design of experiments used to analyse the neurophysiological basis of brain-stimulation reward*

A technique which has been used to analyse the neural basis of brain-stimulation reward is to record from single units during stimulation applied to reward electrodes. If the stimulation current is the same as that used in the self-stimulation test, then it is likely that any neurones activated were also activated in the self-stimulation. Thus pathways activated in self-stimulation can be traced through the brain. The electrophysiological experiments can be performed in the anaesthetized animal or in conscious animals. In the latter case it is possible to analyse the function of activated neurones in natural behaviour, and thus to determine, for example, why electrical stimulation of the brain can be rewarding (see section 5.5).

It can be stressed that in most areas of the brain, neurones are not activated during stimulation applied to reward sites. (For example, an inspection of most of the figures of micro-electrode tracks included here to illustrate the activation of a particular brain area shows that neurones in most of the other brain areas through which the micro-electrode passed were not activated.) There is further evidence that the number of neurones activated by the rewarding stimulation is relatively small. Firstly, evoked potentials (indicative of massive synchronous firing of neurones) are not produced by normal rewarding stimulation (unless the current is increased by a factor of three or four times). Secondly, even single neurones recorded as close as 1 mm to a stimulating electrode are not directly excited by the stimulation field (personal observation). Thirdly, electrical stimulation can produce opposite effects in sites only 1 mm apart (e.g. electrical stimulation of the rat lateral hypothalamus can initiate eating, and stimulation of the ventromedial hypothalamus stops eating). Fourthly, most of the neurones activated at the lowest current which will support self-stimulation have thresholds close to this current. Thus if the electrode is in the right area, the current appears to be able to support self-stimulation as soon as it activates neurones. These points therefore indicate that the electrical stimulation excites neurones (probably mainly fibres) close to (certainly not further than 1 mm from) the tip of the stimulation electrode. The effects of the stimulation may reach distant parts of the brain by ortho- or antidromic conduction in directly excited fibres as well as by fibres of cell bodies which may be directly excited by the stimulation and via neurones trans-synaptically activated by the stimulation. Neurones which are activated by the stimulation could be involved in the reward produced by the stimulation or in the other effects, e.g. arousal and motor movements, which are sometimes produced also. To determine how activated neurones are involved in the effects produced by the stimulation, further evidence from, for example, anaesthetization or lesions of a group of activated neurones, or refractory period determinations, must be considered (see later sections).

To determine whether neurones in the amygdala are activated in self-stimulation, monopolar stainless-steel electrodes insulated (except for 0.5 mm at the tip) with Insl-X varnish were implanted under Equithesin (Jensen-Salsbury Labs. Inc.) anaesthesia. Two electrodes were implanted, one aimed at the lateral hypothalamus and the other at the nucleus accumbens septi. A large exposure of the dura, from the midline to the lateral ridge and from lambda to 3 mm anterior to bregma, was made ipsilateral to the stimulating electrodes to allow the insertion of microelectrodes in later acute electrophysiological experiments. In some experiments, although spaces were left near the stimulating electrodes, the rectangle of bone was not removed until the start of the acute experiment, to minimize the risk of damage to the brain.

2.1.2 *Recordings from single units in the amygdala and pyriform cortex excited by the lateral hypothalamic stimulation*

The electrophysiological experiments were designed to allow investigation of the effects on single units in the amygdala of rewarding lateral hypothalamic and nucleus accumbens septi stimulation. Single-unit activity in the region of the amygdala and pyriform cortex was recorded with a tungsten or capillary micro-electrode lowered through a slit made in the exposed dura. Cathodal stimulus pulses of 0.1 ms duration were applied to the self-stimulation electrodes at the lowest current for which the animal had previously shown a good rate of self-stimulation. This procedure was to ensure that units activated by the electrical stimulation in the acute experiments were also activated in self-stimulation. Whenever a spontaneously active single unit was encountered, the effects of stimulation applied to a self-stimulation electrode were determined and compared, where possible, with stimulation applied to the other electrode. As some activated units were not spontaneously active, stimulus pulses were applied frequently while the micro-electrode was lowered through the brain. Single units activated by the electrical stimulation were classed as directly, synaptically, or indirectly activated (after Rolls, 1971a).

(a) *Activation of the units*

A large number of units in the region of the lateral amygdala and pyriform cortex were directly excited by stimulation of the lateral hypothalamus which elicited eating, drinking, or reward. As shown in Fig. 1a, the all-or-none action potentials of these units followed single-stimulus pulses with short, fixed latencies. (Another example of a directly excited unit is shown in Fig. 21.)

The latency from the start of the stimulating pulse in the lateral hypothalamus to the start of the action potential of the amygdaloid unit was between 0.5 and 2.0 ms. Because the action potentials of each activated amygdaloid unit had a short, fixed latency, each neurone probably passed under both the stimulating and recording electrodes. That is, the neurones from which the recordings were made were directly excited by the hypothalamic stimulation. Excitation could be in either the ortho- or antidromic direction (Fig. 2). With antidromic transmission, action potentials travel in the abnormal direction along the axon towards the cell body (Fig. 2). Sometimes an electrically excited action potential starting from the stimulation electrode will collide with a spontaneous action potential travelling away from the cell body. If collision occurs, the electrically excited action potential fails to propagate past the collision site (because the axon is refractory), and an action potential will not appear at the recording electrode shown in Fig. 2. This forms a very useful test to determine dromicity: if collision occurs, activation is antidromic (see also Rolls, 1971a). An example of collision is shown in Fig. 1b. If collision does not occur, then activation is orthodromic. The critical time parameters for determination that collision has occurred (and that excitation is therefore antidromic) have been given in detail elsewhere (Rolls, 1971a, c).

Evidence for antidromic activation using the collision technique was found in 7 units classed as directly excited by the lateral hypothalamic stimulation. The evidence was inconclusive in an eighth unit, and the other units could not be tested for collision because spontaneous firing was absent. The available evidence thus indicates that at least some of the directly driven amygdaloid units are activated antidromically by the hypothalamic stimulation.

Refractory period measurements can be used to characterize a population of neurones (Lucas, 1917). If a nerve is composed of large nerve fibres, then this will be indicated by short

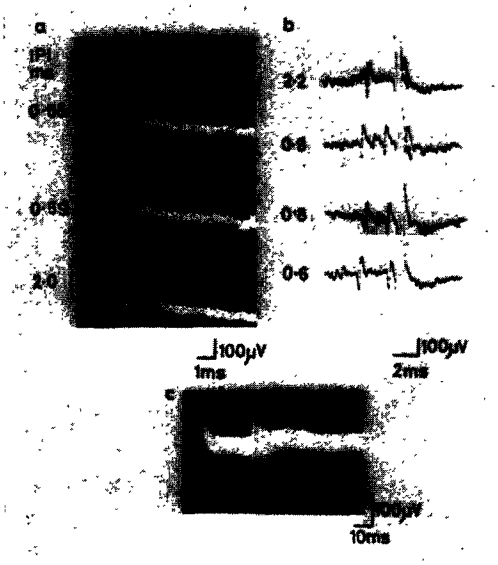

FIG. 1. (a) Absolute refractory period indicated by intermittent firing of the second action potential at 0.59 ms (IPI = intrapair interval). The first stimulus artifact can be seen only at an IPI of 2.0 ms. Approximately 6 superimposed traces. Negative down, as in all other figures. MFB stimulation. (b) Antidromic activation from the MFB of the neurone in (a) is shown by collision of the action potentials produced by MFB stimulation (arrows) with action potentials elicited synaptically in the neurone by nucleus accumbens stimulation. When the synaptically elicited action potentials precede the MFB stimulating pulse (seen as a stimulus artifact) by less than 0.9 ms (indicated by the number to the left of the trace), collision occurs. (c) The unit shown in (a) synaptically driven by nucleus accumbens stimulation. Approximately 10 superimposed traces. This driving was used to produce the collision shown in (b). (From *Brain Res.* **45**, 365–81, 1972.)

refractory period values of the individual fibres. The refractory period (i.e. the shortest time interval following one stimulus pulse when a second stimulus pulse will excite another action potential) was measured for many of the directly excited amygdaloid neurones as shown in Fig. 1a. When the pulse pairs were separated by 2.0 ms (intrapair interval (IPI) 2.0, lowest trace), an action potential (seen as a downward deflection) followed each pulse. At an IPI of 0.59 ms the action potential only sometimes followed the second pulse in an all-or-none manner (middle trace; only the second stimulus artifact is shown). This is therefore the refractory period of the neurone. At a shorter IPI (top trace) no action potentials followed the second pulse. The refractory period of 0.59 ms is the absolute value because increasing the stimulating current further did not reduce the refractory period value. Under the stimulating conditions used, the measured value of refractory period decreases until the current has reached about a twice-threshold value (Rolls, 1971a, Fig. 2). The absolute refractory periods of 49 different directly excited amygdaloid units are shown in Fig. 3. The characteristic absolute refractory period of these units is in the range 0.58–0.67 ms (Fig. 3 for 49 units). Recordings were made from 16 other directly driven units, but refractory periods were not measured because the action potentials were too small.

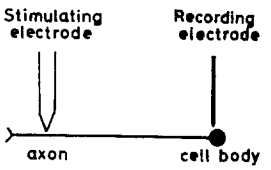

FIG. 2. A neurone antidromically activated by electrical stimulation. Spontaneously occurring action potentials (which travel orthodromically away from the cell body along the axon) may collide with action potentials produced by the stimulation.

A large number of units in the amygdala–pyriform cortex region were classed as trans-synaptically activated by the lateral hypothalamic stimulation. A trans-synaptically activated unit is activated by the stimulus pulses only after transmission across one or more synapses. An example of a trans-synaptically activated unit is shown in Fig. 1c. The features of units classed as trans-synaptically activated are long (usually in the range 2–40 ms), variable latencies. These features are well shown in the superimposed traces of Fig. 1c. In addition, trans-synaptically activated units do not show collision (see Rolls, 1971c) and will fire twice only to pulse pairs separated by long (2–50 ms) IPIs. The latencies of the amygdaloid units trans-synaptically activated by the lateral hypothalamic stimulation were mainly between 2 and 25 ms, as shown in Fig. 4. Some of the trans-synaptically units were not activated by single-stimulus pulses, but did show a long latency change in firing rate following a train of stimulus pulses. These units were classed as indirectly activated (I), and may be polysynaptically driven. It is clear from Fig. 4 that there is strong trans-synaptic activation of neurones in the amygdala by the lateral hypothalamic stimulation known to elicit eating, drinking, or reward.

Many amygdaloid neurones were also trans-synaptically (but not directly) excited by rewarding stimulation of the nucleus accumbens. An example of one of these units is shown in Fig. 1c. The latencies to firing were generally long, with many units having latencies near 17 ms (Fig. 4).

The finding that neurones in the amygdala are activated in eating, drinking, or reward elicited by lateral hypothalamic stimulation suggests that the amygdaloid neurones are involved in the eating, drinking, or reward. The finding that neurones in the amygdala are trans-synaptically activated by the rewarding nucleus accumbens stimulation is a further indication that these neurones are involved in reward.

(b) *Convergence of excitation in lateral hypothalamic and nucleus accumbens septi self-stimulation on to individual amygdaloid units*

In some of the amygdaloid units, convergence from the different self-stimulation sites was demonstrated. An example of convergence on a unit directly driven by the MFB and trans-

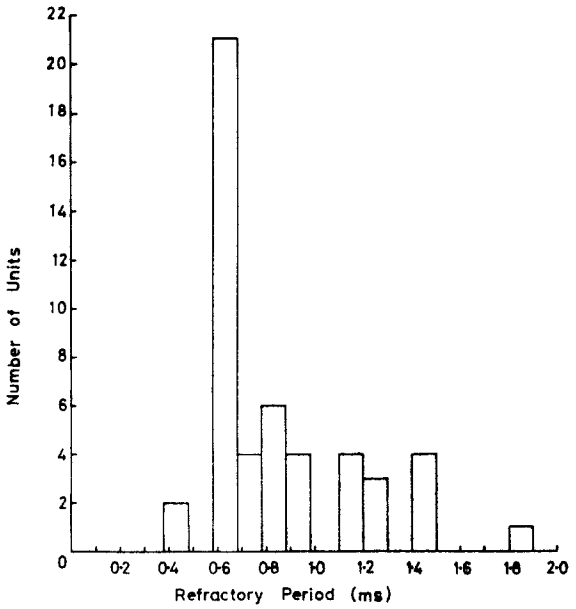

FIG. 3. The absolute refractory periods of amygdala–pyriform cortex units directly excited by the lateral hypothalamic stimulation. The 49 units were recorded in 22 animals. Units with refractory periods of 0.58 or more but less than 0.68 ms are placed in the 0.58–0.68 ms bar of the histogram. (From *Brain Res.* 45, 365–81, 1972.)

synaptically driven by the nucleus accumbens septi stimulation has been illustrated in Fig. 1. Convergence was also seen in units driven trans-synaptically from both the lateral hypothalamus and the nucleus accumbens septi. Convergence was seen in a total of 58 units. Although 302 directly, synaptically, and indirectly driven amygdaloid units were investigated in this study, only 196 of these units were in animals with positive self-stimulation electrodes in both the MFB and the nucleus accumbens. Thus convergence was seen in 58 of a possible 196 units, or 30% of the sample. This convergence on to amygdaloid units from widely separated self-stimulation sites is a further indication that the amygdala–pyriform cortex region may be important in self-stimulation.

(c) *The nature of the activated units in the amygdala and pyriform cortex*

The effects of various stimuli on the firing rates of the units activated from self-stimulation sites were determined to analyse the nature of the units, and, in particular, to test whether the units were arousal units and thus functionally indistinguishable from the arousal units described earlier (Rolls, 1971a). The firing rates of the arousal units change greatly when arousing stimuli are applied to the animal, and are correlated closely with cortical arousal. In addition, as the pyriform cortex receives an input from the olfactory bulb (Powell *et al.*,

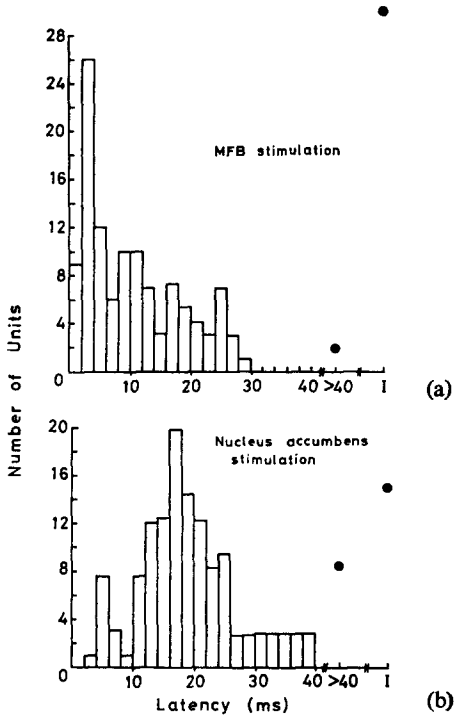

FIG. 4. The latencies of synaptically driven amygdala–pyriform cortex units. (a) Latencies of 115 units synaptically driven from lateral hypothalamic sites in 22 animals. (b) Latencies of 140 units synaptically driven from nucleus accumbens septi sites in 11 animals. Average values are represented for latencies between 30 and 40 ms. I, numbers of units driven indirectly from MFB (17 rats) and nucleus accumbens (6 rats) self-stimulation sites. The indirectly driven units are shown at the end of the latency axis (black dots): in general their latencies were greater than 40 ms. (From *Brain Res.* **45**, 365–81, 1972.)

1965) the effects of olfactory stimuli, e.g. acetone, on the firing rates of the units were also measured.

The majority of units directly driven from MFB self-stimulation sites did not fire spontaneously, even in cortical arousal or after brain stimulation. This leads to the conclusion that the directly excited amygdaloid units are not arousal units. An example of the firing rate of a unit directly driven from a MFB self-stimulation site, and trans-synpatically driven from a nucleus accumbens site, which did show spontaneous firing, is shown in Fig. 5. The average firing rate of the unit was about 5 impulses/s. The firing rate of the unit was decreased by a number of stimuli (e.g. after 3 trains of MFB stimulation, inhalation of acetone

and amyl nitrite, and a pinch to the hind leg), but the changes in the firing rate were rather small compared with the change which would be produced during MFB stimulation. During this stimulation, the unit fired at the stimulus frequency, i.e. 100 Hz (not shown in Fig. 5). Similar results were obtained for other directly driven amygdaloid units with spontaneous firing. Thus the major effects of MFB stimulation on the directly excited amygdaloid units occur during the stimulation, while the unit is being driven, and the after-effects of the stimulation are small and do not last for long periods. Comparable results were found in trans-synaptically activated units, and lead to the following conclusions. Firstly, the firing rates of the units are not correlated in any simple way with arousal. Secondly, the major effects of stimulation on trans-synaptically and indirectly driven units occur during a period of less than 1 s following a brief train of stimulus pulses (e.g. Fig. 1c) and longer post-

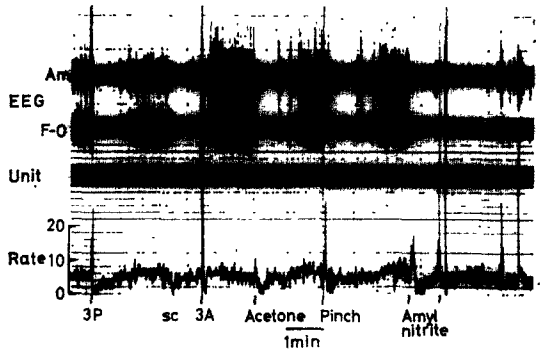

FIG. 5. The firing rate of a unit in the amygdala–pyriform cortex region driven directly from a lateral hypothalamic and synaptically from a nucleus accumbens septi self-stimulation site. Each action potential is represented by a spike in the "unit" record. The unit firing rate (action potentials/s) is shown averaged over 2 s. F–O, EEG recorded between the frontal and occipital cortex. Maximum EEG amplitude is about 500 μV. Am, EEG recorded from the capillary micro-electrode in the amygdaloid region. 3P and 3A, 3 trains of 100 Hz stimulation 0.3 s long applied to the posterior (lateral hypothalamic) and anterior (nucleus accumbens septi) self-stimulation sites respectively. The current was at a level for which the animal had previously self-stimulated. SC, a spontaneous change to arousal. (From *Brain Res.* **45**, 365–81, 1972.)

stimulation effects are of a relatively small magnitude. These characteristics are different from those of arousal units activated in self-stimulation (see section 4) and indicate that, in contrast, the major effects of rewarding stimulation on amygdaloid units cease within about 1 s of the termination of the stimulation.

(d) *Amygdaloid neurones activated in stimulus-bound eating and drinking*

Electrophysiological experiments were performed on 3 rats which ate and 3 which drank during electrical stimulation of the lateral hypothalamus. Units in the amygdala–pyriform cortex region were activated by the stimulation at the intensity which had previously elicited drinking or eating. Twelve directly excited neurones in drinkers and 11 in eaters had absolute refractory periods similar to those measured in the animals tested only for self-stimulation. Recordings were made of the activity of 18 neurones in drinkers and 50 neurones in eaters which were synaptically or indirectly driven by the stimulation. The units had similar

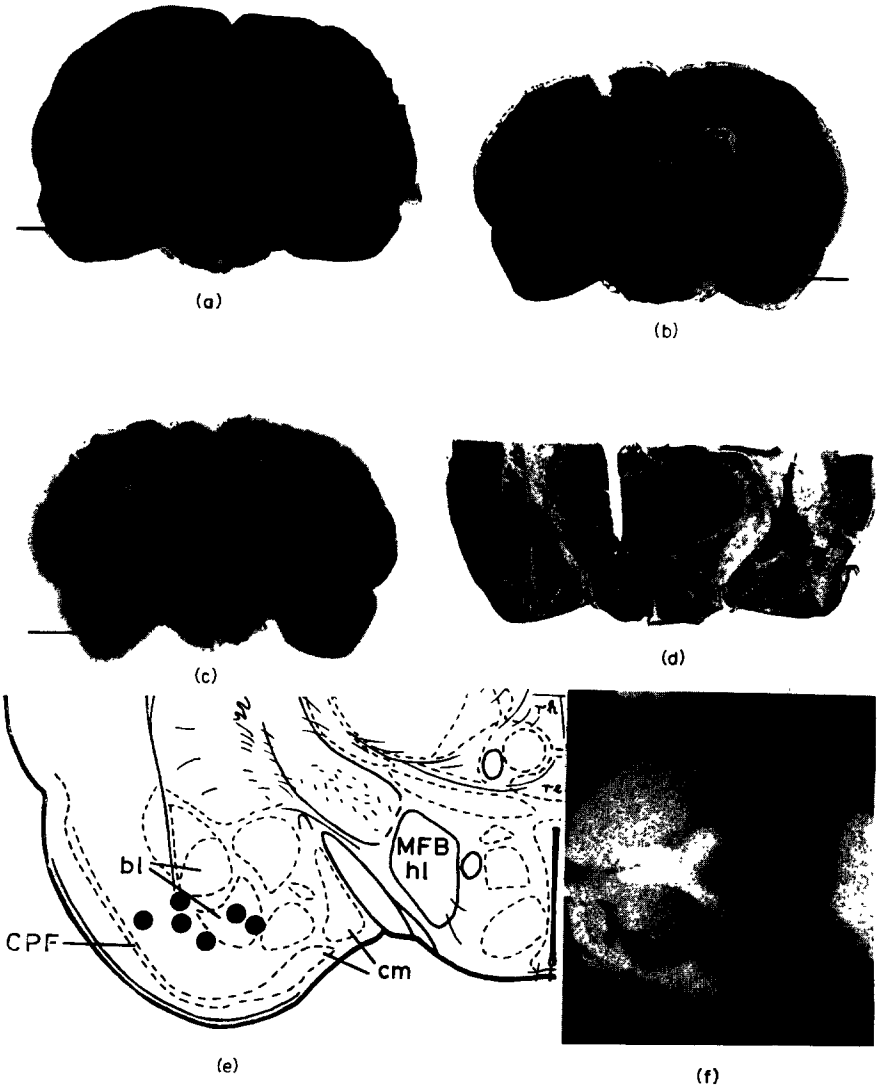

FIG. 6. Examples of sites of units in the lateral amygdala–pyriform cortex region activated from MFB self-stimulation electrodes. (e) (from König and Klippel, 1963, fig. 32b) shows the sites (●) where 6 further activated units were recorded. CPF, pyriform cortex; bl, baso-lateral group of amygdaloid nuclei; cm, cortico-medial group of amygdaloid nuclei; hl, lateral hypothalamus. (f) shows marks (encircled) left at the base of the brain by micro-electrodes with which activated amygdaloid units were recorded. The units were 1–3 mm above the base of the brain. *Brain Res.* **45**, 365–81, 1972.)

latencies and firing-rate characteristics to those of the units recorded in the animals tested only for self-stimulation. Because of these similarities, the results from the rats which drank or ate were combined with those of the rats tested only for self-stimulation, and it can be concluded that similar amygdaloid neural systems are excited in the different groups of animals.

(e) *The sites of activated units and the stimulation sites from which they are driven*

Capillary micro-electrodes were used in the majority of recordings in the amygdaloid region, and histological localization of the micro-electrode tip is not more accurate than 1 mm in the vertical plane (a satisfactory marking method is described in section 3.2). Micro-lesions made with tungsten micro-electrodes indicated that activated units are in the lateral amygdaloid region near the termination of the external capsule (Fig. 6). Tracks made with a capillary micro-electrode are shown in Fig. 6d. Directly activated units were recorded in the more lateral tracks within 3 mm of the base of the brain. These observations indicate that the directly excited units recorded in this study were in the lateral amygdala or pyriform cortex region. Trans-synaptically and indirectly driven units were found in this region and also more medially in the lateral amygdala. Although electrode tracks passed through the medial amygdaloid region, only 4 activated neurones were recorded in it.

The self-stimulation electrodes were mainly in the lateral hypothalamus, but ranged from anterior to posterior hypothalamus along the MFB (see tracks visible in Fig. 6a–d, and Rolls, 1971b), and in, or close to, the nucleus accumbens septi at A 9650, lateral 0.5–1.0 and 0.0–0.5 mm below horizontal zero (stereotaxic atlas of König and Klippel, 1963). Examples of nucleus accumbens sites are shown in Rolls and Kelly, 1972. The electrodes in the animals which showed stimulus-bound drinking or eating were in the lateral hypothalamus.

(f) *Conclusions*

The electrophysiological experiments show that neurones in the region of the basolateral amygdala and pyriform cortex fire during eating, drinking, or reward elicited by lateral hypothalamic stimulation. This suggests that the neurones are involved in the eating, drinking, and reward produced by the lateral hypothalamic stimulation. The finding that neurones in the same region are trans-synaptically activated from a different self-stimulation site, the nucleus accumbens, is a further indication that neurones in this region are involved in reward. As activity in the activated amygdaloid neurones does not simply reflect arousal, the neurones could be involved in the more specific types of behaviour suggested above, namely eating, drinking, and reward.

The neural pathways excited could be as follows (Fig. 7). The amygdaloid neurones directly excited by the lateral hypothalamic stimulation characteristically have absolute refractory periods in the range 0.58–0.67 ms, and are antidromically excited by the stimulation. Although collision tests were not performed on all the directly excited units, no unit was shown to be orthodromically excited. As many amygdaloid units trans-synaptically driven by the lateral hypothalamic stimulation had latencies (1–6 ms) just greater than those of the directly excited units (0.5–2 ms), the pathway may be from directly to synaptically activated amygdaloid units. The driving could be performed by collaterals of the directly excited units (Fig. 7). Alternatively, the driving could be by trans-synaptic activation from amygdaloid afferent fibres. The excitation may then pass from the synaptically activated units through further synapses in the region, as synaptically driven units with latencies up to

30 ms and indirectly activated units were also found here. Some neurones at all levels of this system are also activated in self-stimulation of the nucleus accumbens septi. The activation is usually trans-synaptic (i.e. synaptic or indirect); it is not clear whether some amygdaloid units are directly excited by the nucleus accumbens stimulation.

2.2 AMYGDALOID NEURONES ACTIVATED BY BRAIN-STIMULATION REWARD IN THE MONKEY

In comparable experiments in the squirrel monkey (*Saimiri sciureus*) it has been shown that neurones in the amygdala fire during self-stimulation (M. J. Burton, S. Cooper, E. T. Rolls, and S. G. Shaw). An example of a track through the lateral amygdala is shown in Fig. 8. The amygdaloid units between the two marks M were activated trans-synaptically during self-stimulation of the hypothalamus and the orbitofrontal cortex. In a series of six squirrel monkeys it has been found that amygdaloid neurones are directly excited by reward-

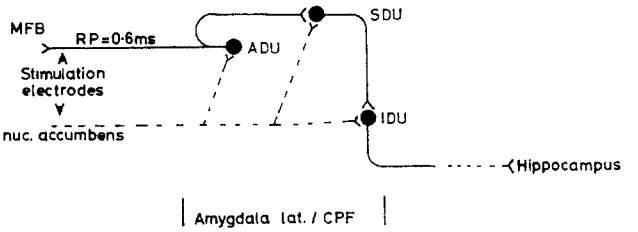

FIG. 7. Schematic diagram to show possible amygdaloid pathways activated in reward, eating, and drinking produced by MFB stimulation. Units in the region of the basolateral amygdala and pyriform cortex (amygdala lat./CPF) antidromically excited (ADU) by the MFB stimulation have absolute refractory periods (RP) of 0.6 ms. Through these, or other neurones, trans-synaptically driven (SDU) and long-latency indirectly driven neurones (IDU) are activated.

ing stimulation of the hypothalamus and trans-synatically activated by rewarding stimulation of the orbitofrontal cortex, nucleus accumbens, lateral hypothalamus, dorsomedial nucleus of the thalamus, and brain stem near the locus coeruleus (Fig. 9). In this way it has been possible to extend work on the rat to a primate.

2.3 THE ABSOLUTE REFRACTORY PERIODS OF NEURONES DIRECTLY EXCITED IN STIMULUS-BOUND EATING AND DRINKING (see Rolls, 1971d, 1973)

2.3.1 *Introduction*

It has been suggested above, on the basis of single-unit recordings in the amygdala, that neurones in the amygdala are involved in eating, drinking, and reward elicited by lateral hypothalamic stimulation. It was shown that the directly excited neurones have a characteristic absolute refractory period of 0.58–0.67 ms. To obtain a further indication of whether these neurones are involved in the eating and drinking, the absolute refractory period of the neurones through which the eating and drinking are elicited was measured. Agreement with

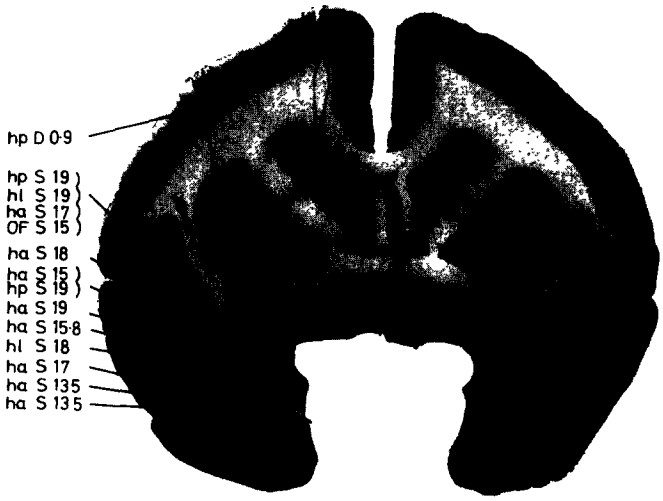

FIG. 8. A micro-electrode track through the squirrel monkey lateral amygdala. Units were trans-synaptically (S) activated from reward sites in the posterior hypothalamus (hp), lateral hypothalamus (hl), anterior hypothalamus (ha), or orbitofrontal cortex (OF) with the latencies (in milliseconds) shown. The track was located by means of the two marks M. The track of the anterior hypothalamic self-stimulation electrode can be seen medially.

the value of 0.58–0.67 ms would provide a further indication that the amygdaloid neurones are involved in the eating and drinking. If another value for the refractory period were found, this would indicate that another group of neurones (e.g. the brain-stem group with a chracteristic absolute refractory period of 0.78–1.0 ms) was involved in the eating and drinking.

The rationale of the refractory period measurements follows that in experiments by Lucas (1917), who measured the refractory periods of axons which innervate the claw of *Astacus*, and by Deutsch (1964), who measured the refractory periods of neurones involved in two different aspects of intracranial self-stimulation (for rationale, see also Gallistel, 1973). If the intrapair interval (IPI) of stimulus pulse pairs exceeds the absolute refractory period of the directly excited neurones, then the neurones fire twice for every pulse pair, and the effects (e.g. eating and drinking) mediated through the neurones will be strong. If the IPI

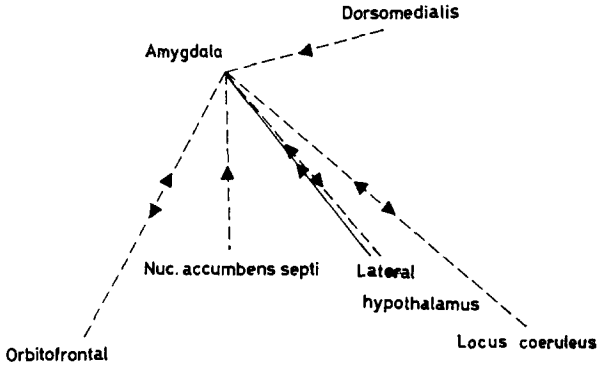

FIG. 9. Summary of self-stimulation sites in the squirrel monkey from which single units in the amygdala are activated. The arrows points towards the recording site. Solid line: neurones directly activated. Dashed line: neurones trans-synaptically activated. Dorsomedialis: nucleus dorsomedialis thalami. Orbitofrontal: orbitofrontal cortex.

is less than the refractory period, then the directly excited neurones will fire once for every pulse pair, and weaker effects will be produced. By measuring the strength of the eating and drinking produced by stimulating with pulse pairs with different IPIs, the absolute refractory period of the neurones involved in eating and drinking was found in the following experiment to be between 0.50 and 0.70 ms.

2.3.2 *Absolute refractory periods of neurones involved in drinking*

Rats which showed drinking during electrical stimulation of the lateral hypothalamus were implanted for the electrophysiological experiments described above and used first in the drinking and eating experiments described here. Negative capacitatively coupled 0.1 ms pulses were applied to the electrode while the rat was in a cage with pellets of laboratory chow and a drinking tube available. The current was increased until the rat showed sniffing and locomotor activity, then set to switch on for 30 s then off for 30 s until a rat ate or drank, or until 1 h had elapsed. If drinking occurred only during the stimulation (stimulus-bound drinking), the rat was used in this experiment.

In an initial experiment conducted with W. K. Beagley, C. R. Gallistel and M. D. Rose at the University of Pennsylvania it was found that the latency to the onset of drinking could be shown to vary with alterations in the IPI of pulse pairs. With short IPIs the rat walked round the cage but did not stop to drink from the tube. With longer IPIs the rat walked round the cage but stopped at the tube and drank until the stimulation was terminated. The latency to the onset of drinking was therefore short. It was as if the stimulation only produced enough thirst to make the rat drink when the IPI was long. The latency to the onset of drinking was therefore used as a measure of the thirst produced by the stimulation.

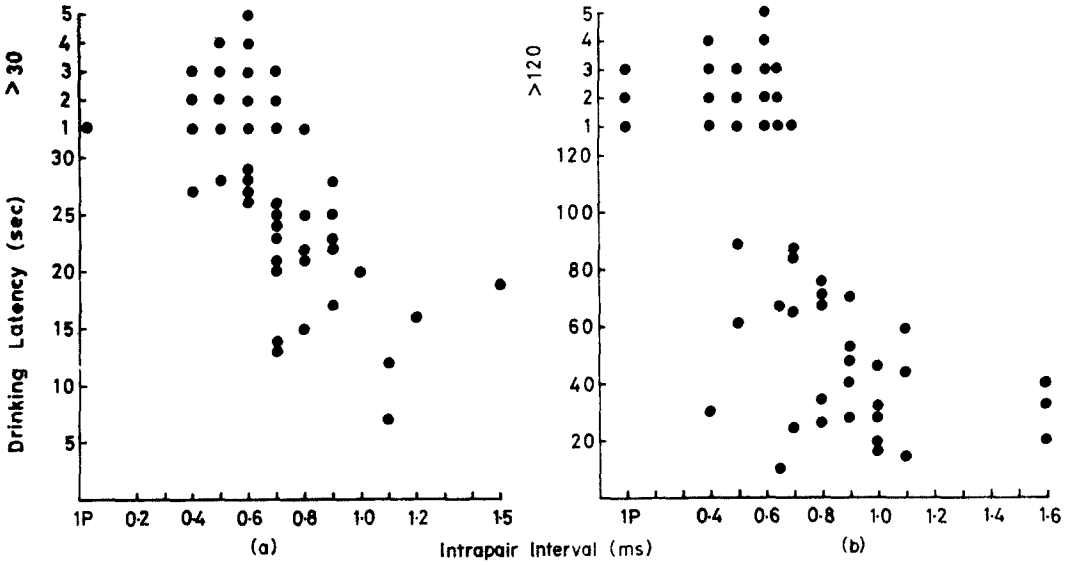

FIG. 10. The latency to drinking in two different rats after the onset of electrical stimulation with pulse pairs with different IPIs. Each point represents one latency measurement. Each time a rat failed to drink in 120 s (or for one rat, 30 s) is shown as a point at the top of the ordinate. The one-pulse (1P) condition is with the second member of each pulse pair omitted. (Modified from *J. comp. physiol. Psychol.* **82**, 15–22, 1973.)

A rat showing stimulus-bound drinking was placed in the test cage with the water tube but not food available. The cage was in a darkened, quiet room. To ensure that an absolute refractory period was measured, the current of the 0.1 ms cathodal pulses was twice that of the threshold value found with a high stimulation frequency (Rolls, 1971b). A frequency of the stimulating pulses was found that elicited drinking only with long latencies (up to 120 s) yet that, when doubled, elicited drinking with much shorter latencies (e.g. 5–20 s) from the onset of the stimulation. This frequency was in the range 10–30 Hz for the different rats. Then pulse pairs at this frequency were substituted for the single pulses. The latency from the start of stimulation to the onset of drinking was measured with a stopwatch as a function of the IPI of the pulse pairs. On each trial the stimulation, with an IPI chosen in random order, was terminated when the animal had shown drinking for 5 s or when a given period (usually 120 s) had elapsed with no drinking. The next stimulation started 1 min later.

The order of IPI was obtained by selecting randomly from the set of values used (Fig. 10). After the set of values had been worked through once, the procedure was repeated a number of times. For some rats, if IPIs were far from the refractory period they were dropped from the set. Trials with the second member of each pulse pair omitted [the one-pulse (1P) condition] were included in the random order of trials.

The latency to the onset of drinking as a function of the IPI of the stimulating pulse pairs for two separate rats is shown in Fig. 10. The number of times drinking did not occur in the given period (usually 120 s) is shown on the extension of the ordinate. It is clear that at the longer IPIs drinking occurs sooner than at the shorter IPIs. The second pulse of each pair starts to become effective (see below) in eliciting drinking at IPIs between 0.55 and 0.70 ms in the different rats. The absolute refractory period of the directly excited neurones involved in the drinking is thus between 0.55 and 0.70 ms.

The refractory period determination on one rat was performed in a Skinner box. The latency to the first bar-press (for 0.05 ml of water) was measured. (After 5 bar-presses the brain stimulation was terminated.) As the results in this rat are similar to those in the other 3 rats, the refractory period determinations hold not only for the consummatory response of drinking water but also for the instrumental response of pressing a bar to obtain water.

The results were tested statistically. To determine the IPI at which the second pulse of each pair became effective, the results for each IPI were compared with the results for the shortest IPIs (usually for 0.4 and 0.5 ms combined) at which it was clear that the second pulse was not effective (Fig. 10). The latter was judged by the observation that IPIs of 0.4 and 0.5 ms were usually not more effective than the one-pulse condition (e.g. rat 122) and that a clear refractory period discontinuity appeared at longer IPIs. Also, very few neurones have absolute refractory periods less than 0.4 ms. The results at the different IPIs were compared with the Mann–Whitney U test, one-tailed (Siegel, 1956). For rat 128 (Fig. 10b), with the results for 0.4, 0.5, and 0.6 ms combined as the base line, $p \gg 0.05$ at 0.65 ms, $P = 0.01$ at 0.70 ms, and $p < 0.01$ at each longer IPI. The refractory period for rat 128 is therefore between 0.65 and 0.70 ms. Similarly (see Rolls, 1973), for the other rats the refractory periods were between 0.55 and 0.60 ms, 0.60 and 0.70 ms, and 0.60 and 0.70 ms. For the 4 rats the values agree closely in giving a value between 0.55 and 0.70 ms for the absolute refractory period of the directly excited neurones involved in the drinking.

In rat 122 the result for IPIs at 0.4 and 0.5 ms are very similar to those for the one-pulse condition, in which the second member of each pulse pair was omitted. In the other rats, the 0.4 and 0.5 ms conditions produced effects that are a little greater than the one-pulse condition (see also section 2.3.3). This latter effect may be due to a small after-effect of the first pulse summating with the second pulse 0.4 or 0.5 ms later.

2.3.3 *Absolute refractory periods of neurones involved in eating*

The procedure was similar to that used for drinking except as stated here. Three rats, different from those used above, showed stimulus-bound eating in the initial test and were the subjects in this experiment. The latency to the onset of eating was measured in the test cage which had a false floor of wire mesh so that unfinished pellets of food would drop through and become inaccessible to the rat. The water-bottle was removed. In one corner of the cage was a watchglass into which 45 mg Noyes food pellets could be introduced through a polythene guide tube. Two pellets were kept in the watchglass and replaced when the rat ate. Sixty seconds after a previous trial the stimulation was switched on with a randomized IPI. It was switched off when the rat had placed a pellet in its mouth and was chewing it, or

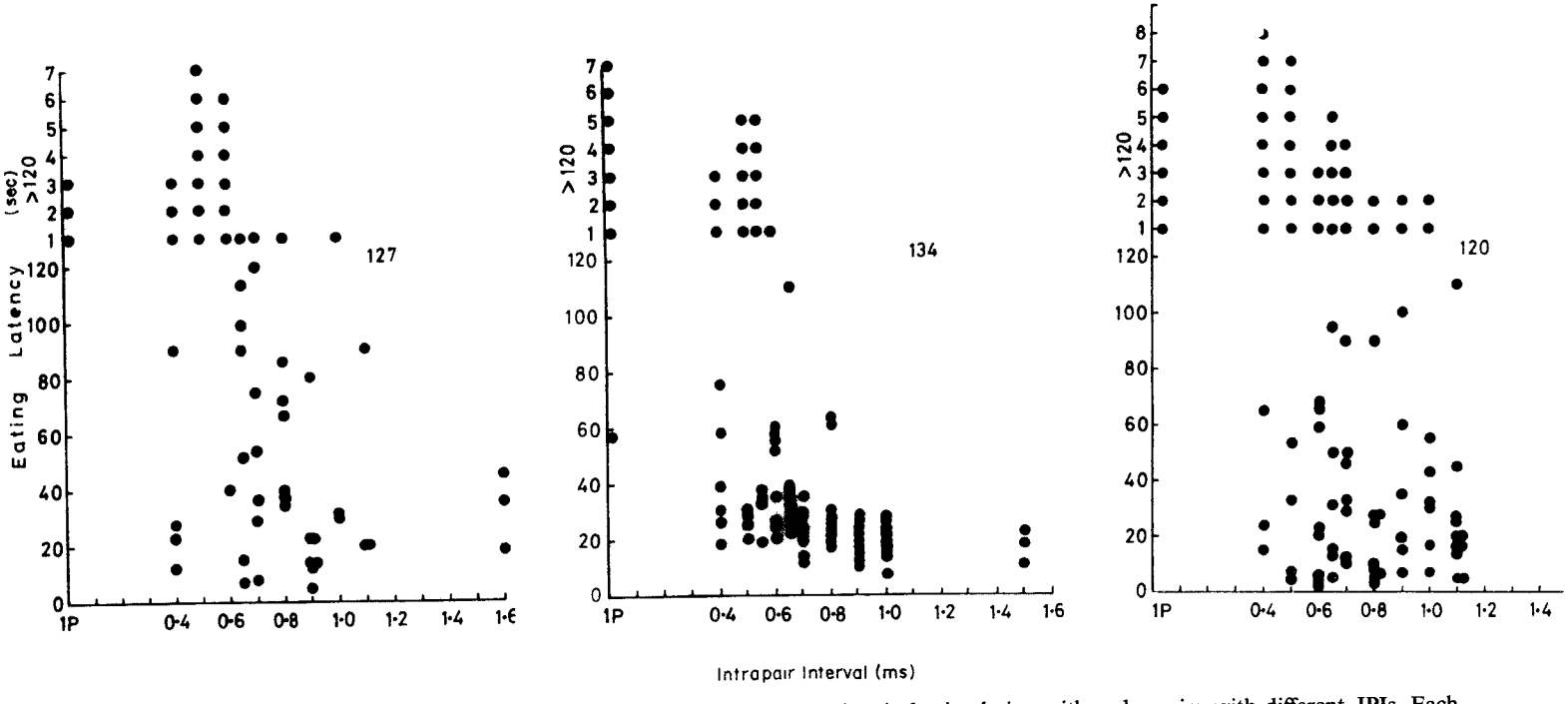

FIG. 11. The latency to eating in three different rats after the onset of electrical stimulation with pulse pairs with different IPIs. Each point represents one latency measurement. Each time a rat failed to eat in 120 s is shown as a point at the top of the ordinate. The one-pulse (1P) condition is with the second member of each pair pulse omitted. (From *J. comp. physiol. Psychol.* **82**, 15–22, 1973.)

when 120 s had elapsed without eating. As in the drinking-test procedure, a stimulation frequency was used which, when doubled, produced shorter latencies to the onset of eating.

The latency to the onset of eating as a function of the IPI of the stimulating pulse pairs for three different rats is shown in Fig. 11. The second pulse of each pair starts to become effective at IPIs in the range 0.50–0.65 ms in the different rats. Statistical analysis, as for the drinking, confirmed this. The absolute refractory period of the neurones involved in eating is thus between 0.50 and 0.65 ms.

2.3.4 *Conclusions*

These experiments show that both eating and drinking become more intense when the IPI of stimulating pulse pairs is greater than 0.50–0.65 ms. This indicates that the absolute refractory periods of the directly excited neurones which mediate the eating or drinking are between 0.50 and 0.70 ms. This value corresponds with that of the amygdaloid neurones directly excited in the eating and drinking. The findings therefore support the suggestion made on the basis of electrophysiological evidence that neurones in the amygdala are involved in eating and drinking elicited by lateral hypothalamic stimulation.

If the amygdaloid neurones whose refractory periods are shown in Fig. 3 are involved in the elicited eating and drinking, then a sudden increase in the strength of the eating or drinking should occur between 0.58 and 0.67 ms, but the strength should increase further as the IPI is increased. This is in general what is seen in Figs. 10 and 11. Other factors which contribute to this effect are discussed elsewhere (section 4.7; Rolls, 1971b).

The main conclusion here is that at IPIs of 0.50–0.65 ms eating and drinking become more intense than at shorter IPIs. This finding is probably due to refractoriness of the directly excited neurones. Neurones with longer refractory periods are excited by the same stimulation (see section 4), and may well be involved in some aspect of the elicited eating and drinking. For example, the duration of time spent drinking and the amount of water consumed in this type of experiment appear to reflect the activation of neurones with refractory periods of 0.8–1.0 ms (Hu, 1971; J. W. Hu, personal communication, 1972). Through these neurones, arousal may be produced (section 4). The general conclusion is that several neural systems may be involved in stimulus-bound drinking (and eating) but that one of the systems has neurones with short refractory periods of 0.50–0.65 ms. This system appears to be specifically related, for example, to thirst, in that animals will only stop at the drinking tube to drink if this system is activated (Rolls, 1973). The conclusion from these experiments is, therefore, that under at least some conditions firing in neurones with absolute refractory periods of 0.50–0.65 ms limits is involved in stimulus-bound eating and drinking. This provides an indication that the amygdaloid neurones directly excited by the hypothalamic stimulation are involved in the eating and drinking. To test this suggestion, the effects of anaesthetization and lesions of the amygdala on eating and drinking were determined.

2.4 EFFECTS OF LESIONS AND ANAESTHETIZATION OF THE AMYGDALA ON EATING, DRINKING, AND REWARD PRODUCED BY ELECTRICAL STIMULATION OF THE BRAIN

2.4.1 *Lesions of the amygdala and brain-stimulation reward*

To determine whether the amygdaloid neurones activated in lateral hypothalamic self-stimulation are involved in the self-stimulation, bilateral amygdaloid lesions were made in

rats previously tested for self-stimulation (Kelly, 1974). The threshold for the self-stimulation, measured by the lowest current for which the rats would maintain steady bar-pressing, was increased markedly in some rats for a few days following the lesions. This suggests that the amygdala may be involved in the reward. Recovery, measured by a return of the threshold to the pre-lesion level, occurred after a few days. This recovery may mean that the amygdala is not essential for brain-stimulation reward, or that only a part of a region essential for self-stimulation was damaged. Because the results were inconclusive and could have been due to a general effect associated with the lesion, the reversible technique of anaesthetization of the brain was applied to the problem instead. The finding with the amygdaloid lesions is consistent with that of Ward (1961), who found that bilateral ablation of the amygdala did not prevent the appearance of tegmental self-stimulation on electrodes implanted later.

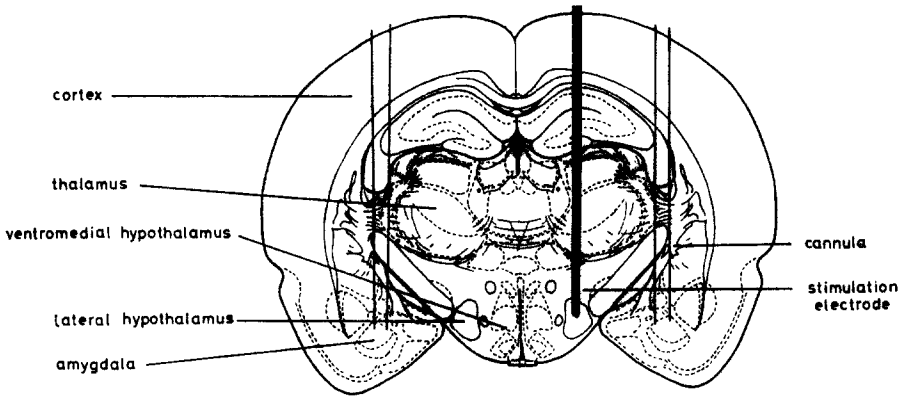

FIG. 12. Local anaesthetic was applied bilaterally through the cannulae to the basolateral amygdala during reward, eating, and drinking produced by lateral hypothalamic stimulation.

2.4.2 *Anaesthetization of the amygdala and brain-stimulation reward*

To obtain further evidence on whether the amygdaloid neurones activated in lateral hypothalamic self-stimulation are involved in the self-stimulation, the region of the activated amygdaloid neurones was anaesthetized during self-stimulation (Kelly, 1974). Guide cannulae (Epstein *et al.*, 1970; Rolls and Jones, 1972) were implanted to end near the amygdala (Fig. 12). During an experiment, injection cannulae filled with 5% procaine HCl, a local anaesthetic, were placed in the guide cannulae with their tips flush with the ends of the guides. The injection cannulae were connected by flexible polythene tubing to Hamilton micro-syringes. After the threshold current for self-stimulation had been obtained, small volumes (usually 1–2 μl) of the procaine were injected bilaterally into the amygdala. A typical finding is shown in Fig. 13. Within 30 s of the injection, the rat stopped self-stimulating, and would not re-start even when priming (free) stimulation was given (P). Only when a higher current was given would the rat start self-stimulating. The effect wore off after 10–15 min. This type of finding was repeated many times in different rats. It is concluded that bilateral anaesthetization of the amygdala attenuates lateral hypothalamic self-stimulation. This finding provides further evidence that the amygdala is involved in lateral hypothalamic self-stimulation.

2.4.3 *Anaesthetization of the amygdala and stimulus-bound eating and drinking*

To provide further evidence on whether the amygdaloid neurones activated in stimulus-bound eating and drinking are involved in the eating and drinking, a local anaesthetic, procaine HCl, was injected into the region of activated neurones (Kelly, 1974). Eating or drinking, which normally occurred during 60 s periods of lateral hypothalamic stimulation, did not occur for approximately 15 min following a bilateral injection of 1–2 μl of 5% procaine hydrochloride into the basolateral amygdala. The effect was not a general suppression of the effects of the stimulation in that there was no regular effect of the injections on locomotor activity elicited by the same stimulation. (This is also relevant to the experiment described in section 2.4.2.) These observations provide further evidence that activation of amygdaloid neurones is involved in eating or drinking produced by lateral hypothalamic stimulation.

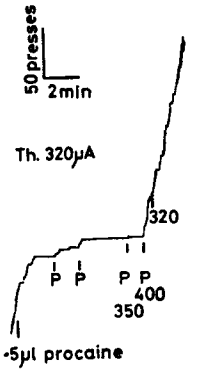

FIG. 13. Effect of bilateral injection of procaine HCl into the basolateral amygdala on lateral hypothalamic self-stimulation. Each time the rat presses the bar, the trace steps up (see calibration). The threshold for self-stimulation was 320 μA. Within 2 min of the injection, self-stimulation ceased. It could not be reinstated, even by priming (P) at 350 μA. After several minutes, as the procaine became ineffective, priming at 400 μA did start self-stimulation.

2.5 EFFECTS OF LESIONS OF THE AMYGDALA ON NATURAL EATING AND DRINKING

(see also Rolls, E. T. and Rolls, B. J., 1973; and Rolls, B. J. and Rolls, E. T., 1973)

2.5.1 *Introduction*

The experiments described above indicate that neurones in the amygdala are involved in eating, drinking, and reward produced by electrical stimulation of the lateral hypothalamus. The experiments suggest that the amygdala is involved in natural eating and drinking. One possibility, consistent with the role of the amygdala in reward, is that the amygdala sends signals towards the lateral hypothalamus which can alter food and water intake, by making food, for example, either rewarding or aversive (see section 7.2). To investigate the role of the amygdala in eating and drinking, bilateral lesions were made in the basolateral region of the amygdala. This is the region in which neurones are activated in eating and drinking produced by lateral hypothalamic stimulation (see Fig. 6).

2.5.2 *General effects of lesions of the amygdala on eating and drinking*

Bilateral lesions were made with platinum–iridium electrodes in the basolateral region of the amygdala of anaesthetized rats. On the basis of the histology performed at the end of the experiments, the rats were retrospectively divided into two main groups. Thirty-three rats with bilateral lesions in the region of the lateral amygdala and pyriform cortex formed the Am group. Thirteen of these 33 rats with lesions which bilaterally and symmetrically destroyed the basolateral region of the amygdala formed the BL group. Examples of lesions in the BL group of animals are shown in Fig. 14. The lesions are in the area in which neurones activated in stimulus-bound eating and drinking are found (section 2.1.2; Rolls, 1972). The body weights and growth rates of the lesioned animals in the BL and Am groups were very similar to the controls (e.g., in 14 days, immediately postoperatively for the lesioned groups, the Am group gained 37 g, the BL group 29 g, and the 19 lesioned control rats gained 34 g). Therefore the lesions in the basolateral region of the amygdala do not appear to produce any major impairment in the control of body weight and food intake. An alteration in feeding behaviour was nevertheless predicted, and so sensitive tests of feeding behaviour (described below) were performed. A similar conclusion was reached about the effects of the lesions on drinking. No major effects on daily water intake were observed (Fig. 15). Some rats drank more after the lesions, and others drank less (note the increased variance of the Am group), and, on average, the lesioned rats drank a little more water than the control rats (Fig. 15).

The controls of thirst in the amygdala-lesioned rats were tested more specifically (Rolls, B. J. and Rolls, E. T., 1973). One control of drinking involves an osmotic (cellular) stimulus (Fitzsimons, 1961a, b). The injection of substances which produce cell shrinkage (e.g. hypertonic NaCl, but not hypertonic urea which crosses cell membranes) stimulates drinking. The experimental procedure followed that of Fitzsimons (1961a). Because the procedure involved nephrectomy, this was the last experiment to be performed on the rats. The number of rats left had decreased in the amygdala-lesioned group to 17 and in the control group to 13. The rats, in water balance at the start of the experiment, were anaesthetized with ether, nephrectomized bilaterally to prevent excretion of the salt load, given an i.p. injection of 0.5 ml per 100 g of 2 M NaCl, replaced in their cages, allowed to recover from the ether, and given access to water in a column, but no food, for 6 h. The water intake at the end of the 6 h period was measured. The water intake of the amygdala-lesioned group was 4.77 ± 0.50 ml per 100 g and of the control group 5.43 ± 0.48 ml per 100 g. There is no significant difference between these means ($t = 0.93, p > 0.3$). It is concluded that there is no deficit in the regulation to a cellular stimulus of drinking in these amygdala-lesioned rats.

A second group of stimuli can also initiate drinking. Extracellular stimuli, e.g. haemorrhage, produce a decrease in extracellular fluid volume without any change in osmotic pressure (Fitzsimons, 1961b). The renin–angiotensin system appears to mediate the response of rats to at least some extracellular stimuli of thirst (Fitzsimons, 1969; Fitzsimons and Simons, 1969). To test whether this drinking system is intact in the amygdala-lesioned rats, isopreterenol (isoprenaline), which is thought to stimulate drinking through the renin-angiotensin system (Houpt and Epstein, 1971), was given to the lesioned and control rats. Fourteen amygdala-lesioned and 12 control rats in water balance were lightly anaesthetized with ether and given a s.c. injection of 0.04 mg/kg of isoproterenol (Suscardia, or isoprenaline hydrochloride, Pharmax Ltd.). After recovery from the anaesthetic they were replaced in their cages with a water column but no food available. Water intake was

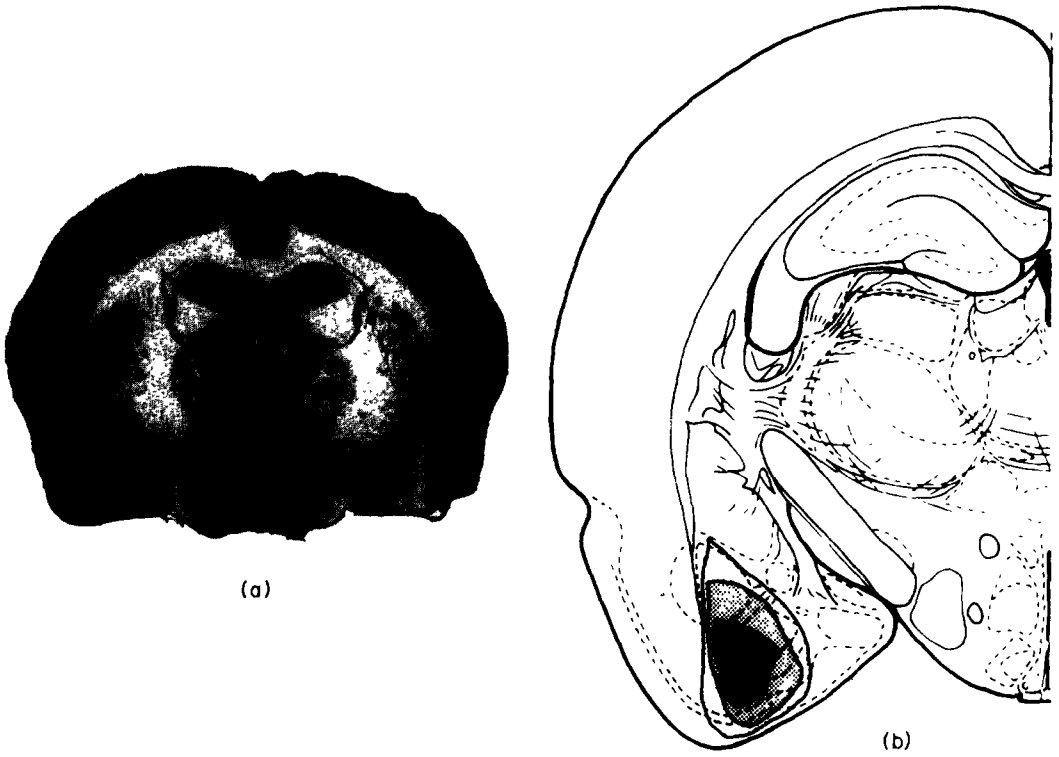

FIG. 14. (a) Example of lesions typical of the animals with lesions in the basolateral region of the amygdala (BL group). (b) Reconstruction of lesions of the 11 rats in the BL group. (The common region damaged bilaterally in 8, 5, and 3 of the 11 rats is shown by the contours. For example, the overlap region of the lesions in 8 of the rats is shown by the innermost, most densely shaded area.) The lesions destroyed a basolateral region of the amygdala. (Outline drawing from König and Klippel, 1963, plate 37b.) (Modified from *J. comp. physiol. Psychol.* **83**, 248–59, 1973.)

measured over 3 h. The water intake of the amygdala-lesioned rats was 1.51 ± 0.14 ml per 100 g and of the control rats 1.60 ± 0.14 ml per 100 g. These means are not significantly different ($t = 0.50$, $p > 0.6$). The standard deviations (0.52 and 0.48) are also very similar. It is concluded that the response to isoproterenol is normal in the amygdala-lesioned group. If isoproterenol acts through the renin-angiotensin system (Houpt and Epstein, 1971), and this is involved in drinking to some extracellular stimuli, then at least this aspect of the extracellular control of water intake is normal in the amygdala-lesioned rats.

In conclusion, no major impairments in the controls of food and water intake were found in the experiments described. Only in different types of test, in which previous experience with food or fluid seemed to be important, were major abnormalities in the ingestive behaviour of the amygdala-lesioned rats found (see sections 2.5.3 and 2.5.4).

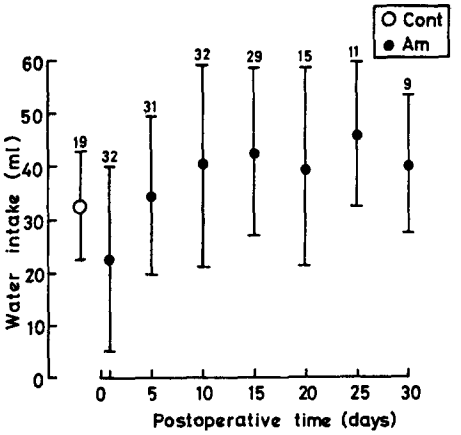

FIG. 15. Overnight water intake ($M \pm SD$) of the amygdala-lesioned rats. The rats were lesioned on day O. For comparison, the overnight water intake ($M \pm SD$) of the control rats averaged over the whole period is shown on the left of the abscissa. The number of rats over which the intake was averaged is shown above each point of the graph. (From *J. comp. physiol. Psychol.* **83**, 240–7, 1973.)

2.5.3 *Altered food preferences after lesions in the basolateral region of the amygdala*

The food preference tests showed that rats with the bilateral amygdaloid lesions were willing to accept new foods, in contrast to normal rats which eat only small quantities of new foods, and instead eat familiar food. The "neophobia" of normal rats probably ensures that rats do not ingest large quantities of dangerous material (Barnett, 1958; Rozin, 1968). Because the amygdala-lesioned rats do not show this neophobia, it appears that the amygdala is involved in the effects of previous experience on food intake.

For a food-preference test a rat was deprived of food overnight and tested in the morning. The rats were tested in a cage which contained 6 food cups. Each food cup contained about 5 g of chopped uncooked food as shown in Fig. 16. A stopwatch was started when the rat was placed in the cage, and the time when a rat started and stopped eating each type of food was noted. Eating was defined as picking up food, biting and chewing it, and ingesting it. After 10 min the rat was removed from the cage, and the times spent eating each type of food were determined. The normal food of the rats, laboratory chow, was given to the animals much

later in the afternoon. A rat was tested only once a day with a minimum of 2 days between tests.

In all the food tests the general behaviour of the three groups of animals in the test cage was similar. On being placed in the test cage, a rat typically explored the cage for the first 30–90 s, sniffing and sometimes tasting the foods during this period. Then the rats started to eat the foods, typically eating a particular food for 15–60 s, then moving on to eat another food. Thus in almost all the tests every food was sampled by the rats. Differences between groups of rats arose because some rats repeatedly returned to a particular food to eat it rather than other foods.

The three groups of animals ate for very similar lengths of time (controls for 196 $\pm$ 21 s, Am for 231 $\pm$ 16 s, BL for 245 $\pm$ 27 s). (The variance figure given throughout is the standard error of the mean.) These times are not significantly different from each other (i.e. $p > 0.05$) (two-tailed t-tests are used here).

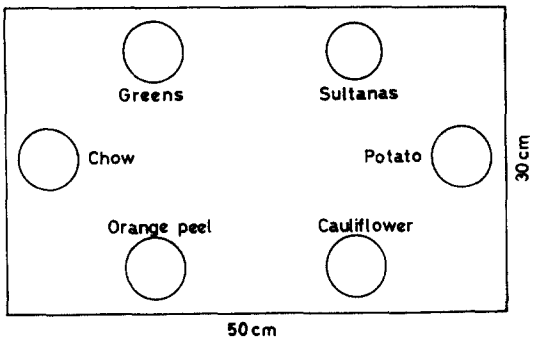

FIG. 16. Plan of arrangement of foods in the wire-mesh test cage. Each food was in a container 1.0 cm high. (From *J. comp. physiol. Psychol.* **83**, 248–59, 1973.)

The Am and BL groups show very different preferences from the controls. The food preferences of a rat were expressed by converting the time on each food to a percentage of the rat's total eating time. In Fig. 17 the percentages for each food have been averaged over the different animals in each group. As well as the mean, the standard deviation of the mean percentage of the time a group of rats ate each food was also calculated. A two-tailed t-test was used to determine whether a group of rats ate a particular food for a different time to another group of rats. The Am group ate less chow than the controls ($p < 0.001$) and more sultanas ($p < 0.02$) and more cauliflower ($p < 0.05$). The BL group ate less chow than the controls ($p < 0.001$) and more sultanas ($p < 0.01$) and more cauliflower ($p < 0.01$). Other differences were not significant. The altered food preferences were more extreme in the BL than the AM group (Fig. 17) although a direct comparison of the BL and Am groups on each of these foods just failed to reach significance (at the 0.05 level).

It can be concluded that the rats with amygdala lesions, particularly in the basolateral region of the amygdala, spend much less time eating their familiar chow and more time eating sultanas and cauliflower than the controls when placed in the test situation for the first time.

The control group of rats ate little of the unfamiliar food, consuming chow for 64% of the eating time. They just sampled the unfamiliar foods. It may be stressed that the chow was

familiar because it was normally available in the home cages. The rats with amygdala lesions sampled and ate the new foods, eating chow for only 34% (Am) or 20% (BL) of their eating time.

It is possible that when the normal rats sampled the new foods they found them unpalatable and therefore ate chow. To determine whether a palatable food would coax the normal rats away from the chow in the second food preference test given to the rats, chocolate chip cookies, which are reputed to be highly palatable to rats (Teitelbaum and Epstein, 1962), were included in the food test. The food preferences of the rats showed that although the amygdala-lesioned rats found the cookies very palatable, the normal rats could not be coaxed away from their familiar chow (Fig. 18).

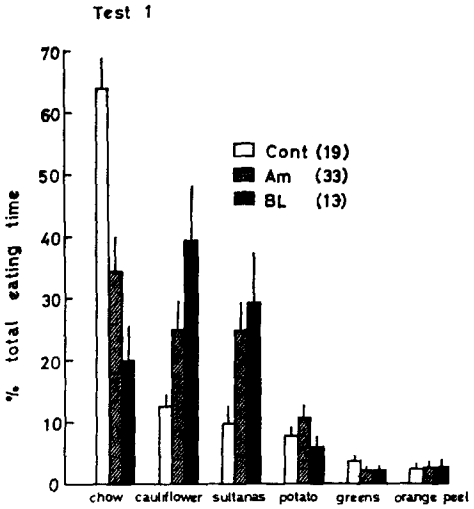

FIG. 17. Food preferences of amygdala-lesioned rats (Am and BL) and control rats. The BL group had symmetrical lesions in the basolateral region of the amygdala. The number of rats in each group is indicated in parentheses. In this and subsequent figures preferences are indicated by the mean percentage of the total times (histograms ± SE) that the rats ate each food. (From *J. comp. physiol. Psychol.* **83**, 248–59, 1973.)

To determine whether lack of familiarity with the foods apart from the chow was the factor which made the normal rats eat chow, a group of the normal rats were repeatedly re-tested in the food preference situation. The normal rats gradually started to eat a greater proportion of the previously unfamiliar foods. As shown, e.g. in Fig. 19, the 12 normal rats ate a smaller proportion of chow than they ate in test 2 ($p < 0.05$) and greater proportions of cookies and cauliflower. Other examples of this gradual acceptance of previously unfamiliar foods by the normal rats are shown in Rolls, E. T. and Rolls, B. J. (1973), figs. 5 and 8. It is also shown there that after repeated testing of the amygdala-lesioned rats and the normal rats, their food preferences become very similar (*ibid.*, fig. 8). These experiments suggest that the basolateral region of the amygdala is involved in ingestive behaviour, and, in particular, mediates the effects of previous experience on food intake. In particular, the rats with amygdala lesions did not show the normal response to unfamiliar foods, "neophobia". Whether the amygdala also is involved in the effects of previous experience on drinking is considered below.

2.5.4 *Alterations in drinking produced by lesions in the basolateral region of the amygdala*

As shown above, specific thirst tests failed to show a deficit in regulatory drinking in the lesioned animals. To determine whether the fluid ingestion of amygdala-lesioned rats is guided normally by experience, a "learned aversion" experiment was performed. Normal

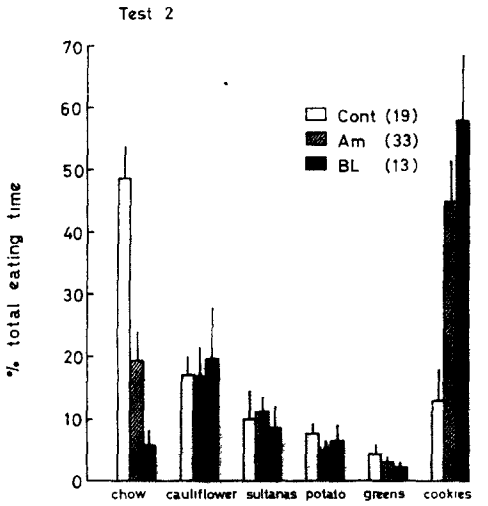

FIG. 18. Food preferences of the amygdala-lesioned (BL and Am groups) and control rats in test 2 in which cookies replaced the orange peel of test 1. (From *J. comp. physiol. Psychol.* **83**, 248–59, 1973.)

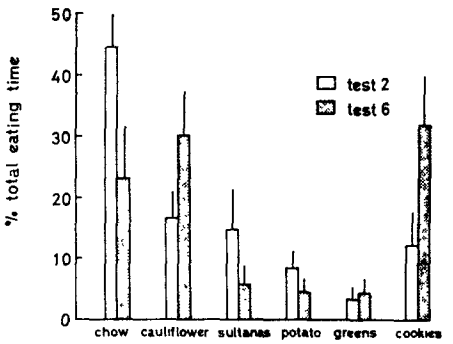

FIG. 19. Food preferences of 12 control rats in test 6, in which the foods were the same as those available in test 2. For comparison, the food preferences of the same 12 control rats in test 2 are shown in the unshaded histogram. (From *J. comp. physiol. Psychol.* **83**, 248–59, 1973.)

rats poisoned by the ingestion of LiCl subsequently avoid LiCl and NaCl (Nachman, 1963). In this type of learning, the experience of ingesting LiCl and feeling ill comes to guide subsequent behaviour.

Ten of the amygdala-lesioned and 16 of the control rats were the subjects of this experiment. On day 1 the rats were put on a 23 h water deprivation schedule, with chow continu-

ously available. On day 4, 0.12 M LiCl instead of water was available in the drinking column. The columns were removed when the rats had drunk 8 ml or after 15 min, whichever was sooner. Because some of the amygdala-lesioned rats drank only small volumes of the LiCl solution, the intakes of 6 of the control rats were restricted to 2–3 ml (see Fig. 20). The 8 ml value was chosen so that the sickness should not be severe, and no pronounced sign of sickness was seen. Nachman's (1963) albino rats showed sickness by lying down on the floors of their cages, but they consumed an average of 9 ml of 0.12 M LiCl solution. Food and water were available *ad lib* for the night of day 4, and for days 5 and 6. On night 6 the rats were water deprived, and on day 7 the drinking response to 0.12 M NaCl was measured. At the

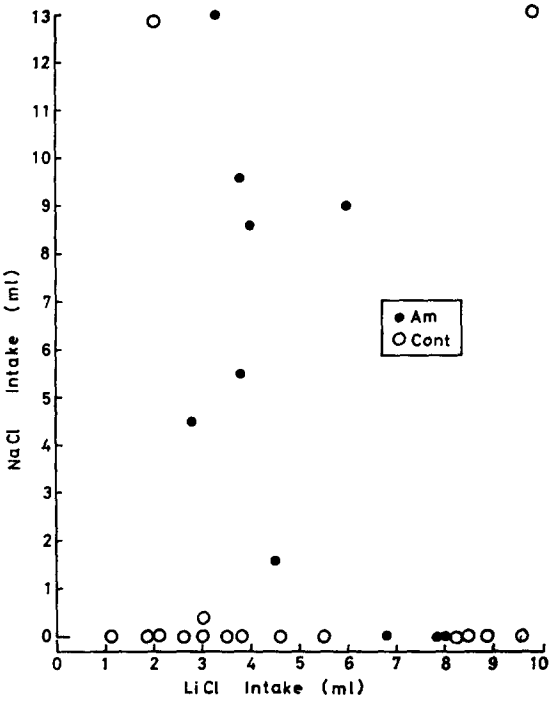

FIG. 20. The NaCl intake on the second test as a function of LiCl intake on a first test in a learned-aversion experiment. (From *J. Comp. Physiol. Psychol.* 83, 240–7, 1973.)

end of 30 min the amount drunk was noted and the experiment was terminated. The NaCl solution was used because rats react to it as to LiCl when tested for learned aversion, yet the NaCl does not make the rats sick a second time (Nachman, 1963).

It is shown in Fig. 20 that in general the amygdala-lesioned rats drank the NaCl solution when tested for the learned aversion and the control rats did not. If the animals which drank 6 ml or less of LiCl are considered, the 7 amygdala-lesioned rats drank significantly more NaCl than the 11 controls ($p < 0.001$, Mann–Whitney U-test, one-tailed). (The result is also significant when all the rats are considered.) It is clear from Fig. 20 that all these Am rats drank the NaCl and failed to show learned aversion, and that all but one of the control rats drank almost no NaCl, and showed learned aversion.

Three of the rats in the Am group drank more than 6 ml of LiCl, and subsequently drank no NaCl. It appears that the intake of the poisonous LiCl necessary to produce learned aversion in these animals is at least three times that which is effective in the control rats (Fig. 20).

In this experiment it was found that in the Am rats the ingestion of a poison had little effect on the subsequent intake of a solution like the poison. The control of fluid intake by previous experience appeared to be deficient in the lesioned rats. With large LiCl intakes, learned aversion was apparent, and thus learning was not completely impossible in the lesioned animals. Although it is possible that the amygdala lesions resulted in less sickness after ingestion of LiCl, it appears more likely that it was learning which was impaired in the situation.

2.6 CONCLUSIONS AND DISCUSSION ON THE ROLE OF THE AMYGDALA IN BEHAVIOUR

The experiments described above form a sequence starting with the electrophysiological demonstration that neurones in the basolateral amygdala are activated by electrical stimulation which produces eating, drinking, and reward, proceeding through the refractory period and anaesthetization experiments which suggest that the activated amygdaloid neurones are involved in the eating, drinking, and reward, and coming to the lesion experiments which indicate that the basolateral region of the amygdala is involved in the effects of previous experience on natural eating and drinking. Taken together, the experiments suggest that neurones with cell bodies in the basolateral region of the amygdala project to or through the lateral hypothalamus, and suppress eating or drinking under conditions dependent on previous experience. Two specific examples of the type of previous experience are neophobia and learned aversion. The evidence that the lateral hypothalamus is on this functional pathway is, firstly, that the amygdaloid neurones are excited by lateral hypothalamic stimulation, and, secondly, that lesions of the lateral hypothalamus also impair learned aversion (in "recovered lateral" rats—Teitelbaum, 1971; Roth *et al.*, 1973). The above indications of the nature of the pathways running between the amygdala and the hypothalamus are consistent with what is known of the anatomy (Cowan *et al.*, 1965; Lammers, 1972) and neurophysiology (Dreifuss, 1972; Egger, 1972; Murphy, 1972; van Atta and Sutin, 1972) of amygdalo-hypothalamic connections.

To be able to alter the intake of a particular food or fluid on the basis of previous experience, the basolateral region of the amygdala would appear to need an input of incoming sensory information. Information from memory about the consequences of the previous ingestion of the food or fluid would also have to be provided, either from within the amygdala or by the incoming pathways. Among the known inputs to the amygdala are olfactory inputs in the rat (Powell *et al.*, 1965), and an input from visual regions of the temporal lobe in the monkey (Jones and Powell, 1970). A function of the basolateral region of the amygdala in ingestive behaviour could be to produce a signal to inhibit ingestion from these sources. This signal would then be led to the hypothalamus by the amygdalo-hypothalamic pathways, as described above, to modulate ingestion on the basis of incoming sensory information and previous experience. Alteration of this modulatory influence on the hypothalamus by, for example, anaesthetization of the amygdala, could affect hypothalamic self-stimulation. But because the amygdalo-hypothalamic pathways may normally only modulate hypothalamic systems, the pathways may not be essential for the operation of these systems

in eating, drinking, and reward. The pathways appear to be more critically involved in the modulation of hypothalamic systems on the basis of previous experience, and this function may extend to the formation of stimulus-reinforcement associations in general (see section 7.3).

3. The Role of the Prefrontal Cortex in Brain-stimulation Reward

3.1 INTRODUCTION

During electrophysiological experiments in which a search was made for neurones activated by brain-stimulation reward (Rolls, 1970, 1971a, 1972) it was noticed that in general rather few activated neurones were found in the neocortex. One exception is the cingulate cortex (see section 5.3), in which a number of activated neurones are found. But in experiments on the prefrontal cortex it has been shown that a large number of prefrontal neurones are activated by brain-stimulation reward (Rolls and Cooper, 1973). Further, neurones in the prefrontal cortex are activated from many different self-stimulation sites as described below.

The prefrontal cortex in the rat, defined as the projection field of the mediodorsal nucleus (MD) of the thalamus, has been identified by Leonard (1969) using the Fink–Heimer silver technique for tracing degenerating fibres. The sulcal prefrontal cortex forms the dorsal bank of the rhinal sulcus. It is reciprocally connected with the medial division of MD, and in this respect is similar to the caudal orbitofrontal cortex of the rhesus monkey. The medial cortex forms the medial wall of the hemisphere anterior and dorsal to the genu of the corpus callosum. It is reciprocally connected with the lateral division of MD. The dorsal sector of this medial cortex (the "shoulder" region) may be comparable to the caudal prefrontal cortex (Brodmann's area 8, the frontal eye-field) of the monkey, while the remainder of the medial cortex may be homologous with the major part of the monkey's frontal convexity cortex (Leonard, 1969, p. 338).

3.2 ACTIVATION OF NEURONES IN THE PROFRONTAL CORTEX BY BRAIN-STIMULATION REWARD

To determine whether neurones in the prefrontal cortex are activated in brain-stimulation reward, rats were implanted with electrodes and tested for self-stimulation. Then recordings from single units in the prefrontal cortex were made in the anaesthetized animal while stimulation was applied to the self-stimulation electrodes. To ensure that all the neurones activated in the electrophysiological experiment had also been activated during self-stimulation, only currents near the threshold value for self-stimulation were used during the electrophysiology. To determine whether activation of neurones in the prefrontal cortex was characteristic of self-stimulation, a number of different self-stimulation sites were used, and also effects from a non-reward site were investigated. In the only other electrophysiology performed on the prefrontal cortex during brain-stimulation reward, Ito and Olds (1971) found approximately 6 neurones in the pregenual frontal (4 probably in the medial prefrontal) cortex which were activated in hypothalamic self-stimulation.

In the present experiments (Rolls and Cooper, 1973, 1974b) one self-stimulation electrode was aimed at the lateral hypothalamus (level head coordinates, 3.0 mm behind bregma, 1.5 mm lateral to the sagittal sinus, and 7.6 mm beneath the dura, (i.e. −3.0:1.5:7.6 mm down). Other electrodes were aimed at the medial prefrontal cortex (+2.5:0.5:2.5 mm down),

the midbrain tegmentum ventrolateral to the central grey (−5.5:1.2:5.5 mm down) and sometimes at the nucleus accumbens (+1.6:1.0:4.6 mm down). A large exposure of the dura was not made at this stage, but enough skull was removed round each electrode shaft to ensure that the dura could be exposed later for the insertion of micro-electrodes without touching the stimulating electrodes. The electrodes were held in an electrode assembly which was cemented to the skull contralateral to and thus clear of the stimulating electrodes. Two days later the rats were tested for self-stimulation. Each rat was placed in a cage which contained a lever. A 0.3 s train of 0.1 ms constant current cathodal pulses, at a frequency of 100 Hz, was applied to the electrode under test when the rat pressed the lever. Current return was by the screws in the skull which held the electrodes. Lateral hypothalamic and tegmental electrodes, classed as positive for self-stimulation, supported self-stimulation rates of more than 30 lever-presses per minute, and positive nucleus accumbens and medial prefrontal cortex sites produced rates of more than 10 lever-presses per minute. The current and the voltage of the stimulating current, which just supported self-stimulation, were found for each positive electrode.

The electrophysiological experiments on the prefrontal cortex followed methods similar to those used for the amygdala (see section 2.1), except that single-unit activity was recorded with capillary micro-electrodes filled with pontamine sky blue dye (6BX, George T. Gurr Ltd., London) made up as a 2% solution in 0.5 M sodium acetate so that marks could be made to locate units. Passage of a cathodal current of up to 50 μA for 60 s, higher than that previously used (Hellon, 1971), was found to increase the chance of producing a mark which could be found easily. The method enabled the location of single units recorded with capillary micro-electrodes to be determined satisfactorily. Single units activated by the 0.1 ms stimulus pulses applied to the reward sites were classed as directly excited or trans-synaptically activated.

In electrophysiological experiments on 19 rats previously tested for self-stimulation, it was found that single units in the sulcal and the medial prefrontal cortex were excited during self-stimulation of the lateral hypothalamus, midbrain tegmentum, pontine tegmentum near the locus coeruleus, nucleus accumbens, and medial prefrontal cortex (Rolls and Cooper, 1973, 1974b). Two further points indicate that activation of neurones in the prefrontal cortex appears to be closely related to brain-stimulation reward. First, units in other neocortical areas (apart from the cingulate cortex, section 5.3) have not been found to be activated by the reward. Second, there is some evidence (see below) that activation of the prefrontal cortex is found more often from reward sites than from non-reward sites in the tegmentum.

An example of a recording of a single unit in the sulcal prefrontal cortex is shown in Fig. 23. The unit was directly excited by stimulus pulses applied to a self-stimulation site in the pontine tegmentum. The short, fixed latency of the action potentials after the stimulus pulses, and the short, absolute refractory period (Fig. 23a) led this to be classed as a directly excited unit. In Fig. 23b collision evidence shows that this neurone was antidromically activated by the pontine stimulation. Other prefrontal units, classed as trans-synaptically activated, were activated with longer, more variable latencies by the stimulus pulses.

In micro-electrode tracks aimed at the sulcal prefrontal cortex, which forms the dorsal bank of the rhinal sulcus, many units activated from self-stimulation sites were recorded (Figs. 21 and 22). The units indicated in Figs. 21 and 22 were activated directly (D) or trans-synaptically (S) by stimulation applied to self-stimulation sites in the lateral hypothalamus (Lh), medial prefrontal cortex (Fr), nucleus accumbens (NA), midbrain tegmentum (Teg), or

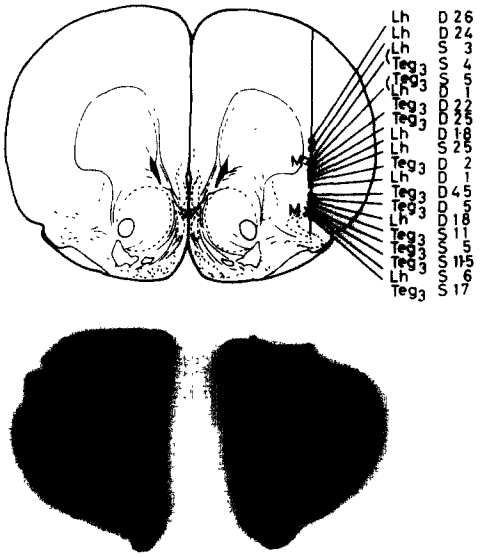

FIG. 22. A micro-electrode track passing through the sulcal prefrontal cortex, which forms the dorsal bank of the rhinal sulcus. Units were activated from a self-stimulation site, either in the pontine tegmentum (Teg_3) or in the lateral hypothalamus (Lh). The latency (milliseconds) of the action potentials from the stimulus pulses is indicated for each unit. Groups of units recorded at one depth are bracketed. Pontamine sky-blue marks are indicated by a cross and labelled M. The outline is from König and Klippel's (1963) atlas. The histological section shows the marks used to locate the units.

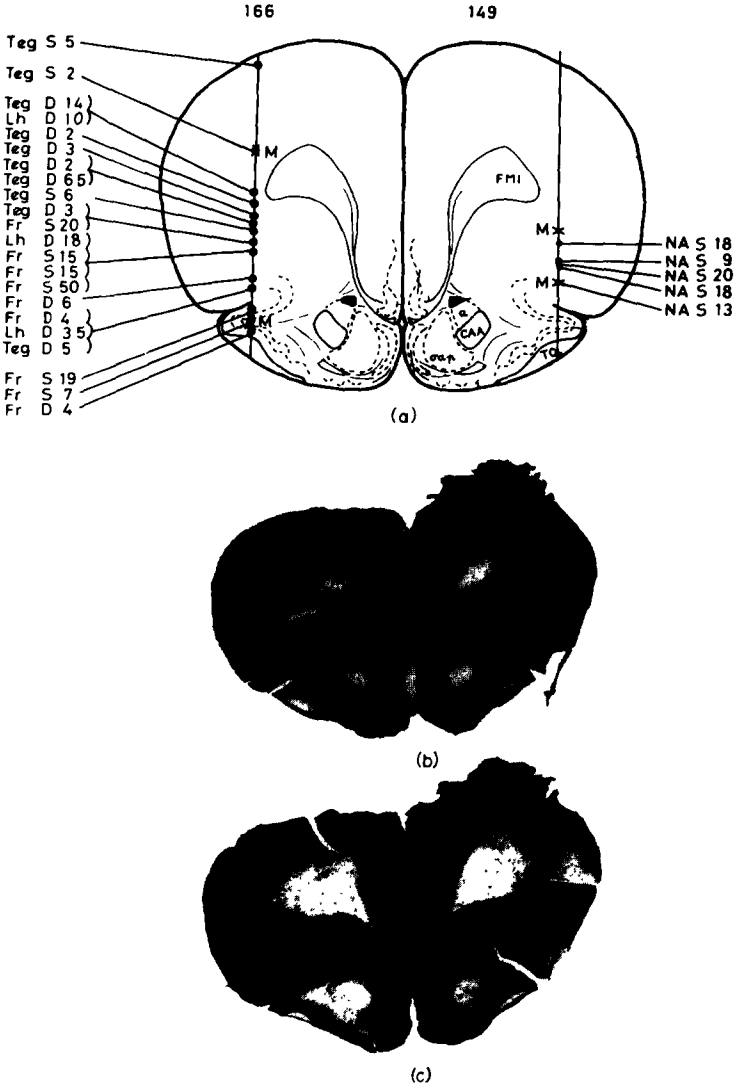

FIG. 21. (a) Micro-electrode tracks passing through the sulcal prefrontal cortex. Units were directly excited (D) or trans-synaptically activated (S) from self-stimulation sites in the midbrain tegmentum (Teg), lateral hypothalamus (Lh), medial prefrontal cortex (Fr), or nucleus accumbens (NA). (Outline from König and Klippel, 1963, fig. 8b.) (b) and (c) Brain sections stained with safranin (b) and thionin (c) to show location of pontamine sky-blue marks. The marks were made to locate the units shown in the diagram of a track made in rat 149 shown schematically immediately above. In the safranin section both upper and lower marks are visible. In the thionin section only the lower mark (in sulcal prefrontal cortex) is clear. (From *Brain Res.* **60**, 351–68, 1973.)

pontine tegmentum (Teg_3). Good localization of the units was obtained by making marks in the tracks, as shown in the histological sections in the figures. A first interesting finding therefore is that units in the sulcal prefrontal cortex are activated from a wide variety of self-stimulation sites. To show the nature of the activation, the latencies of 85 sulcal prefrontal units activated by rewarding lateral hypothalamic stimulation in 8 animals are shown in Fig. 24. Most of the directly excited units had short latencies of less than 2 ms, and where collision tests could be performed were shown to be antidromically activated. Many of the

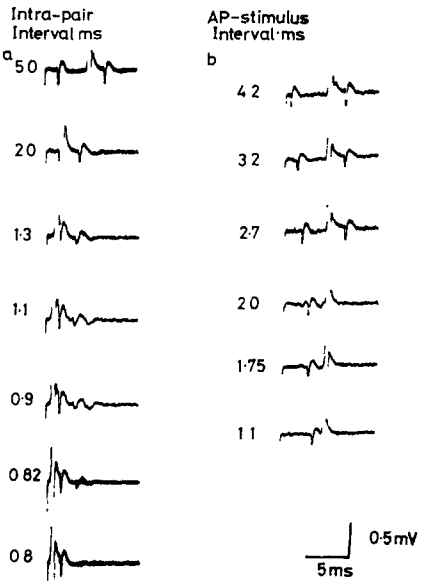

FIG. 23. Recording from a single unit in the sulcal prefrontal cortex directly excited by the pontine stimulation. (a) The absolute refractory period is shown to be 0.82 ms by the intermittent firing of the all-or-none action potentials when the intrapair interval of the twice-threshold pulse pairs is 0.82 ms. Negative down. Approximately 5 superimposed traces. (b) Collision evidence showing antidromic activation of the same neurone. When a spontaneous action potential preceded the twice-threshold stimulus pulse by 2.0 ms or less (AP-stimulus intervals of 2.0, 1.75, and 1.1 ms), the electrically elicited action potential (shown following the stimulus pulse in the upper three traces) failed to appear. Because the neurone had an absolute refractory period of 0.82 ms and was driven with a latency of 2.0 ms, collision of the electrically elicited action potential with the spontaneous action potential must have occurred. Therefore activation is antidromic.

trans-synaptically activated units had slightly longer latencies of 2–4 ms, but some had latencies as long as 50 ms. Units activated from the reward sites in the midbrain tegmentum and pontine tegmentum showed a similar pattern of activation but had longer latencies associated with the greater transmission distances (Rolls and Cooper, 1973, 1974b). The pattern of activation shown from these three reward sites is consistent with the antidromic activation of neurones with cell bodies in the sulcal prefrontal cortex which have axons passing to or through the different reward sites. The activation of the trans-synaptically activated neurones is equally consistent with driving by collaterals of the directly excited neurones and with trans-synaptic activation by other neurones with axons afferent to the

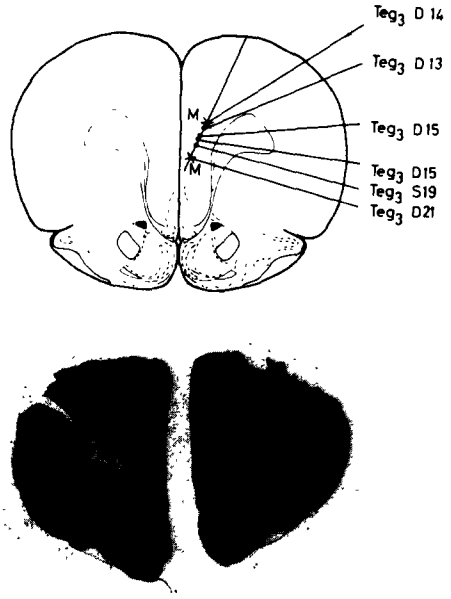

FIG. 27. A micro-electrode track passing through the medial prefrontal cortex. Units were directly excited (D) or trans-synaptically activated (S) from a self-stimulation site in the pontine tegmentum (Teg_3). The latency (milliseconds) of the action potential from the stimulation pulses is indicated for each unit. Pontamine sky-blue marks are indicated by a cross and labelled M. The outline is from König and Klippel's 1963 atlas. The histological section shows the marks used to locate the units.

sulcal prefrontal cortex. A point of interest is that in general a single unit in the prefrontal cortex was activated from only one of these three reward sites. This suggests that axons which reach the pontine or midbrain tegmentum do not pass through the lateral hypothalamic reward sites en route.

A summary of these connections is shown in Fig. 25. Units were activated from the nucleus accumbens with a different pattern. Only trans-synaptically driven units were found, and these units had long latencies, between 8 and 100 ms (Fig. 26). The pattern of activation is consistent with polysynaptic activation of the prefrontal neurones via neurones with axons afferent to the sulcal prefrontal cortex. This is included in the schematic representation

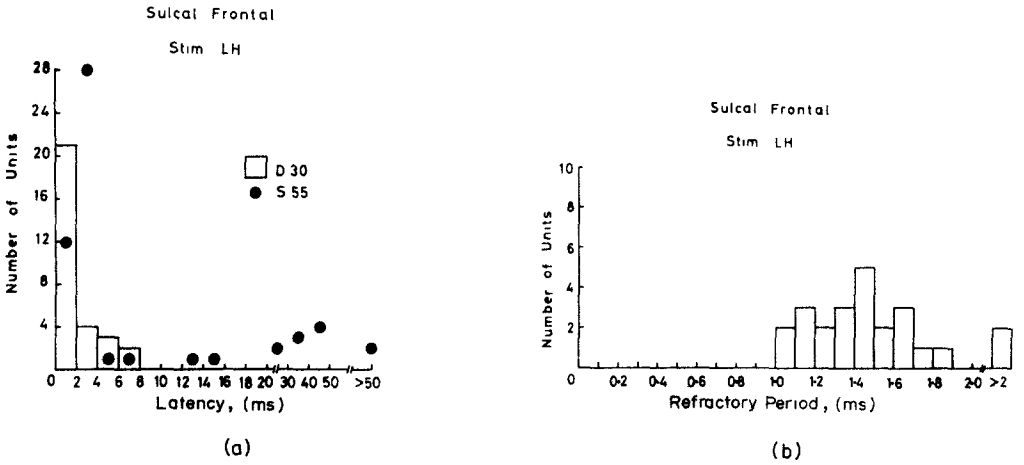

FIG. 24. (a) The latencies of 85 units in or near the sulcal prefrontal cortex directly excited (bar histogram, D) or trans-synaptically activated (S) in lateral hypothalamic self-stimulation. The directly excited units were recorded in 7 animals and the synaptically activated units in 6 animals. The numbers beside the key give the numbers of units in each class. Units with latencies of 2 or more but less than 4 ms are placed in the 2–4 ms bar of the histogram. (b) The absolute refractory periods of 24 sulcal prefrontal cortex units directly excited by the lateral hypothalamic stimulation. Units with refractory periods of 1.0 or more but less than 1.1 ms are placed in the 1.0–1.1 ms bar of the histogram. (From *Brain Res.* **60**, 351–68, 1973.)

of Fig. 25. With rewarding stimulation of the medial prefrontal cortex, units in the sulcal prefrontal cortex were usually activated trans-synaptically with latencies between 2 and 8 ms (Rolls and Cooper, 1973). Oligosynaptic activation via axons afferent to the sulcal prefrontal cortex with cell bodies in the medial prefrontal cortex is possible here, but some antidromic activation occurs (Fig. 25).

Units in the medial prefrontal cortex are also activated from reward sites. A microelectrode track in which units were activated from a reward site in the pontine tegmentum is shown in Fig. 27. The units were clustered deep in the medial prefrontal cortex, and were localized with the aid of the two marks shown in the histological section of Fig. 27. Units in this region were activated in a comparable manner to their activation in the sulcal prefrontal cortex from reward sites in the lateral hypothalamus (Fig. 28), nucleus accumbens, midbrain tegmentum, and pontine tegmentum (Rolls and Cooper, 1973; 1974a).

The absolute refractory periods of neurones in the sulcal and medial prefrontal cortex directly activated from the lateral hypothalamic reward sites were measured to aid their classification as directly excited, and so that the values could be compared with values obtained for neurones in other areas of the brain also activated from the lateral hypothalamus. The refractory period measures are shown in Figs. 24 and 28. The values range in general between 1.0 and 1.9 ms. This is longer than the values characteristic of the directly excited amygdaloid neurones (0.58–0.68 ms, section 2) and brain-stem neurones (0.78–1.0 ms, section 4).

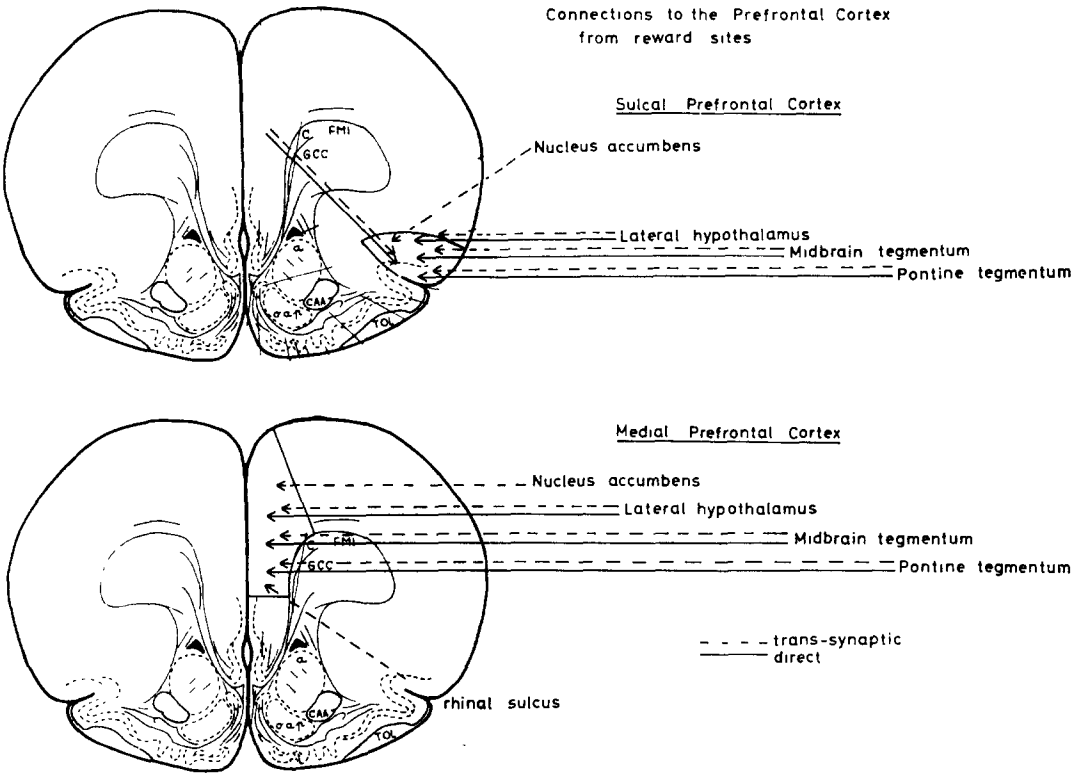

FIG. 25. Summary of connections to the prefrontal cortex from reward sites. Recordings from single units in the prefrontal cortex showed that they were directly (solid line) or trans-synaptically (dashed line) activated from the different reward sites. The approximate extent of the medial and sulcal prefrontal cortex is indicated, although in the lateral tracks some of the activated units were dorsal to the enclosed region.

Some evidence that activation of the prefrontal neurones is characteristic of reward sites comes from animals implanted with electrodes in the midbrain tegmentum. In 4 animals which showed self-stimulation, 51 activated units (some in every animal) were found in the sulcal prefrontal cortex. Of 8 animals in which the stimulation did not induce reward but only motor effects such as flexion of the leg, activated units were found in the sulcal prefrontal cortex of only one animal (18 activated units were found). Similarly, in the medial prefrontal cortex 26 activated units were found in 3 animals positive for self-stimulation, and only 6 units were found in 9 motor-effect animals. The observations indicate that activation

of neurones in the prefrontal cortex is more characteristic of rewarding than of non-rewarding stimulation of the brain.

The prefrontal regions in which neurones were found to be activated by brain-stimulation reward are indicated in Fig. 25. The areas are similar to those found to receive fibres from the mediodorsal nucleus of the thalamus and called sulcal and medial prefrontal cortex by Leonard (1969). Examples of the different reward sites from which the prefrontal neurones are activated have been given elsewhere (lateral hypothalamus: Rolls, 1971b; nucleus accumbens: Rolls and Kelly, 1972; pontine tegmentum: Rolls and Cooper, 1974b; medial

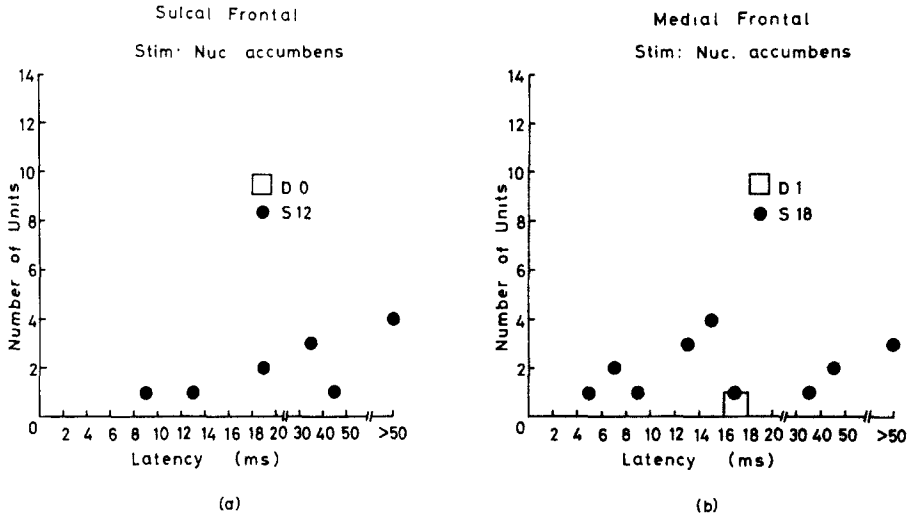

FIG. 26. (a) The latencies of 12 units in the sulcal prefrontal cortex activated from nucleus accumbens self-stimulation sites. The units were recorded in 2 rats. Conventions as in Fig. 24. (b) The latencies of 19 units in the medial prefrontal cortex activated from nucleus accumbens self-stimulation sites. All but one of the units were classed as synaptically activated. The units were recorded in 2 rats. (From *Brain Res.* **60**, 351–68, 1973.)

prefrontal cortex and midbrain tegmentum: Rolls and Cooper, 1973; sulcal prefrontal cortex: Rolls and Cooper, 1973; see also Rolls *et al.*, 1974).

3.2.1 *Summary*

Single units in the sulcal and medial prefrontal cortex are directly or trans-synaptically activated in self-stimulation of the lateral hypothalamus, midbrain tegmentum, and pontine tegmentum. Units in the prefrontal cortex are trans-synaptically activated in self-stimulation of the nucleus accumbens. Units in the prefrontal cortex are in general not activated from non-reward sites in the midbrain tegmentum. This powerful activation of neurones in the prefrontal cortex is in contrast to other neocortical areas, most of which do not appear to be similarly activated by brain-stimulation reward. These observations indicate that activation of neurones in the sulcal and medial prefrontal cortex is closely related to, and thus may be involved in, brain-stimulation reward.

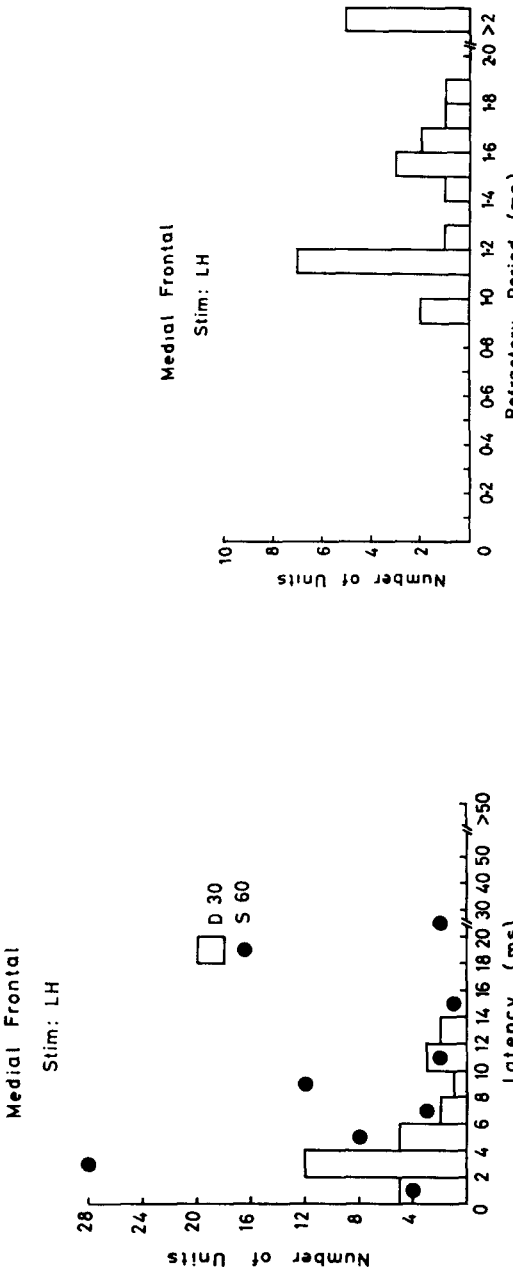

FIG. 28. (a) The latencies of medial prefrontal cortex units directly excited in 8 rats (bar histogram, D) and synaptically (S) activated in 9 rats from lateral hypothalamic self-stimulation sites. The numbers beside the key give the number of units in each class. (b) The absolute refractory periods of 23 medial prefrontal cortex units directly excited by the lateral hypothalamic stimulation. The units were recorded in 8 animals. (From *Brain Res.* **60**, 351–68, 1973.)

3.3 ACTIVATION OF NEURONES IN THE PREFRONTAL CORTEX AND DORSOMEDIAL NUCLEUS OF THE THALAMUS BY BRAIN-STIMULATION REWARD IN THE MONKEY

In the squirrel moneky (*Saimiri sciureus*) it has been found that neurones in the oribtofrontal cortex are activated in brain-stimulation reward of many different sites (experiments of M. J. Burton, S. J. Cooper, E. T. Rolls, and S. G. Shaw). The activation has been studied in unanaesthetized animals and in animals anaesthetized with nitrous oxide. An example of a track through the orbitofrontal cortex is shown in Fig. 29. The mark used to locate the track can be clearly seen. It is of interest that individual neurones were often activated from a number of different reward sites. For example, one of the neurones in the track shown in Fig. 29 was activated trans-synaptically from reward sites in or near the nucleus accumbens, lateral hypothalamus, mediodorsal nucleus of the thalamus, and locus coeruleus. A summary of the activation found in experiments on 9 animals of orbitofrontal neurones from reward sites is shown in Fig. 31. The direct (probably antidromic) activation of neurones was regularly seen from the lateral hypothalamus. This powerful activation of orbitofrontal neurones from many different reward sites is an indication that the orbitofrontal cortex is involved in reward mechanisms in primates. The corresponding area in the rat is the sulcal prefrontal cortex. The experiments on the monkey orbitofrontal cortex were designed partly on the basis of the results in the rat.

The mediodorsal nucleus of the thalamus (MD) is the nucleus which projects to the orbitofrontal cortex. Therefore recordings were also made from the mediodorsal nucleus during brain-stimulation reward. An example of a track through MD is shown in Fig. 30. Neurones here have so far been shown to be activated in self-stimulation of the orbitofrontal cortex, lateral hypothalamus, nucleus accumbens, amygdala, and locus coeruleus. These results provide evidence that the mediodorsal nucleus together with one of its projection areas, the orbitofrontal cortex, is closely related to reward mechanisms in primates.

3.4 ANAESTHETIZATION OF THE PREFRONTAL CORTEX AND BRAIN-STIMULATION REWARD

To test whether the prefrontal neurones known to be activated in brain-stimulation reward (Ito and Olds, 1971; Rolls and Cooper, 1973, 1974b; see also section 3.2) are involved in brain-stimulation reward, experiments have been performed in which the region of activated neurones is anaesthetized during self-stimulation (Rolls and Cooper, 1974a). Bilateral anaesthesia of the sulcal prefrontal cortex was found to attenuate self-stimulation of both the lateral hypothalamus and the pontine tegmentum. The experiments indicate that the sulcal prefrontal cortex is involved in brain-stimulation reward. Few comparable experiments have yet been performed on the medial prefrontal cortex.

Ten male hooded rats were implanted bilaterally in the sulcal prefrontal cortex with guide cannulae. The rats were implanted under Equithesin (Jensen-Salsbury Labs. Inc.) anaesthesia. The cannulae have been described previously (Epstein *et al.*, 1970; Rolls and Jones, 1972) and consist of a 0.6 mm o.d. stainless-steel guide tube fitted with an obturator, which is removed and replaced with a 0.3 mm o.d. injection cannula prior to injection. The injection cannula is inserted so that its tip is flush with the tip of the guide cannula. The coordinates of the tips of the guide cannulae were 2.5 mm anterior to bregma, 3.0 mm lateral to the saggital sinus, and 4.0 mm beneath the dorsal surface of the brain (+2.5:3.0:4.0 mm

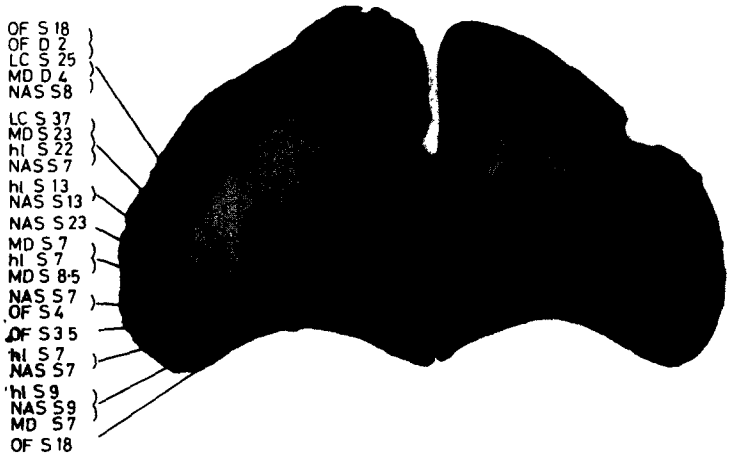

FIG. 29. Micro-electrode track through the orbitofrontal cortex of the squirrel monkey. Single units were directly (D) or trans-synaptically (S) activated with the latencies shown (milliseconds) from self-stimulation sites in the orbitofrontal cortex (OF), nucleus accumbens (NAS), lateral hypothalamus (hl), mediodorsal nucleus of the thalamus (MD), or in the region of the locus coeruleus (LC). A lesion marked the position of the track.

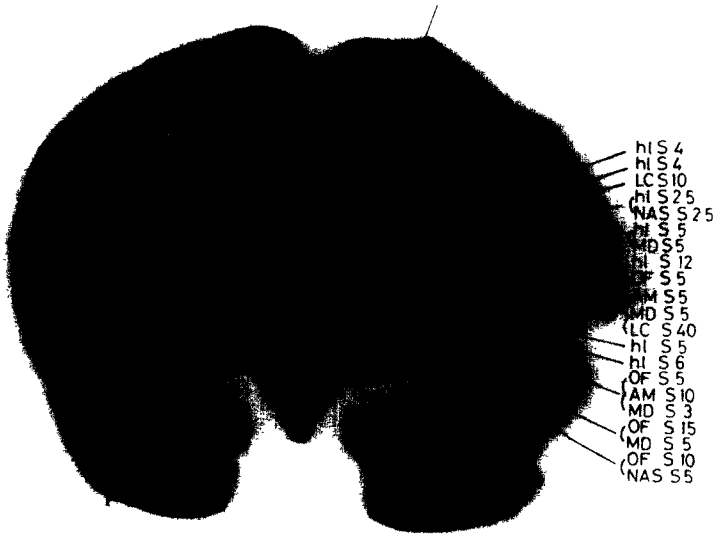

FIG. 30. Micro-electrode track through the dorsomedial nucleus of the thalamus of the squirrel monkey. Single units were activated from the self-stimulation sites indicated. Conventions as in Fig. 29. AM: self-stimulation site in the amygdala. It is not clear whether this is the medial or lateral division of MD. Similar activation has been found confirmed in the medial division of MD.

down). Some rats had uni- or bilateral cannulae in the medial prefrontal cortex (+2.5:0.8: 2.0 mm down). In the same operation monopolar stimulation electrodes were implanted in self-stimulation sites in the lateral hypothalamus (−3.0:1.5:7.6 mm down) or in the pontine tegmentum just rostral to the brachium of the superior colliculus, near the locus coeruleus (−8.5:1.0:5.0 mm down). The latter site was chosen for this investigation because it is so far distant from the prefrontal cortex that any effect obtained in the experiments would not be due to local factors.

Before each experiment with the anaesthetic, two polythene tubes, each with an injection cannula at one end and a 10 μl Hamilton micro-syringe at the other, were filled with 5% procaine hydrochloride made up in 0.9% saline. The injection cannulae were inserted into the guide cannulae so that they were flush with the tips of the guide cannulae. A near-threshold stable baseline of self-stimulation was obtained by reducing the stimulation current so that continuous self-stimulation occurred with few pauses, and with no pauses greater than 3 s. The average rates of self-stimulation were 30 presses/min. Injections of 1 μl of the

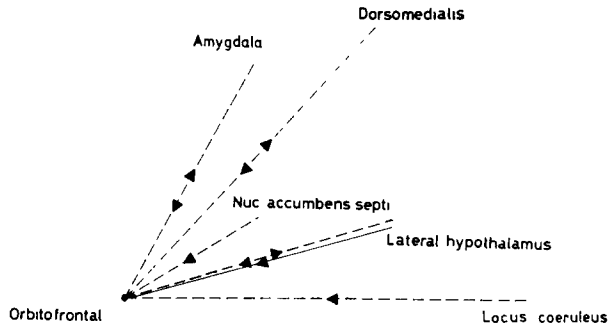

FIG. 31. Summary of activation of single units in the orbitofrontal cortex from reward sites in the squirrel monkey. The arrows point to the recording sites. Direct excitation: solid line. Trans-synaptic activation: dashed line. Dorsomedialis: nucleus medialis dorsalis thalami.

5% procaine hydrochloride were given bilaterally. If the rat stopped self-stimulating within 10 min, either priming stimulation was given to determine whether he would start pressing again at that current or the current was increased to determine whether self-stimulation would occur at a higher current. In the latter case, any change in the threshold for self-stimulation could be plotted as a function of time after the injections. The experiments continued until the baseline level of self-stimulation returned. If the 1 μl injections produced no effect, injections of 2 μl then 3 μl were given bilaterally at 45 min intervals. Each rat was tested at least twice.

In 4 rats with lateral hypothalamic self-stimulation, bilateral injections of 1–2 μl of 5% procaine hydrochloride attenuated the self-stimulation. In 3 rats with self-stimulation of the pontine tegmentum, bilateral injections of 1–2 μl (or in one case 4 μl) of 5% procaine hydrochloride attenuated the self-stimulation. The attenuation took the form of a cessation of self-stimulation, which could sometimes be reinstated by a large increase in the self-stimulation current, or the attenuation was seen as a decrease in the rate of self-stimulation, or the attenuation was seen as repeated stopping of self-stimulation even when the rat was started again by the experimenter giving priming (free) stimulation. The injections of anaesthetic usually took effect within 30 s and lasted for less than 30 min.

An example of attenuation of lateral hypothalamic self-stimulation by the bilateral injection of 1.5 μl of 5% procaine hydrochloride into the sulcal prefrontal cortex is shown in Fig. 32. The cumulative record of lever-presses shows that the rat bar-pressed rapidly for the 5 min before the injection of procaine (the pen resets after 300 presses). The current was 180 μA, which was sufficient to maintain the very steady responding shown. Within 1 min of the injection the rate of self-stimulation fell, and after 5 min two pauses in self-stimulation occurred. After this the rate of self-stimulation gradually increased. Approximately 21 min after the bilateral anaesthesia, self-stimulation was back to the pre-injection rate of 300 presses in 4 min. While the anaesthetic was active the general behaviour of the rat did not appear to be normal—locomotor activity occurred and the pauses in self-stimulation could be removed by giving priming stimulation or by increasing the self-stimulation current (see below). This shows that the anaesthetic did not make the rats incapable of self-stimulation,

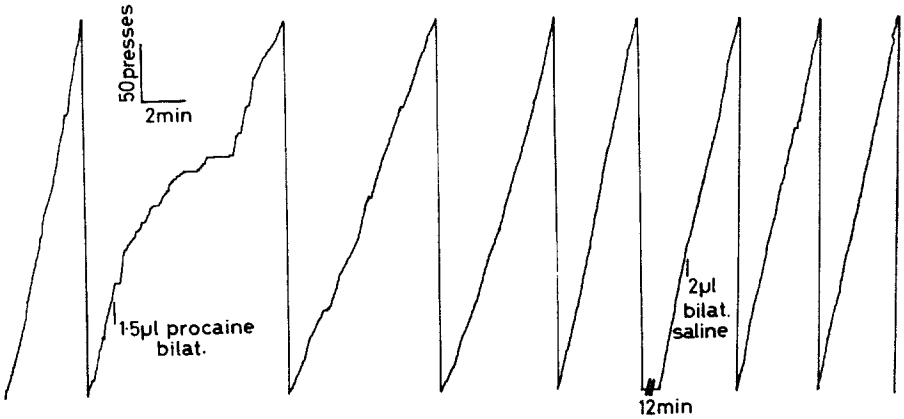

FIG. 32. An example of attenuation of lateral hypothalamic self-stimulation by the bilateral injection of 1.5 μl of 5% procaine HCl into the sulcal prefrontal cortex. A control injection of 0.9% saline is also shown.

but did produce a partial attenuation of the effects of the brain-stimulation reward. In Fig. 32 a control injection of 0.9% saline is also shown. Although larger in volume than the previous procaine injection, the saline did not produce any attenuation of self-stimulation. Similarly, control injections of saline into other rats had no effect. It is concluded that the effect following a procaine injection is not due just to the injection of a volume of fluid through the cannulae.

In further experiments it was shown that unilateral anaesthetization of the sulcal prefrontal cortex did not attenuate self-stimulation. Further, it was found that with bilateral anaesthesia the attenuation of self-stimulation could be measured as an increase in the threshold current of self-stimulation.

To determine which region near the sulcal prefrontal cortex was critical for brain-stimulation reward, the sites of the cannula tips in animals in which the anaesthetic had attenuated self-stimulation were compared with those in which the injections of anaesthetic had no effect. Animals in which the injections of procaine HCl did attenuate self-stimulation of the lateral hypothalamus (Fig. 33, row A) and pontine tegmentum (Fig. 33, row B) had cannulae placed in general symmetrically near the sulcal prefrontal cortex. Cannulae through

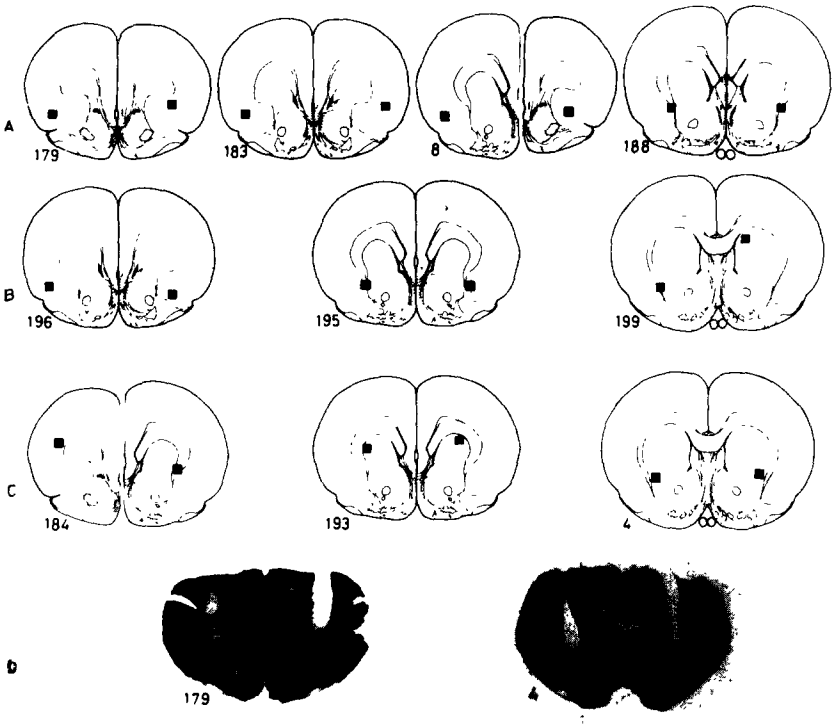

FIG. 33. Through the cannulae shown in row A lateral hypothalamic self-stimulation was attenuated by small bilateral injections of procaine HCl. Through the cannulae shown in row B self-stimulation of the pontine tegmentum was attenuated by small bilateral injections of procaine HCl. Injections of procaine HCl through the cannulae shown in row C did not effectively attenuate self-stimulation. Examples of the histology are shown in row D. (The brain outlines are from König and Klippel, 1963.)

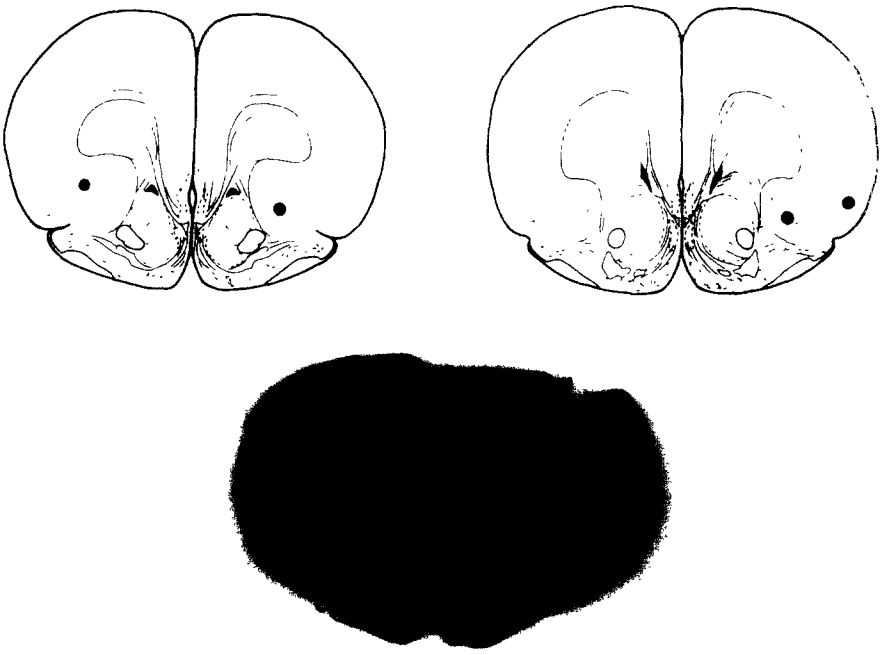

FIG. 34. Sites of electrode tips in 4 rats which showed self-stimulation of a region n or near the sulcal prefrontal cortex. An example of the histology is shown below. (The brain outlines are from König and Klippel, 1963.)

which the injections did not attenuate brain-stimulation reward had one or both cannulae dorsal to or caudal to the sulcal prefrontal cortex (Fig. 33, row C). It can be concluded that a critical frontal site for self-stimulation is in or near the sulcal prefrontal cortex.

3.4.1 *Summary*

Bilateral anaesthetization of the sulcal prefrontal cortex, but not of other nearby sites, attenuates self-stimulation of the lateral hypothalamus and the pontine tegmentum. Therefore the sulcal prefrontal cortex may be involved in brain-stimulation reward.

3.5 SELF-STIMULATION OF THE PREFRONTAL CORTEX

If the prefrontal cortex is involved in brain-stimulation reward, as suggested by the electrophysiological experiments (sections 3.2 and 3.3) and the observations with local application of anaesthetic (section 3.4), then stimulation of the prefrontal cortex should at least affect reward, and could support self-stimulation. It has been shown previously that stimulation of the medial prefrontal cortex can support self-stimulation (Routtenberg, 1971; Rolls and Cooper, 1973). To determine whether the sulcal prefrontal cortex can support self-stimulation, monopolar electrodes were implanted in the sulcal prefrontal cortex (+2.5:3.0:4.0 mm beneath the dura) of 5 male hooded rats.

Four of the rats showed good self-stimulation, and bar-pressed more than 30 times/min for 0.3 s trains of 0.1 ms stimulus pulses at 100 Hz. Histological examination showed that the electrode tips in these 4 rats were in or close to the sulcal prefrontal cortex, as shown in Fig. 34. One rat showed vibrissa twitching during stimulation, but would not self-stimulate. The electrode tip in this animal was outside the sulcal prefrontal cortex, about 1 mm dorsolateral to it. This experiment shows that rats will show self-stimulation of a region in or very near to the sulcal prefrontal cortex. The same finding has recently been reported by Routtenberg and Sloan (1972) in the rat, and in the squirrel moneky (*Saimiri sciureus*) it has been found that electrodes in the regions of reward-related neurones in the orbitofrontal cortex and mediodorsal nucleus of the thalamus support self-stimulation. These observations provide further evidence that the orbitofrontal cortex and mediodorsal nucleus in primates are related to reward mechanisms.

3.6 THE ROLE OF THE PREFRONTAL CORTEX IN REWARD

There is now considerable evidence that the prefrontal cortex is involved in intracranial self-stimulation. Ito and Olds (1971) recorded from single units during posterior hypothalamic self-stimulation in rats, and with only a very small number of relevant recording sites found some evidence that units in the medial prefrontal cortex were activated. Routtenberg (1971) found that self-stimulation of the medial prefrontal cortex occurred, and traced experimental fibre degeneration from here caudally to the lateral portion of the MFB and the medial tip of the internal capsule. In the electrophysiological experiments described here (section 3.2; Rolls and Cooper, 1973, 1974b) it was shown that units in both the sulcal and the medial prefrontal cortex are activated in self-stimulation of a wide variety of self-stimulation sites. The sites were the lateral hypothalamus, midbrain tegmentum, pontine tegmentum, nucleus accumbens, and medial prefrontal cortex. Consistent with this is the observation of Routtenberg (1971) that fibre degeneration from reward sites in the medial prefrontal cortex runs through reward sites in the medial part of the internal capsule. Because

anaesthetization of the region of the sulcal prefrontal cortex attenuated self-stimulation of the lateral hypothalamus and pontine tegmentum, Rolls and Cooper (1974a) concluded that the sulcal prefrontal cortex or a nearby structure is involved in self-stimulation. Consistently with this it was shown that self-stimulation of the sulcal prefrontal cortex occurred (section 3.5). In the monkey, Routtenberg *et al.* (1971) showed that orthograde degeneration from lesioned self-stimulation sites in the medial tip of the internal capsule coursed to the dorsomedial nucleus of the thalamus and to the orbitofrontal cortex. In electrophysiological experiments on the squirrel monkey it has been found that neurones in the orbitofrontal cortex are activated in self-stimulation (see section 3.3). It has also been found that self-stimulation of the squirrel monkey orbitofrontal cortex occurs (section 3.5). Given that the rat sulcal prefrontal cortex may be homologous with the monkey orbitofrontal cortex in that both receive a projection from the medial part of the mediodorsal nucleus of the thalamus (Leonard, 1969), the evidence given above suggests that these regions of the brain have similar functions in intracranial self-stimulation.

The function of the prefrontal cortex in brain-stimulation reward can be considered together with the known functions of the prefrontal cortex. In the monkey, lesions of the orbitofrontal cortex lead to poor performance in an object discrimination reversal task because the lesioned monkeys continue to select the previously rewarded but now unrewarded stimulus (Jones and Mishkin, 1972); the poor extinction measured by prolonged bar-pressing when reward is no longer available (Butter, 1969); and to deficits in a go/no-go task in which the lesioned monkeys cannot learn not to reach out on a no-go trial. These tasks appear to share an "unlearning" factor. In each task the lesioned monkeys appear to be unable to change their behaviour when reward is no longer associated with a stimulus or a type of behaviour. The animals cannot break a stimulus-reinforcement association, i.e. "unlearn". In order to perform this suggested function, the orbitofrontal cortex would need to know when reward arrived so that it could operate on the omission of a reward. The electrophysiological experiments show that the orbitofrontal cortex (and the sulcal prefrontal cortex in the rat) does receive a signal when reward arrives. The orbitofrontal cortex could then influence other reward neurones (e.g., in the hypothalamus) if a stimulus is no longer associated with reinforcement. Thus one reason why the orbitofrontal cortex (and perhaps also the sulcal prefrontal cortex in the rat) is closely connected with brain-stimulation reward may be that it normally signals when expected reward does not arrive.

The role of the rat medial prefrontal cortex, in which neurones are activated by brain-stimulation reward, is more difficult to assess. There is little evidence on whether anaesthetization of this region affects self-stimulation. The region which may be homologous with it in the monkey, the dorsolateral prefrontal cortex (Leonard, 1969), appears to be involved in tasks which involve a delay factor and a spatial factor (e.g. Goldman *et al.*, 1971). Thus spatial delayed alternation, in which the animal must respond alternately left and right with a delay interposed before the next alternation in order to obtain a reward, is performed poorly by monkeys with lesions in the dorsolateral prefrontal cortex (Butters and Pandya, 1969; Goldman *et al.*, 1971). The relation, if there is any, of this type of operation to brain-stimulation reward remains to be determined.

3.7 SUMMARY

Neurones in the sulcal and the medial prefrontal cortex in the rat are activated in self-stimulation of many different brain sites. Self-stimulation of the sulcal and the medial pre-

frontal cortex occurs. Bilateral anaesthetization of the region of the sulcal prefrontal cortex attenuates brain-stimulation reward. Therefore the sulcal prefrontal cortex (and possibly also the medial prefrontal cortex) may be involved in brain-stimulation reward. Similarly, in the monkey neurones in the orbitofrontal cortex are activated during self-stimulation and the orbitofrontal cortex supports self-stimulation. In the monkey the orbitofrontal cortex appears to be involved in breaking a learned association between a stimulus and reinforcement. Thus the orbitofrontal cortex in the monkey and the sulcal prefrontal cortex in the rat may be closely related to brain-stimulation reward because these parts of the brain must normally monitor reward so that they can operate as soon as a reward fails to occur. These parts of the cortex can be considered as high-level controls of reward which are concerned with changing behaviour when reward is no longer associated with the behaviour. Because of the role in reward, the monkey orbitofrontal and rat prefrontal cortex may not be essential for reward. The function of these areas in reward is analogous to that of the amygdala except that the amygdala may be concerned with the formation (as opposed to the disconnection) of stimulus-reinforcement associations (see section 2).

4. The Functions of a System in the Midbrain and Pons activated in Self-stimulation

4.1 INTRODUCTION

During experiments in which recordings were made from neurones in many different parts of the brain in investigations of the nature of brain-stimulation reward, it was found that neurones in the midbrain and pons were excited by rewarding lateral hypothalamic stimulation (Rolls, 1971a; Gallistel *et al.*, 1969). Gradually evidence accumulated which indicated that arousal was also produced by the stimulation, and that it was through these brain-stem neurones that the arousal was produced (Rolls, 1971a, c). The arousal produced by the stimulation is an important effect of lateral hypothalamic stimulation, for probably this arousal affects self-stimulation rate (Rolls, 1971b) and stimulus-bound motivational behaviour (Rolls, 1973), and may at least partly mediate the priming effect seen with lateral hypothalamic self-stimulation (Rolls, 1971a) as well as locomotor activity produced by lateral hypothalamic stimulation (Rolls and Kelly, 1972). There is no evidence to indicate that activation of this neural system is directly involved in reward effects produced by brain stimulation, but there is considerable evidence that the activation affects self-stimulation. The evidence relevant to these conclusions is reviewed below.

4.2 ACTIVATION OF A NEURAL SYSTEM IN THE MIDBRAIN AND PONS BY REWARDING STIMULATION OF THE LATERAL HYPOTHALAMUS AND OTHER SITES NEAR THE MEDIAL FOREBRAIN BUNDLE (see also Rolls, 1971a, c)

In rats which showed self-stimulation of the lateral hypothalamus and other sites near the medial forebrain bundle (MFB), neurones in the midbrain and pons were found to be antidromically activated. This type of activation was found in the course of micro-electrode tracks as soon as the electrode was deeper than the deep layers of the colliculi and as far ventral as 1 mm from the base of the brain (Fig. 35). Other neurones in the same area were trans-synaptically activated. When stimulation was applied to reward sites in or near the nucleus accumbens, only few neurones in the midbrain and pons were activated. This is

illustrated in Fig. 36, in which the absolute refractory periods and latencies of the brain-stem neurones driven from the two types of site are shown: only a small number of this type of neurone is activated from the nucleus accumbens.

When recordings were made from neurones in the brain-stem driven with long latencies, it was found that the neurones showed increased firing rates for several minutes following a train of stimulation of the sort received by the animal during self-stimulation. Recordings of cortical EEG were made, and it was found that these trains of stimulation produced EEG desynchronization for several minutes following trains of lateral hypothalamic stimulation (Fig. 37). The firing rates of the long latency "indirectly driven" units (they did not follow single stimulus pulses in phase) correlated with the degree of desynchronization of the EEG (Fig. 37). A pinch, or the inhalation of amyl nitrite, produced similar effects to the stimulation (Fig. 37). These indirectly driven units, found in the brain stem and medial posterior thalamus, were therefore called arousal units. Neither the arousal units nor the EEG were affected by stimulation of the nucleus accumbens (Fig. 37), even at very high current intensities (last 10A of Fig. 37). Therefore the elicitation of arousal and the activation of the brain-stem units is caracteristic of the MFB but not of the nucleus accumbens self-stimulation sites. Routtenberg and Huang (1968) also found that brain-stem neurones were activated from diencephalic but not nucleus accumbens self-stimulation electrodes, but did not relate their findings to arousal.

To investigate how the indirectly driven ("arousal") neurones are activated, the refractory period of the directly excited neurones through which they were driven was estimated. The value obtained could then be compared with that of different populations of neurones measured directly to give an indication of the activated pathways. For example, an indirect refractory period value of 0.8 ms would indicate that the indirectly driven neurone was driven through directly excited neurones with refractory periods of 0.8 ms. An indirect refractory period determination was performed by measuring the response of an indirectly driven neurone to trains of pulse pairs. If the intra-pair interval (IPI) of the pulse pairs exceeded the refractory period of the directly excited neurones, then these would fire twice for every pair and large postsynaptic effects (on indirectly driven neurones) would be produced. IPIs shorter than the refractory period of the directly excited neurones would produce only small postsynaptic effects because the directly excited neurones would fire only once for every pulse pair. An example of a refractory period measurement on an indirectly driven unit is shown in Fig. 38. The response of the single unit to a train of 4 pulse pairs with a long IPI (1.5 ms) is shown in Fig. 38b. The unit showed no spontaneous activity so the stimulation clearly produced a large increase in activity. The post-stimulation response of the unit as a function of IPI is shown in Fig. 38c, and average post-stimulus time histograms are shown in Fig. 38a. It is clear that with IPI greater than 1.0 ms, much more post-stimulation firing was produced than with shorter IPI or than with the one-pulse condition (in which the second pulse of each pair was omitted). Because the stimulus pulses were at a twice-threshold value, this finding indicates that the absolute refractory period of the directly excited neurones through which the indirectly driven response was produced was 1.0–1.1 ms. The results of 13 indirect determinations of refractory period on 13 indirectly driven arousal units in 13 different rats are shown in Fig. 39. The values fall in the range 0.8–1.1 ms. These values are the values which would be produced if the arousal neurones were driven through the directly excited brain-stem neurones whose refractory periods (Fig. 39) fall mainly between 0.78 and 1.0 ms. This finding provides an indication that the arousal units are driven through the directly excited brain-stem units. It is, of course, possible that other un-

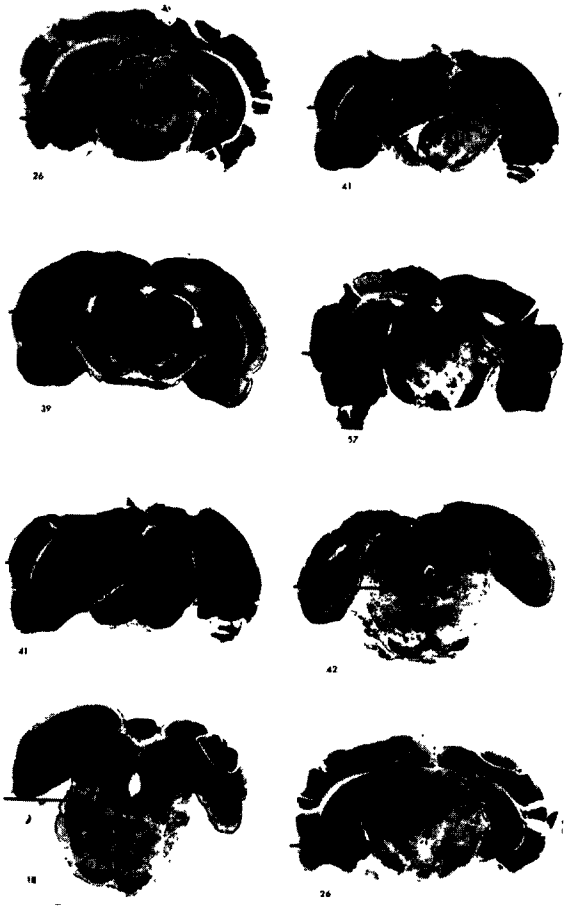

FIG. 35. Sites (marked by arrows) in the brain stem of neurones directly excited through MFB self-stimulation electrodes. (From *Physiol. Behav.* 7, 297–310, 1971.)

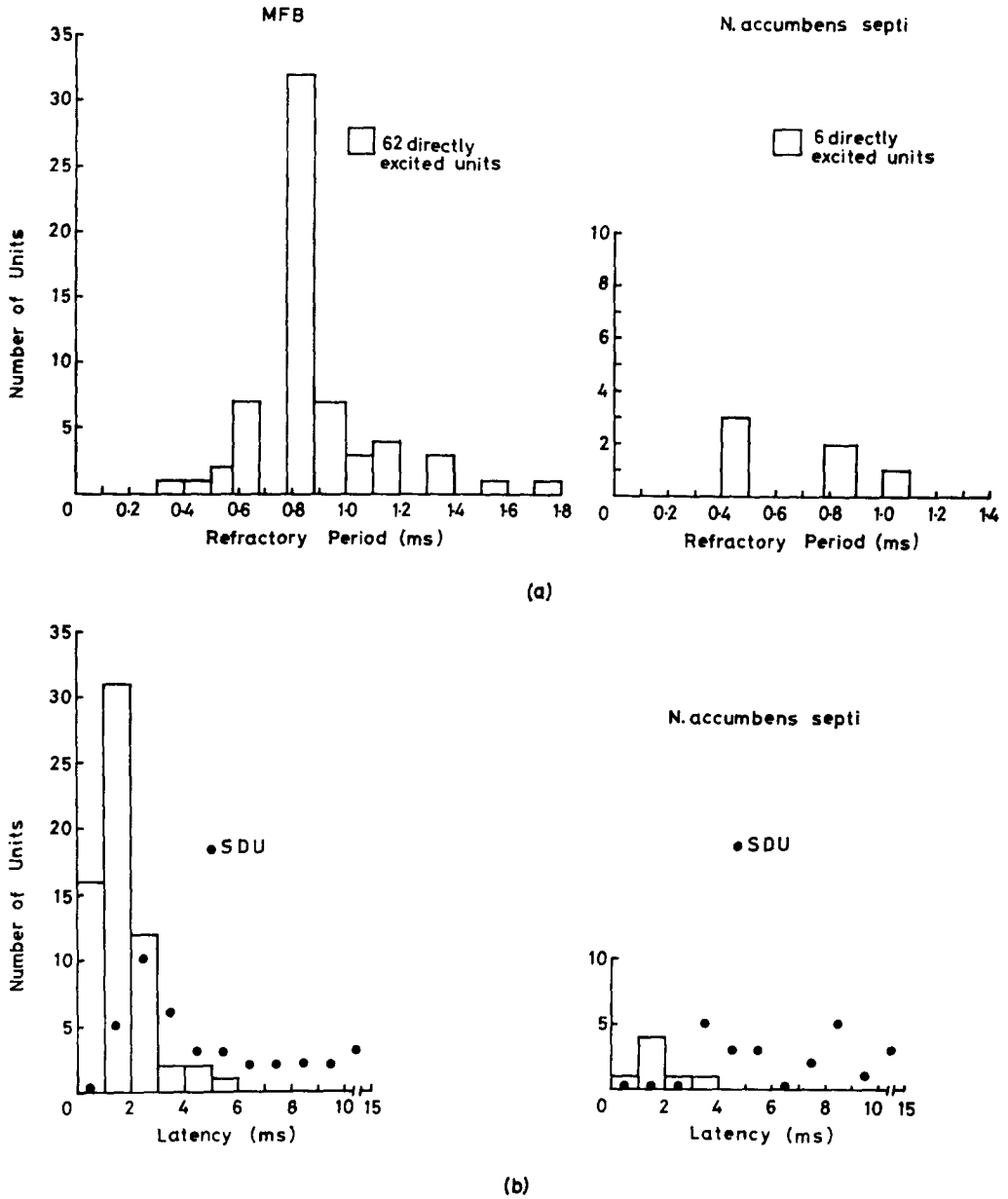

FIG. 36. Absolute refractory periods (a) and latencies (b) of units in the midbrain and pons activated from MFB (left, approximately 18 rats) and nucleus accumbens (right, 8 rats) self-stimulation sites. In 7 of the 8 rats with nucleus accumbens reward sites, almost no brain-stem units were activated in contrast to the strong activation of these units from the MFB reward sites. (Modified from *Brain Res.* **31**, 275–85, 1971.)

identified directly excited units have this refractory period, so that this method can only serve as one indication of functional pathways. The method is useful in that it allows effects of stimulation to be traced across synapses so that tracing of a pathway need not stop at a synapse.

There are several different types of evidence which indicate that the activation of arousal neurones (and the production of arousal) is mediated through the brain-stem directly excited neurones. Firstly, the refractory period similarities described above provide one

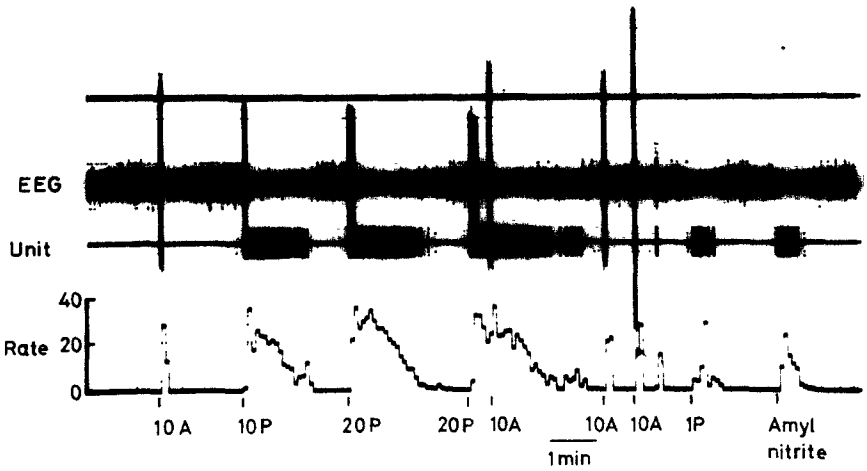

FIG. 37. Arousal is not produced by stimulation applied to a nucleus accumbens septi self-stimulation site. One, ten, or twenty trains of stimulation applied to the posterior, MFB, self-stimulation electrode (1P, 10P, 20P) increased the firing rate of this unit (see "unit" and "rate" traces) and produced cortical desynchronization. Ten trains applied to the anterior, nucleus accumbens septi, electrode (10A) did not produce a similar arousal effect. (Only stimulus artifact was counted in the rate trace.) The same stimulation did not inhibit the arousal effect (20P followed by 10A). Each 0.3 s train of pulses at 100 Hz was just above the threshold of self-stimulation. The unit, which was indirectly driven by MFB stimulation, had general arousal properties in that its firing rate was correlated with cortical synchronization, and stimuli which altered arousal level (e.g. amyl nitrite) always produced a correlated change in the firing rate of the unit. (From *Brain Res.* **31**, 275–85, 1971.)

point. Secondly, when motor effects (e.g. leg flexion) are produced through electrodes near the lateral hypothalamus which do not support intracranial self-stimulation, the directly excited brain-stem units are not activated and arousal is not produced (Rolls, 1971a). (In fact these motor effects are produced through neurones with refractory periods of 0.5–0.6 ms and are associated with the direct activation of brain-stem units with refractory periods of 0.5–0.67 ms; see Rolls, 1971a.) These motor-effect experiments provide a useful control for refractory period methods. Thirdly, the directly excited brain-stem units are activated from lateral hypothalamic reward sites from which arousal is produced but not from nucleus accumbens reward sites from which arousal is not produced (Figs 36 and 37). Fourthly, some of the short latency trans-synaptically activated units found close to the directly excited units in the brain-stem were arousal units. These units were found only in the animals with electrodes in the MFB self-stimulation sites.

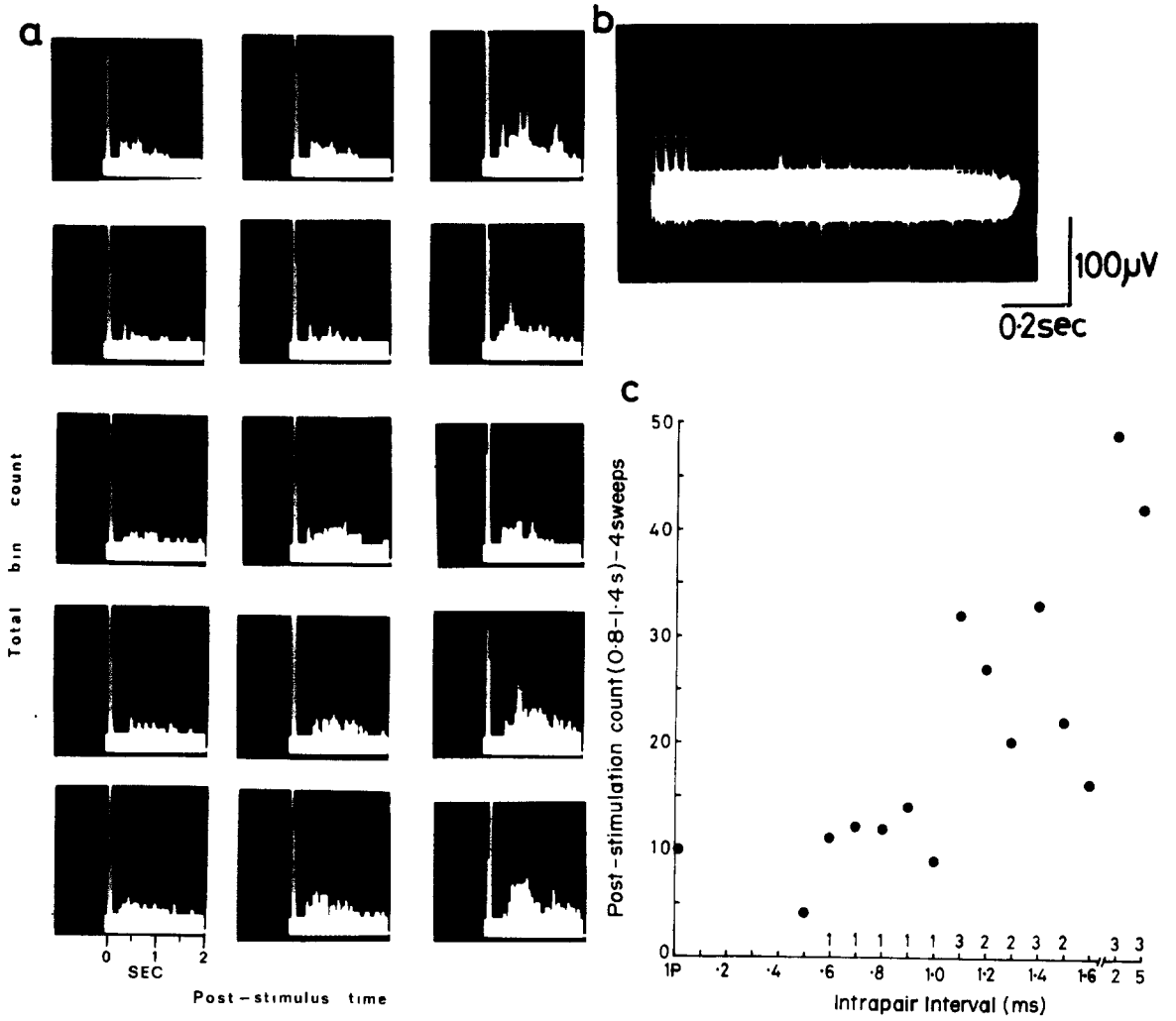

FIG. 38. Indirect measurement of refractory period. The response (shown retouched in (b)) of the long latency indirectly driven unit to a train of 4 pulse pairs was measured in (a) and (c) to determine the refractory period of the neurones driving the unit. The unit showed no spontaneous activity. In (a) the inset IPI values are in milliseconds. In (c) the significance of the difference of the firing at a given IPI from the single-pulse (1P) condition is shown by the numbers, 1, $p > 0.2$; 2, $p < 0.03$; 3, $p < 0.001$. Thus significantly more firing than in the single-pulse condition is found when the IPI of the stimulating pulse pairs is greater than 1.0 ms. (From *Physiol. Behav.* 7, 297–310, 1971.)

4.3 FUNCTION OF THE BRAIN-STEM AROUSAL SYSTEM IN REWARD

Reward produced by stimulation of the nucleus accumbens is not associated either with activation of the brain-stem neurones or with the elicitation of arousal (Rolls, 1971c). It is concluded that activation of the brain-stem arousal system is not necessary for brain-stimulation reward. Further, the arousal produced by MFB stimulation may take several minutes to decay (Fig. 37). This gradual decay is probably different from the time course of the decay of reward because animals may cease pressing for brain-stimulation reward very soon after the stimulation is disconnected. One example of this rapid extinction is given in an experiment by Gibson *et al.* (1965) in which rats pressed only a few times in extinction.

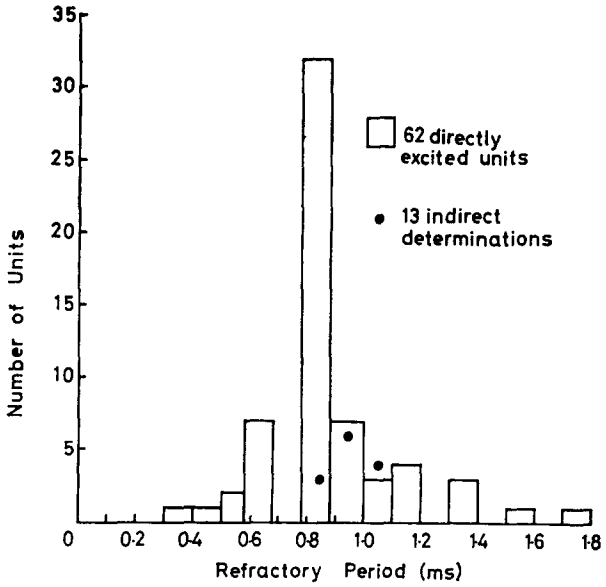

FIG. 39. Refractory periods of 62 brain-stem neurones directly excited through MFB self-stimulation electrodes (bar histogram). The units were recorded in 28 different rats. Indirect determinations of refractory period made on 13 indirectly driven units recorded in 13 different rats are shown by solid circles (●). (From *Physiol. Behav.* **7**, 297–310, 1971.)

Although it is concluded that activation of the brain-stem arousal system is not necessary for the production of brain-stimulation reward, it is very likely that the arousal produced by stimulation of some reward sites will affect the self-stimulation seen at that site (see below).

4.4 FUNCTION OF THE BRAIN-STEM AROUSAL SYSTEM IN THE PRIMING EFFECT

If a rat is connected for self-stimulation and placed in its test cage, it may not start self-stimulating until the experimenter gives a few trains of free or priming stimulation. Thus in addition to its reward effect, the stimulation also has a priming effect. In the example of priming given above, the effect is called the overnight decrement effect. Priming is also seen in a runway, when (priming) stimulation given at the start of a runway may increase running

speed for the (reward) stimulation given at the end of the runway. The priming effect shows a gradual decay for several minutes after the stimulation, as shown, for example, in Fig. 40 (Gallistel, 1969a). A rat ran in the runway for a small amount of brain-stimulation reward given at the end of the runway. When a relatively large amount of priming stimulation (1–20 trains) was given immediately before the first run, subsequent running speed along the runway for the reward was high, and gradually decreased as a function of time since the priming. It is shown in Fig. 40 not only that the priming effect shows a gradual decay, but also that the magnitude and duration of the priming effect depend on the amount (in this case the number of trains) of priming stimulation given. The priming effect is also seen in

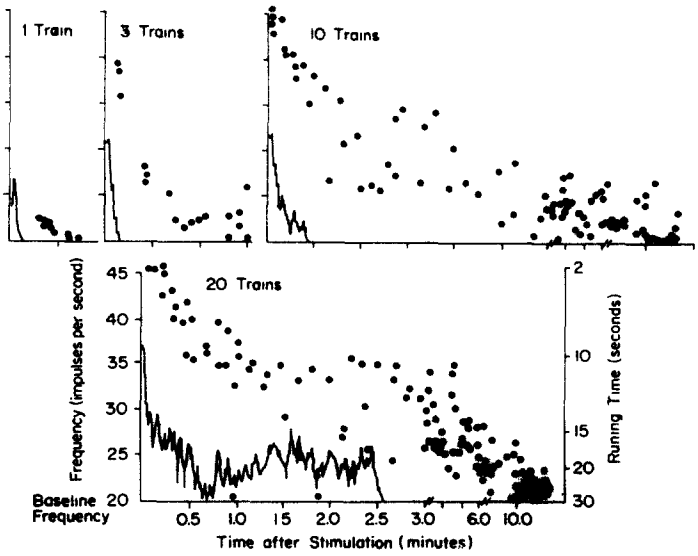

FIG. 40. Running speed (●) for a small brain-stimulation reward on massed trials as a function of time after different numbers of priming trains of stimulation given before the first trial. The abscissa has been shortened (data from Gallistel, *J. comp. physiol. Psychol.* **69**, 713–21, 1969). The firing rate of an arousal unit (solid line) as a function of time after different numbers of trains of stimulation delivered to a MFB self-stimulation site is shown for comparison.

the intertrial interval effect, in which rats running in a runway for brain-stimulation reward run faster after a decrease in intertrial interval, and more slowly after an increase (Gallistel, 1967). (A similar effect was not found in thirsty rats running for water reward.) As the effect occurs on the first trial after a change in intertrial interval, before an animal has been able to sample the reward at the end of the runway the effect is ascribed to a decaying pro-active (priming) effect of the last brain stimulation (Gallistel, 1967). The priming effect may also be involved in the poor performance often found with low density reward schedules. In this type of schedule the priming effect produced by a train of brain-stimulation would decay before the next train of stimulation was available. The long intervals without brain-stimulation may be bridged by allowing the priming effect to accumulate before the non-reward period, as occurs, for example, on a chain fixed-interval-10-min/continuous-reinforcement-1000-trains schedule (Pliskoff *et al.*, 1965).

The priming effect may be partly mediated by arousal produced through activation of the brain-stem arousal system (Rolls, 1971a). The evidence is as follows. Firstly, the arousal effect, measured by changes in the firing rates of indirectly driven arousal neurones and the correlated changes in the EEG, continues after the termination of stimulation for periods of the order of minutes (Figs. 37 and 40). Similarly, the priming effect, measured by its effect on subsequent running for a fixed brain-stimulation reward (Fig. 40), or on subsequent bar-pressing (Deutsch, 1964), or on subsequent choice of brain-stimulation reward (Deutsch *et al.*, 1964), is a pro-active effect of the stimulation. Secondly, the directly excited neurones which mediate the arousal effect have absolute refractory periods in the range 0.78–1.1 ms (Fig. 39) as do those neurones which mediate the priming effect (Deutsch, 1964; Gallistel

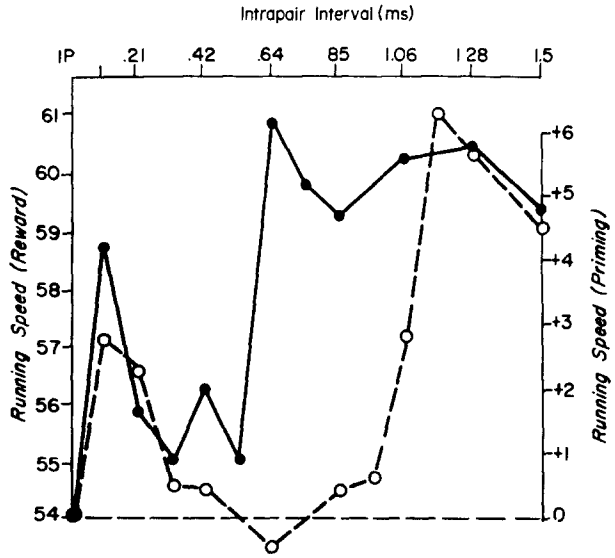

FIG. 41. Total running speed of a male albino rat as a function of IPI in the reward stimulation (solid line) given at the end of a runway for running, and as a function of IPI in the priming stimulation (broken line) given before running. Each point is the mean over 4 blocks of 10 trials each. The priming running-speed is expressed as a difference from the mean of blocks of 10 "baseline" trials, in which the second stimulus pulse in each pair was omitted. The speed scores are 100/(total latency in seconds). (Modified from *Science* **166**, 1028–30, 1969.)

et al., 1969; Rolls, 1971b; see below). For example, in a runway situation, in which the priming and reward effects can be separated (Gallistel, 1969a), running speed was measured as a function of the IPI of the pulse pairs in the priming stimulation given before each run (Gallistel *et al.*, 1969; Fig. 41, broken line). The running speed became greater than with priming with only the first pulse of each pair (1P) when the IPI was greater than 0.95 ms (Fig. 41). Thus the refractory period of the neurones mediating the priming effect was in the the range 0.95–1.06 ms. In the same experiment variation of the IPI of the reward stimulation produced a different value of the refractory period of the neurones involved in reward (Fig. 41, solid line). In an experiment which used the rate of self-stimulation to measure the priming effect, the refractory period values obtained were in the range 0.8–1.1 ms (Deutsch, 1964). Similar values were found in another rate of self-stimulation experiment in which the

same lateral hypothalamic sites as those used in the electrophysiological refractory period measurements were used (Fig. 42; Rolls, 1971b). In order to approach the absolute refractory period of the neurones, twice-threshold pulse pairs were used in this experiment. As the priming effect is at least a general activation of the EEG and behaviour, it must influence how rapidly an animal bar-presses, and in the two experiments above the self-stimulation rate is used to provide a measure of the priming effect. Thirdly, the decay of the arousal effect (seen in the gradual return to pre-stimulation firing rates of indirectly driven neurones and the gradual return of the EEG to synchronization, Figs. 37 and 40) is similar to the decay of the priming effect in self-stimulation (Fig. 40; Gallistel 1969a) and to the gradual reduction in the choice of the brain-stimulation after priming stimulation (see below, Deutsch *et al.*, 1964; Fig. 43). Fourthly, the magnitude and duration of the priming effect (Fig. 40) and of the arousal effect (Fig. 40) depend on the duration (or number of trains) of the priming stimulation. The duration of the priming effect illustrated in Fig. 40 is very long, and was therefore useful in the behavioural experiments of Gallistel (1969a). Fifthly, both the priming and the arousal effects accumulate over long periods of stimulation, of the order of 10 s in previous behavioural studies (Gallistel, 1969a; see Fig. 40; Hodos, 1965) and in the electrophysiological experiments (Figs. 37 and 40).

Because of the similar characteristics of the priming and arousal effects, it is likely that the priming effect often found with intracranial self-stimulation is mediated at least partly by the general arousal produced by the stimulation. The general arousal measured electrophysiologically consisted of EEG desynchronization and activation of arousal units (Figs. 37 and 40). (A behavioural measure of this general arousal is locomotor activity produced by the stimulation—see section 4.5.) It is therefore of interest to determine whether the priming effect has a general effect on behaviour equivalent to an increase in general activity or whether the priming effect is a more specific drive-like effect, similar, for example, to hunger or thirst. That is, does priming stimulation produce a drive for more brain-stimulation reward or does it produce a general facilitation of behaviour equivalent to increased arousal? One experiment shows that the priming effect at least produces a facilitation of behaviour which is different from thirst. Deutsch *et al.* (1964) gave rats a choice between water and brain-stimulation reward. When thirsty rats were given priming stimulation, they chose brain-stimulation reward rather than water (Fig. 43, 0 s delay). This priming effect decayed, so that with a delay between priming and the choice, the rats chose water (Fig. 43). The next question is whether the priming effect, which is distinguishable from a specific natural drive such as thirst, is specific in the same way as a natural drive. If so, then hunger could correspond to priming at one site, and thirst to priming at another. Gallistel (1969b) found no evidence that rats did choose to be rewarded on an electrode on which they had recently been primed. Thus the priming effect was a general one—the rats did not distinguish between priming at the two sites. (He has found very convincing evidence that the reward effect produced by the stimulation is specific—see Gallistel and Beagley, 1971, and section 7.2.) To summarize, there is no evidence that the priming effect is like a specific natural drive, but there is evidence that it is distinguishable from it. This is consistent with the view that the priming effect is at least partly mediated by the elicited general arousal.

Although the evidence given above indicates that general arousal produced by stimulation of self-stimulation sites near the MFB must affect self-stimulation and at least partly mediates the priming effect, other factors may also be involved in the priming effect. One possible factor is incentive motivation (or the "salted-nut" phenomenon). Panksepp and Trowill (1967b) have shown that satiated animals working for a highly palatable reward of

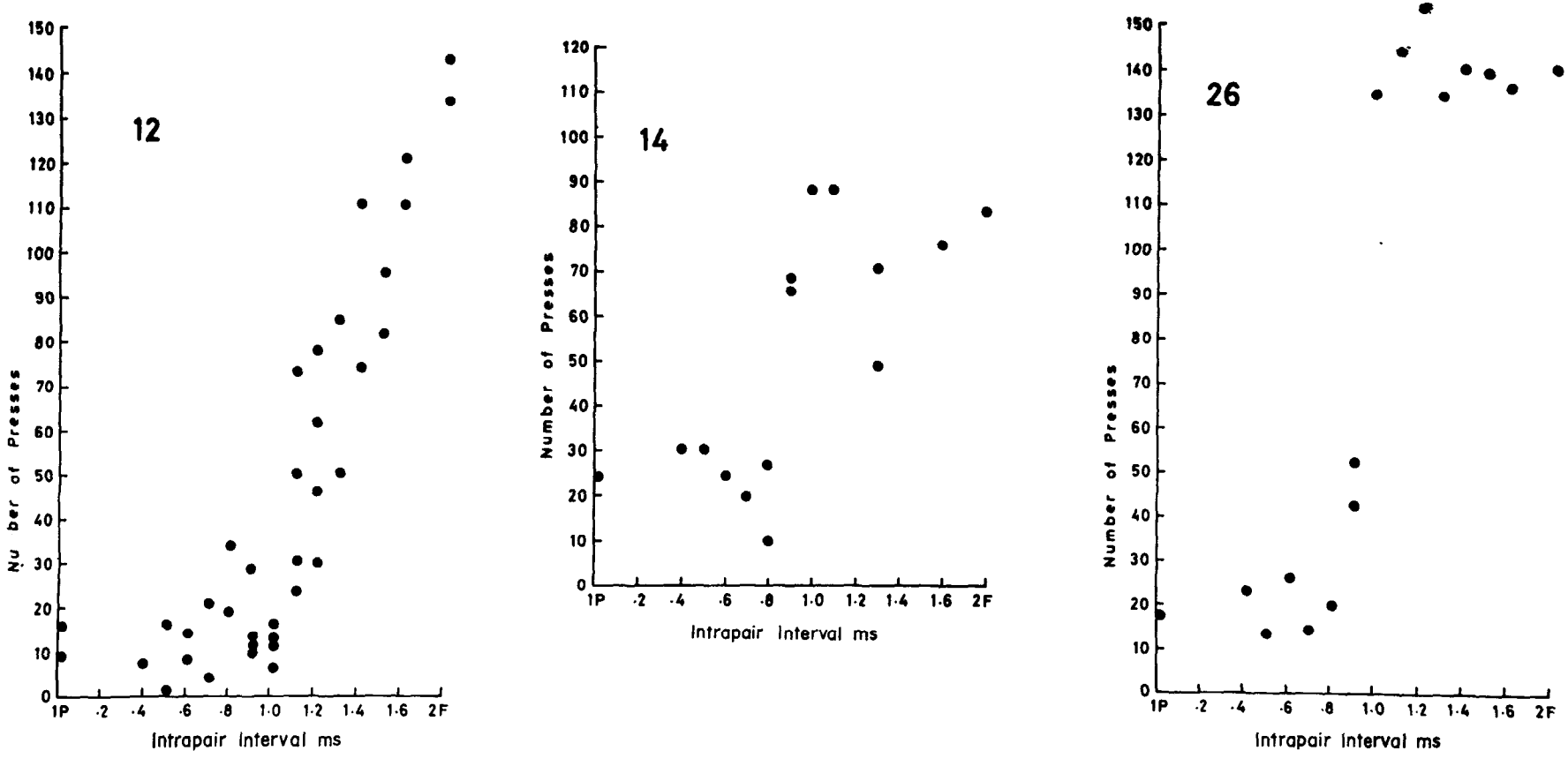

FIG. 42. Number of bar-presses in a 90 s test period for a 0.3 s train of twice-threshold pulse pairs as a function of the IPI of the pulse pairs. Results for three different rats with lateral hypothalamic self-stimulation are shown here. (Modified from *Physiol. Behav.* 7, 311–15, 1971.)

chocolate milk delivered intraorally sometimes need priming. Another possible factor is aversion produced by the stimulation. Kent and Grossman (1969) reported that rats which needed priming showed that the stimulation was aversive by squealing, and showed an approach–avoidance conflict at the bar. These factors are not mutually exclusive, and it is likely that arousal, incentive motivation, and aversion produced at some brain-stimulation reward sites can contribute to the priming effect. Further, it is probable that aversion and arousal are to some extent correlated. In their work on aversion, Kent and Grossman (1969) found that only some animals showed an overnight decrement effect. Although some

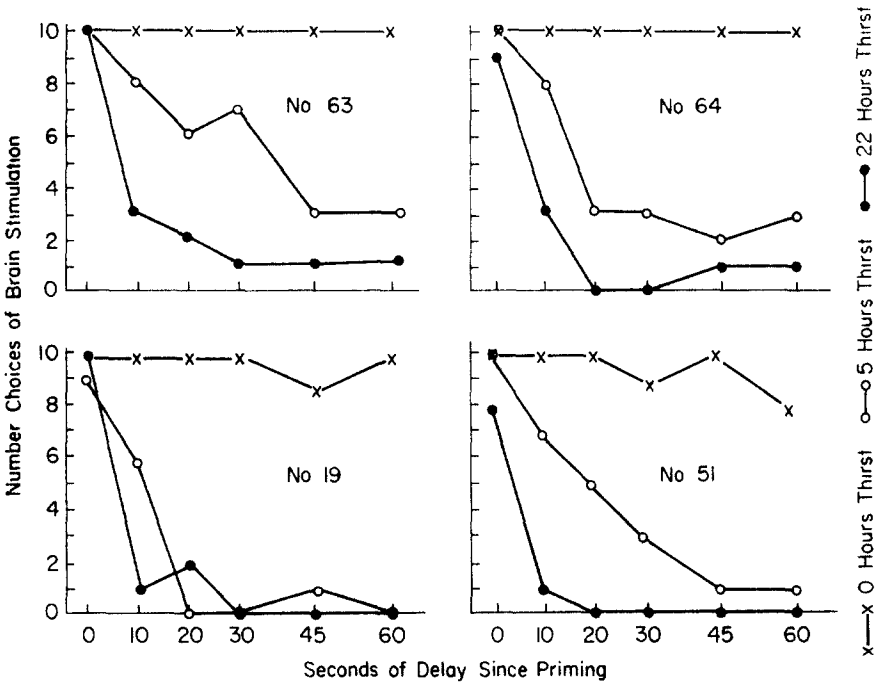

FIG. 43. Choice behaviour of 4 rats as a function of degree of water deprivation and time since priming at a self-stimulation site. The number of times brain-stimulation reward is chosen rather than water decreases for about 60 s following the priming (see, for example, curves for 5 h water deprivation). This appears to show the decay of a specific drive-like process. (From Deutsch *et al.*, *J. comp. physiol. Psychol.* **57**, 241–3, 1964.)

of their animals thus did not need priming, the animals might still have shown a priming effect (subsequent facilitation of self-stimulation) if priming had been tried in the experiments. One experiment of interest in this context would be to determine to what extent an animal in which rewarding stimulation does not produce arousal (e.g. with an electrode in the nucleus accumbens) shows a priming effect.

It has been suggested that the rapid extinction sometimes seen with intracranial self-stimulation is related to the priming effect (Deutsch, 1960; Howarth and Deutsch, 1962). The hypothesis was that the rapid extinction is due to the decay of the activation which is needed (in the absence of the natural relevant drive) to produce the next instrumental act producing reward. Clearly one factor of importance is the presence of a relevant natural

drive (e.g. hunger at a self-stimulation site where food deprivation increases self-stimulation rate), for in hungry rats extinction from self-stimulation is comparable to extinction of a food-rewarded response (Olds, 1956a, b; Deutsch and DiCara, 1967). (The presence of a specific natural drive also makes secondary reinforcement with brain-stimulation reward more normal—see DiCara and Deutsch cited in Deutsch and Deutsch, 1966, p. 128.) Another factor of importance in the rapid extinction from self-stimulation is the lack of delay between pressing the bar and obtaining the stimulation. Similarly, rapid extinction is seen in rats which must lick a dipper to obtain sucrose solution (Gibson *et al.*, 1965). In this case there is also no delay between the operant response and reinforcement, so that the animal has immediate information that the response produces no reinforcement, and extinction is rapid. Although it is possible that the response of licking the dipper produced odd results in this experiment (Panksepp and Trowill, 1967a, b), it does appear that rapid extinction from self-stimulation can be influenced by relevant natural drives and by the prompt reinforcement. It is therefore unclear to what extent arousal produced by stimulation of some reward sites is necessary to explain, or is involved in, extinction from intracranial self-stimulation.

4.5 FUNCTION OF THE BRAIN-STEM AROUSAL SYSTEM IN STIMULUS-BOUND LOCOMOTOR ACTIVITY

The most prevalent behaviour elicited by electrical stimulation of the lateral hypothalamus is locomotor activity. Stimulus-bound wheel running (Rosenquist and Hoebel, 1968) and locomotor exploration (Christopher and Butter, 1968) are obtained from hypothalamic self-stimulation sites. Conversely, other activities such as eating, drinking, gnawing, and sexual behaviour (Valenstein *et al.*, 1969; Madlafousek *et al.*, 1970) are elicited from a smaller proportion of electrode sites. In the absence of the required goal object, stimulation at these sites also produces locomotor activity (Hoebel, 1969). To analyse the neural basis of the stimulus-bound locomotor activity and to determine the relation of the activity to reward and motivation induced by lateral hypothalamic stimulation, the characteristics of the locomotor activity were determined (Rolls and Kelly, 1972). These characteristics were then compared with those of neural systems known to be activated by the stimulation.

Firstly, the absolute refractory period of the neurones whose direct excitation leads to locomotor activity during rewarding lateral hypothalamic stimulation was measured. Twice-threshold 0.1 ms pulse pairs were applied to a reward electrode for 60 s, and then switched off for 90 s. The repetition frequency of the pulse pairs was one which when doubled in the one-pulse condition led to increased locomotor activity. The locomotor activity was then measured on subsequent trials as a function of the IPI of the pulse pairs. Figure 44 shows the locomotor activity measured by the number of counts in a locomotion apparatus during the trial period. The longer IPIs produce more locomotor activity than the short IPIs or the one-pulse condition. That this increase in locomotion is not apparent at 1.0 ms but is generally present at 1.1 ms, is an indication that the directly excited neurones fire more at 1.1 ms and, therefore, that the absolute refractory period of the directly stimulated neurones is in the range 1.0–1.1 ms.

The results for 6 rats agreed closely in showing increased locomotor activity when the IPI was in the range 0.75–1.1 ms (Rolls and Kelly, 1972). This value corresponds with that of the brain-stem neurones in the arousal system directly excited by the hypothalamic stimulation

(0.78–1.0 ms). This provides an indication that the brain-stem arousal system is involved in the stimulus-bound locomotor activity.

The refractory period experiment gave an indication that the brain-stem arousal system was involved in the locomotor activity. To gain further evidence on this, experiments were

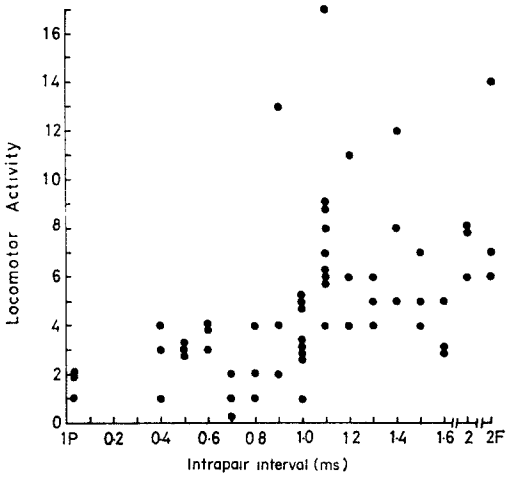

FIG. 44. Locomotor activity produced by rewarding lateral hypothalamic stimulation as a function of the IPI of twice-threshold pulse pairs (results for one rat are shown here). 1P = one-pulse condition. 2F = repetition frequency doubled. (Modified from *J. comp. physiol. Psychol.* **81**, 173–82, 1972.)

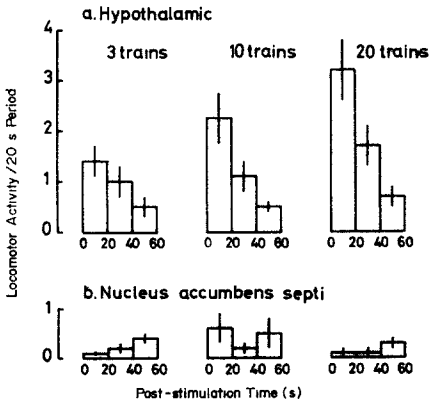

FIG. 45. Post-stimulation locomotor activity (means and standard errors) as a function of time since stimulation and amount of stimulation delivered to (a) hypothalamic sites, and (b) nucleus accumbens sites. (Each train was 0.5 s long, 100 pulses/s.) (From *J. comp. physiol. Psychol.* **81**, 173–82, 1972.)

performed to determine whether the locomotor activity also had other characteristics of the brain-stem arousal system, namely, gradual decay of activity after the end of stimulation, activity whose magnitude and duration are dependent on the number of trains of stimulation applied, and lack of activation by stimulation applied to nucleus accumbens sites. In 4 rats

series of 0.5 s trains of 0.1 ms constant-current cathodal pulses at 100 pulses/s and at a current which supported self-stimulation were delivered to the hypothalamic electrode. Three series were used for each rat: 3 trains, 10 trains, and 20 trains, with 0.5 s between each train in a series. Sixty seconds elapsed between the termination of one series and the onset of the next. After the animal's behaviour had stabilized each series was repeated 10 times with the order of the different series randomized. The results are shown in Fig. 45a. They show that the magnitude of the locomotor effect was significantly greater following 20 trains than following 3 trains (Mann–Whitney U-test on total locomotor activity scores; $p = 0.011$). Thus the locomotor effect is similar to the arousal effect in that increasing the number of trains produces an effect of greater magnitude. It was not possible to assess the absolute duration of the locomotor activity as the locomotor activity following one series did not decline to zero before the next series was delivered. Qualitatively, within the 60 s period it is clear that the results have a similar form to those found for the arousal effect (Figs. 37 and 40). The results also emphasize the decay of locomotor-exploratory activity following hypothalamic stimulation. Mean activity in the initial 20 s period was significantly greater than in the final 20 s period following 3, 10, or 20 trains (Mann–Whitney U-tests; $p = 0.017$, 0.004, 0.0003 respectively). It is shown in Fig. 45b that very little locomotor activity is produced by rewarding nucleus accumbens stimulation, which does not produce general arousal.

The marked similarities between the locomotor activity and the arousal which are produced by stimulation of lateral hypothalamic sites provide evidence that activation of the brain-stem arousal system at least partly mediates the locomotor activity.

It has been noted that sometimes rewarding lateral hypothalamic stimulation produces turning locomotor activity (Grastayán *et al.*, 1968; see also Molnár, 1973). The turning was generally contraversive (with respect to the electrode), and was followed at the end of the stimulation by more contraversive turning (rebound after-effects). (Ipsiversive rebound turning was associated with sites where stimulation was aversive.) The rebound effect was associated with activity in the hippocampus (see section 5.1).

4.6 EFFECT OF ACTIVATION OF THE BRAIN-STEM AROUSAL SYSTEM ON MFB SELF-STIMULATION

Sites near the MFB support very different self-stimulation to that seen with rhinencephalic sites including, for example, the hippocampus, amygdala, and probably nucleus accumbens. Differences between MFB and rhinencephalic self-stimulation have been summarized by Olds and Olds (1965). MFB self-stimulation occurs at much higher rates than rhinencephalic self-stimulation: under similar conditions rates may be 10,000 vs. 500 responses/h. Rhinencephalic self-stimulation may show "satiation" and stop for the day after several thousand bar-presses, while MFB animals continue until exhausted (although MFB animals requiring priming may show a decline in rate; Kent and Grossman, 1969). MFB reward is accompanied by hyperactivity, whereas at least during intracranial stimulation, rhinencephalic rewarding stimulation is accompanied by hypoactivity. Pain or anxiety relief in man is obtained from stimulation of some rhinencephalic reward sites, and no relief is obtained from some MFB sites (Brady, 1961). This situation also occurs in the rat, in which rewarding rhinencephalic stimulation suppresses the aversive effects of tegmental stimulation (Routtenberg and Olds, 1963), but rewarding MFB stimulation augments the behavioural response to the aversive stimulation (Olds and Olds, 1962; see also section 1.2.1). Finally, the eating, drinking, or sexual activity which may be produced by stimulation of

MFB reward sites is stimulus-bound (for review see Valenstein *et al.*, 1969), while feeding produced by stimulation of some hippocampal reward sites occurs for 3–40 s after a 1 s period of stimulation, and may be regarded as a rebound phenomenon (Milgram, 1969).

It has been shown above that the hyperactivity and the high rates of self-stimulation typical of MFB self-stimulation depend on activation of the brain-stem arousal system. The lack of satiation of MFB self-stimulation may be partly because an animal is kept awake and active during the self-stimulation. Stimulus-bound motivated behaviour can be influenced by activation of the brain-stem arousal system, as shown by refractory period measurements (Rolls and Kelly, 1972; see sections 4.5 and 2.3.3), the effects of lesions (see section 1.2.2), and the evidence that stimulus-bound motivated behaviour is produced from reward sites from which the brain-stem arousal system is activated. One possible hypothesis is that stimulus-bound motivational behaviour is produced when neurones which code a specific natural reward (e.g. food) are excited in conjunction with general arousal produced by activation of the brain-stem arousal system. This hypothesis explains stimulus-bound motivational behaviour as incentive motivation coupled with general activation of behaviour. Arousal changes produced by the stimulation may also account for the alterations in sensory evoked potentials seen during self-stimulation (Ball, 1967) as arousal may affect evoked potential magnitude (Horn, 1965). Thus a number of the effects obtained by stimulation of some reward sites may be produced not by activation of reward neurones but by activation of arousal neurones.

4.7 THE USE OF REFRACTORY PERIOD DETERMINATIONS

Refractory period measurements are clearly of use in distinguishing electrophysiologically between directly driven and trans-synaptically driven neurones. Directly driven neurones have a short refractory period, usually less than 2 ms, in the neural systems described here. In contrast, trans-synaptically activated neurones only show good following of pulse pairs at longer IPIs, usually longer than 5 ms. The criteria used to judge direct or trans-synaptic activation for the above statements are presence or absence of collision (present only in antidromically activated neurones; Rolls, 1971a, c), variability of latency, and value of latency. Refractory period determinations are equivalent in this context to tests with trains of high frequency (e.g. 1000 Hz) stimulus pulses which are characteristically only followed by directly excited units.

Refractory period measurements have also been useful in relating the activation of a trans-synaptically activated neurone to the activation of a given population of units (Gallistel *et al.*, 1969; Rolls, 1971a). By determining the response of indirectly driven arousal neurones to trains of pulse pairs as a function of the IPI it was shown that the arousal neurones fired more when the IPIs were greater than 0.8–1.1 ms (Rolls, 1971a). The straightforward explanation of this is that the refractory period of the directly excited neurones is in the the range 0.8–1.1 ms. This value was then taken as one indication that the arousal neurones were driven through the brain stem directly excited neurones with absolute refractory periods of 0.78–1.0 ms (Rolls, 1971a). This indication was, in fact, useful, for further tests were then performed to determine whether other evidence supported the suggestion. It has been shown above (section 4.2) that the suggestion was supported, e.g. by the experiment with nucleus accumbens stimulation. Early use of this type of evidence was made by Lucas (1917) on the nerve-muscle preparation (see also Gallistel, 1973).

Refractory period measurements have also been useful in relating behavioural effects produced by electrical stimulation to the underlying neural mechanism. For example, as the refractory period of one group of neurones involved in stimulus-bound eating and drinking (Rolls, 1973) corresponded with that of amygdaloid neurones directly excited by the stimulation, further tests (anaesthesia, lesions—see section 2.4) were performed to test the hypothesis. Similarly, when it became clear that the absolute refractory period of the neurones involved in stimulus-bound locomotor activity was 0.8–1.1 ms (Rolls and Kelly, 1972; section 4.5), the hypothesis that activation of the brain-stem arousal system mediated the locomotor activity was tested (by determining the post-stimulation nature of the locomotor activity: section 4.5). In these examples the refractory period measurements have provided a useful indication of the nature of the neural system underlying a type of behaviour. The observations have been used as indications and have been followed up to determine whether there is supportive evidence for the suggestion generated. Further examples are given in the recent review by Gallistel (1973).

A number of points over which care must be taken with indirect refractory period measurements have been made by Rolls (1971b). At least twice-threshold pulse pairs should be used to increase the probability of measuring an absolute rather than a relative refractory period. The rather long refractory period values (1.0–1.4 ms) found with indirectly driven (arousal) neurones in an early study (Gallistel *et al.*, 1969) were probably due to a rather low value of stimulating current relative to the threshold of the directly excited neurones. At short IPIs (e.g. 0.2 and 0.3 ms) more activation than with the one-pulse condition is frequently found. This is probably because of latent addition (Deutsch, 1964; Rolls, 1971b). The failure of Wetzel (1972) to obtain clear refractory period determinations for self-stimulation rate in the cat may be due to inattention to these points. It is not clear, for example, that at least twice-threshold current pulses were used (see further, Rolls, 1971b). The use of lower frequency stimulus pulses and the recognition that postsynaptic effects (such as temporal summation, see Kestenbaum *et al.*, 1970; Smith and Coons, 1970; Ungerleider and Coons, 1970) must influence performance at the longer IPIs, might also have been useful.

The exact form of the results found in an indirect refractory period determination (see, for example, Figs. 10, 11, 38, 41, 42, 44, and 48) is likely to be sigmoid rather than a step function for the following reasons. Firstly, the form of the curve must reflect the distribution of the refractory periods of the directly excited neurones. For example, for the directly excited neurones shown in Fig. 39 the number of neurones excited as the IPI of pulse pairs is increased becomes much greater at 0.78 ms. Yet at smaller IPIs some neurones would be excited, and as the IPI is increased beyond 0.78 ms, more and more neurones would be excited. Cumulation over the number of neurones excited produces a sigmoid curve, which has a sharp rise in this case at 0.78 ms. Secondly, neurones at the edge of the stimulation field may not be excited with a sufficiently suprathreshold current to fire twice at their absolute refractory period. That is, relative refractoriness may be shown. This would tend to produce a sigmoid curve, and would also tend to move it towards longer refractory period values. Given these points, care must be taken in reading indirect refractory period curves. The first sharp rise which occurs relative to the one-pulse stimulation as the IPI is increased gives an indication that many neurones fire twice at that IPI. This is the main information which can be gained from the curve. At shorter and longer IPIs increases in effectiveness of pulse pairs may be related to the excitation of the other neurones contained in the refractory period distribution. However, extrapolation from the curve back to the original form

of the refractory period distribution cannot be exact because of latent addition, relative refractoriness, and postsynaptic effects (see above). Thus if the distribution of refractory periods of the directly excited neurones has a sharp peak, then this can be detected with an indirect refractory period measurement, but other inferences are probably not justified. (In particular, changes occurring at IPIs greater than at the first major inflection of the curve could be due to longer refractory period fibres, relative refractoriness of short refractory period fibres, postsynaptic effects, or ceiling effects. Spuriously long determinations could arise similarly.)

Some points which suggest that refractory period determinations can be useful in relating neuronal function to behaviour follow. Firstly, when a relatively simple preparation is used, the nerve-muscle preparation, the refractory period of the nerve fibres can be measured equally well by the electrical activity of the nerve and by the contractile behaviour of the muscle (Boycott, 1899; Gotch and Burch, 1899; Bramwell and Lucas, 1911). Secondly, different populations of neurones excited through the same electrode can have different refractory period distributions (see, for example, Figs. 3 and 39). Thirdly, when refractory period experiments suggested that the amygdala is involved in stimulus-bound eating and drinking (section 2), and that brain-stem neurones are involved in EEG arousal and locomotor activity produced by hypothalamic stimulation (section 4), subsequent experiments confirmed the suggestion. For example, the brain-stem neurones were only activated from sites from which EEG arousal and locomotor activity were produced. Further, a different population of brain-stem neurones was excited from non-reward hypothalamic sites from which motor effects (but no EEG arousal or locomotor activity) were elicited, and the refractory period characteristic of this neuronal population (0.6 ms) corresponded with that measured indirectly using the strength of the motor contraction elicited (Rolls, 1971a; section 4). Fourthly, when refractory period determinations are performed on different types of behaviour, different refractory period values are obtained. For example, 0.55–0.60 ms is the refractory period value characteristic of the motor effect elicited from motor effect sites (Rolls, 1971a); 0.8–1.1 ms is the refractory period value characteristic of the arousal (section 4.2), priming effect (section 4.4), locomotor activity (section 4.5), and under some experimental conditions of the eating and drinking (Hu, 1971) produced by stimulation of MFB self-stimulation sites; and 0.6 ms is the refractory period characteristic of the eating and drinking elicited under other experimental conditions (when latency to the onset of drinking or eating is measured, section 2.2) and perhaps of reward (Deutsch, 1964; Gallistel *et al.*, 1969) elicited by stimulation of MFB self-stimulation sites.

A further point about refractory period determinations has been made by Szabó (1973). He suggests that neurones in the subliminal fringe to the first pulse of a pair could receive a trans-synaptic input from neurones fired by the first pulse. If this trans-synaptic input is excitatory (i.e. produces an EPSP), then this increased excitability could result in firing to the second pulse of the pair. In this way increased performance (e.g. behaviour) could be produced by a pulse separated from a first pulse by a delay including synaptic transmission time (e.g. a delay of 0.5 ms). The extent to which this type of mechanism accounts, for example, for the facilitation of self-stimulation seen as the IPI is increased beyond 0.6 ms (Deutsch, 1964) is not known. The hypothesis that neurones with refractory periods as short as 0.5–0.6 ms could not be involved in lateral hypothalamic self-stimulation is clearly incorrect because refractory periods of this value are measured distant from the stimulating electrode in neurones directly excited by the stimulation (see, for example, section 2.1.2). Further relevant evidence to Szabó's point is that when the refractory period of neurones

involved in motor effects was estimated indirectly to be 0.5–0.6 ms it was found that a population of brain-stem neurones directly excited by the stimulation had refractory periods of 0.5–0.6 ms (Rolls, 1971a; section 4.2). Thus indirectly measured refractory periods of 0.5–0.6 ms can be associated with the direct excitation of neurones with this absolute refractory period (sections 4.2, 2.1, and 2.3). The main point which arises is that although refractory period evidence may be useful in relating behaviour to activation of given neural tissue from which recordings have been made (see above), it should only be used to give an indication of activated structures, and should be followed up with further investigations (see above).

A minor point about refractory period determinations is that care must be taken when extrapolations are made to fibre diameter in the central nervous system. Most of the evidence on this point comes not from measurements made in the central nervous system but from work on peripheral nerves.

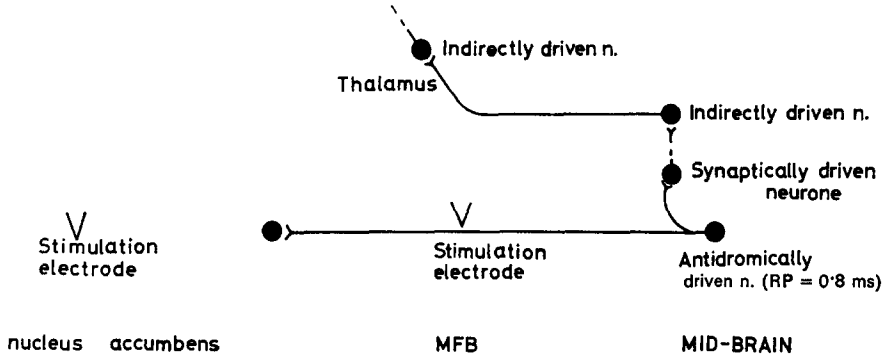

FIG. 46. Schematic diagram of a brain-stem neural system through which arousal is produced by rewarding MFB stimulation. RP = absolute refractory period.

4.8 SUMMARY

Neurones with cell bodies in the midbrain and pons are excited by stimulation at self-stimulation sites along the MFB (Fig. 46). These neurones probably trans-synaptically drive other neurones in the brain stem and, finally, activate brain stem and thalamic neurones which have general arousal propoerties. Arousal was measured by EEG desynchronization and by the responses of the units to a pinch and other arousing stimuli. Activation of this brain-stem arousal system is not necessary for brain-stimulation reward, for rewarding nucleus accumbens stimulation does not excite the brain-stem neurones nor does it produce arousal. The brain-stem arousal system may be involved in the priming effect often seen with self-stimulation because the arousal and the priming effect have similar post-stimulation temporal characteristics and are produced through neurones with absolute refractory periods of 0.75–1.0 ms. Similar evidence indicates that the brain-stem arousal system at least partly mediates stimulus-bound locomotor activity produced by MFB stimulation. Activation of the brain-stem arousal system affects the rate of self-stimulation, and may also account for some of the characteristics of MFB self-stimulation, namely, high rates of self-stimulation, hyperactivity, and lack of satiation.

5. The Function of Other Limbic and Related Areas in Brain-stimulation Reward

It has been shown in previous sections that the prefrontal cortex and the amygdala are involved in brain-stimulation reward. It is therefore of interest to examine whether neurones in other areas closely related to the hypothalamus, e.g. the hippocampus and the cingulate cortex, are also involved in brain-stimulation reward. Although neurones in some of these areas are activated in brain-stimulation reward (see below), the currently available lesion evidence (see section 1) suggests that these areas are not critical for brain-stimulation reward.

5.1 THE HIPPOCAMPUS

The activation of neurones in the hippocampus by brain-stimulation reward has been described by Rolls (1970a, b) and Ito and Olds (1971).

An example of a hippocampal unit which was activated by brain-stimulation reward is shown in Fig. 47. The unit was activated only by a train of stimulus pulses, not by single stimulus pulses, and was therefore classed as indirectly driven. Following a 10 ms train of pulses applied to a lateral hypothalamic site, the unit showed a post-stimulation increase in rate with a latency of 30 ms followed by inhibition (see unit trace and post-stimulus time histogram). The same unit was inhibited with a latency of 70 ms by stimulation applied to a nucleus accumbens reward site. Because the stimulation currents used were those which had previously supported self-stimulation, this type of activation is characteristic of the rewarding stimulation. The EEG and unit rate measurements below show that an arousing stimulus, a pinch, and the inhalation of acetone have only small effects on the firing rate of the unit. Five trains of stimulation (100 Hz for 0.3 s as in self-stimulation) applied to the nucleus accumbens electrode (5A) and to the lateral hypothalamic electrode (5P) produced only small long-term effects (Fig. 47).

This indirect activation of hippocampal units by brain-stimulation reward was found in a large sample (14) of animals. Latencies of 30–100 ms from the start of a stimulus train were common. The units often had high spontaneous firing rates (up to 100 per s) and were inhibited by the stimulation. The sites of some activated hippocampal units are shown in Fig. 48. Consistent with this type of activation is the finding of Ito and Olds (1971) that the spontaneous firing rates of 14 hippocampal units were decreased during rewarding posterior hypothalamic self-stimulation, and only one unit showed an increased rate. In their study, 8 units were unaffected by the stimulation. Convergence on to single hippocampal neurones of the effects of lateral hypothalamic and nucleus accumbens stimulation is usual. The activation of hippocampal neurones was clearly not simply a correlate of arousal, as shown, for example, in Fig. 47.

Very few hippocampal neurones have been found to be activated with short latencies, either directly or trans-synaptically, by rewarding stimulation of the lateral or posterior hypothalamus. Rolls (1970a) found short latency (3–6 ms) trans-synaptic driving in only two of 16 rats, and Ito and Olds (1971) found only 1 driven neurone in a sample of 23 neurones. These results suggest that the activation of hippocampal neurones in general involves several synapses, and that antidromic activation of pyramidal cells through the fornix is an unlikely route of activation. Neurones in the entorhinal area are activated in brain-stimulation reward (see below), and activation of the hippocampal neurones could be mediated through these neurones. In an attempt to identify the pathway through which the hippocampal neurones are indirectly driven, Rolls (1970a, b) performed indirect refractory

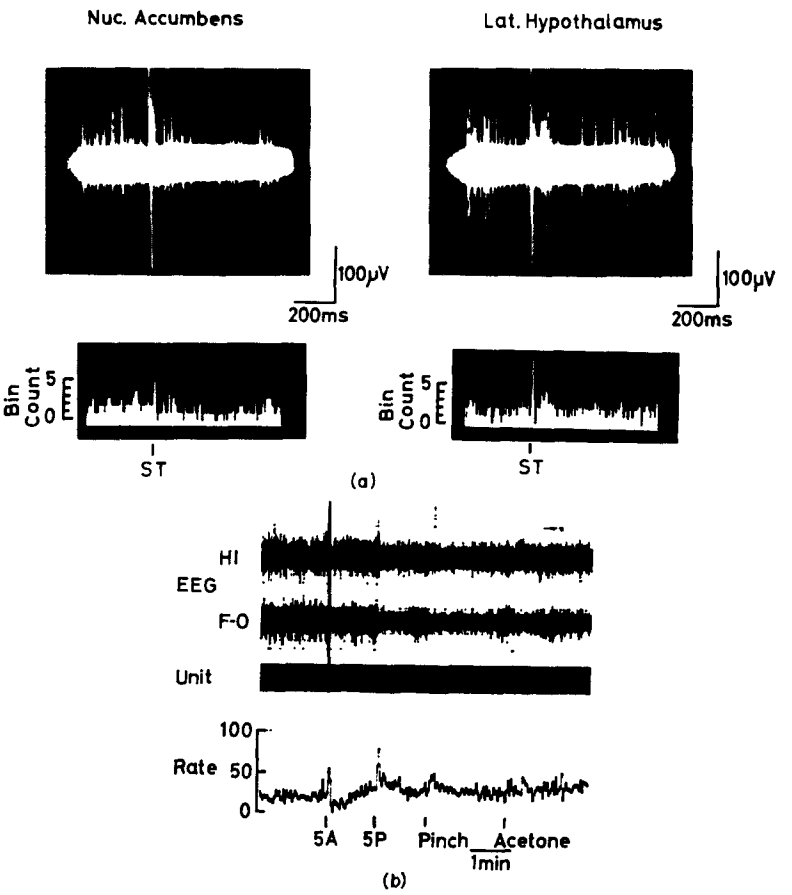

FIG. 47. (a) An indirectly (trans-synaptically) driven hippocampal unit inhibited by nucleus accumbens stimulation with a latency of 70 ms and excited by MFB stimulation with a latency of 30 ms. An example of the response of each unit is shown in a photograph of a single sweep above. A pre- and post-stimulus time histogram of 10 sweeps with a bin width of 4 ms is shown below for each unit. The 10 ms stimulation train, of 0.1 ms pulses at 1000 Hz at the self-stimulation current threshold, occurred at ST. (b) The firing of the unit illustrated above. F–O: EEG recorded between the frontal and occipital cortex. HI: EEG recorded from the single-unit capillary microelectrode in the hippocampus. Unit: spikes here correspond to action potentials. Rate: firing rate of the hippocampal unit in action potentials/s. 5A: 5 trains of stimulation applied to the nucleus accumbens reward electrode. 5P: 5 trains of stimulation applied to the MFB reward electrode. Acetone: olfactory stimulation. The rat was lightly anaesthetized with urethane. (From Rolls, 1970b.)

period determinations on activated hippocampal neurones. An example is shown in Fig. 49. The duration of the inhibition of spontaneous activity was measured as a function of the IPI of the pulse pairs in a stimulus train. The inhibition became more intense relative to the one-pulse condition with IPI greater than 0.55 ms. Thus the absolute refractory periods of the directly excited neurones through which the driving was produced was near 0.55 ms. In a series of 7 indirect refractory period determinations on hippocampal units (in 7 different rats) the values obtained were between 0.5 and 0.7 ms. Thus the limited evidence available

suggests that the hippocampal neurones activated in lateral hypothalamic self-stimulation are activated through directly excited neurones with absolute refractory periods between 0.5 and 0.7 ms. This would be consistent with activation through the directly excited neurones in the region of the basolateral amygdala and pyriform cortex (see section 2), but it is, of course, possible that other as yet unidentified activated pathways have a similar refractory-period characteristic. A possible pathway for this activation would be via the intracortical links between the pyriform cortex and entorhinal area, and then via the temporoammonic tract or the temporoalvear tract to the hippocampus (for anatomy see Raisman *et al.*, 1965, 1966).

The finding that lesions of the fornix do not affect self-stimulation of the lateral hypothalamus (Boyd and Gardner, 1967) or basal tegmentum (Ward, 1960) indicates that this pathway is not crucial for brain-stimulation reward. Similarly, the findings that lesions of the hippocampus increase septal (Asdourian *et al.*, 1966) and lateral hypothalamic (Molnár and Grastayán, 1966; see Molnár, 1973) self-stimulation rate, and that lesions of the hippocampus lower the current levels required to maintain lateral hypothalamic self-stimulation (Molnár and Grastayán, 1966; Jackson, 1968), suggest that the activation of hippocampal neurones described here may affect but not be crucial for brain-stimulation reward.

The role of the hippocampus in motivation and reinforcement has been discussed recently by Molnár (1973). The above lesion evidence is interpreted as showing that while the hippocampus is not essential for self-stimulation, it does influence the regulation of motivational processes (on other evidence, particularly in relation to attention). Following earlier work of Grastayán *et al.* (1965), Molnár (see Molnár, 1973) showed that rewarding lateral hypothalamic stimulation was associated with contraversive turning behaviour during and as a "rebound" from the stimulation and with an increase of hippocampal theta activity. (In contrast aversive stimulation—probably of the periventricular system—led to ipsiversive turning and hippocampal delta activity.) Although hippocampal epileptic manifestations were supposed to be "extreme indicators of reinforcement", they are presumably not present in the lesioned animals which self-stimulate (see above), nor are they necessarily present in self-stimulation. (For example, septal self-stimulation occurs equally well when the stimulation produces a definite theta rhythm or theta blocking in the hippocampus: Ball and Gray, 1971.) Molnár (1973) suggests further that it is a rebound process occurring usually at the termination of stimulation which is reinforcing on the evidence of Grastayán *et al.* (1968) that animals showed approach behaviour to objects seen at the termination of stimulation. The rebound was correlated with hippocampal epileptic activity. This hypothesis that the termination of the stimulation is rewarding provides one possible explanation of the observation that animals self-stimulate with repeated short trains of stimulation rather than with one continuous train. Another possible explanation is that adaptation of reward neurones occurs. This is consistent with the observation that rats usually prefer to increase rather than turn off persistent brain-stimulation reward (Deutsch and Hawkins, 1972).

5.1.1 *Summary*

Very few neurones in the hippocampus are activated with short latencies either directly or trans-synaptically by rewarding stimulation of the lateral hypothalamus or nucleus accumbens. Many hippocampal neurones are indirectly activated (i.e. by a train of stimulus pulses) with long latencies, commonly between 30 and 100 ms, by the rewarding stimulation.

Activation of the neurones is not related to arousal, and must be related to another effect produced by the the stimulation. Lesion evidence indicates that the activation of hippocampal neurones may not be crucial for brain-stimulation reward.

5.2 THE ENTORHINAL CORTEX

A weak projection from MFB self-stimulation sites, and a stronger projection from nucleus accumbens sites, has been found in the region of the entorhinal cortex in the rat (level head coordinates 5.5–6.0 mm behind bregma: 4–5 mm lateral: more than 7 mm below the dura) (Rolls, 1970b). The activation from the MFB was similar to that found in the region of the basolateral amygdala and pyriform cortex in that the small sample of directly excited entorhinal units had absolute refractory periods in the range 0.58–0.68 ms. Eighteen units with latencies of 6–30 ms were trans-synaptically activated from nucleus accumbens reward sites, and further units were indirectly activated. A small number of units with short latencies of 4–15 ms and absolute refractory periods of 1.5–2.0 ms appeared to be directly excited by the nucleus accumbens stimulation.

The role of the entorhinal cortex in brain-stimulation reward is not known, but it could form a link from the region of the basolateral amygdala and pyriform cortex to the hippocampus, as suggested above (section 5.1).

5.3 THE CINGULATE CORTEX

A weak projection from MFB reward sites to the cingulate cortex has been found (Rolls, 1970b). The cingulate cortex is taken as the projection area of the anterior nucleus of the thalamus, and is posterior to the medial prefrontal cortex, which receives from the mediodorsal nucleus of the thalamus (Domesick, 1969; Leonard, 1969). Three units antidromically driven from MFB self-stimulation sites had latencies of 1–3 ms and absolute refractory periods of 0.85, 1.02, and 1.5 ms. Four trans-synaptically activated units had latencies of 2–4 ms. Three indirectly driven units were driven through neurones with refractory periods of 0.7–0.8, 0.8–0.9, and 1.0–1.1 ms. Examples of sites where these units were recorded are shown in Fig. 50. In addition, Ito and Olds (1971) have recorded from a small number of cingulate units which were trans-synaptically activated in posterior hypothalamic self-stimulation. (Most of their "cingulate units" were in the medial prefrontal cortex or the septal region.)

As so few trans-synaptically and indirectly driven units were found in the cingulate cortex, it is probable that activation of the mammillothalamic tract–anterior nucleus of the thalamus–cingulate cortex system is not important in MFB self-stimulation. The finding of Coons and Fonberg (1963) that lateral hypothalamic lesions block cingulate self-stimulation but not vice versa, suggests that the pathways recorded from above may mediate cingulate but not lateral hypothalamic self-stimulation.

5.4 UNITS IN THE REGION OF THE RETICULAR NUCLEUS OF THE THALAMUS AND THE THALAMIC RADIATIONS

A number of directly, synaptically, and indirectly driven units activated from MFB sites have been found in this region. Three small amplitude units, which may have been fibres, were found. They had latencies of 0.6–1.0 ms and absolute refractory periods of 0.58–0.59 ms. These may have been fibres passing through the thalamic radiations. Two trans-

synaptically driven units with latencies of 2–4 ms were found. A number of indirectly driven units in the region were inhibited (a few were excited) by MFB stimulation. The firing rates typically recovered over several seconds, in the course of which bursts of firing followed by a silent interval occurred repeatedly. It is not clear whether these units were driven from the directly driven fibres in the region or whether their activation was a result of the arousal produced by MFB stimulation.

Examples of the sites in which these units were found are shown in Fig. 51. The directly driven units are in the region through which fibres from the pyriform cortex and lateral amygdala pass on their route to the hypothalamus (Powell *et al.*, 1965), and may be axons of the directly excited units found in the region of the basolateral amygdala and pyriform cortex. The units recorded in the "lateral tracks" of the study by Gallistel *et al.* (1969) were examples of activated units in this reticular region.

5.5 PRE-OPTIC AREA, SEPTAL REGION, AND HYPOTHALAMUS

Single units in the pre-optic area were trans-synaptically driven through self-stimulation electrodes along the MFB and in the nucleus accumbens (Rolls, 1970b). The latencies of driven units are shown in Fig. 52. Convergence from both self-stimulation regions was seen in three units. Figure 52 includes the latencies of 5 units driven directly from MFB self-stimulation sites.

Ito and Olds (1971) found activated units in the septal region and nucleus accumbens, but they found surprisingly few activated units in the hypothalamus of rats during posterior hypothalamic self-stimulation. Ito (1972) recorded from hypothalamic units which were inhibited during lateral hypothalamic self-stimulation.

The importance of these activated units in brain-stimulation reward is indicated by the findings that intense reward is produced by stimulation of regions near the MFB as far forward as the pre-optic area and that lesions near the pre-optic area produce some attenuation of self-stimulation (Boyd and Gardner, 1967; Olds and Olds, 1969).

In experiments aimed at elucidating the nature of brain-stimulation reward, the activity of neurones in the hypothalamus (and also the amygdala and prefrontal cortex) was recorded during naturally rewarded behaviour (e.g. eating and drinking) and during brain-stimulation reward in the monkey (experiments in progress of M. J. Burton, A. Edelson, E. T. Rolls, and S. G. Shaw on the squirrel monkey, *Saimiri sciureus*). A number of neurones recorded in the hypothalamus were activated both by brain-stimulation reward and by a specific natural reward. An example is shown in Fig. 53. The neurone was activated trans-synaptically during self-stimulation of the nucleus accumbens (latency 10 ms), orbitofrontal cortex (latency 10 ms), and lateral hypothalamus (latency 5 ms). The monkey was hungry and thirsty. The neurone fired while water was in the mouth or being swallowed (Fig. 53). The neurone showed only small inconsistent changes in firing rate during the ingestion of 5% glucose (Fig. 53) and isotonic saline (presented with the same syringe) and during stimulation of the mouth with air from the syringe. Thus this hypothalamic neurone appears to fire to the sensory input of water but not glucose or saline, and thus could guide the thirsty animal to consume water. Thus one effect of the brain-stimulation reward is to mimic the effects of a specific natural reward—the electrical stimulation mimics the effects of water for a thirsty animal. This observation provides an explanation of why electrical stimulation of the brain can act as a reward—it can mimic the effects of a specific natural reward. Other neurones of this general type, including units activated by the sight of food, have been

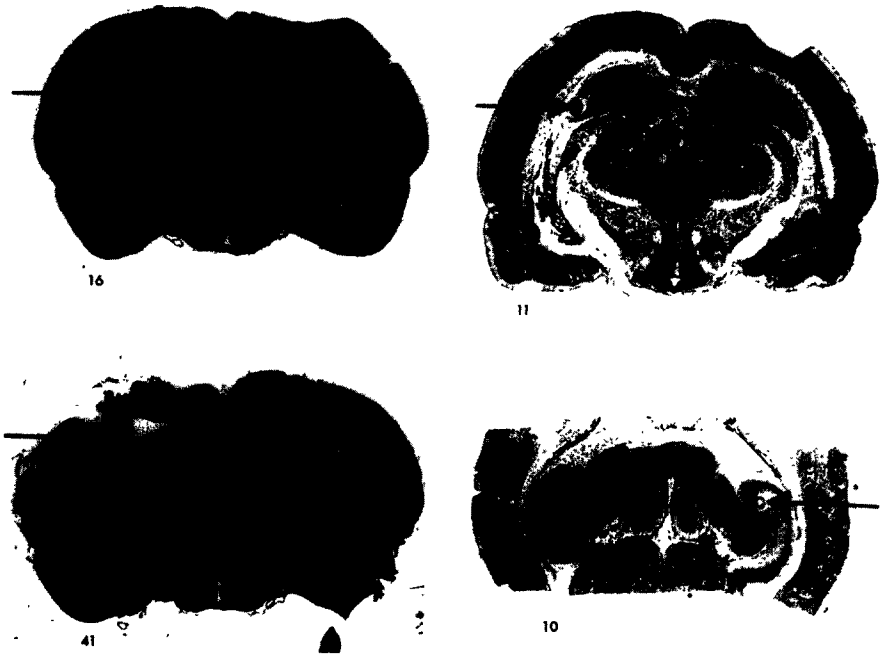

FIG. 48. Examples of recording sites of hippocampal units indirectly driven by rewarding MFB stimulation in the rat. The lower right brain was sectioned in the horizontal plane. (From Rolls, 1970b.)

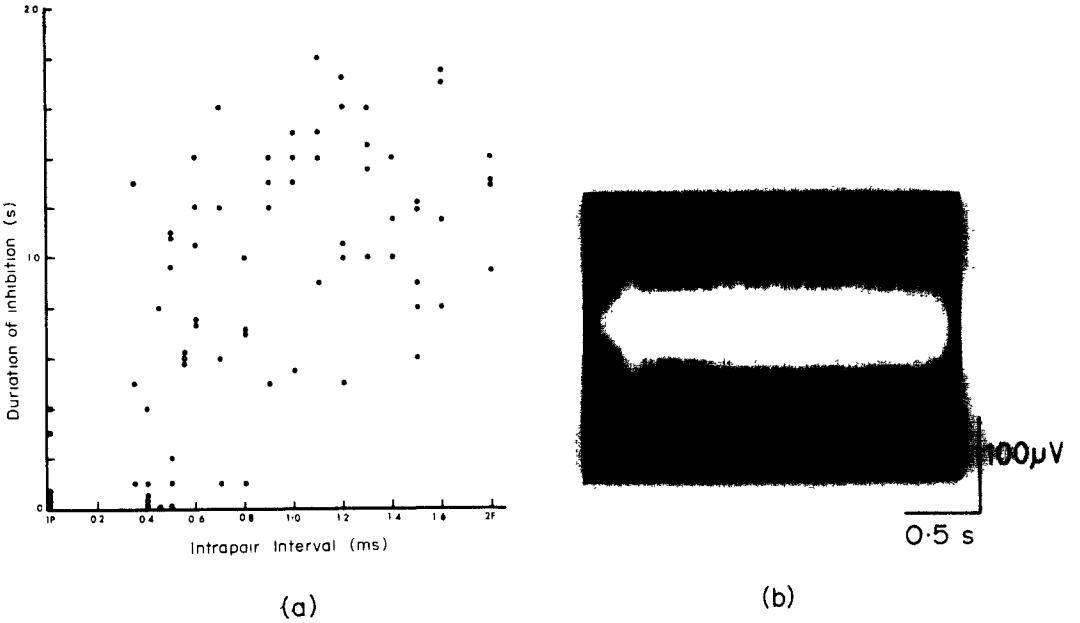

FIG. 49. Indirect measurement of the refractory period of the directly excited neurones through which rewarding MFB stimulation inhibited a hippocampal unit. (b) Example of the inhibition of the firing of a hippocampal unit when stimulation was a train of pulse pairs with an IPI of 1.2 ms. Four pulse pairs were delivered in a 100 ms train. (a) Duration of the inhibition produced by pulse pairs with different IPIs. A significant difference relative to the one-pulse condition is seen with IPIs of and greater than 0.55 ms. (From Rolls, 1970b.)

FIG. 50. Examples of sites of units in the cingulate cortex activated from MFB self-stimulation sites in the rat. (From Rolls, 1970b.)

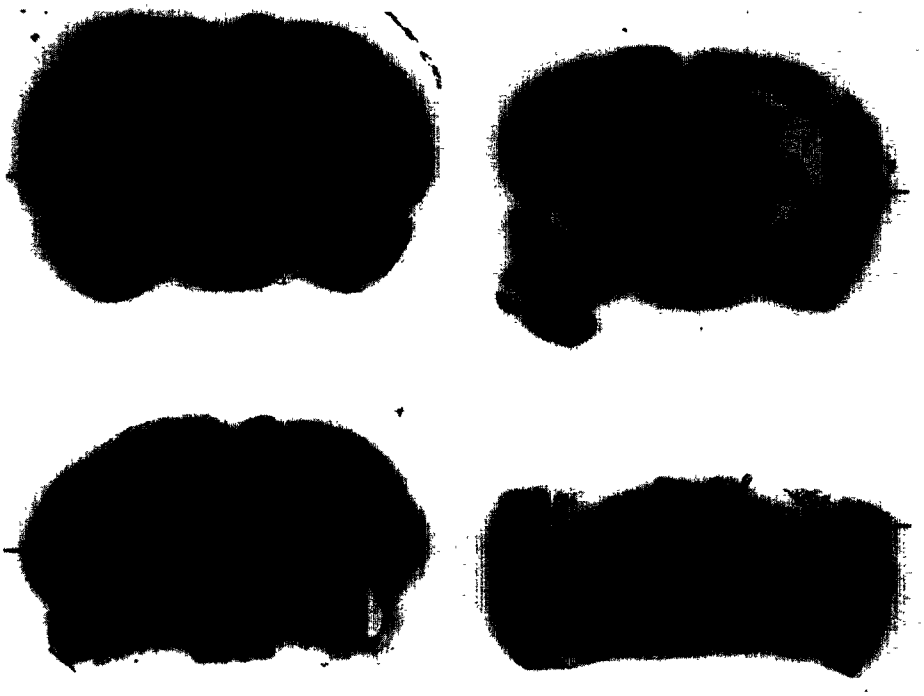

FIG. 51. Examples of sites of units in the region of the reticular nucleus of the thalamus activated from MFB self-stimulation sites in the rat. (From Rolls, 1970b.)

found in the hypothalamus, and not so far in the prefrontal cortex. This type of observation provides direct evidence that the hypothalamus is a focus for brain-stimulation reward, and excitation of certain types of hypothalamic neurone may be sufficient for brain-stimulation reward.

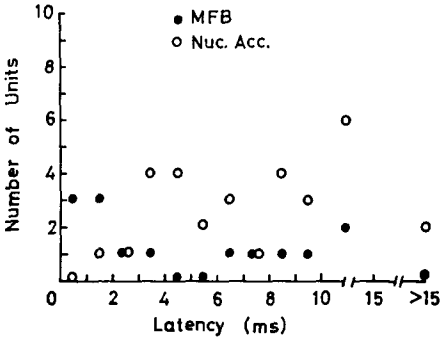

FIG. 52. Latencies of 45 units in the pre-optic area driven from MFB (6 rats) and nucleus accumbens (3 rats) self-stimulation sites (From Rolls, 1970b.)

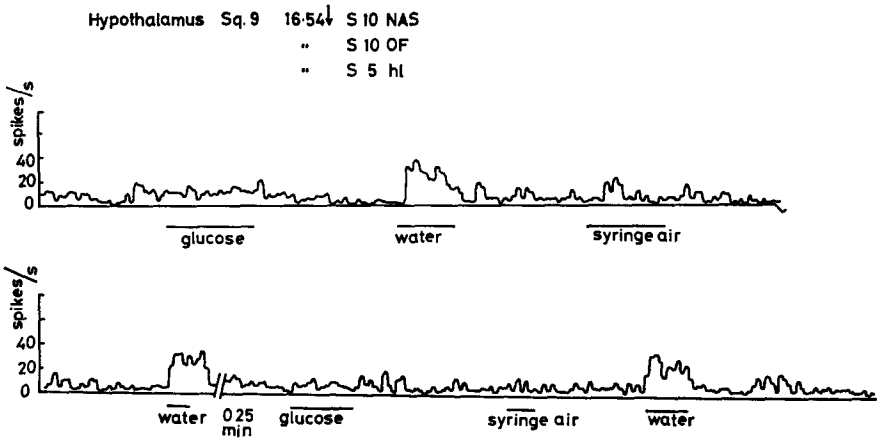

FIG. 53. Unit in the hypothalamus of the squirrel monkey trans-synaptically (S) activated during self-stimulation of the nucleus accumbens (NAS), orbitofrontal cortex (OF), and lateral hypothalamus (hl) with the latencies (milliseconds) shown. The unit fired more when the hungry and thirsty monkey drank water, but little change was seen when 5% glucose (or isotonic saline) was drunk or when air was blown on the mouth from a syringe (this latter is aversive). The unit fired most rapidly while the water was in the mouth. Time scale: the stimuli were presented for approximately 30 s.

5.6 PONS AND MEDULLA

The hypothesis that self-stimulation is mediated by axons of noradrenergic neurones which ascend through the MFB to reach the cingulate area from cell bodies in the pons and medulla, in particular the locus coeruleus, was proposed by Stein (see Stein, 1969). To test the hypothesis electrophysiologically, single-unit activity was recorded in the pons and medulla to determine whether cells in the locus coeruleus are antidromically activated in

self-stimulation (Cooper and Rolls, 1974). Massive antidromic activation of units in the region of the locus coeruleus was not found in these experiments, but neurones as far caudal as the locus coeruleus were shown to be directly excited in self-stimulation of many different sites. In previous work on this region, Routtenberg and Huang (1968) had found brain-stem units activated in posterior diencephalic self-stimulation, and because of activation from non-reward sites had concluded that the (anatomically defined) reticular formation may not represent a critical area of convergence for rewarding stimulation of the brain.

In tracks near the locus coeruleus in the pons or medulla, some units were recorded which were directly excited or trans-synaptically activated in self-stimulation of the lateral hypothalamus, the midbrain tegmentum, as well as the pontine tegmentum near the locus coeruleus. Units in the same region were trans-synaptically activated in self-stimulation of the sulcal and the medial prefrontal cortex. An example of a track in this region is shown in

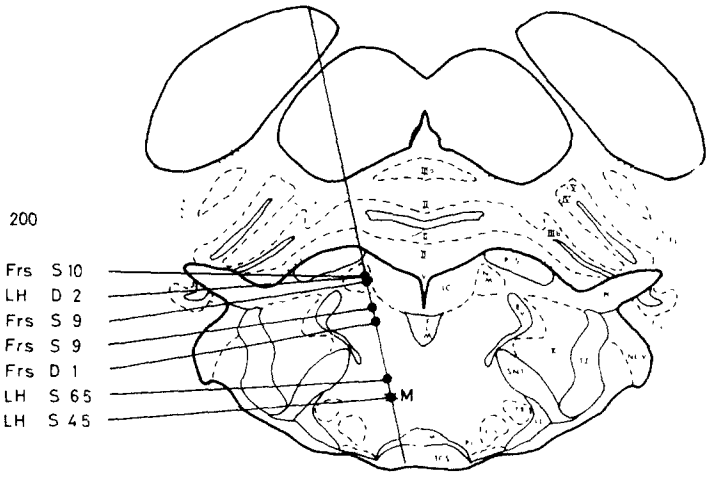

FIG. 54. Micro-electrode track through the region of the locus coeruleus in the rat in which units were found to be activated from self-stimulation sites in the sulcal prefrontal cortex (Frs) and lateral hypothalamus (LH). Only the three most dorsal units were in or close to the locus coeruleus.

Fig. 54. The first two units recorded in the track were in or close to the locus coeruleus. The region in which these units were found extended in a lateral position in the pons and medulla, from the locus coeruleus dorsally to the base of the brain ventrally (Fig. 54). The region appeared to include the nucleus reticularis parvocellularis in the medullary reticular formation, the locus coeruleus, and the mesencephalic nucleus of the trigeminal nerve. As units in this region were not found to be activated from sites in the midbrain tegmentum from which motor effects but not reward were elicited, the activated units could be involved in self-stimulation. This suggestion is supported by the finding that self-stimulation of a region in or near the locus coeruleus occurs (Crow *et al.*, 1972; Rolls and Cooper, 1973). Self-stimulation of a brain-stem region in or near the locus coeruleus also occurs in the squirrel monkey (observations of M. J. Burton, E. Rolls, and S. Shaw). The activation of units in the nucleus reticularis parvocellularis may be related to the organization of motor responses used, for example, in motivated behaviour. In a more medial part of the reticular

formation (nucleus reticularis pontis caudalis and nucleus reticularis gigantocellularis of the medulla—Fig. 55) units were activated from the self-stimulation sites or from motor effect sites in the midbrain tegmentum. The activation of these units may therefore be related to the motor effects which are sometimes produced by stimulation at reward sites.

5.7 SUMMARY

Neurones in the hippocampus (and entorhinal cortex) are trans-synaptically activated with long latencies (e.g. 30–100 ms) by brain-stimulation reward. This activation is not necessary for but may affect brain-stimulation reward, as lesions of the hippocampus

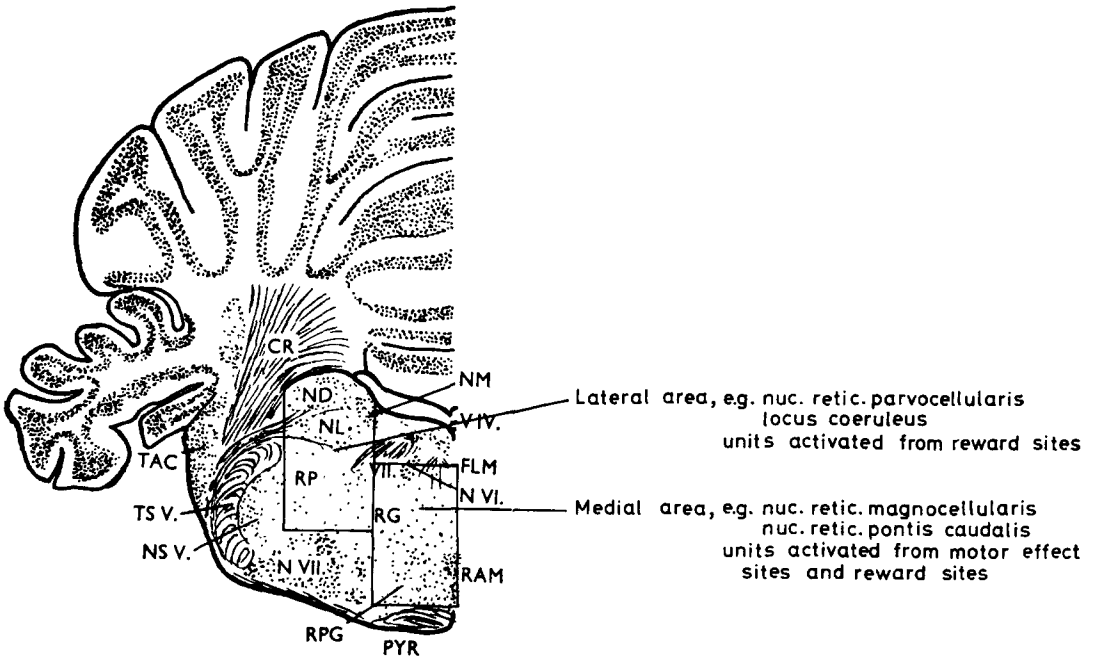

FIG. 55. Summary of activation of units in the pons and medulla from reward sites. RP = nucleus reticularis parvocellularis. RG = nucleus reticularis gigantocellularis. The locus coeruleus is in the region dorsal to the nucleus reticularis parvocellularis.

generally facilitate self-stimulation measured by the rate of bar-pressing. Neurones in the cingulate cortex are activated (some antidromically) with short latencies by rewarding hypothalamic stimulation. The hypothalamus may be necessary for cingulate self-stimulation but not vice versa. Single units in the reticular nucleus of the thalamus are activated directly or trans-synaptically by rewarding hypothalamic stimulation. Their role in self-stimulation is not known. Units in the pre-optic area and hypothalamus may be excited or inhibited with short latencies during brain-stimulation reward. The importance of hypothalamic units in brain-stimulation reward is indicated by the findings that these units are also activated by natural rewards and that lesions in this area may attenuate self-stimulation (see also sections 1.2.1 and 7.1). Neurones in the lateral parts of the pons and medulla (near or in the nucleus reticularis parvocellularis and locus coeruleus) were activated directly or

trans-synaptically from many different reward sites. Neurones in the more medial parts of the pons and medulla (e.g. the nucleus reticularis gigantocellularis) were activated by both self-stimulation and during motor effects produced from non-reward sites, and may be related to the elicitation of motor effects.

6. The Functions of Catecholamines in Self-stimulation

6.1 INTRODUCTION

There is considerable evidence that central catecholamines are involved in intracranial self-stimulation. Evidence that noradrenaline is involved in the reward produced by the stimulation is weak in two respects. Firstly, many of the treatments used to support the view are not specific, and affect catecholamines apart from noradrenaline (e.g. dopamine). Secondly, it has not been shown that noradrenaline affects reward directly and not by a side effect, e.g. by producing sedation. Before the noradrenergic theory can be accepted, more evidence on these points is required. Much of the evidence is consistent with the view that dopamine is related to brain-stimulation reward, as described below.

6.2 EVIDENCE THAT CATECHOLAMINE TRANSMISSION IS INVOLVED IN INTRACRANIAL SELF-STIMULATION

Treatments which release catecholamines from nerve terminals facilitate self-stimulation. Examples are: D-amphetamine (Stein, 1964; 1967); L-amphetamine (Stein, 1964); D-methamphetamine (Stein, 1967); α-methyl-*m*-tyrosine after inhibition of monamine oxidase (MAO) (Poschel and Ninteman, 1964); and tetrabenazine after MAO inhibition (Poschel and Ninteman, 1964; Stein, 1967). The facilitation is seen as an increase in low rates of self-stimulation. Conversely, self-stimulation is attenuated by treatments which decrease brain concentrations of catecholamines, e.g. α-methyl-*p*-tyrosine (Poschel and Ninteman, 1966; Gibson *et al.*, 1970); reserpine (Stein, 1962; Gibson *et al.*, 1970); and tetrabenazine (Stein, 1967); and by treatments which produce catecholamine receptor blockade, e.g. haloperidol (Stein, 1967) and chlorpromazine (Stein and Ray, 1960; Stark *et al.*, 1969).

6.3 THE ROLES OF NORADRENALINE AND DOPAMINE IN INTRACRANIAL SELF-STIMULATION

Much of the evidence cited above showing that catecholamines are involved in self-stimulation has been interpreted as showing that transmission in noradrenergic neurones mediates the reward produced by the stimulation (Stein, 1962, 1964, 1967, 1969, 1971; Poschel and Ninteman, 1964, 1966; Wise and Stein, 1969; Stein and Wise, 1971). Most of the treatments are not specific for noradrenaline (NA). For example, D-amphetamine probably releases dopamine as well as NA (locomotor activity test: Carlsson, 1970; release into perfusate: McKenzie and Szerb, 1968; rat rotation test: Christie and Crow, 1971). Similarly, L-amphetamine and D-methamphetamine release DA (rat rotation test: Christie and Crow, 1971), and α-methyl-*m*-tyrosine (Andén, 1964; Weissman and Koe, 1965; Nickerson, 1970; Chan and Webster, 1971a) and tetrabenazine (Chan and Webster, 1971a) release both NA and DA (direct assay method). Brain concentrations of both NA and DA are reduced by reserpine (Nickerson, 1970; Chan and Webster, 1971b). Similarly, inhibition of tyrosine

hydroxylase by α-methyl-*p*-tyrosine decreases brain concentrations of both NA (Weissman and Koe, 1965; Spector *et al.*, 1965; Persson and Waldeck, 1970) and DA (Weissman and Koe, 1965; Persson and Waldeck, 1970). Further, chlorpromazine blocks NA and DA receptors about equally (Andén *et al.*, 1970), and haloperidol blocks DA receptors more effectively than NA receptors (Andén *et al.*, 1970). 6-hydroxydopamine (6-OHDA) has also been shown to reduce self-stimulation (Stein, 1971). In the doses used, single intraventricular injections of 200–400 μg or repeated 25–400 μg doses, it is clear that both NA and DA concentrations in the brain are reduced (Uretsky and Iverson, 1970; Breese and Traylor, 1970, 1971). The treatments described above therefore provide only poor evidence that one particular catecholamine, NA, is involved in brain-stimulation reward. They are equally consistent with the view that another catecholamine (e.g. DA) is involved in brain-stimulation reward.

There have been few studies of the effects on brain-stimulation reward of treatments which alter the activity in specific catecholaminergic systems. One agent, disulfiram, which depletes the brain of NA but not DA (Fig. 56) by inhibiting the enzyme dopamine-β-hydroxylase (Musacchio *et al.*, 1966; Goldstein and Nakajima, 1967), can abolish self-stimulation (Wise

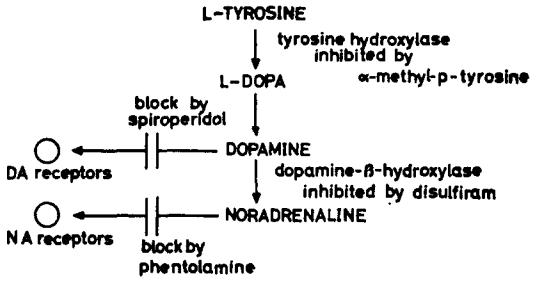

FIG. 56. Catecholamine biosynthetic pathways: effects of some pharmacological agents.

and Stein, 1969). This indicates that an agent which specifically decreases brain NA can attenuate self-stimulation. Roll (1970) showed that after disulfiram, rats had many pauses of greater than 60 s between lever-presses for brain-stimulation reward. The animals appeared to be sleepy in the long interpress intervals. She interpreted this as showing that disulfiram decreases self-stimulation by making animals drowsy. In the experiments of Wise and Stein (1969) it was also noted that the injections of disulfiram and the similar agent diethyldithiocarbamate (DEDTC) which attenuated self-stimulation produced sedation, and that reversal of the attenuation by intraventricular injections of *l*-norepinephrine also rapidly produced a state of arousal and alertness. Thus in these experiments it has not been shown that noradrenergic transmission mediates reward produced by brain-stimulation. (The hypothesis under test is that the rewarding stimulation activates noradrenergic neurones, and that the release of NA which occurs for each bar-press mediates the reward.) It is possible that the effects on self-stimulation of the treatments are produced by a decrease in arousal, which is known to markedly affect self-stimulation rate (Rolls, 1971a, b, c; see section 4).

To investigate how noradrenergic and dopaminergic transmission are involved in reward and arousal, Kelly *et al.* (1974) measured the effects on self-stimulation rate and two meas-

ures of sedation of disulfiram (which decreases the synthesis of NA but not DA), phentolamine (which blocks receptors sensitive to NA but not DA receptors—Nickerson and Hollenberg, 1967), and spiroperidol (which blocks DA but not NA receptors—Andén *et al.*, 1970). The level of sedation was measured by spontaneous locomotor activity (see section 4.5) and by spontaneous rearing, a good measure of arousal/sedation (Benešová *et al.*, 1967; Cole and Dearnaley, 1971). Eight rats were tested while each of the drugs was active or after a placebo. A test consisted of a 5 min measurement of spontaneous locomotor activity and rearing followed by a 10 min test of lateral hypothalamic self-stimulation rate.

The bar histograms in Fig. 57 show that when disulfiram or phentolamine produced a modest reduction in self-stimulation rate (from 70 to about 42 bar-presses/min), the animals were very drowsy as measured by the decrease in rearing and the decrease in locomotor activity. The animals also looked drowsy. Therefore inhibition of the synthesis of NA

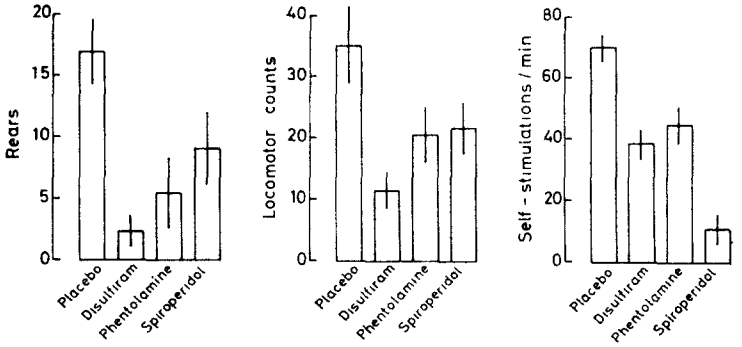

FIG. 57. Effect of disulfiram (200 mg/kg i.p. injected 3 h before testing), phentolamine mesylate (10 mg/kg i.p. injected 40 min before testing) and spiroperidol (0.1 mg/kg i.p. injected 2 h before testing) on two measures of arousal/sedation (rearing and locomotor activity) and on lateral hypothalamic self-stimulation rate. Eight rats were tested in counterbalanced order. Bars represent mean with SE of the mean indicated.

(disulfiram treatment) or blockade of noradrenergic receptors (phentolamine treatment) does reduce self-stimulation rate, but at the same time produces drowsiness. (The effect produced by the i.p. phentolamine is reproduced by the bilateral intracranial injection of 10 μg of phentolamine mesylate. The conclusion follows that the blockade of central noradrenergic receptors produces drowsiness together with some reduction in self-stimulation rate.)

Whether the drowsiness accounts for the whole of the decrease in self-stimulation rate is not known. It is clear that the treatments by producing drowsiness would decrease self-stimulation rate (see section 4), and this type of experiment poses the question of whether noradrenergic transmission plays any role in self-stimulation other than by modifying arousal level. Although noradrenergic transmission could mediate reward, the present experiment suggests that such a role has never been proved in that the treatments have massive effects on other types of behaviour. Rather, the effects obtained previously have probably been due at least partly to effects on arousal.

It is also shown in Fig. 57 that treatment with spiroperidol reduced self-stimulation rate from 70 to 10 stimulations/min and left rearing and locomotor activity relatively high (compared to disulfiram and phentolamine). Therefore pharmacological treatments can be

found which appear to attenuate reward aspects of self-stimulation more specifically with respect to arousal than disulfiram. It is interesting that spiroperidol produces a blockade of dopamine receptors (Andén *et al.*, 1970). This evidence therefore suggests that dopaminergic pathways are involved in brain-stimulation reward. Although sedation probably does normally reduce self-stimulation rate, Wise and Stein (1969) noted that some sedative drugs, e.g. barbiturates, may not decrease self-stimulation rate. Thus attenuation of self-stimulation by these drugs is probably more usual (Mogenson, 1964), and the facilitation sometimes seen may not be related to the sedation produced. These pharmacologically non-specific treatments have some stimulant properties (Machne *et al.*, 1955) and may affect many aspects of behaviour, e.g. frustrative non-reward (Gray, 1971).

When dose–response curves of the effects of disulfiram and spiroperidol on measures of arousal and self-stimulation rate (Kelly *et al.*, 1974) are compared (Fig. 58) it is found that treatment with disulfiram produces a relatively greater effect on arousal relative to self-stimulation rate than spiroperidol. These observations support the above conclusions. A point of interest is that some rats treated with spiroperidol self-stimulate for 1–3 min when first tested and then suddenly stop self-stimulation. This observation may not be consistent with the view that spiroperidol attenuates self-stimulation only by DA receptor blockade. A further observation was that some treated animals then assumed a posture facing the lever and could not be induced to bar-press either by priming or by placing the animal on the lever. The hypothesis that spiroperidol attenuates self-stimulation by attenuating operant behaviour (although not general activity) rather than reward, cannot be rejected.

The main conclusions of these studies therefore are as follows. Firstly, treatments which alter noradrenergic transmission and attenuate self-stimulation produce major effects on other types of behaviour. Secondly, pharmacological agents can be found which affect self-stimulation much more selectively. Thirdly, agents which produce DA-receptor blockade attenuate self-stimulation. Fourthly, DA-receptor blocking agents do not attenuate self-stimulation merely by producing sedation (compare dose–response curves for spiroperidol and disulfiram, Fig. 58), and may therefore affect brain-stimulation reward more specifically. Fifthly, although dopaminergic transmission could be involved in reward produced by brain stimulation, it has not been proved that spiroperidol (and pimozide) attenuate self-stimulation by blocking dopaminergic transmission in reward pathways.

There is now other evidence that DA is involved in self-stimulation of at least some sites. Crow *et al.* (1972) obtained self-stimulation when electrodes were near the DA-containing cell bodies (especially the group A10) in the ventral mesencephalon. Wauquier and Niemegeers (1972) showed that the DA-receptor blocking agent pimozide attenuates MFB self-stimulation. We (Rolls, Shaw, and Burton) have recently extended the observations with spiroperidol to the monkey, showing that in the squirrel monkey a dose of 4 μg intracranially attenuates self-stimulation. Phillips and Fibiger (1973) found that self-stimulation of sites near the substantia nigra was differentially facilitated by the administration of amphetamine, which differentially affects DA.

In a further investigation of the role of DA in self-stimulation it was found that spiroperidol attenuated self-stimulation of many different brain sites (the nucleus accumbens, septal area, anterior hypothalamus, and ventral tegmental area) (Rolls *et al.*, 1974). Thus DA may be involved in self-stimulation of these different sites. The spiroperidol did not appear to produce its effect because of motor impairment in these experiments, because at a particular dose of spiroperidol (e.g. 0.05 mg/kg) the rats could still bar-press quite fast (e.g. 40 presses/min for tegmental stimulation), yet showed an attenuation of nucleus accumbens

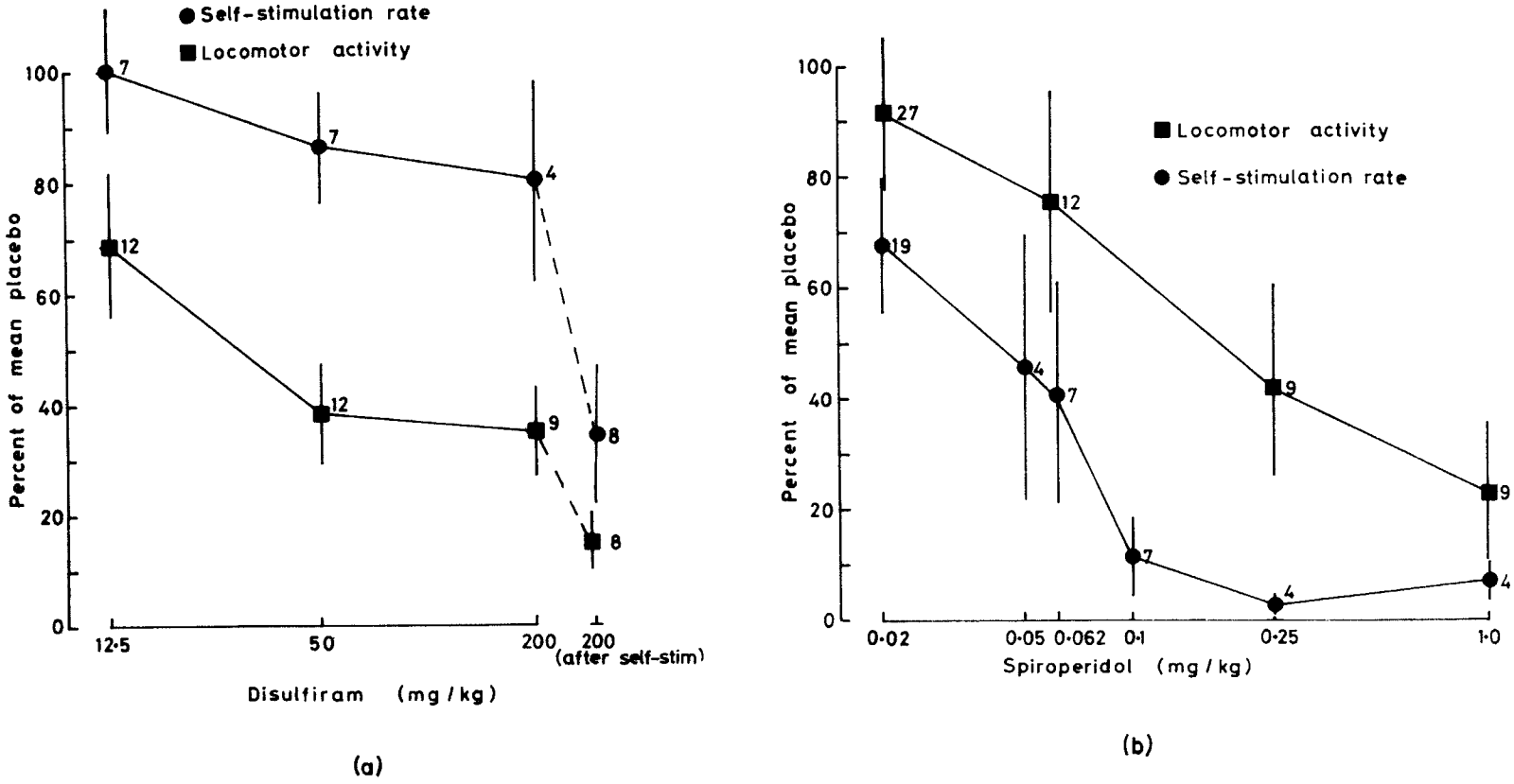

FIG. 58. (a) Disulfiram (injected i.p. 3 h before testing) has a greater effect on locomotor activity than on self-stimulation rate. One group of 8 rats was allowed to self-stimulate continuously following the disulfiram injection: after 3 h locomotor activity was also more depressed than the self-stimulation (see 200 mg/kg after self-stimulation). (b) Spiroperidol (injected i.p. 2 h before testing) has a greater effect on self-stimulation rate than on locomotor activity. The numbers of animals tested is shown beside each point. The points represent the mean (±SE) locomotor activity or self-stimulation rate of the different rats, expressed as a percentage of the group's average locomotor activity or self-stimulation rate

self-stimulation below the 10 press/min baseline. Thus DA-receptor blockade does not appear to attenuate self-stimulation because it limits how fast an animal can bar-press for the stimulation. With intracranial injections of spiroperidol it was found that self- stimulation was attenuated by smaller volumes in the preoptic area than in the caudate nucleus. This suggests that a structure near the preoptic area is more closely related to the blockade of self-stimulation than the caudate nucleus. Yet it was not possible to separate the effects of spiroperidol on motor behaviour (in particular catalepsy, measured by waxy flexibility—the tendency of an animal to maintain any position into which it is put—and time spent hanging motionless on a rod) from its effects on self-stimulation (Kelly *et al.*, 1974). As it was not possible to dissociate the effects of spiroperidol on catalepsy and on self-stimulation, the dopamine-receptor blockade could have interfered with self-stimulation by interfering with the organization of complex motor responses. This view is consistent with the observations that dopamine-receptor blockade interferes also with tasks in which animals can learn to avoid foot-shock (Wauquier and Niemegeers, 1972), and that a more severe impairment of eating and drinking occurs if a complex motor response is required to obtain the food or water (Rolls *et al.*, 1974).

The conclusion which can be made at present is that DA receptors are involved in self-stimulation but not necessarily in the reward produced by the stimulation. The role of DA receptors in self-stimulation could be in the high-level organization of the motor responses involved in self-stimulation, in line with the finding on catalepsy above. However, none of the experiments described here rules out the possibility that DA (or even NA) is involved in reward produced by electrical stimulation of the brain.

In a different type of experiment taken to support the noradrenergic theory of reward, Stein and Wise (1971) found that central NA turnover increased during MFB self-stimulation. The method involved perfusion of labelled NA precursor into the ventricles and recovery of labelled NA from the brain. Although this is an interesting observation, it was not shown that the measured effect was due to reward rather than, for example, arousal, and there are difficulties with this type of experiment, e.g. substances may be released non-specifically (Chase and Kopin, 1968).

There has been an extrapolation from the noradrenergic theory of reward to abnormal human emotional behaviour (Stein and Wise, 1971; Stein, 1971). Following the observation that intraventricular injections of 6-OHDA, which lead to degeneration of catecholamine-containing pathways, permanently attenuate self-stimulation, it was suggested the lack of emotional responsiveness (lack of response to reward) found in schizophrenia could be produced as a result of degeneration of NA-containing reward pathways. The mechanism of degeneration postulated was the abnormal endogenous production of 6-hydroxydopamine (6-OHDA). Chlorpromazine was held to have a therapeutic effect clinically because of its ability to prevent the uptake of 6-OHDA by the noradrenergic terminals. Given that the evidence for the noradrenergic theory of reward is weak, this type of extrapolation must be treated with caution.

6.4 SUMMARY

There is considerable evidence that central catecholamines are involved in intracranial self-stimulation. Much of the evidence which has been cited to show that the release of the particular catecholamine noradrenaline mediates brain-stimulation reward is weak in two respects. Firstly, many of the treatments which decrease self-stimulation rate (e.g. α-methyl-

p-tyrosine, chlorpromazine, haloperidol) or increase self-stimulation rate (e.g. amphetamine) affect DA as well as NA. Secondly, most of the treatments affect arousal, and it has not been shown, for example, that sedation does not account for the attenuation of self-stimulation produced by agents which decrease the synthesis of noradrenaline. Thus the evidence available at present does not provide support for the view that the release of noradrenaline mediates brain-stimulation reward. Dopamine-receptor blockade attenuates self-stimulation of many different brain sites without producing major sedation. Whether this represents a true block of reward or is a result of interference with high-level motor behaviour is not yet clear.

7. Review—Nature and Neural Basis of Brain-stimulation Reward

7.1 THE FOCUS OF BRAIN-STIMULATION REWARD

Because sites close to the general course of the MFB between the levels of the pre-optic area and midbrain support intense self-stimulation, neurones in or with axons which pass through this region are probably involved in the self-stimulation (see section 1). This does not mean that axons which run in the MFB itself must be involved in the self-stimulation. One problem with this type of argument is that the "intensity" of the self-stimulation is seen as a high rate of self-stimulation, and the high rate appears to be produced at least partly by activation of the brain-stem arousal system, which may not be directly involved in reward (section 4). Because lesions in or near the MFB anterior or posterior to self-stimulation sites attenuate self-stimulation (Boyd and Gardner, 1967; Olds and Olds, 1969), the hypothalamic region is again indicated as a focus for self-stimulation. A further point is that axons from most sites which support self-stimulation (see section 1) pass to or through the hypothalamus. Rather little recording of single-unit activity in the hypothalamus and preoptic area has been performed during self-stimulation, but neurones in these areas are activated in reward (see section 5.5 and Ito, 1972) and neurones in some hypothalamic areas show inhibition during lateral hypothalamic self-stimulation (Ito, 1972). Preliminary experiments in which single-unit activity in these areas is recorded during self-stimulation, and correlated with the effects of the presentation of natural reward, show that one effect of brain-stimulation reward is to activate neurones concerned with specific natural reward (section 5.5). It may be sufficient for self-stimulation that neurones concerned with a specific natural reward are activated by the stimulation. Until further evidence is available, the view that neural structures in or near the hypothalamus provide a focus for brain-stimulation reward can be accepted. The view will be put below that these hypothalamic neural systems provide the regulation of basic rewards, e.g. of food reward, and that inputs to these regions from, for example, the amygdala and prefrontal cortex, allow stimuli to affect the basic rewards and allow the formation or disconnection of stimulus-reinforcement associations. Through such inputs the sight or smell of a poisoned food could come to reduce the intake of that food, or a stimulus could become associated with an emotional response. These high-level inputs probably need not be intact for reward processes to operate, as forebrain ablated rats can self-stimulate (Huston and Borbély, 1973).

7.2 RELATION OF BRAIN-STIMULATION REWARD TO EATING AND DRINKING

In normal eating and drinking, reward or reinforcement appears to be provided by sensory input, usually from taste and smell. That this is so is shown by experiments with oesophageal fistulae which prevent food reaching the stomach but which allow taste and smell to operate normally. Animals with oesophageal fistulae eat at least as much food as normal animals (see Epstein, 1967), so that the reward or reinforcement provided by the food is associated with the act of feeding (taste, smell, swallowing, etc.) and not with stomach distension or absorption of the food. Further evidence of this is provided by the injection of food directly into the stomach, which does not reward or reinforce bar-pressing unless large volumes are given (Epstein and Teitelbaum, 1962). (For example, volumes of at least 0.5 ml were needed to maintain bar-pressing in the rat, and the capacity of the stomach is only about 8 ml. In contrast, volumes as low as 1/200 ml given orally will maintain bar-pressing.) Similarly, intragastric injections do not guide intake normally in that the sucrose preference–aversion function is absent with intragastric self-administration (see Epstein, 1967). This evidence shows that sensory input, e.g. from taste and smell, provides reinforcement for and maintains eating, and that stomach factors are relatively unimportant in reward. Although secondary reinforcement may complicate the interpretation of these experiments with oesophageal fistulae, the point remains that the sensory input normally guides intake (to food or water)—and maintains intake. Thus oropharyngeal sensations normally provide reward in ingestive behaviour—they are normally required to detect food and to discriminate between different types of food.

To regulate food intake it appears that the reward value of food is adjusted by the level of hunger, so that a hungry animal eats because it finds food rewarding, and a satiated animal does not eat because it finds food is aversive. Some evidence for this follows. In the rat, self-stimulation of areas related to feeding in the lateral hypothalamus becomes slower when liquid diet is injected into the stomach (see Hoebel, 1969). Thus a decrease in hunger is associated with a reduction in reward produced by lateral hypothalamic stimulation. A satiated animal will show an increased tendency to escape from the stimulation. Conversely, an animal made hungry by food deprivation shows increased lateral hypothalamic self-stimulation (see Hoebel, 1969). Normal feeding can be considered as self-stimulation of the lateral hypothalamus produced by the sensory stimuli associated with eating. The observation that hypothalamic neurones in the monkey fire while water is in the mouth of a thirsty animal supports this view (see section 5.5). Further the firing of these neurones to sensory stimuli is probably modulated by thirst. Human subjects indicate that food (e.g. a sucrose solution) is pleasant when hungry and less pleasant or aversive when satiated (Cabanac, 1971). Thus in man also the level of hunger (varied by food deprivation) affects the reward value of food.

The factors which adjust the level of food reward are closely related to the absorption of food and to the subsequent utilization of the food. Glucose level or utilization may affect the reward level of food, as shown by the s.c. injection of insulin which decreases blood glucose and increases food intake and lateral hypothalamic self-stimulation, and by s.c. injections of glucagon which have the opposite effects. The possible delay before absorbed glucose reaches the bloodstream may not be a problem, for in the rat glucose is released from the liver within a very few minutes of glucose entering the stomach (Steffens, 1970), and may even be released when a sweet solution is placed on the tongue (Nicolaidis, 1969). A factor

associated with the body weight of an animal, perhaps the total body fat, also appears to alter the reward level of food, because force-fed rats show decreased lateral hypothalamic self-stimulation and decreased food intake (McNeil, 1966; see Hoebel, 1969). Stomach distension is also capable of reducing the reward associated with feeding and thus can reduce food intake (see Hoebel, 1969), although this factor may only be used to inhibit food intake when an exceptionally large meal has been eaten (Janowitz and Grossman, 1949). In man metabolic factors may not provide the only control of the pleasantness of food, for Wooley *et al.* (1972) have shown that subjects intubed with saccharin find subsequently that the taste of glucose becomes less pleasant.

Thus in the normal regulation of food intake factors such as glucose utilization, body weight, and stomach distension control feeding by adjusting the reward value of food. In other terms, the level of motivation, or hunger, adjusts the reward value of food, and level of motivation is equivalent to the state produced by the combined effect of the factors such as glucose utilization, body weight, and stomach distension. That is, sensory input (e.g. taste) is modulated by motivation to make the sensory input either rewarding or aversive. The experiments of Hoebel described above show that stimulation of the lateral hypothalamus produces reward like food in that lateral hypothalamic self-stimulation and the reward value of food co-vary as a function of hunger. This is an important conclusion about the nature of brain-stimulation reward—that it can be equivalent to a specific natural reward such as food. Direct evidence of this comes from the observation that hypothalamic neurones concerned with a specific natural reward (e.g. water for a thirsty animal) are activated by brain-stimulation reward (section 5.5). This means, of course, that brain-stimulation reward can be useful in analysing specific reward pathways in the brain, and it has clearly been useful in understanding the relation between motivation and reward as set out above.

Given that lateral hypothalamic stimulation can be equivalent to food reward, it is next of interest to determine whether brain-stimulation reward can mimic other types of reward. This has been determined, for example, by making an animal either thirsty or hungry, and showing that it chooses brain-stimulation reward on one electrode when hungry ("food-reward electrode") and on a different electrode when thirsty ("water-reward electrode") (Gallistel and Beagley, 1971). Similarly, castration reduces posterior MFB self-stimulation rate ("sex-related reward"?) but not lateral hypothalamic self-stimulation rate (Caggiula, 1967; see also Olds, 1961; Hoebel, 1969). If it cannot be shown that self-stimulation at a particular site interacts with this type of shift of hunger, thirst, etc., then it could be that the nature of the reward produced is "pleasure". In man, stimulation at reward sites is said sometimes to produce reports of "pleasure", "happiness", and "relaxation" (Heath, 1964; Mark *et al.*, 1972).

It can be concluded that at least in some areas of the hypothalamus brain-stimulation reward is equivalent to stimulation of pathways which normally signal food or water reward, and that the reward level of the stimulation (and of food or water) is adjusted at the hypothalamic level by factors such as glucose utilization, body weight, tonicity, stomach distension, and perhaps also by recent taste inputs. The latter type of factor is equivalent to motivation, and is named, for example, hunger or thirst.

The mechanism by which hypothalamic stimulation produces stimulus-bound eating, drinking, or sexual behaviour remains unproven, but it has been suggested above (section 4.6) that the simultaneous activation of specific reward neurones (e.g. food-reward neurones) and the brain-stem arousal system could result in stimulus-bound motivational behaviour. The stimulation does at least this. It is, of course, possible that in addition the stimulation

also mimics the action of decreased glucose utilization and the other factors which control reward level, so that "hunger" is also produced.

7.3 ROLE OF THE AMYGDALA IN REWARD

The experiments described in section 3 indicate that when previous experience affects ingestive behaviour, as in neophobia and learned aversion, the amygdala is involved. The amygdala receives sensory inputs; e.g. an olfactory input from the pyriform cortex in the rat (Powell *et al.*, 1965), a major visual input via the inferotemporal cortex in the monkey (Jones and Powell, 1970), and an auditory input in the cat (O'Keefe and Bouma, 1969). Thus sensory stimuli reach the amygdala–pyriform cortex region, and from here are able to influence the control systems for reward in or near the hypothalamus by the amygdalo-hypothalamic pathways. It is probably in this way that the sight or smell of a new food or of a poisoned food is able to inhibit ingestion (see section 2). Because of the close relation of the amygdala to reward (see section 2), it is likely that it controls food intake on the basis of previous experience by adjusting reward level. Thus the amygdala can be considered as a system which allows a sensory stimulus (coded, for example, through areas 17, 18, 19, and the inferotemporal areas of the visual system) to influence reward level. In this sense the amygdala allows stimulus-reinforcement associations to act on ingestive behaviour. The way in which the amygdala is involved in the original formation of these connections (a memory operation) is unclear, but single units in the amygdala do alter their responsiveness during the formation of stimulus-reinforcement associations (Fuster and Uyeda, 1971; Ben Ari and le Gal la Salle, 1972).

The amygdala may be involved more generally in the operation of stimulus-reinforcement associations, and a number of the features of the Klüver–Bucy syndrome in monkeys (Klüver and Bucy, 1939) may be due to a failure to make stimulus-reinforcement associations (Weiskrantz, 1956; Rolls, 1970b; Jones and Mishkin, 1972). Thus after temporal pole-amygdala lesions monkeys become tame (the sight of a human is not aversive); they mouth and sometimes eat raw meat, faeces, and inedible objects (the sight and smell of the objects is not associated with edibility, and is similar to the deficit of amygdala-lesioned rats which do not show neophobia and learned aversion); and they show indiscriminate sexual behaviour, approaching male and female monkeys and animals of other species (visual stimuli do not provide the correct guiding function of normal reinforcement). The nature of the impairment is shown more clearly in formal behavioural tests in which animals with amygdala lesions fail to show normal conditional avoidance and conditioned emotional responses (Weiskrantz, 1956; Bagshaw and Coppock, 1968; Kellicutt and Schwartzbaum, 1963). In these animals the stimulus probably did not produce the appropriate emotional response—fear. For example, in the conditional emotional response test a tone previously paired with a shock does not interfere with (or suppress) bar-pressing for food, i.e. conditioned fear does not disrupt the behaviour. Similarly, the amygdala appears to be involved in the operation of connections between stimuli and positive reinforcement. For example, monkeys with temporal pole–amygdala lesions do not acquire an object discrimination normally, i.e. they cannot associate easily one of two objects with food reward (Jones and Mishkin, 1972). As the amygdala does appear to be involved in the operation of stimulus-reinforcement operations in general, it is probably very important in emotional behaviour. For example, when a particular object arouses the emotion of fear, the amygdala is probably involved.

As a result of recent research it is possible to link perceptual systems with motivational and emotional systems. Thus anatomically it is clear that there is a series of connections through the visual cortex, from area 17 (striate) to 18 and then to 19 (both are prestriate), and from there, through several stages, including the inferotemporal cortex, to the amygdala (Jones and Powell, 1970). Connections from the amygdala to the hypothalamus are well known (see Eleftheriou, 1972). Behavioural experiments indicate that the prestriate cortex is involved in visual pattern discriminations and that the inferotemporal cortex, if lesioned, leads to a deficit on concurrent visual discriminations which could indicate a memory function (Cowey and Gross, 1970; see also Mishkin, 1966, 1970; Gross, 1973). The amygdala appears to be involved in stimulus-reinforcement associations (see above). The work on the neural basis of brain-stimulation reward indicates that the hypothalamus or a closely related system is involved in basic aspects of reward, and that an input to this region from the amygdala can adjust reward level (see section 2). In this way, work on basic aspects of motivation and reinforcement has progressed back from the hypothalamus to the amygdala, where it has linked with work progressing in the other direction from sensory systems towards the amygdala. The result is that some understanding of how stimuli affect motivation and emotion is possible. Coded stimuli may be linked by the amygdala to the basic controls of emotion and reinforcement in the region of the hypothalamus. In this system the amygdala would not be essential for basic reinforcement, and self-stimulation without large parts of the amygdala has been obtained (Ward, 1961; Huston and Borbely, 1973).

In man, stimulation of the amygdala can lead to emotional feelings, e.g. pleasure (Mark *et al.*, 1972), and it has been claimed that bilateral damage in the amygdala can reduce violent behaviour without impairing intelligence (Narabayashi, 1972). The apparent similarity of the human and animal data are of interest, but much more research is needed on animals before a conclusive picture can emerge even in animals.

7.4 ROLE OF THE PREFRONTAL CORTEX IN REWARD

It was concluded in section 3 that the sulcal and medial prefrontal cortex in the rat are activated in (electrophysiological evidence), and that the sulcal prefrontal cortex is involved in (evidence from anaesthetization), brain-stimulation reward. In the monkey, neurones in the orbitofrontal cortex are activated in brain-stimulation reward, and self-stimulation occurs with electrodes in the region of the orbitofrontal cortex. The function of this activation may be to signal whether or not reinforcement arrives, so that the orbitofrontal cortex can operate when reinforcement changes. Lesion evidence indicates that the orbitofrontal cortex is involved in disconnecting stimulus-reinforcement associations, for lesioned monkeys show prolonged extinction (Butter, 1969), difficulty on the reversal part of object-discrimination reversals (Jones and Mishkin, 1972), and deficits in the no-go components of go–no-go tests. Thus the function of the orbitofrontal cortex in reward may be to disconnect stimuli from reward (or punishment), and this could explain its relation to brain-stimulation reward. The basic reward (or punishment) from which disconnection must occur may be represented at the hypothalamic level. Thus the prefrontal cortex may provide a high-level control of reward-aversion, and is probably not essential for reward-aversion (Huston and Borbely, 1973). In this sense the prefrontal cortex is at an analogous level to the amygdala. Given this role in reward (and punishment), it is likely that the prefrontal cortex is very important in emotional behaviour. Its correct function could ensure that stimuli are dis-

connected from emotional responses when appropriate. Its malfunction could produce insufficient or prolonged perseveration of emotional responses to stimuli.

In man, frontal-lobe damage can lead to perseveration of strategies, seen in inability to change the categories into which cards are sorted, and in inability of the patients to learn a maze correctly (see Nauta, 1971). Perseveration of a strategy when inappropriate is very similar to the failure to disconnect stimulus-reinforcement associations seen in orbitofrontal monkeys. Whether this type of perseveration is related to orbitofrontal damage is unclear. An interesting characteristic of the human patients, which may have relevance to the interpretation of animal experiments, is that the patients realize and state that their strategy is wrong, yet still persist in their strategy.

7.5 ROLE OF THE BRAIN-STEM AROUSAL SYSTEM IN INTRACRANIAL SELF-STIMULATION

Although activation of the brain-stem arousal system is probably not directly involved in reward aspects of self-stimulation (self-stimulation of the nucleus accumbens does not produce arousal—see section 4), it does affect self-stimulation. The arousal produced affects the rate of self-stimulation (section 4), and more generally mediates, at least in part, the priming effect. The activation also at least partly mediates stimulus-bound locomotor activity, and may be involved in stimulus-bound motivational behaviour. The effects of pharmacological agents on intracranial self-stimulation require careful interpretation because of the influence of arousal on self-stimulation and because self-stimulation of some sites produces arousal.

7.6 IMPLICATIONS FOR THE NEURAL BASIS OF EMOTIONAL BEHAVIOUR

Emotional behaviour often involves the formation of stimulus-reinforcement associations. For example, the sight of a dog may come to elicit fear after a dog-bite or the sound of a melody may come to elicit happiness because of the formation of a stimulus-reinforcement association. Any malfunction in the formation or disconnection of stimulus-reinforcement associations would therefore lead to abnormal emotional behaviour. For example, a deficit in the formation of stimulus-reinforcement associations would mean that signals normally associated with pleasure or punishment and danger would not be operative (a dangerous situation might be repeatedly approached) and flatness of affect or emotional response would be apparent. In contrast, a deficit in the disconnection of stimulus-reinforcement associations would mean that associations of stimuli with fear and danger or pleasure would be persistent, so that perhaps a phobia (in which, for example, a spider comes to produce persistent fear) or obsessive behaviour (in which long, unnecessary sequences of behaviour persist) would result. In general, the perseveration of inappropriate responses or strategies would be expected.

In that the work described above on the amygdala and prefrontal cortex suggests that they may play some part in the formation and disconnection respectively of stimulus-reinforcement associations, the work is relevant to the neural basis of emotional behaviour.

8. Summary

The hypothalamus is a critical area for brain-stimulation reward in that it contains self-stimulation sites, lesions in or caudal to it can attenuate self-stimulation, fibres from many

self-stimulation sites course to or close to it, and single neurones in the hypothalamus fire during self-stimulation of many different sites. Some hypothalamic neurones which are activated by specific natural rewards, e.g. water for a thirsty animal or the sight of a banana for a hungry animal, are also activated by brain-stimulation reward. It is suggested that brain stimulation can provide reward because it activates neurones of this general type—neurones fired by specific natural rewards. The effects of natural stimuli and of brain stimulation on some specific natural reward neurones can probably be gated in that food or brain-stimulation at one site may only provide reward if the animal is hungry, and water or brain-stimulation at another site may only provide reward if the animal is thirsty.

The amygdala can modulate brain-stimulation reward. Neurones in the amygdala project to the lateral hypothalamus and are activated in self-stimulation of the lateral hypothalamus and of some other reward sites. The amygdala modulates ingestion on the basis of previous experience in that rats with lesions in the basolateral amygdala do not avoid new foods and show deficits in learning to reduce the intake of a particular food which has been associated in the past with sickness. (On this type of and on electrophysiological evidence, parts of the amygdala may be involved in the formation of stimulus-reinforcement associations in general.) The amygdala can modulate lateral hypothalamic self-stimulation in a way which may be comparable with its influence on food intake. The modulation can be demonstrated by local anaesthesia of the amygdala, which attenuates the self-stimulation. The amygdala does not appear to be essential for self-stimulation in that self-stimulation can still occur after bilateral removal of the amygdala.

The prefrontal cortex is closely related to brain-stimulation reward in that in the rat and monkey self-stimulation of it can be obtained, and electrophysiological and fibre degeneration experiments show that it is closely connected with many different self-stimulation sites. In the rat anaesthesia of the sulcal prefrontal cortex attenuates self-stimulation, but the prefrontal cortex is not essential for self-stimulation, which can occur even when much of the forebrain is ablated. It has been suggested that in the monkey the orbitofrontal cortex is involved in the disconnection of stimulus-reinforcements associations. As in the case of the amygdala, the prefrontal cortex may modulate reward, but in relation not to the formation but to the disconnection of stimulus-reinforcement associations.

Through neurones in the midbrain and pons arousal is produced by hypothalamic self-stimulation. Activation of this arousal system at least partly mediates stimulus-bound locomotor activity in that the arousal and activity show a similar post-stimulation decay, are produced through directly excited neurones with the same absolute refractory period, and are not produced by rewarding stimulation of the nucleus accumbens. There is some similar evidence that activation of this arousal system partly mediates the priming effect in self-stimulation, although other factors such as incentive motivation may also contribute to the priming effect. Activation of this arousal system is not essential for reward in that the arousal system is not activated in self-stimulation of the nucleus accumbens.

Although neurones in most areas of the brain are not activated as described above in self-stimulation, some activation of neurones in the hippocampus, cingulate cortex, reticular nucleus of the thalamus, and the medulla and caudal pons by brain-stimulation reward has so far been found. The function of activation of these neurones in self-stimulation is not yet known.

There is considerable evidence that central catecholamines are involved in intracranial self-stimulation. Much of the evidence which has been cited to show that the release of the particular catecholamine noradrenaline mediates brain-stimulation reward is weak in two

respects. Firstly, many of the treatments which decrease self-stimulation rate (e.g. α-methyl-*p*-tyrosine, chlorpromazine, haloperidol) or increase self-stimulation rate (e.g. amphetamine) affect dopamine as well as noradrenaline. Secondly, most of the treatments affect arousal, and it has not been shown, for example, that sedation does not account for the attenuation of self-stimulation produced by agents which decrease the synthesis of noradrenaline. Thus the evidence available at present does not provide support for the view that the release of noradrenaline mediates brain-stimulation reward. Dopamine-receptor blockade attenuates self-stimulation of many different brain sites without producing major sedation. Whether this represents a true block of reward or is a result of interference with high-level motor behaviour is not yet clear.

The main sections of this account of the neural basis of brain-stimulation reward are summarized in sections 1.2.1, 1.2.2, 2.6, 3.7, 4.8, and 5.7.

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