PROCEEDINGS OF THE NUTRITION SOCIETY

The Four Hundred and Third Scientific Meeting (One Hundred and Fifty-seventh Scottish Meeting) was held in Cowan House, Pollock Halls, Holyrood Park Road, Edinburgh, on 25/26 September 1984

SYMPOSIUM ON
‘FOOD IntAKE, AND ITS CONTROL BY FARM ANIMALS’

Neural and hormonal mechanisms regulating food intake

By B. A. Baldwin, AFRC Institute of Animal Physiology, Babraham, Cambridge CB2 4AT

In this outline of the neural control of food intake, no attempt has been made to provide a comprehensive survey of the literature since there are several symposia and reviews available which summarize the extensive work in this field (Grossman, 1975; Novin et al. 1976; Silverstone, 1976; Morgane & Panksepp, 1980; Hoebel & Novin, 1982). Instead some current concepts of the neural control of food intake are presented. Almost all the work on the neural control of feeding has been carried out on laboratory animals but experiments on farm animals will be emphasized where appropriate.

The brain region most extensively investigated in relation to feeding behaviour is the hypothalamus. Hetherington & Ranson (1942) and Brobeck et al. (1943) demonstrated that bilateral lesions in the ventromedial region of the rat’s hypothalamus (VMH) resulted in hyperphagia and adiposity, and Anand & Brobeck (1951) reported that bilateral lesions in the lateral hypothalamus of rats and cats produced profound adipsia and aphagia. These seminal experiments led to the concepts of excitory and inhibitory centres in the hypothalamus with a ‘satiety centre’ in the ventromedial region and a ‘feeding centre’ in the lateral hypothalamus (Steller, 1954). These early concepts have been modified and replaced by the hypothesis that although the hypothalamus is a major part of the neurological system involved in the regulation of food intake, it is not fruitful to search for precise regions entirely responsible for ‘hunger’ and ‘satiety’.

Lesion studies of the hypothalamus

VMH syndrome. The first effect of bilateral VMH lesions is the ‘acute dynamic phase’ which lasts a few hours and is characterized by frantic ingestive behaviour and, if food is not available, the animals may eat non-nutritive material (Balagura & Devenport, 1970). In relation to the early phase, it is of interest that local
anaesthesia of the VMH in rats (Epstein, 1960) and chickens (Snapir et al. 1973) results in an immediate increase in food intake in both sated and deprived animals. In sheep, Seoane & Baile (1972, 1973) demonstrated that injection of magnesium and calcium ions or barbiturates into the third ventricle resulted in immediate feeding and a similar transient hyperphagia has been produced by injection of these agents into the lateral ventricle of pigs (Baldwin et al. 1975). These effects are probably due to transient depression of the VMH.

Gold (1973) demonstrated that hypothalamic lesions which cause hyperphagia and obesity need not involve the ventromedial nucleus itself and that the most effective lesions are located lateral and somewhat ventral to it. In sheep it has been shown that when only the ventromedial nuclei are destroyed no change in food intake occurs (Tarttelin, 1969; Bell, 1971). Hyperphagia has been produced in goats by lesion of the VMH region (Baile et al. 1969). Following a VMH lesion the animal exhibits a pattern of hyperphagia known as the ‘dynamic phase’ and during this period it becomes fat and gains weight. The animal’s over-consumption eventually diminishes to a maintenance level and the abnormal increase in weight ceases. This period, which can last until senescence, is known as the ‘static phase’. In pigs, the effects of VMH lesions have been studied by Auffray (1969) and Khalaf (1969). Auffray (1969) used pigs weighing 80–96 kg and reported that a bilateral lesion induced a 70% increase in food intake. The hyperphagia reached its maximum 1 week after the lesion. No dynamic phase followed by a static phase was seen, and food intake remained high during the 8-week course of the experiment. The lack of a static phase was probably due to the use of growing immature animals. Khalaf (1969), using 8-week-old pigs, reported that VMH-lesioned animals increased their body-weight only 13% more than controls over a 7-week period. The young pig may be near its ceiling rate of growth and it is known that VMH lesions do not cause weight gain in weanling rats although metabolic changes occur (Han et al. 1965). Auffray & Blum (1970) and Snapir et al. (1976) have induced VMH lesions in geese and observed a dynamic and static phase of hyperphagia. VMH lesions also caused hyperphagia in chickens (Lepkovsky & Yasuda, 1966).

The VMH lesion has profound metabolic effects, and Powley et al. (1980) have stated that ‘hyperinsulinaemia is a central and perhaps defining trait of the VMH syndrome’. For a full discussion of the metabolic effects of VMH lesions, see Powley et al. (1980).

Recently, it has been suggested (Ahlskog & Hoebel, 1973; Marshall, 1976) that part of the VMH syndrome may be due to damage to the ventral ascending noradrenergic bundle described by Ungerstedt (1971a). However, there are some important differences (reviewed by Marshall, 1976) between the results of VMH lesions and depletion of noradrenaline in the hypothalamus.

The lateral hypothalamic (LH) syndrome. Anand & Brobeck (1951) reported that bilateral lesions of the ventrolateral hypothalamic region in rats and cats resulted in complete cessation of eating and death within 10 d: the initial adipsia and aphagia were not permanent and animals could be kept alive by intragastric
administration of liquid nutrients and would eventually eat and drink spontaneously. The process of recovery from LH lesions has been described in detail by Teitelbaum & Epstein (1962). The lesions that were most effective in producing aphagia and adipsia were localized in the far lateral aspect of the hypothalamus, a region consisting largely of ascending and descending fibres of passage rather than cells. In pigs (Khalaf, 1969) and goats (Baile et al. 1968), it has been demonstrated that aphagia and adipsia occur following LH lesions and aphagia also occurs in chickens (Feldman et al. 1957).

Ungerstedt (1971a,b) pointed out that LH lesions would interrupt dopamine-containing neurones of the nigrostriatal bundle as they passed through the ventral diencephalon. He depleted striatal dopamine by injection of 6-hydroxydopamine (6-OHDA) and produced aphagia and adipsia. In lesioned animals, Marshall et al. (1971, 1974) described sensorimotor defects, particularly impaired orientation to stimulation, and injection of 6-OHDA, which depleted dopamine neurones, also produced similar ‘sensory neglect’. However, recent work indicates that there are significant differences between the LH syndrome produced by lesions and that produced by depletion of dopamine (Stricker & Zigmond, 1976). The size and location of the lesions are also critical factors. It is possible that the feeding defects following LH lesions or dopamine depletion are one dramatic facet of a general impairment affecting several behavioural systems.

Lesions of the amygdala

Fonberg (1976) demonstrated in dogs that lesions in the dorsomedial part of the amygdaloid complex produced aphagia and adipsia lasting several days, followed by prolonged hypophagia, finickiness and decreased body-weight. The dogs became depressed, hostile to man and uninterested in their environment. The changes resembled those seen in dogs after lesions of the LH and the ‘sensory neglect’ caused by LH lesions in rats. By contrast, lesions in the lateral amygdala produced hyperphagia, increased body-weight and playful, friendly dogs.

Neurophysiological studies

A significant recent advance in the study of the neural control of feeding has been the development of methods for recording the activity of neurones in conscious animals (Rolls, 1980; Ono et al. 1981). Rolls (1980) has shown that a small proportion of the neurones in the LH and substantia innominata of the conscious monkey respond specifically to the sight and taste of food. Similar cells have been found in the LH of conscious sheep by Maddison & Baldwin (1983). The cells in the sheep responded to the sight of sheep nuts and hay and a few neurones were found which only responded to the approach of food to the sheep’s mouth. In monkeys, using a visual discrimination task, it has been demonstrated that the neuronal responses can become associated with the sight of food by learning (Mora et al. 1976) and the cells only responded to the sight of food when the animal was hungry (Burton et al. 1975).
Rolls (1975) postulated that the food-responsive neurones in the LH or substantia innominata are involved in the control of feeding in the following manner. Sensory inputs from the sight or taste of food reach the hypothalamus but only influence LH food-reward neurones if the animal is hungry. This modulation of the effects of sensory input on hypothalamic reward neurones is performed by neurones which indicate hunger and are influenced by stimuli such as stomach distension, glucose utilization, etc. which indicate the internal state of the animal. These hunger neurones could be in the LH as neurones responsive to glucose levels have been found there (Anand et al. 1964). The study of neuronal responses in conscious-behaving animals provides a powerful method for the investigation of the neural control of food intake.

**Thermal stimulation of the hypothalamus**

Many mammalian species increase their food intake in cold environments and decrease it in hot conditions. Brobeck (1960) has suggested that changes in body temperature may be important in the regulation of food intake and speculated that animals may eat to keep warm and stop eating to avoid hyperthermia. This hypothesis has been tested by examining the effect of localized thermal stimulation of the hypothalamus on food intake. In farm animals, experiments have been carried out on goats (Andersson & Larsson, 1961; Andersson et al. 1962), pigs (Ingram, 1968) and sheep (Baldwin & Cooper, 1982).

The previously-mentioned experiments did not provide uniform results and do not strongly support Brobeck’s (1960) hypothesis. Abrams & Hammel (1964) have questioned the contribution of brain temperature to the initiation and termination of meals as they found no correlation between changes in hypothalamic temperature and feeding in rats.

**Chemical stimulation by catecholamines**

The role of neurotransmitters in the control of food intake is an active area of current research (see Leibowitz, 1980). Only work on noradrenaline will be mentioned here as this substance has been studied in ruminants and the evidence that it can increase food intake in laboratory animals is well established. The effect of noradrenaline in rats has been studied by direct microinjection into hypothalamic nuclei and the most effective sites are in the anterior hypothalamus (Booth, 1976). In sheep, Baile et al. (1972) and Simpson et al. (1975) demonstrated that injection of noradrenaline into the hypothalamus resulted in increased food intake but, by contrast, in cattle, noradrenaline appeared to cause satiety and suppressed feeding. Driver et al. (1979) have shown that small doses of noradrenaline injected into the lateral ventricles of sheep stimulated food intake.

**Electrical stimulation**

In many species, electrical stimulation of the lateral hypothalamus elicits feeding (Hoebel, 1976). It was initially considered that the stimulation made the animals hungry but this view has been challenged by Valenstein (1976) who demonstrated,
in rats, that feeding induced by stimulation of the lateral hypothalamus, with food and water available, could be converted into drinking if the food was removed. Valenstein (1976) considers that ingestive behaviour induced by electrical stimulation is due more to the reward derived from the execution of built-in, or well rehearsed, response patterns than ingestion to satisfy a biological need. The question of whether animals can be made hungry by electrical stimulation of the hypothalamus remains controversial. In pigs (Baldwin & Parrott, 1979), sheep (Larsson, 1954; Baldwin & Parrott, 1983) and goats (Wyrwicka et al. 1960), feeding has been elicited by stimulation of the hypothalamus.

**Sensory factors—taste and olfaction**

Palatability can be important in determining food intake and some work has been done on taste and olfaction in farm animals. Taste preferences have been examined in goats (Bell, 1959; Goatcher & Church, 1970a,b), sheep (Goatcher & Church, 1970a,b,c,d) and pigs (Kare et al. 1965; Kennedy & Baldwin, 1972; Houpt & Houpt, 1976).

In man, Cabanac (1971) has shown that internal states can influence the hedonic rating of foods and has termed this effect ‘alliesthesia’. These experiments may indicate that we stop eating because the food is no longer attractive. Similar effects may occur in farm animals.

The role of olfaction in food intake has been investigated in sheep and pigs by examining the effects of removal of the olfactory bulbs on feeding behaviour. Sheep were studied by Tribe (1949), who concluded that olfaction was only of supplementary importance in influencing food selection during grazing. The effect of olfactory bulbectomy on the diet of sheep grazing on different swards was examined by Milne et al. (1982). The bulbectomized sheep ate a higher proportion of weed species than control animals but it was concluded that olfaction played a minor part in influencing the diet selected. Kreuger et al. (1974) also considered that olfaction did not significantly influence the diet of grazing sheep. Arnold (1968, 1970) has studied the role of the chemical senses in relation to grazing behaviour in sheep and suggested that the selection of particular plants for food depended on a combination of all the orosensory factors. Olfactory bulbectomy in sheep housed indoors and fed on a pelleted diet did not alter total daily intake or meal size (Baldwin et al. 1977). In pigs, olfactory bulbectomy did not significantly alter total daily intake or the pattern of feeding (Baldwin & Cooper, 1979). In rats, bulbectomy induced a marked and persistent pattern of nibbling at their food and this result emphasizes the importance of species differences (Larue & Le Magnon, 1972).

**Hormonal and neuropeptide influences on the neural regulation of food intake**

Only a selective outline is presented of endogenous agents which may act directly on the brain to influence feeding.

**Gonadal hormones.** These hormones can influence body-weight, body composition and food intake (Wade, 1972; Baile & Forbes, 1974; Fishman, 1976).
Diencephalic oestrogen implants decrease food intake in rats (Wade & Zucker, 1970), and in sheep (wethers) Forbes (1974) demonstrated that intraventricular injection of oestradiol increased food intake at low doses but decreased it at higher doses. Kay (1979) has described the marked seasonal changes of appetite seen in deer and sheep and the neural basis of this behaviour requires further investigation.

**Insulin.** Plasma insulin levels are related to the amount of body fat and Woods & Porte (1976) proposed that, although plasma insulin levels are labile, if basal levels rise, as in adiposity, insulin levels in the cerebrospinal fluid (CSF) slowly increase and could indicate the level of the body fat stores. It has been shown that injection of insulin into the CSF of baboons suppressed their food intake (Woods et al. 1979). The brain contains insulin receptors: plasma insulin can reach some brain sites and locally applied insulin can alter hypothalamic electrical activity and change noradrenaline turnover (Schneider et al. 1983). Thus, insulin may be involved in both short-term regulation of feeding and the long-term regulation of body fat.

**Cholecystokinin (CCK).** The peptide hormone that has received most attention as a putative satiety agent is CCK (for review, see Smith et al. 1981). CCK is released from the duodenum during feeding and could act as a satiety signal. It has been shown by Gibbs et al. (1973) that peripherally-administered CCK produced satiety in rats and as CCK does not pass the blood–brain barrier it must have acted at some peripheral site (Oldendorf, 1981). In pigs, intraventricular injection of CCK suppressed food intake but did not influence drinking (Parrott & Baldwin, 1981). Anika et al. (1981) demonstrated that intravenous injection of CCK reduced meal size in pigs and Houpt (1983) has shown that the peripheral sites of action of CCK in inducing satiety in pigs are in the duodenum and ileum. However, the specificity of CCK as a satiety agent in pigs is doubtful as intravenous CCK not only reduced operant feeding but also water, sucrose solution or radiant heat demand (Baldwin et al. 1983).

In sheep, CCK administered intracerebroventricularly suppressed feeding (Della-Fera & Baile, 1979) and similar injections of antibodies against CCK can inhibit satiety (Della-Fera et al. 1981). These workers have proposed that, during feeding, CCK is released into the CSF and then reaches brain sites concerned with satiety (Della-Fera & Baile, 1980). The peripheral sites of action of CCK in sheep have been studied by Grovum (1982) and Cottrell & Iggo (1984).

**Bombesin.** This peptide has been implicated in the control of feeding (Schneider et al. 1983) and intraventricular injection of bombesin reduces food intake in sheep (Baile & Della-Fera, 1981) and pigs (Parrott & Baldwin, 1982). However, in pigs, intraventricular bombesin had averse properties which suggested that it was not acting as a satiety agent.

**Endogenous opiates and other peptides**

In several species, it has been shown that endogenous opiates act on the brain and influence feeding behaviour (for review, see Morley et al. 1983). Schneider
et al. (1983) briefly mentioned some of the effects of thyrotropin-releasing hormone and related peptides. The release of growth hormone in relation to feeding has been investigated in sheep by Driver & Forbes (1981), and Lotter et al. (1981) have shown that somatostatin may play some part in the regulation of food intake in rats and baboons. Other peptides which have been shown to reduce food intake in rats by direct action on the brain, include neurotensin (Stanley et al. 1983), neuropeptide Y (Clark et al. 1984) and calcitonin (Levine & Morley, 1981). Glucagon reduces food intake in rats when injected into the hepatic portal vein (Martin & Novin, 1977) but had no effect in pigs when given intraventricularly (R. F. Parrott and B. A. Baldwin, unpublished results). It is obvious that a major field of research during the next decade will be the evaluation of the role of numerous neuropeptides in the regulation of feeding behaviour.

REFERENCES

Physiology 207, 1146–1154.
177–188.
R310–R318.
Sciences 270, 2362–2365.
357–364.
and Behaviour 3, 915–918.
831–853.


Vol. 44 Food intake, and its control by farm animals 311


Printed in Great Britain