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THE REGULATION OF VOLUNTARY FOOD INTAKE

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Hypothalamic control of food intake

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This brief review of the neural control of food intake is prepared as an introduction to this symposium and is not to be considered as a complete coverage of all the aspects of anatomy, physiology, behavioural and metabolic studies which have provided information on the influence of the hypothalamus on feeding behaviour. Readers who are interested in greater detail will find appropriate references in numerous reviews, of which the following are recent examples, Brobeck (1960), Kennedy (1966), Anand (1967) and Stevenson (1969) so, that in this essay, references will be kept to a minimum.

In the eighteenth and nineteenth centuries it was thought that food intake was governed by the sensation of hunger originating from peripherally placed receptors situated somewhere in the alimentary canal. Another school, including the powerful nineteenth century French neurophysiologists, believed that the control of food intake was invested in the brain. Foster adopted a 'generalist' viewpoint which suggested that afferent impulses from many regions affected the brain but, in addition, the brain itself could be affected by the circulating blood (see Anand, 1961). As a result of clinical observation in man, it had been noticed that injury or some other lesion of the base of the brain resulted in obesity. In 1901, Fröhlich described a syndrome in man of which adiposity and infantilism were features and postulated that the change was due to the destruction of the hypophysis by a tumour. On further investigation it was realized that in Fröhlich's syndrome the hypophyseal loss was only incidental and that the obesity resulted from hypothalamic damage (Brobeck, Tepperman & Long, 1943).

In the 1930's techniques were developed which allowed investigation of the depth of the brain with some precision. Hess (1932) showed that midline hypothalamic structures could be stimulated electrically and he initiated a vigorous study to separate various aspects of behaviour using this technique. In Chicago, Ranson rediscovered the stereotaxic instrument designed by Clarke and used by Clarke & Horsley (1906), and placed large electrolytic lesions in the hypothalamus

of rats and produced obesity (Hetherington & Ranson, 1940). The exploitation of Clarke's invention to study hypothalamic physiology moved to New Haven where Brobeck *et al.* (1943) showed that the obesity following small ventromedial hypothalamic lesions led to the onset of hyperphagic behaviour and that the adiposity which occurred was due to increased food intake and not to a disturbance of metabolism. They suggested that this area of the ventromedial hypothalamus was concerned in the inhibition of food ingestion so that, when it was removed, the animal was insatiably hungry and showed this by its hyperphagic behaviour.

The earlier clinical observations had noticed that hypothalamic lesions (usually tumours) did not always produce obesity and, in fact, sometimes they caused opposite effects such as inappetence, weight loss and cachexia. Anand & Brobeck (1951) showed that these latter effects could easily be reproduced when bilateral lesions were placed in the lateral part of the lateral hypothalamus in the frontal plane of the ventromedian nuclei. Rats with this type of lesion showed complete aphagia, cachexia and death from starvation, and it was postulated that this behaviour was due to destruction of a 'feeding center'. When rats are made hyperphagic by medial hypothalamic lesions they become aphagic when bilateral lateral lesions are added.

The combination of these experimental studies of diencephalic lesions on feeding behaviour was utilized to propound the concept that the regulation of food intake is controlled by a central hypothalamic mechanism. The hypothalamic centre was itself divisible into a lateral 'feeding center' and a medial 'satiety center', with the two centres reciprocally innervated but with the medial satiety centre being dominant since it could override feeding (Brobeck, 1955).

The early experimental work has been verified and extended with the object of precisely delimiting the brain areas and pathways involved, especially in establishing an anatomical basis for this physiological mechanism set in the hypothalamus (Anand, 1961). There is a close similarity in the cytoarchitecture, cellular arrangement and axonal connectives in the hypothalamus of mammals which suggests that physiological mechanisms might be comparable (Krieg, 1932; Diefen, 1962).

It has been noted that it is unnecessary to destroy completely the ventromedial nuclei bilaterally to produce weight gain in rats, but usually unilateral or partial destruction of the ventromedial area of the hypothalamus causes only short-lived or slight hyperphagic effects (Mayer & Barnett, 1955; Wagner & de Groot, 1962). It is now accepted that provided animals are kept hydrated by stomach-tube feeding they will recover sooner or later from the aphagia of lateral hypothalamic lesions. It has been shown that a mere introduction of an electrode into the brain-stem may cause an effect without the production of an electrolytic lesion (Morrison & Mayer, 1957). The original experiments in rats have been extended to the cat and monkey (Anand, Dua & Schoenberg, 1955; Morgane & Kosman, 1959), rabbits (Balinska, Lewinska, Romaniuk & Wyrwicka, 1961), goat (Baile & Mayer, 1968), sheep (Tarttelin & Bell, 1968) and chicken (Feldman, Larsson, Dimick & Lepkovsky, 1957).

Anand & Brobeck (1951) particularized in claiming that the ventromedial nuclei

of the ventromedial area of the hypothalamus was the 'satiety centre' of the feeding centre, although in the same paper they presented evidence that bilateral lesions restricted to the hypothalamus lateral to the ventromedial nuclei also produced hyperphagia and obesity. Holmes & Fraser (1965) placed large lesions in the ventromedial hypothalamus of sheep but were unable to demonstrate hyperphagia. On the other hand, large lesions involving the ventromedial region of the sheep and goat have been associated with transient hyperphagia, but when the ventromedial nuclei are destroyed with precision in sheep, then no change in food intake occurs (Tarttelin & Bell, 1968; Baile, Mahoney & Mayer, 1968). This latter finding agrees with many other authors that the ventromedial nucleus of the hypothalamic constellation of neuronal 'nuclei' is not the anatomical locus of the physiological entity designated the ventromedial hypothalamic 'satiety centre'.

The neuroanatomical delimitation of the lateral hypothalamic centre is even more difficult to ascertain. This region of the hypothalamus lacks cellular uniformity and the numerous neurones show no aggregation so that they can be regarded only as part of the neuropil or the bed nucleus of tracts such as the medial forebrain bundle. Nevertheless, it requires very precise positioning of the electrolytic lesions bilaterally in a frontal plane at the level of the ventromedial nucleus to produce lasting aphagia even in rats. Single, unilateral lesions may produce hypophagia for a short period. Fibres of the median forebrain bundle were thought to be implicated by Morrison & Mayer (1957), but Morgane (1961*a,b*) brings strong evidence that centrifugal fibres from the globi pallidi at the level of the feeding centres are critical in the feeding reaction, and it is interruption of the impulses carried by these fibres which produces aphagia. Electrical stimulation of the lateral hypothalamus as well as producing hyperphagia causes licking, chewing, swallowing described as 'eating automatisms' which suggests that the hypothalamus is linked to other brain regions such as the posterior brain-stem.

There has been much speculation and a great deal of experimentation directed at the factors which influence the short-term regulation of the hypothalamic feeding mechanisms. At first, various biochemical influences were considered which could trigger one of the two components of the hypothalamic feeding centre. These factors included: the specific dynamic action of food, the availability of glucose in body fluids, the concentration of fat metabolites in body fluids, and the concentration of serum amino acids in body fluids. It was thought that variations of these factors in the *milieu interieur* could affect specific receptor neurones in the hypothalamic satiety centre which, when thus stimulated, inhibited the 'feeding' centre and conversely when the biochemical influence on the 'satiety' centre was removed, the 'feeding' centre was released from inhibition and the animal was motivated to feed again (Brobeck, 1955).

Further positive evidence of hypothalamic feeding centres has come from stimulation studies of unanaesthetized animals. Delgado & Anand (1953) showed that stimulation of the lateral hypothalamic area of cats increased food intake, and Larsson (1954) produced a similar response in goats. Wyrwicka & Dobrzeczka (1960) showed that stimulation of the medial hypothalamus in goats inhibited feeding

whereas stimulation of the lateral hypothalamus evoked feeding. The feeding responses elicited from lateral stimulation could be blocked by concomitant medial stimulation which supported the view of satiety centre dominance.

It has been possible by placing small cannulas into the hypothalamus to inject chemical substances, pharmacological agents or metabolites into specific sites. Andersson (1953) was the first to use this method, using the Hess technique of implantation, to show the effects of saline solutions on food and water intake. Larsson (1954) showed that ATP and creatine phosphate are important in hunger activity, and Grossman (1962) and Wagner & de Groot (1963) showed that nor-adrenaline applied to the lateral hypothalamus produced eating. Pharmacological effects have also been shown to produce feeding responses by differential perfusion of the brain via the ventricles.

The glucostatic theory was favoured because of the known relationship of hunger in man with variation with the level of glucose in the blood. This was correlated with the activity of the dorsal motor nucleus of the vagus and the activity of the gastric musculature. This stand received further support when it was shown that the ventromedial nucleus of rats, but especially mice, was so affected by gold thioglucose that hyperphagia occurred (Liebelt & Perry, 1967). Gold thioglucose does not affect the ventromedial nucleus of goats and this may be due to a lack of glucose receptors in these animals (Baile & Mayer, 1970). During hunger there is an increased utilization of oxygen and glucose by the feeding centre which shows parallel activity in the electrical activity of this centre (Anand, Dua & Singh, 1961). The biochemical activity of the hypothalamus is difficult to study during satiety or feeding but evidence to date does not suggest that any single metabolite controls the activity of the neural regulating process.

It has been suggested that the neurones of the hypothalamic feeding centres, in addition to being affected by circulating metabolites, might be affected by peripherally placed receptors. Apart from gustatory and ocular effects, it has been shown that peripherally placed receptors, for example in the liver, may modulate feeding behaviour. Gastric distension can affect tension receptors and changes in the intestinal contents affect both osmoreceptors and many types of chemoreceptors. For example, Baile & Mayer (1970) produced evidence that acetic acid production may affect food intake in the goat through ruminal chemoreceptors. These signals generated during the intake of food have been shown to affect the activity of hypothalamic neurones and this has been interpreted as a possible feedback system which controls the continuation or cessation of food intake. The rate of firing of hypothalamic neurones can also be affected by activation of many other parts of the brain and it is reasonable to suggest that integration of nervous activity is carried out here.

In addition to the hypothalamus, food intake can be affected by stimulation or inhibition of many other parts of the brain, including the cortex, basal ganglia, and structures in the brain-stem and medulla oblongata. Recently, the limbic system has been closely investigated and because of its influence on the activity of several visceral functions, including the gastro-intestinal tract, it has been called the 'visceral

brain' (MacLean, 1949). It is now known that elements of the limbic system and the forebrain project to the hypothalamus as well as ascending influences from the tegmentum and posterior brain-stem through the reticular activating system. As a result of the extension of investigations to examine feeding behaviour it was soon realized that although there may be regulation of short-term feeding behaviour by the hypothalamus, the control was more widespread. This is manifest by the behaviour of a hungry animal which becomes restless whereas a satiated animal normally is immobile. The cerebral cortex obviously plays a part in feeding behaviour and in the subprimates the effects are restricted to reflexes generated by the special senses. In the goat, the motor cortex controls the lip musculature so that on ablation the animal is unable to prehend food even when hungry, but food placed in the mouth can be chewed and swallowed (Bell & Lawn, 1957).

The investigation of food intake using the techniques of experimental psychology have greatly advanced our understanding of the whole consummatory act of feeding. Olds (1958) showed that hungry rats could be trained to press a bar to obtain food and, if food was not available, would continue to press a bar to activate implanted electrodes which stimulated the ventromedial hypothalamus. In other words, self-stimulation of the hypothalamus substituted for the ingestion of food. Many other physiological patterns can be demonstrated by the self-stimulation technique of implanted hypothalamic electrodes, including thermoregulation and sexual behaviour, so that it is probable that the hypothalamus acts to integrate a variety of 'visceral processes'. Morgane (1969) has combined the self-stimulatory techniques with the placement of hypothalamic lesions and shown close anatomical connection between the brain-stem, hypothalamus and limbic area. Electroencephalographic phenomena dependent upon feeding shown by Serman, Wyrwicka & Roth (1969) can be correlated with the activity of the cortex and reticular activating system and thus showing feeding behaviour to be a whole animal reaction.

It appears that the hypothalamic food centres act as a balancing mechanism set in the depth of the midbrain which acts somewhat like a thermostat, or more fancifully as a 'homeostat', so that the animal responds to the concentration of metabolites in the extracellular fluid affecting specific or non-specific hypothalamic receptors. In addition to being stimulated by blood-borne cues, there is an input of nervous impulses from peripheral receptors as well as from all other parts of the brain. The sum of all these effects on the hypothalamus produces a drive seen as behavioural activity in the animal whereby it moves by a series of reflexes to ingest food. The reflexes associated with the ingestion of food and the consequences of food ingestion producing gastric fill together with the products of digestion, modulate the hypothalamic drive by 'facilitating' neurones in the ventromedial area of the hypothalamus, so that the 'feeding drive' either wanes or disappears. This facilitatory effect on the satiety centre is transmitted to the lateral hypothalamus but causes inhibition of feeding mechanisms. When the stimulus to the satiety centre is removed either by changes in the fluid bathing the cells or by lack of impulses from the alimentary tract, then the inhibitory action of the lateral hypothalamic feeding centre is removed so that once again the feeding mechanisms are facilitated and the

animal shows a pattern of action which culminates in the ingestion of food.

The hypothalamus is not only invested in drives which are associated with the renewal of regulation of food and water intake, but it also controls other vegetative mechanisms such as the production of gonadotrophic hormones from the hypophysis, thermoregulatory activity as well as behavioural changes such as rage, sleep and nursing (Hess, 1932). These other forms of behaviour probably either reinforce or inhibit the feeding consummatory act.

There is an interrelationship between these other vegetative drives and feeding behaviour, especially in the long-term control of food intake as well as short-term control. For example, in the sheep it has been shown by Tarttelin (1968) that with oestrus there is a diminution in food and water intake so that a cycle of food intake is seen with a periodicity of 18 d. In addition Tarttelin (1969) has shown that there is an even longer cycle of food intake in the female sheep whereby demonstrable increases in food intake can be shown in the summer months when compared to the winter months. It is possible that this long-term control of food intake is associated with hormonal control, possibly through the pituitary/thyroid axis, although, considering thermoregulation, it is paradoxical that there is greater food intake in the summer months than in the colder winter months.

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Physiological mechanisms for the regulation of energy balance

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No one will dispute that whether or not an animal or man is eating at a particular moment depends upon many factors. In this sense, control of food intake is highly multifactorial. It is, however, sometimes valuable to isolate a single factor from the multitude which govern real events, even though this seems to lead to a theoretical abstraction. This paper will be concerned only with regulation of food intake in relation to energy balance; that is, with the factors which regulate energy ingested in correspondence with energy expended.

A theoretical need for regulation of energy balance arises from the conservation of energy. It seems inescapable that:

$$\text{energy intake of body} = \text{energy output from body} + \Delta \text{energy in body.}$$

This is so without regard to the important differences in thermodynamic level of the energy, which are – speaking teleologically – the whole point of energy exchange. Since energy stored in the body is, like food, in chemical form, predominantly fat, changes in its amount must be perceptible as changes in body-weight; more accurate measurement is of course possible by carcass analysis. Inasmuch as adult animals do not change greatly in body-weight and composition, it follows that their intake and output of energy must be equal within a calculable degree of precision. Because the energy store in the bodies of larger animals such as man is large compared with the energy turned over in a day – representative figures for a man could be