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CENTRAL NERVOUS MECHANISMS RELATED TO FEEDING AND APPETITE

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1 Concept of Feeding and Satiety Centres in the Brain

From clinical evidence it has been known since early this century that damage to the base of the brain in or near the hypothalamus can lead to overeating and obesity in man. Later, it was demonstrated that the critical region is in the ventromedial hypothalamus (VMH), for bilateral lesions here in animals led to hyperphagia and obesity (see Grossman, 1967, 1973). Then Anand & Brobeck (1951) discovered that bilateral lesions of the lateral hypothalamus (LH) can lead to eating, whereas electrical stimulation of the VMH can stop eating. Evidence of this type led in the 1950s and 1960s to the view that food intake is regulated by two interacting hypothalamic "centres": a feeding centre in the LH and a satiety centre in the VMH (see Stellar, 1954; Grossman, 1967, 1973).

2 Problems with the "Dual-Centre" Hypothesis

Soon, problems with the "dual-centre" hypothesis appeared. Morgane (1961a,b,c) showed that the LH lesions, which were particularly effective in producing aphagia, were far lateral and damaged pallidofugal fibre pathways. Damage to these pathways outside the LH could also produce aphagia. Thus the possibility arose that LH aphagia was due to damage to fibre pathways which merely coursed near the hypothalamus. Marshall *et al.* (1974) showed that the dopaminergic nigrostriatal bundle close to the far LH region was also damaged by LH lesions that produced aphagia, and that damage to this pathway outside the hypothalamus could also produce aphagia. The damage was associated with a complex sensorimotor dysfunction in which the rats could not orientate correctly to visual or somatosensory stimuli, including food. It was suggested that this sensorimotor disturbance at least partly accounted for the aphagia produced by LH lesions, and consistent with this view is the finding that LH lesions impair drinking as well as feeding. Thus by the middle 1970s it was clear that the lesion evidence for a LH feeding centre was not straightforward, for at least part of the effect of the lesion was due to damage to fibres of passage travelling through or near the LH (e.g. Stricker & Zigmond, 1976).

3 Direct Neurophysiological Evidence on the Role of the Lateral Hypothalamus in Feeding

Using the neurophysiological approach to complement and to add to the lesion evidence, several investigators have established that the firing rates of some LH neurones alter during (Oomura *et al.* 1969; Hamburg, 1971; Oomura, 1973) or immediately before (Olds *et al.* 1969; Rolls *et al.* 1976) feeding in the rat, cat and monkey. These changes could be related to various factors, some of which have now been investigated in the monkey. Some neurones had activity related to movements made by the monkey, or to touch (E T Rolls *et al.* 1976, 1980; Rolls & Rolls, 1977; Rolls, 1981a,b). One population of LH neurones had activity more specifically related to feeding (see section 3v), and they extended out lateral to the LH into the substantia innominata.

i *Responses Associated with the Taste of Food*

The activity of some neurones in the LH and substantia innominata of the hungry monkey is associated with the taste of food (Burton *et al.* 1976; E T Rolls *et al.* 1980), as they respond when some, but not other, solutions are tasted and ingested, even though similar movements are made to drink the different solutions. Gustatory responses to water, glucose and saline occur in the rat LH (Norgren, 1970). In a sample of 764 neurones in the monkey LH and substantia innominata, 33 responded in association with the taste of food, and 19 also responded in association with the sight of food (E T Rolls *et al.* 1976, 1980).

ii *Responses Associated with the Sight of Food*

In the hungry monkey some neurones in the LH and substantia innominata responded immediately before feeding, that is, as soon as the monkey saw the food, and while he looked at the food (Rolls *et al.* 1976). These neurones responded most to the monkey's most preferred foods, and comparable responses did not occur when the monkey looked at or reached for non-food objects. These neurones did not respond if the monkey smelled, grasped and then tasted and ate the food in the dark. The results of these and other tests suggest that the responses of these neurones are associated with the sight of food and are not due to olfactory, gustatory or motor responses associated with feeding, or to anticipatory responses, such as salivation (Rolls *et al.* 1976).

iii *Modulation by Hunger of the Responses of Lateral Hypothalamic Neurones to the Sight and Taste of Food*

The neurones in the LH and substantia innominata, which respond when food is seen and/or tasted if the monkey is hungry, do not respond if he is satiated (Burton *et al.* 1976). The responses of these neurones associated with food diminish in intensity as satiety, measured by whether the food is rejected, progresses. The spontaneous base-line firing rate of these neurones is little affected by the transition from hunger to satiety. Rather it is the sensitivity of these neurones to their visual and/or taste inputs which is modulated by satiety. These experiments suggest the following principle: at the hypothalamic stage of processing, visual and gustatory responses to food-related sensory inputs are modulated by the hunger (or need, in terms of physiological variables, or motivational state) of the animal. This modulation by hunger of responsiveness to food-related sensory inputs suggests that these hypothalamic neurones could mediate the responses that occur in the hungry animal to food. These responses include autonomic and

endocrine as well as feeding responses to the sight (or taste) of food.

iv *Sensory-Specific Modulation of the Responsiveness of Lateral Hypothalamic Neurones and of Appetite*

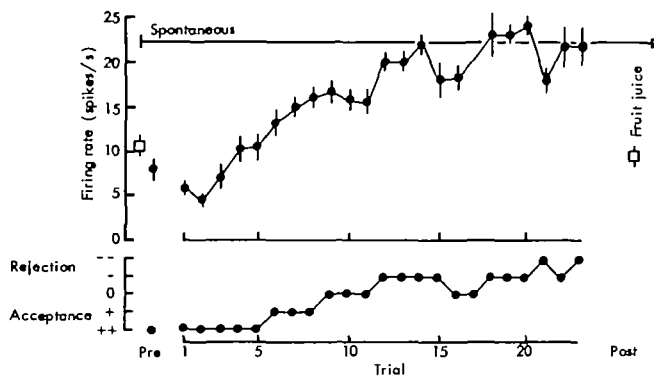
During these experiments on satiety, it was observed that, if a LH neurone had ceased to respond to a food on which the monkey had beed fed to satiety, then the neurone might still respond to a different food. This occurred for neurones with responses associated with the taste (see fig. 1) or sight (see Rolls & Rolls, 1981) of food. Corresponding to this neuronal specificity of the effects of feeding to satiety, the monkey rejected the food on which he had been fed to satiety, but accepted the other foods which he had not been fed.

As a result of these neurophysiological and behavioural observations showing the specificity of satiety in the monkey, experiments were performed to determine whether satiety was specific to foods eaten in man (see E T Rolls & Rolls, 1981; B J Rolls *et al.* 1981a,b). It was found that the pleasantness of the taste of food eaten to satiety decreased more than for foods that had not been eaten. Because sensory factors, such as similarity of flavour and texture, are usually relatively more important than metabolic equivalence in terms of protein, carbohydrate and fat content in influencing how foods interact in this aspect of satiety, it had been called "sensory-specific satiety" (E T Rolls & Rolls, 1977, 1981; B J Rolls *et al.* 1981a,b).

One implication of these findings is that if one food is eaten to satiety, appetite reduction for other foods will "at best" be incomplete, and this should mean that at least some of the other foods will be eaten. This has been confirmed in an experiment in which either sausages or cheese with crackers were eaten for lunch. The liking for the food eaten decreased more than for the food not eaten and, when an unexpected second course was offered, more was eaten if a subject had not been given that food in the first course than if he had been given that food in the first course (98% vs 40% eaten in the second courses, $P < 0.01$). In fact, there was a highly significant ($P < 0.001$) correlation ($r_s = 0.68$) between the depression in liking for a food in the first course (which was high for foods eaten) and the amount of it subsequently eaten in the second course (which was low for foods eaten) (Rolls *et al.* 1981a,b).

If followed through, the implication of this sensory-specific satiety is that, if a wide variety of foods is available, the total amount consumed will be more than when only one food is offered repeatedly. This prediction has been confirmed by several studies in man and the rat (B J Rolls *et al.* 1980, 1981a,b). This enhanced eating when a variety of foods is available, as a result of the operation of sensory-specific satiety, may have been advantageous in evolution in ensuring that different foods with different important nutrients were consumed, but today in man, when a wide variety of food is readily available, it may be a factor that can lead to overeating and obesity.

FIG. 1. Sensory-specific decrease in the responsiveness of a lateral hypothalamic neurone produced by feeding



The firing rate was measured on each trial in a 7–10s period in which the monkey drank 10ml of 20% glucose solution. At the start of the experiment (pre) the neurone responded (by decreasing its firing rate below the spontaneous rate) while the monkey drank glucose (●) or blackcurrant juice (□). The firing rate (mean ± S.E M.) decreased when the glucose was tasted on the early trials of the satiety experiments in which the monkey was still hungry but, as the monkey became satiated because of drinking the glucose (trials 5–15), the response when the glucose was tasted diminished to nil (for further details see E T Rolls *et al.* 1980). However, at the end of the experiment (post), the neurone still responded when the monkey drank the blackcurrant juice. The monkey's acceptance or rejection of the glucose is shown in the lower graph

v *Role of these Hypothalamic Neurones in Feeding*

This type of neurophysiological analysis shows that some LH neurones (13.6% in one sample of 764 neurones) respond to the sight and/or taste of food, responding most to the most preferred foods; that these responses occur only if the monkey is hungry, and in fact are modulated by sensory-specific satiety, so that they respond only to foods for which an appetite can be demonstrated; and that the visual responses occur only to objects which the animal has learned are foods (Mora *et al.* 1976). These neurones respond to food-related visual stimuli with relatively short latencies (150–200ms) compared with the animal's feeding responses to the same stimuli (300–400ms) (Rolls *et al.* 1979a), so that these neuronal responses could be involved in producing the responses of the hungry animal to food. These responses include autonomic and endocrine responses (such as the release of insulin), as well as feeding responses to the sight of food. Some role in the autonomic and endocrine responses is likely, because there are hypothalamic neurones that project towards brain-stem systems controlling these responses (Jones *et al.* 1976; Saper *et al.* 1976, 1979) and hypothalamic lesions and stimulation do influence autonomic and endocrine function. Some role in the feeding responses is also possible, for not only do the responses of these hypothalamic neurones show the food-, appetite- and learning-related responses described above, but in a visual discrimination for food their responses precede and predict the responses of the hungry monkey to food (Rolls *et al.* 1979a). Consistent with this possibility is evidence that damage to the LH with kainic acid injections, which spare fibres of passage, leads to some aphagia and adipsia (Grossman *et al.* 1978), and that there are projections from the LH to the frontal and parietal cortex (Divac, 1975; Kievit & Kuypers, 1975) and to the substantia nigra (Arbuthnott *et al.* 1976; Swanson, 1976; Nauta & Domesick, 1978), through which the hypothalamus could influence the initiation of feeding responses. Also consistent with this possibility is the evidence on brain-stimulation reward and the hypothalamus. Nevertheless the hypothalamus is not essential for simple reflex acceptance of sweet solutions during hunger, and of rejection of these solutions during satiety, as this can occur in decerebrate animals, in which the hypothalamus can no longer influence the brain-stem (Grill & Norgren, 1978). Rather, the importance of the hypothalamus in feeding appears

to be in its close relation to the forebrain, through which it must receive the highly coded food- and learning-related visual inputs described above in the primate (Rolls, 1981b). The fact that these inputs reach the hypothalamus emphasizes the important role of visual stimuli and learning in the responses to food and selection of foods in primates, including man.

4 Responses to Food Reward and to Brain-Stimulation Reward in the Lateral Hypothalamus

These experiments show that a population of LH neurones responds when food reward is given to an animal. The food is rewarding in that the monkey will work for it. Factors that determine whether food or an object is rewarding include those that influence the responses of the LH neurones, e.g. association with food during learning and whether the monkey is hungry. Therefore it is significant that electrical stimulation of the LH can be rewarding, in that the animal will work to obtain it. It is also important that the electrical stimulation is similar to food for a hungry animal, in that the animal will work to obtain stimulation in this region if he is hungry, but will work much less if he is satiated (Olds, 1962, 1977; Hoebel & Teitelbaum, 1962; Hoebel, 1965, 1976; E T Rolls, 1975, 1979, 1981b; Rolls *et al.* 1980). Therefore it was interesting that (i) all the food-related LH neurones were activated by brain-stimulation reward of some forebrain sites; (ii) this activation was more likely to occur from self-stimulation than from non-self-stimulation sites; (iii) self-stimulation through the recording electrode occurred when it was in the region of the neurones activated by food, and became less as the electrode was raised or lowered from this region; and (iv) self-stimulation in the region of these neurones in the LH was attenuated after the monkey was fed to satiety (i.e., until food was no longer rewarding as the monkey would no longer work for or accept the food) (E T Rolls *et al.* 1980). All this evidence is consistent with the hypothesis that the behaviour of the animal is directed in order to obtain activation of these neurones either by food reward or by brain-stimulation reward of some brain regions. This hypothesis would account for why animals will work to obtain stimulation of some brain-stimulation reward sites, and implies that activation of these hypothalamic neurones by food reward or by brain-stimulation reward is something for which the animal will work.

5 Role of the Ventromedial Hypothalamus in Feeding

Apparently the bilateral lesions of the VMH which lead to hyperphagia and obesity do so at least partly by altering endocrine mechanisms. The lesions lead to lipogenesis throughout the day as well as the night, and this is associated with hyperinsulinaemia (Le Magnen *et al.* 1973). If the hyperinsulinaemia is abolished by destruction of the β cells of the pancreas with streptozocin, the hyperphagia and obesity are abolished (York & Bray, 1972). However, these results may be misleading because the hypoinsulinaemia impairs normal metabolism; and, although Inoue *et al.* (1977) did not find that transplantation of a functional (but of course denervated) pancreas into experimentally diabetic rats allowed VMH obesity to develop, Vilberg & Beatty (1975) were able to demonstrate that VMH lesions still led to obesity in diabetic animals whose insulin levels were maintained by exogenous insulin injections. Further, although there are reports that subdiaphragmatic vagotomy (which would prevent neurally mediated release of insulin by the pancreas produced, for example, by food given to the hungry animal) can prevent MVH hyperphagia (Powley & Opshal, 1974; Inoue & Bray, 1977), Wampler & Snowdon (1979) did obtain obesity in vagotomized VMH lesioned rats, and suggested that earlier failures might be due to surgically produced damage to the oesophagus during vagotomy. Thus the hyperinsulinaemia that is produced by VMH lesions may not fully account for the overeating and obesity produced, and there may be some other effect of the lesions which tends to produce obesity (see Panksepp *et al.* 1979). Nevertheless, the neurally mediated increase in secretion of insulin produced by giving food to a hungry animal (one of the cephalic phase alimentary reflexes) could lead to more intense eating, and may be enhanced by VMH lesions (Powley, 1977).

6 Neural Control of Eating in Man

Although the studies described above on the neural control of feeding have been on animals, many were on non-human primates, and therefore are relevant for explaining the control of feeding and body weight in man. The direct evidence available for man is consistent with the evidence from animal studies (although of course precise localization is usually not possible in the human material). For example, Reeves & Plum (1969) described a patient with a VMH tumour who ate 8000–10000 cal/day[1], and in one two-month period of hospitalization gained 24 kg. Bray & Gallagher (1975) described eight cases of obesity associated with hypothalamic damage, and found in detailed metabolic studies of four of the hyperphagic patients that the fasting insulin concentration was higher than in control obese patients. This is consistent with the possibility that hyperinsulinaemia produced by the hypothalamic damage at least contributed to the obesity in these patients. Of course, these findings do not imply that in most obese humans there is hypothalamic damage. In patients with anorexia, Mecklenburg *et al.* (1974) have provided indirect evidence for hypothalamic damage (impaired thermoregulation and partial diabetes insipidus), and White & Hain (1959) and Kamalian *et al.* (1975) have provided direct evidence for brain damage which included the LH. Quaade (1974) and Quaade *et al.* (1974) electrically stimulated the LH in (obese) humans, and reported in three of five patients "convincing hunger responses", such as "I am so hungry that I could eat a whole fried chicken with chips", and "I am so hungry that my entire belly feels as a vacuum". In two patients unilateral LH lesions produced a transient suppression of feeding, but no significant weight reduction.

Although these observations are consistent with our understanding of the neurology of feeding in animals, we still cannot advocate direct therapeutic intervention in obesity. (i) Our understanding of the neurology of feeding in animals is limited. (ii) It is clear that anatomically the hypothalamus is a heterogeneous region, with many fibre systems coursing through or near it, so that there is no one centre which can be separated from other systems. It is not even yet clear to what degree damage to the different cell and fibre systems in and near the hypothalamus contributes to the effects of lesions on eating. (iii) It is clear from the neurophysiological studies that only a small proportion of the hypothalamic neurones recorded are feeding-related, and that these are widely distributed from the anterior commissure anteriorly to the LH posteriorly, and laterally into the substantia innominata (see e.g. Rolls *et al.* 1979a), and are intermingled with neurones with other functions (see Rolls, 1981a), so that again no one centre which can be isolated from other systems can be identified, and damaged by

[1] 1 cal ≈ 4.2 J.—ED.

lesions. Therefore it is inappropriate to conceive of feeding centres in man, and to attempt to disrupt them selectively.

7 Role of Catecholamine Pathways in Feeding

Damage to the dopaminergic nigro-striatal bundle leads to a complex sensorimotor deficit, which includes an inability to orientate to environmental stimuli and to initiate behaviour, and to aphagia and adipsia, which are probably secondary to these changes (Ungerstedt, 1971; Marshall *et al.* 1974). When recordings are made in the caudate nucleus and putamen, the structures to which the nigro-striatal bundle projects, a partially topographical organization of neurones is found. These neurones respond to visual stimuli (in the tail of the caudate nucleus, which receives from visual inferotemporal cortex), to environmental stimuli which the animal uses as cues for the initiation of behaviour including feeding responses (in the head of the caudate nucleus), and in relation to movements (e.g. in the putamen) (Rolls *et al.* 1979b; Rolls, 1981b). Taken together with evidence on the effects of nigro-striatal bundle damage, these and other neurophysiological findings suggest that the striatum (a system which receives from all areas of the cerebral cortex and has major efferent projections to structures involved in movement such as the globus pallidus and thus indirectly to motor cortex) is involved in the initiation of behavioural responses to environmental stimuli (Rolls *et al.* 1979b; Rolls, 1981b), and that this function is modulated by the dopaminergic input. The aphagia and adipsia produced by nigro-striatal bundle lesions probably result from disruption of the normal function of these neurones in the initiation of behavioural responses, rather than from disruption of a system concerned primarily or specifically with feeding.

8 Conclusions

Evidence from lesion studies on the role of the hypothalamus in feeding is difficult to interpret because damage to many different neural systems is produced. Neurophysiological evidence, based on recordings of the activity of single neurones during feeding, shows that one population of hypothalamic neurones has responses to the sight and/or taste of food, and that these responses are influenced by hunger and food-related learning. The neuronal responses to the sight of food precede and predict the responses of the hungry animal to food. These responses provide evidence that these neurones are involved in the initiation of autonomic, endocrine or feeding responses made to food. To analyse the neural control of feeding further, it will be necessary to determine the input pathways to these hypothalamic neurones, which may be via the inferior temporal visual cortex, and the systems to which these hypothalamic neurones project (see Rolls, 1981b).

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