Endocrine factors in the modulation of food intake

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Food intake is controlled by multiple factors. Such a state of affairs has obvious advantages in assuring back-up control mechanisms should one or another of the systems become damaged or non-functional. This redundancy in control mechanisms is manifested by the fact that both humoral and metabolic messages are integrated with neural systems modulating the cyclic events of initiation, ingestion and termination of eating. For the present discussion, however, I shall focus on the putative hormonal factors which might be involved in regulation of food intake as though they were operating independently of messages derived from food nutrients or from the neural substrate and internal homeostatic mechanisms which are obviously also playing a role. Four groups of endocrine factors will be considered: peptide hormones arising from the gastrointestinal tract; pancreatic hormones; steroid hormones arising from the gonads and/or adrenal; and thyroid hormones.

Intestinal hormones and the regulation of food intake

Since foods which enter the body are absorbed across the intestine, it is reasonable to suppose that gastrointestinal hormones, might play a major role in regulation of food intake, especially in the termination of a meal. This is not a new idea since an important role for the gastrointestinal tract was postulated more than 50 years ago by Carlson (1912) and by Cannon & Washburn (1912). Several gastrointestinal hormones have been identified and isolated. More recently, the chemical structure for many of them has been determined, and chemical synthesis achieved (Pearse *et al.* 1977). Among this group are gastrin, cholecystokinin, secretin, vasoactive intestinal polypeptide (VIP), enteroglucagon (gut glucagon or glicentin), motilin, and gastrointestinal inhibitory polypeptide (GIP). In addition, two of these hormones (cholecystokinin and VIP) have been identified in neuronal tissue (Straus & Yalow, 1978; Hughes & Iverson, 1978). Moreover, three peptides, somatostatin (Arimura *et al.* 1975), neurotensin (Carraway & Leeman, 1976), and thyrotropin-releasing hormone (TRH) (Morley *et al.* 1977), originally isolated from hypothalamic tissue are now known to occur in other tissues including intestine and pancreas. Although several of these hormones have been proposed as factors in regulation of food intake, data are at best suggestive for only three of them.

Cholecystokinin. Gibbs *et al.* (1973) provided the first evidence suggesting that

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the gastrointestinal hormone, cholecystokinin, might participate in terminating a meal. In rats prepared with a gastric fistula, the quantity of liquid diet ingested remains at high levels of between 8 and 12 ml/min for up to 60 min. If the gastric cannula is closed, however, intake of liquid diet occurs in regular meals lasting from 15 to 30 min followed by an intermeal interval with no food intake. Even when the gastric fistula is open, intake of food can be terminated by infusing liquid diet into the intestine or when cholecystokinin (or its octapeptide) are injected. Pentagastrin and gastrin have only weak effects, whereas secretin and pancreatic glucagon have no effect at all in this system. Two features of the response to cholecystokinin are particularly noteworthy. First, it is dose-related. Second, to inhibit eating, the hormone has to be injected just before or up to 12 min after the onset of eating (Antin *et al.* 1977). If the cholecystokinin is injected too early, or too late, it has much less effect on food intake. Injections of cholecystokinin into monkeys also produces a dose-related suppression of feeding, but the effect appears to require pharmacological levels (Gibbs & Smith, 1977). Results in humans are less clear. In one study, impure preparations of cholecystokinin were found to produce either an increase or decrease in feeding depending on dose (Sturdevant & Goetz, 1976). Using the pure octopeptide of cholecystokinin, Greenway & Bray (1977) could find no effect in food intake in normal subjects at doses that produced abdominal cramps in some.

Enteroglucagon and neurotensin. Enteroglucagon (gut glucagon-like radioimmunoactivity) as a satiety factor was suggested by the clinical observations of an increase in enteroglucagon following intestinal bypass surgery (Barry *et al.* 1977). This increased secretion of enteroglucagon could be a consequence of the weight loss or it could be related in some way to the bypass surgery and altered intestinal function. To separate these possibilities, patients scheduled for bypass surgery entered a study in which a period of dieting preceded the surgery. The secretion of enteroglucagon after eating a standardized meal was significantly greater following surgery than during the tests conducted before or after dieting. Indeed, dietary weight loss alone had no significant effect on enteroglucagon release. This evidence, although only tentative, would be consistent with an effect of gut-glucagon on food intake to be described later (Figure 1). Neurotensin, a peptide which like enteroglucagon is located mainly in the ileum, also shows an exaggerated increase in obese patients who have had a jejunoileal by-pass.

The data on cholecystokinin, enteroglucagon and neurotensin open up the possibility that these two or other gastrointestinal hormones might play a role in the regulation of food intake.

Pancreatic hormones

At least five hormones can now be identified in the pancreas. The most prominent is insulin whose isolation in 1921 led to the successful treatment of diabetes mellitus. The second most common is glucagon, a hyperglycemic peptide synthesized and released from the alpha cells in contrast to the location of insulin in the beta cells. The third most common peptide is a recently isolated polypeptide

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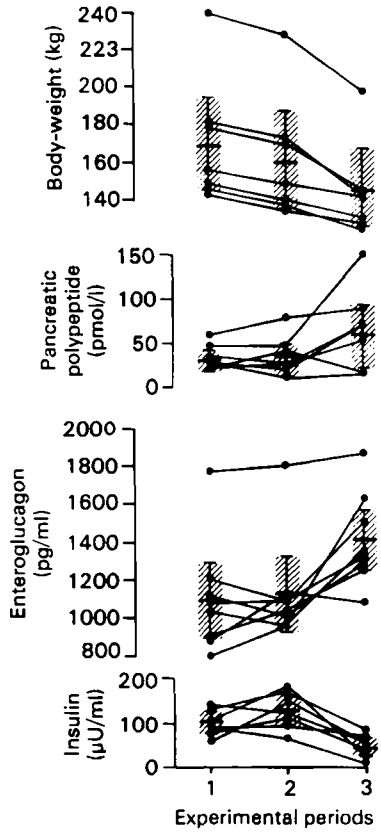

Fig. 1. Endocrine response to intestinal bypass for three experimental periods (1, 2, 3). The effect of a standard 1·47 kJ (350 cal) breakfast on insulin, pancreatic polypeptide and enteroglucagon (gut GLI) are shown in individuals who have lost weight by dieting and by bypass surgery. The points are mean values with standard deviations represented by vertical bars. It is clear that after bypass surgery, but not after a comparable dietary weight loss, the rise in enteroglucagon and pancreatic polypeptide was increased. In contrast, the rise in insulin and glucose was reduced.

called pancreatic polypeptide. In addition, gastrin and somatostatin have also been identified in pancreatic tissue.

Insulin. It has been known for many years that injections of long-acting protamine zinc insulin are followed by increased food intake and if the injections are continued by the development of obesity (MacKay *et al.* 1940). This mechanism for induction of obesity has been used to study the problem of corpulence. Of more relevance is the possibility that insulin may be a pathogenetic factor for the development of hyperphagia and obesity following bilateral ventromedial hypothalamic injury (Inoue, Bray *et al.* 1977). This syndrome of hypothalamic obesity results from destruction of regions in the hypothalamus which carry fibre tracts which appear to originate in the paraventricular nucleus of the anterior hypothalamus. The ventromedial nucleus originally was thought to be the focal point in this syndrome but it is now clear that the major essential site for

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injury is outside the ventromedial nucleus (Gold *et al.* 1977; Sclafani & Berner, 1976). If secretion of insulin is diminished, reduced or prevented after hypothalamic injury, and a high carbohydrate diet is provided, the development of obesity is markedly impaired (York & Bray, 1972). Moreover, the development of hyperinsulinemia and obesity after hypothalamic lesions do not require hyperphagia and can be produced in animals which are tube-fed or whose dietary intake is restricted (Han & Frohman, 1970; Hustvedt & Løvø, 1976; Bernardis & Goldman, 1976). Finally, when islets are removed from their neural innervation in the pancreas and transplanted to diabetic rats under the renal capsule, hypothalamic lesions no longer produce obesity (Inoue, Bray *et al.* 1977, 1978). This series of findings suggests a neurally mediated role for insulin secretion in the development of obesity following bilateral ventromedial hypothalamic injury. This concept is schematized in Figure 2. The hypergastric acidity (Ridley & Brooks, 1965; Powley & Opsahl, 1974; Inoue & Bray, 1977) and reversal of the syndrome

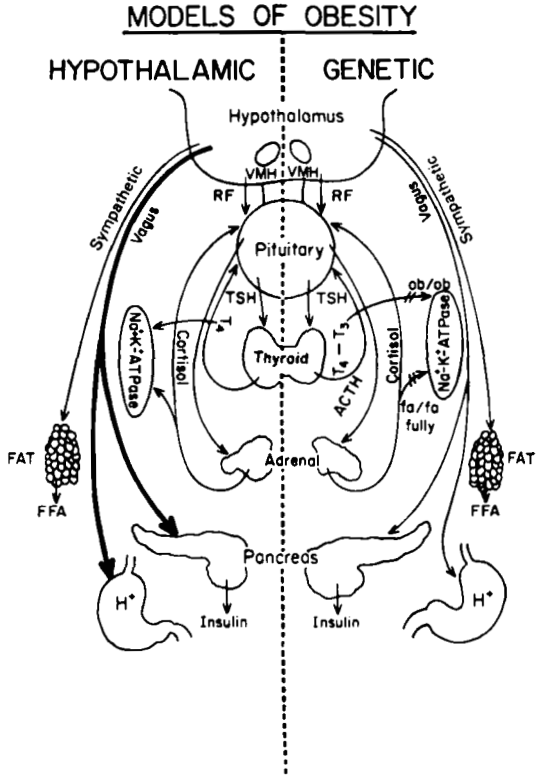

Fig. 2. A schematic model comparing genetic and hypothalamic obesity. The pituitary adrenal axis appears to play a key role in the development of genetic obesity but is relatively unimportant in hypothalamic obesity. This pituitary-adrenal axis may well be involved along with resistance to thyroid hormones in the modulation of systems involved in sodium and potassium transport ($Na^+ + K^+$)-ATPase. In contrast for the hypothalamic obese model, the vagus and sympathetic nervous system seem to be of major importance. There appears to be vagal hyperactivity and a reduction in the activity of the sympathetic component of this system.

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of hypothalamic obesity after subdiaphragmatic vagotomy (Powley & Opsahl, 1974; Inoue & Bray, 1977) suggests that vagal overactivity may be involved in mediating the hyperinsulinemia. Recent evidence has suggested impairment of the sympathetic nervous system after hypothalamic injury (Inoue, Campfield *et al.* 1977; Nishizawa & Bray, 1978*a*,*b*). The syndrome of hypothalamic obesity may thus be largely the result of an imbalance in the control of the autonomic nervous system.

Glucagon. Glucagon may also play a role in the development of obesity. When this hormone is injected into humans, it leads to decreased food intake (Schulman *et al.* 1957). Intraportal infusion of glucagon into experimental animals can also modulate food intake (Martin & Novin, 1977). This biological effect of glucagon suggests that enteroglucagon, the intestinal hormone with glucagon-like activity, which was discussed above may produce its effects through changing concentrations in the portal vein which in turn modulates hepatic neural outputs to the brain.

Pancreatic polypeptide. Pancreatic polypeptide contains thirty-six amino acids in a single chain with amide linkage at the carboxyl terminal end. That it may play a role in the regulation of food intake and the development of obesity has been suggested by four different studies. First, decreased concentrations of immunofluorescent pancreatic polypeptide are found in the pancreatic cells from obese animals compared to lean animals (Larsson *et al.* 1977). Restriction of food intake to produce weight loss leads to appearance of the immunofluorescent granules containing pancreatic polypeptide. The second line of evidence is the observation that injections of pancreatic polypeptide into the genetically obese (*ob*/*ob*) mouse will lead to a decrease in food intake and a loss of weight (Malaisse-Lagae *et al.* 1977). Of more physiological interest are the findings of nearly complete reversal of the syndrome of obesity in the New Zealand Obese (NZO) mouse (Gates & Lazarus, 1977). In this animal, the circulating concentrations of pancreatic polypeptide are low and injection of this hormone normalizes blood glucose and reduces the food intake and weight gain. The fourth observation is summarized in Figure 1. In this study, pancreatic polypeptide concentrations were measured before and after dieting and again after intestinal bypass when food intake is reduced. The changes in pancreatic polypeptide following dieting were not significantly different than from the untreated state. However, after intestinal bypass, there was a significantly greater rise in pancreatic polypeptide than after dieting. Thus, both pancreatic polypeptide and enteroglucagon need to be considered as candidates for hormonal factors in satiety.

Steroids

The third group of compounds for discussion are the steroidal hormones. These include oestrogen and progesterone from the gonads and corticosterone from the adrenal gland.

Progesterone. The injection of progesterone into rodents produces a dose-related increase in food intake (Hervey & Hervey, 1967). This increased food intake is

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deposited both as increased lean tissue and as fat. As indicated below, it may also have an important interaction with oestrogen.

Oestrogen. Oestrogen secretion from the ovaries has the opposite effects of progesterone. During the oestrus cycle in the rodent, diestrus is associated with low levels of oestrogen and with reduced running and increased food intake. At the time of oestrus, there is a rise in oestrogen, an increase in running activity and a decrease in food intake (Tarttelin & Gorski, 1971; Wade, 1972). This cyclic oscillation in weight gain and loss, which parallels the changes in oestrogen concentration, can be obliterated by castration. In the lean animals, castration is followed by significant increase in weight gain which can be reversed by the injection of small doses of oestrogen. The weight gain after castration can be prevented by adrenalectomy (Figure 3) (Mook & Blass, 1968). This has been

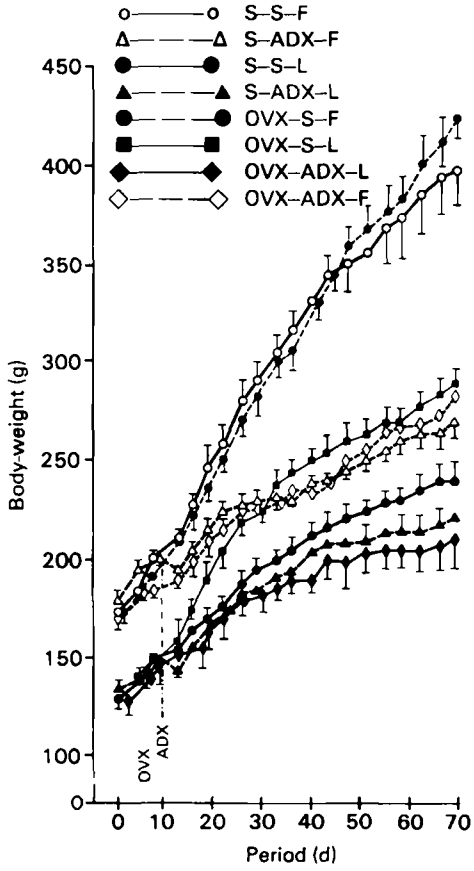

Fig. 3. Effects of adrenalectomy and castration in the fatty rat.

The points are mean values with standard deviations represented by vertical bars. Fatty rats, F; lean rats, L; sham operation, S; adrenalectomy, ADX; ovariectomy, OVX.

Castration in the fatty rat is without effect but in the lean animals was followed by an increase in body-weight. In contrast, adrenalectomy completely restored food intake and rate of weight gain in fatty rats to levels seen in normal animals, but this operation had almost no effect on the weight gain in lean animals.

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explained by the removal of progesterone which in the rat is secreted largely by the adrenals. Finally, injections of oestrogen themselves to lean animals can significantly reduce food intake and produce weight loss (Wade, 1972).

Adrenal Corticosteroids. Adrenalectomy in the normal animal fed supplements of salt has only a modest effect on food intake under appropriately controlled circumstances (Figure 3). Moreover, injections of corticosteroids have only small effects on body weight unless large doses are used. In the animal with a ventromedial hypothalamic obesity (Figure 2) neither adrenalectomy nor hypophysectomy (Bray, 1974) prevented the development of this syndrome. However, in the genetically obese animals, adrenalectomy has a profound effect on the phenotypic expression of this syndrome (Figure 3) (Solomon & Mayer, 1973; Naeser, 1973; Yukimura & Bray, 1978*b*). This figure compares the effects of castration and adrenalectomy in lean and genetically obese fatty rats (Yukimura & Bray, 1978*a*). The results on lean animals show that adrenalectomy had little effect on the rate of weight gain although the animals tended to gain weight at a slightly slower rate than the intact animals. Castration of lean animals was followed by an increase in body-weight gain and food intake. Adrenalectomy in the castrated animal, however, prevented the weight gain after castration so that animals with the combined operation showed almost the same weight gain as those which were only adrenalectomized (Mook & Blass, 1968). In the genetically obese (Zucker) rat, however, weight gain after adrenalectomy was restored to normal and food intake declined (Yukimura, Bray *et al.* 1978). In contrast to normal animals, castration in the Zucker rats did not augment the already high level of food intake, or body-weight. Thus, the effects of adrenalectomy and castration are very different in lean and genetically obese animals. A model comparing the genetically obese (Zucker) fatty rats with the rat with ventromedial hypothalamic injury is depicted in Figure 2. In the fatty rat, adrenal secretory function appears to be entirely normal but peripheral responsiveness to corticosterone is distinctly altered (Yokimura, Bray *et al.* 1978), with an increase in food intake and increased weight gain. In contrast, in the animals with ventromedial hypothalamic injury, neither the adrenal nor pituitary are essential for the development of this syndrome. Increased activity of the vagus nerve (Inoue, Bray *et al.* 1977, 1978) and decreased activity of the sympathetic nerves (Nishizawa & Bray, 1978*a*,*b*) are followed by hyperinsulinemia and the manifestation of many of the metabolic and hyperphagic features of this syndrome.

Thyroid Hormones

Thyroxine and triiodothyronine are the principal active thyroid hormones. After thyroidectomy, food intake declines and weight gain is slower (Bray, 1964). Excessive quantities of thyroid hormone, on the other hand, increase food intake and metabolic rate but may lead to weight loss due to inadequate caloric compensation for the higher metabolic rate (Bray, 1964). The hypothermia and cold-sensitivity of the obese (*ob/ob*) mouse (Kaplan & Leveille, 1973; Ohtake *et al.* 1977; Trayhurn *et al.* 1977) have suggested the possibility that these animals may

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be hypothyroid (Joosten & Van der Kroon, 1974). However, circulating levels of thyroid hormone are normal (Ohtake *et al.* 1977; York, Otto *et al.* 1978). The finding of an impaired response to thyroid hormones in these animals (Ohtake *et al.* 1977) suggested that the thyroid-induced system for sodium transport in the membrane might be defective (Edelman & Ismail-Beigi, 1974). The thyroid induced ($Na^+ + K^+$)-ATPase in *ob/ob* mice was absent, but α-glycerolphosphate dehydrogenase, another thyroid induced enzyme, was normal (York, Bray *et al.* 1978). Moreover, other nongenetic types of obesity had no impairment of response, whereas one other genetic type of obesity showed (Bray *et al.* 1978) a similar change. The number of ouabain-binding sites in muscle of *ob/ob* mice is also reduced (Lin *et al.* 1978). These observations are schematized in Figure 2 as a block in response to thyroid hormones at the site of ATPase activity.

In this review, I have examined the role of some hormones in the regulation of food intake. Since food is absorbed across the intestine, they are likely candidates for 'terminating' of meals. Pancreatic hormones are highly influenced by food ingestion and absorption. In addition, they reach peripheral tissues only after passing through the liver. Thus, insulin, glucagon, and possibly pancreatic polypeptide are in an ideal situation to respond to and modulate eating patterns. Steroids and thyroid hormones also modulate energy storage. Castration, hypophysectomy, adrenalectomy and resistance to thyroid hormones all produce changes in food intake and energy storage under different circumstances. If there is a message from this review of hormonal factors and food intake, it might be summarized as follows. There are many ways to skin a cat. That is, there are a variety of control systems that operate normally. Disturbances in any of these control systems can result in obesity, but its consequence differs from one condition to another.

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