Neuroviews

Neurophysiology of feeding

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In investigations of the neural processes underlying various behavioural phenomena, it is often very difficult to separate cause from effect, especially when the part of the nervous system central to this control is distant from both the sensory and the motor ends of this behaviour. Overcoming these difficulties, Edmund Rolls, with his colleagues, has carried out a series of very elegant experiments which have succeeded in dissecting apart the various types of neurones involved in feeding behaviour, and, in doing so, has provided intriguing information as to the separate roles of these different neurones.

Lesions of the lateral hypothalamus reduce or abolish feeding, and of the ventromedial hypothalamus lead to hyperphagia and obesity. Conversely, electrical stimulation of the lateral hypothalamus can induce feeding, and of the ventromedial hypothalamus can stop feeding. These observations led in the 1950's and 1960's to the concept of a hunger centre in the lateral hypothalamus and of a satiety centre in the ventromedial hypothalamus.

Problems with this evidence for the dual centre hypothesis of the control of feeding are that the lateral hypothalamic lesions which disturb feeding are associated with a complex sensory-motor dysfunction, and damage many pathways (such as the nigrostriatal dopamine-containing fibres) running through, and lateral to, the lateral hypothalamus. In fact, damage to these pathways outside the lateral hypothalamus can lead to a syndrome similar to the lateral hypothalamic syndrome, with a reduction in feeding and a sensory-motor disturbance[5,10]. A more direct approach to the neurology of feeding is to analyse the activity of single neurones in different regions of the brain during feeding, to determine how neurones in different brain areas are involved in the control of feeding. This approach is likely to be particularly useful in regions such as the hypothalamus where a great many systems are intermingled, and is the subject of this article.

Neuronal responses to feeding

When recordings are made of the activity of single neurones in the monkey during feeding, a population of neurones is found in the lateral hypothalamus with activity which is related to feeding[7]. Interestingly, these neurones stretch out laterally through the substantia innominata (see Fig. 2). In one sample of 764 neurones in this region, approximately 13% had activity related to feeding[8]. The other neurones either had activity which did not change during feeding, or which were related to other factors such as movements made by the monkey, touch to the face or body, or arousal[7]. Of the neurones with activity related to feeding, a small proportion (2% of the 764) had activity which altered only during the ingestion of some fluids (e.g. glucose), and were classified as being associated with taste.

Sight of food responses

The responses of the majority of the neurones in the lateral hypothalamus and substantia innominata with activity related to feeding (11% of the 764) occurred before the food was placed in the monkey's mouth, while the monkey was looking at the food, for example at a peanut, mash, or fruit. These neurones did not respond while the monkey looked at non-food objects, did not respond simply in relation to movements made by the monkey, did not respond when arousal was elicited in control tests, and in many cases did not respond while the monkey had food in his mouth so that salivation could not have elicited the response[8]. Thus the activity of these neurones, which either increased or decreased their firing rate when the monkey looked at food, was classified as being associated with the sight of food.

To investigate whether these neurones could be involved in the responses of the hungry monkey to food, the monkeys were fed until they were satiated: the neurones ceased to respond to the food as the monkeys became satiated! We also found in visual discrimination learning experiments performed while we were recording from these neurones, that the neurones' activity came to be associated, during learning, with visual stimuli which indicated food[3].

A causal question

At this stage neurones had been found in the lateral hypothalamus and substantia innominata of the monkey which responded to the sight of food if the monkey was hungry, and if he recognized the visual stimulus as a food object. The question then was whether these neurones could mediate some of the responses of the hungry monkey to food, such as the initiation of feeding and the autonomic and endocrine responses, or whether the activity of these neurones simply reflected these responses. This causal type of question is crucial when analysing brain function, and was investigated in two ways as follows. Firstly, the latency of activation of these neurones when food was shown to the monkey was measured, to determine whether it was shorter than the latency of the initiation of the monkey's responses to the sight of the food. Secondly, the activity of these neurones was compared with the activity of neurones in sensory and motor structures in the same test situation, to determine whether the hypothalamic neurones were particularly closely related to the initiation of feeding, and to compare the latencies of activation in the different regions. The final aim here was to trace the test-signal through visual and learning stages to the hypothalamus, and then from the hypothalamus to neurones in structures which could provide a clear indication of the types of response mediated by the hypothalamic neurones. This tracing could lead us to neurones involved in the initiation of feeding responses, or in the autonomic and endocrine responses.

The latency of activation of hypothalamic neurones

To measure the latency of activation of the hypothalamic neurones with activity associated with the sight of food, a large aperture shutter was placed in front of the monkey. When the aperture opened to reveal food objects, the neurones responded with a latency of 150-200 msec; there was no significant response when the shutter opened to reveal non-food objects.

The next stage was to determine if this latency was short relative to the latency at which the monkey could initiate motor responses to obtain food. This was done by turning the test into a visual discrimination test, so that when the shutter opened to reveal one arbitrary stimulus, e.g. a 2 ml syringe, or a square white plate, the monkey could lick a tube in front of his mouth to obtain fruit juice, and when the shutter opened to reveal a different visual stimulus, aversive hypertonic saline was obtained if the monkey licked the tube. In this situation, the hypothalamic neurones responded with latencies of 150-200 msec to the food-related visual stimulus, and for a typical monkey the latency to the lick contact on the fastest trials was 400 msec (see Fig. 1), and to the electrical activity in the muscles which produced the lick response (which were the only relevant muscles, given the head restraint) was 300 msec.

Thus the response of the hypothalamic neurones to the sight of the food preceded the earliest sign of the initiation of a correct response to obtain food (150-200 v. 300 msec), and could be used to predict the response of the monkey to the food. This showed that the activity of these hypothalamic neurones did not simply reflect movements made by the animal to obtain food, and is consistent with the view that these hypothalamic neurones respond to the sight of food in the hungry monkey and mediate some of the responses of the monkey to the food, such as the initiation of feeding, and the autonomic and endocrine responses[4,5,7].

Activity of neurones in input and output structures during the initiation of feeding

After the primary visual cortex, there are visual projections via prestriate visual areas to the inferotemporal visual cortex, an area of the visual association cortex. This area has connections to a dorsolateral area of the amygdala, a subcortical temporal lobe nucleus which in turn has connections to the lateral hypothalamus and substantia innominata (see Fig. 2). Because of these connections, and because lesions of the temporal lobe can produce monkeys which do not distinguish correctly in visual discriminations between food and non-food objects, single-unit recordings have been made in the inferotemporal cortex and amygdala. In the inferotemporal cortex, neurones responded with latencies of 100-140 msec which were independent of whether the visual stimuli were food or non-food objects, or whether they signified food during visual discrimination learning, and which were also independent of hunger[9].

In many cases physical properties of the stimuli could be used to predict neuronal responses. In the dorsolateral amygdala, a region of neurones with visual responses with latencies of 110-150 msec were found, and although there was a tendency for some (22%) of the neurones to respond primarily to rewarded or aversive objects, neurones were not found which responded uniquely to food objects.

These findings show that the response of hypothalamic neurones with activity associated with the sight of food are different from those of neurones in the visual inferotemporal cortex in the same test situation, so that the responses of the hypothalamic neurones do appear to be closely related to the control of responses to the sight of food, and are not due to general changes in the monkey's behaviour which influence activity throughout the visual system when he sees food. Further, the findings are consistent with the hypothesis that visual information related to feeding which is important in the initiation of feeding in the primate reaches hypothalamic neurones via the inferotemporal cortex and the amygdala.

Investigations of where the significance of visual stimuli first affects neuronal responses will now be important, given that the significance has no effect on inferotemporal neuronal responses, a possible small effect at the amygdaloid level, and that it determines the responses only a very short time later at the hypothalamic level[10].

Movement-related responses

When recordings are made during feeding in structures such as the globus pallidus and in the region of the substantia nigra, neuronal activity which alters during feeding can be related to movements made by the monkey. For example, neurones in these regions may have activity related to mouth or arm movements[2,8], so that during the initiation of feeding these neurones fire relatively late, at about the time when electrical activity starts in the relevant muscles. Further, this type of response

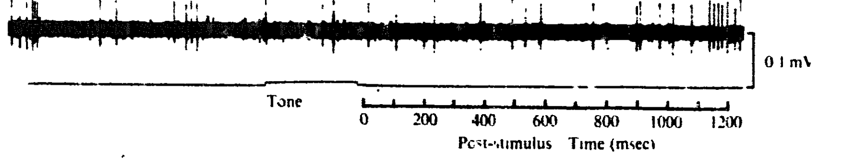

Fig. 1. Activity of a neurone with food-related activity in the substantia innominata during visual discrimination. Top trace: food trial. At the end of the signal tone the shutter opened at time 0 to reveal a food-associated visual stimulus: the unit responded to the stimulus with a latency of 150 msec, and the monkey licked the tube in front of his mouth at approximately 470 msec to obtain fruit juice. Lower trace: non-food trial. When the shutter opened it revealed a saline-associated visual stimulus, and correctly the monkey did not lick the tube, or he would have obtained hypertonic saline.

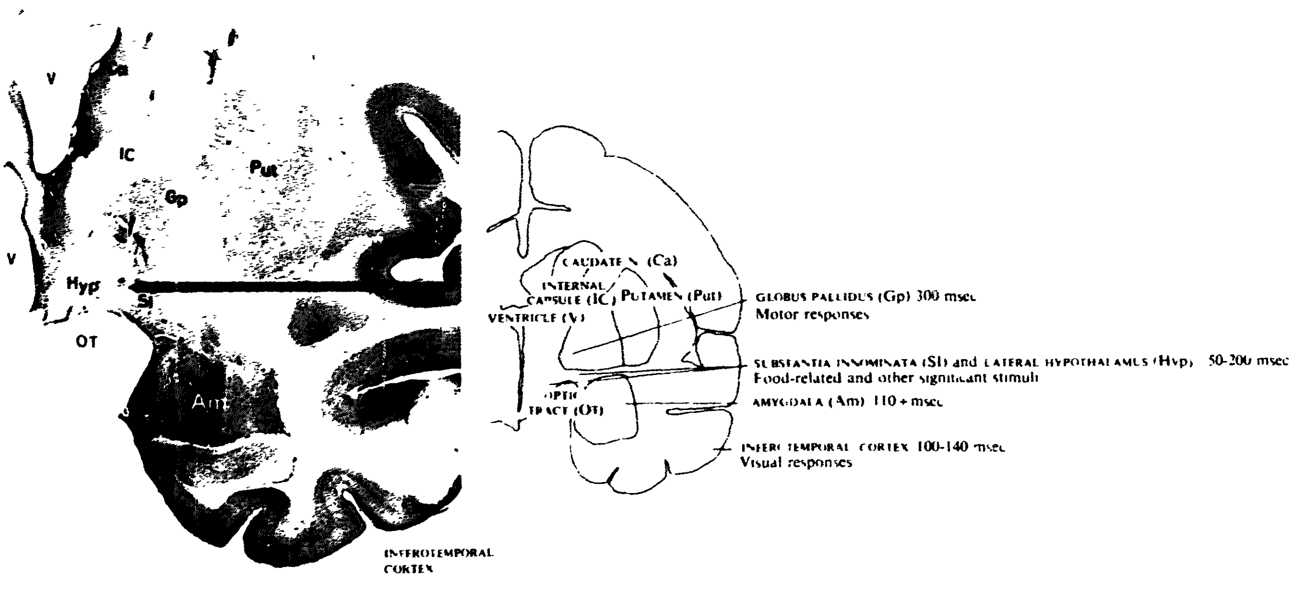

Fig. 2. Brain areas related to different processes involved in feeding. The latencies of activation of neuronal activity in response to seeing food are indicated for various of these areas.

occurs whenever the movement is made, and does not depend on the hunger of the monkey[1,2]. These observations show that the movement-related responses of neurones in these structures follow, and can be distinguished from, the responses of hypothalamic neurones to the sight of food. It now becomes important to follow the output connections of hypothalamic neurones more precisely to subsequent stages in order to understand further their function and the initiation of the responses to food.

Stimulation-reward

Because the activity of the hypothalamic neurones occurred when the monkeys would work for food, that is when the food was rewarding, it was interesting to find that these neurones were activated by electrical stimulation of some brain sites which produced reward, and that self-stimulation, which was decreased by satiety, was found in the region of these hypothalamic neurones[4,6]. These observations suggest that a sufficient reason for self-stimulation of some brain sites is that the stimulation mimics the effect of food reward on the activity of neurones in the lateral hypothalamus and substantia innominata[4,6]. Equally, the observations are consistent with the view that activation of the neurones in the lateral hypothalamus and substantia innominata by food in the hungry animal could provide an important signal in the initiation of feeding, in that the hungry monkey would work to obtain a sensory input, produced by food, which would activate these neurones.

Routes to neurophysiological understanding

The type of problem which arises when investigating the neurophysiology of the central nervous system is how one can determine what the function is of the neurones from which the recordings are made. This is particularly important when the brain region being studied is not close to either sensory input or the motor output. Methods which have been useful in the work described above include comparisons of the latencies of the neuronal responses, as well as the types of responses obtained in different brain regions during the same experimental conditions, and then tracing the processing through the nervous system from sensory input through control or decision stages to motor output. The function of the nervous system as a system can only be understood by the ability to trace processing through the different stages of the system, and this clarifies the function of each part of the system, and must be a goal for future research. When applied to the neurology of feeding, these methods show that the activities of neurones in the lateral hypothalamus and substantia innominata are closely related to the presentation of food in the hungry animal, and precedes and predicts the responses of the monkey to the food (see Fig. 2). Such studies clearly indicate that these neurones in the lateral hypothalamus and substantia innominata are important in the neurology of feeding

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