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SYMPOSIUM ON 'REGULATION OF ENERGY BALANCE'

Regulation of energy balance: studies on genetic, hypothalamic and dietary obesity

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Energy balance deals with the relationships between energy intake and energy expenditure, and includes the processes for storage and utilization of energy containing compounds (Garrow, 1978). Clinical interest in this problem results from the disturbances which manifest themselves as corpulence, anorexia and malnutrition (Bray, 1976). The psychologist is interested in energy balance as a problem in the behavioural control of events leading to or stopping eating; the physiologist is interested in the cellular and chemical mechanisms involved in regulation of eating.

A simple scheme of energy intake, energy storage and energy utilization is shown in Fig. 1. All energy intake occurs as food or infused nutrients. Energy expenditure, on the other hand, can be divided into the energy used for resting metabolic functions, the energy required for physical work and the heat losses due to the thermic effects of food and maintenance of body temperature. Fat is the principal storage form of energy.

The over-all control of energy intake is integrated in the central nervous system (Fig. 2). External information provided by the sense of smell and sight plays an important role in identifying the presence and quality of food during food seeking activities. When the hungry animal searches for food it uses information provided by these senses as well as the sense of taste in choosing its food. The hypothalamus provides an important integrating and relay station in this process. Destruction of the ventromedial hypothalamus is followed by hyperphagia and obesity. On the other hand, damage to the lateral hypothalamus reduces or abolishes food intake and destroys food seeking behaviour in animals made hypoglycemic by the injection of insulin (Bray, 1980).

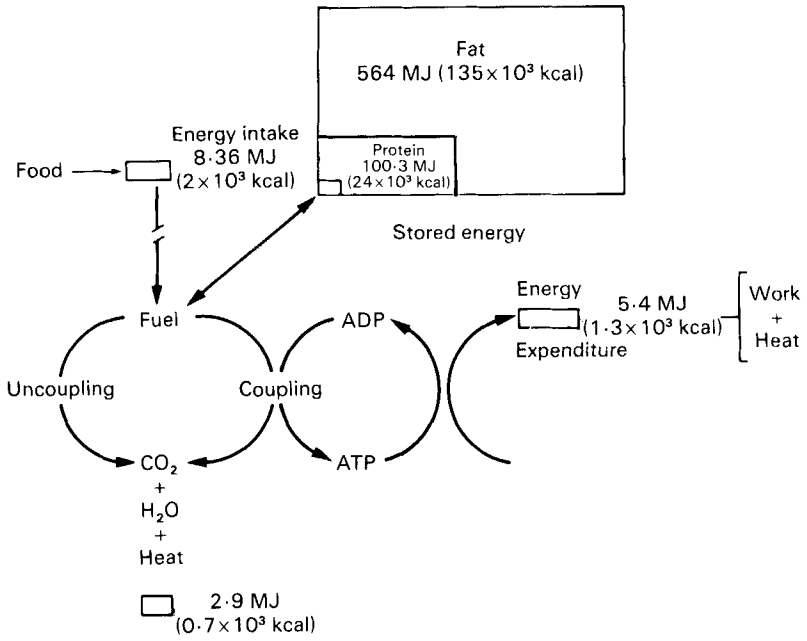

Fig. 1. A schematic representation of energy intake and expenditure. Food intake is shown at 8·36 MJ (2000 kcal)/d, and the relative dissipation through coupled and uncoupled sources is shown. The energy stores in this individual of normal weight are sixty-five times the level of daily energy intake.

Control of energy intake

The anatomic substrate for control of food intake is similar in all homeothermic species. Destruction of the ventromedial hypothalamus produces hyperphagia in mice, rats, dogs, cats, monkeys, chickens and human beings (Bray & Gallagher, 1975; Bray, 1976). The hyperphagic part of the syndrome of hypothalamic obesity involves destruction of fibre tracts which run lateral to the ventromedial nucleus of the hypothalamus (Sclafani & Berner, 1977). Destruction of the ventromedial nucleus itself is associated with hyperinsulinaemia, which is also associated with this syndrome (Bray & York, 1979).

Destruction of either the ventromedial nucleus or the adjacent fibre tracts is also associated with changes in the autonomic nervous system. The vagus nerve appears to become hyperactive after damage to the ventromedial nucleus (Bray & York, 1979). Vagotomy will reverse the obesity of animals with ventromedial hypothalamic lesions (Powley & Opsahl, 1974; Inoue & Bray, 1977) and will prevent the development of obesity during controlled experiments with constant intragastric feeding in animals with hypothalamic injury (Cox & Powley, 1981).

The sympathetic nervous system is also affected by ventromedial hypothalamic lesions (Nishizawa & Bray, 1978). The mobilization of free fatty acids and depletion of fat stores during starvation or during other 'stressful' situations is reduced after damage to the ventromedial hypothalamus (Bray & Nishizawa,

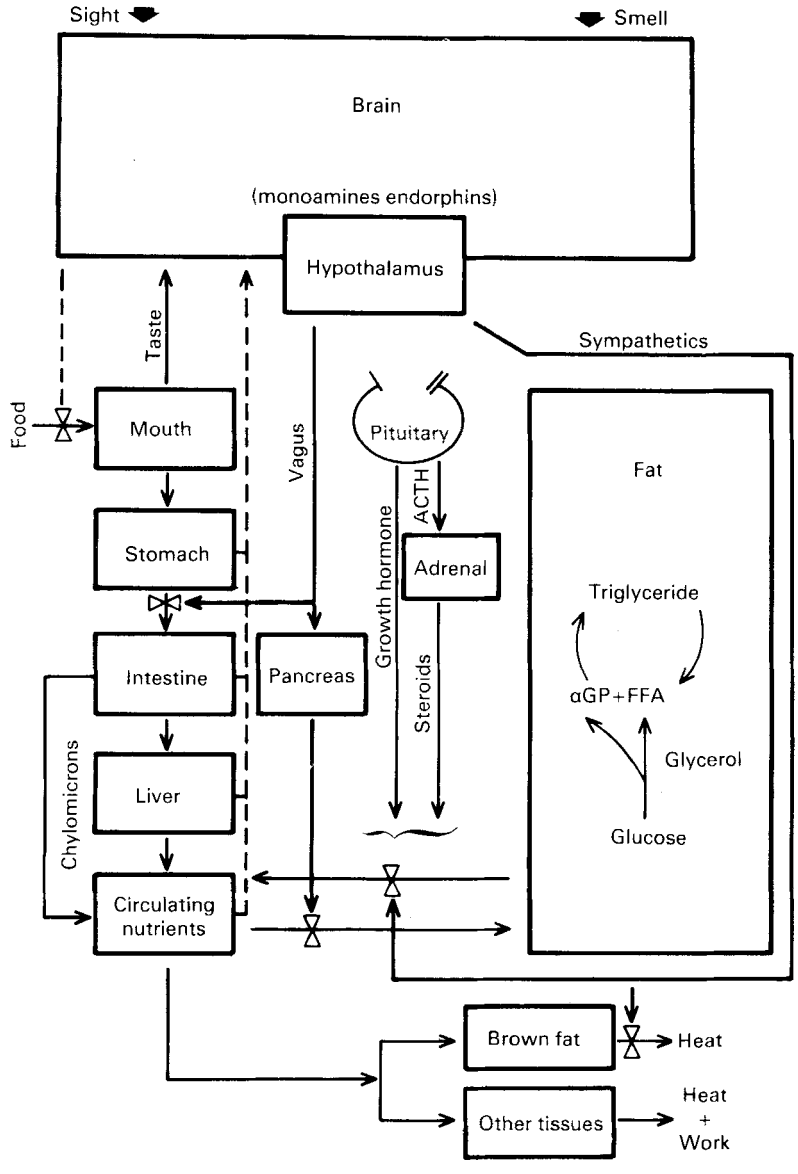

Fig. 2. A schematic representation of the components involved in the control of energy intake. The principal components of this system are the brain and hypothalamus, the gastrointestinal tract, the fat stores, the endocrine and autonomic nervous system and the systems which control energy dissipation.

1978). These alterations in the autonomic nervous system provide the basis for the Autonomic Hypothesis for the development of hypothalamic obesity (Bray & York, 1979; Bray, Inoue *et al.* 1981). Damage to the ventromedial hypothalamus also slows the turnover of peripheral catecholamines (Landsberg *et al.* 1980).

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Destruction of the lateral hypothalamus produces graded hypophagia, which is related to the size of the lesion (Keesey & Powley, 1975). A small lesion will reduce food intake and body-weight will decline and then recover, but not to the normal level (Bray, Inoue *et al.* 1981). Large lesions can even produce complete aphagia (Teitelbaum *et al.* 1969). Recovery, albeit with a number of residual neurological deficits, will occur in animals that are tube-fed during the early period after large lateral hypothalamic lesions. Electrical stimulation of the lateral hypothalamus has the opposite effect. During stimulation in this region of the brain food intake increases and, if the stimulation is continued, body-weight and body fat increase (Steffens, 1975). When the electrical stimulation is stopped, however, food intake and body-weight decline.

The biochemical messages involved in neural transmission within the feeding system include both monoamines and peptides. Serotonin, dopamine, norepinephrine and acetylcholine may all be involved in this control process. Destructive lesions in the lateral hypothalamus which impair feeding also destroy significant components of the dopaminergic fibre tracts which pass through this region of the brain (Ungerstedt, 1971). Injections of norepinephrine into the periventricular region of the brain can initiate feeding in the satiated animal, and similar injections can inhibit feeding if administered into the lateral hypothalamus (Leibowitz & Brown, 1980).

In addition to these clear-cut effects involving the monoamine containing neurons, there is evidence for involvement of several peptides in the feeding system. Interest in this area was stimulated by the observation that cholecystokinin (CCK) injected peripherally could reduce food intake (Smith & Gibbs, 1979), and the subsequent controversial finding that the concentration of the peptide might be reduced in the brains of animals with genetic obesity (*ob/ob*) (Schneider *et al.* 1979; Straus & Yalow, 1979; Oku *et al.* 1980). Injection of CCK into the cerebral ventricle reduces food intake in sheep (Della-Fera & Baile, 1979) and in rats (Maddison, 1977). Bombesin, a peptide originally isolated from frog skin, but also found in brain and gut, will lower food intake when injected into cerebral ventricles (Gibbs *et al.* 1979). In contrast with CCK, however, the effect of bombesin is not reduced by adrenalectomy or vagotomy. Other peptides including thyrotropin releasing hormone (TRH) (Vijayan & McCann, 1977), calcitonin substance P, pancreatic polypeptide and somatostatin (Lotter *et al.* 1981) have also been implicated in the control of food intake (Smith & Gibbs, 1979).

In most cases these peptides inhibit feeding. Beta-endorphin, on the other hand, has been shown to stimulate feeding (Olson *et al.* 1980; Morley, 1981). Experiments with injections of endorphin into the cerebral ventricles suggest that its acute effects may be mediated through intermediary neurons since the rise in feeding can be inhibited with bicuccline, a drug which blocks the action of gamma-aminobutyric acid (Grandison & Guidotti, 1977).

Injections of naloxone, a drug which blocks opioid receptors, have been used to study the role of endorphins in control of feeding. Acute injections of naloxone

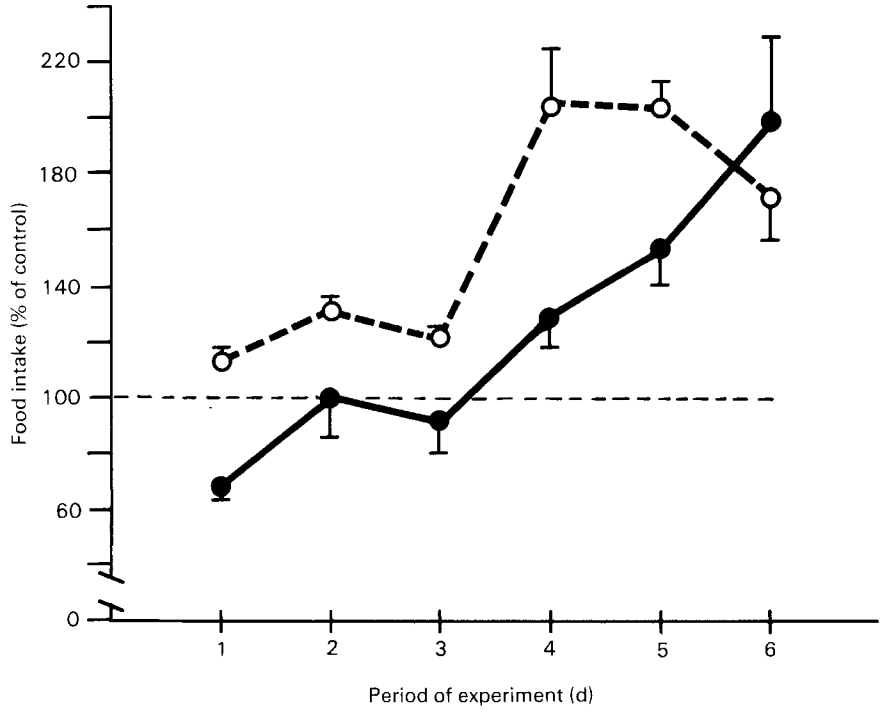

Fig. 3. Effect of naloxone in food intake of *ob/ob* (●——●) and lean (○– – –○) mice. Animals trained to eat their daily food ration in 8 h were injected at 09.00 and 13.00 hours with naloxone (10 mg/kg body-weight). Food intake of control animals was set at 100% and the changes in the treated groups were shown to rise to values nearly twice as high.

reduced food intake of both the obese (*ob/ob*) and lean mouse and in rats (Margules *et al.* 1978). This effect is dose dependent, competitively modified by morphine, and does not interact with the suppression of food intake seen with d-amphetamine.

Because naloxone has a short biological half life, we approached its use in chronic treatment by giving animals their total food during an 8 h period (09.00 hours to 17.00 hours). After the animals had been adapted to this regimen for 6 d, doses of 10 mg naloxone/kg body-weight were given at the beginning of the feeding period (09.00 hours) and again 4 h later (13.00 hours). By the fourth day the cumulative food intake for the entire 8 h period in the lean mice had risen to twice the control levels where it remained for the rest of the study (Fig. 3), (Shimomura *et al.* 1982). In the naloxone-treated *ob/ob* mice, the rise in food intake occurred more slowly.

The finding that naloxone, a drug which is known to antagonize morphine by interaction with the opioid receptors, increased food intake, raised the question of whether the drug was acting specifically on the opioid receptors or by some other mechanism. If the effect did involve opioid receptors, it should be blocked by morphine. To answer this question, mice were treated with naloxone (10 mg/kg

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body-weight), morphine (10 mg/kg body-weight) or a combination of these drugs, injected at 09.00 hours and 13.00 hours, with food available from 09.00 to 17.00 hours. The food intake over the 8 h is shown in Fig. 4. After the initial suppression of food intake on the first day, the morphine-treated group had a mean intake at 90% of control. The naloxone-treated group, on the other hand, showed the same response observed in the previous experiment with a rise in food intake to 160% of the control by the fourth day. Simultaneous injections of morphine and naloxone were associated with a level of food intake that was close to control.

Morphine and heroin both lower food intake and body-weight (Thornhill *et al.* 1976). Upon withdrawal of these drugs there is a transient further weight loss, followed by a weight gain which is more rapid than observed in pair-fed control animals (Brands *et al.* 1979). These results have been interpreted as supporting the presence of a food-reward system with which morphine interacts; our results fit into this same framework. The effects of naloxone may be interpreted as partially

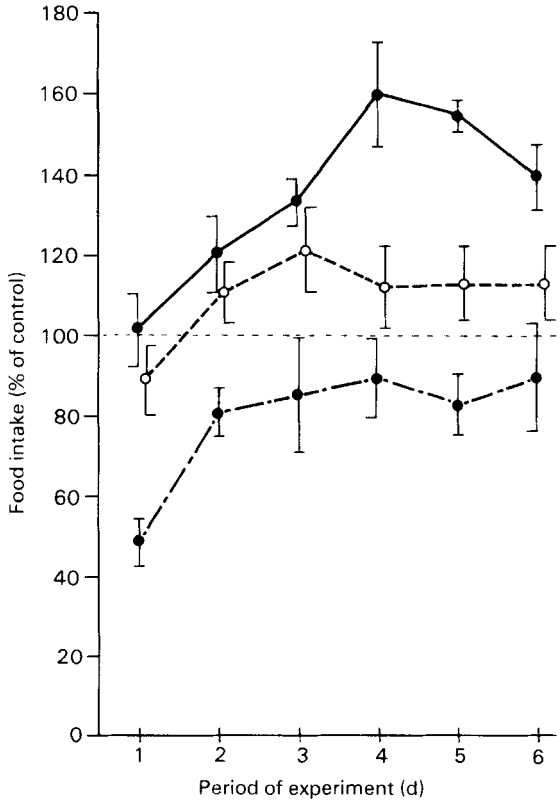

Fig. 4. The effects of morphine (●– – –●), naloxone (●——●) and both (○– – –○) on food intake of schedule-fed lean mice. Animals trained to eat their daily food ration in 8 h were injected at 9.00 and 13.00 hours at 10 mg/kg body-weight. Food intake of control animals was set at 100%. Food intake of the animals treated with naloxone rose above controls. Morphine blocked the effect of naloxone. (Shimomura *et al.* 1982).

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blocking the opioid receptors in this food-reward system. This suggests that the endogenous system signalling satiety may contain opioid receptors. Satiety might thus be viewed as the result of a rise in the concentration of opioid-like compounds (endorphins or enkephlins) interacting with these receptors. When exogenous opiates are administered, these receptors would be partly activated and the animals would have the sensation of 'satiety'. Thus less endogenous stimulation would be needed to produce the level of receptor stimulation associated with satiety and less food would be eaten. Morphine and heroin treatment might thus be expected to produce lower body-weight. Conversely blockade of these receptors in the satiety centre would require larger amounts of endogenous stimulation (endorphins or enkephalins) to signal satiety. In this case the animal would have to eat more food to produce satiety. Thus chronic endogenous stimulation of opioid receptors may be related to the quantities of food which are being eaten and provide a mechanism for long-term regulation of satiety and energy balance.

Peripheral regulation of food intake

Now let us turn to the peripheral components involved in the regulation of food intake. The left-hand side of Fig. 2 depicts the processes of food intake, including digestion and assimilation of nutrients. Taste and smell of appetizing foods activate the autonomic nervous system to prepare the intestine and circulation for the anticipated nutrients. Smell and taste of food can elevate insulin secretion (Powley, 1977; Krotkiewski *et al.* 1980) as well as intestinal motility.

Entry of food into the stomach or intestine may control food intake further by at least two mechanisms. On the one hand, distention of the stomach, determined by the rate of entry of food from the mouth and rate of exit through the pylorus, will reduce subsequent food intake. When food is put into the stomach prior to ingestion of a meal, the subsequent intake of food is reduced although not by an amount sufficient to offset completely what was put into the stomach (Spiegel, 1973). The temporal relationships between putting food into the stomach and the inhibitory effects on the further intake have been delineated. Food intake was reduced to the greatest degree when the preload was given 15 min before the meal. When it was introduced into the stomach 1 min or at 60 min beforehand the effect was less apparent (Jordan, 1973).

The concentration of energy in food may also play an important role in the quantity of food ingested. In classic studies Adolph (1980) demonstrated that addition of indigestible substances to food would increase the quantity of food ingested in order to maintain a constant intake of energy. However, during the first meal after the dilution or concentration of energy there is inappropriate energy intake, indicating that some component of the ingested energy must be measured physiologically to provide a relation between intake and need (Adolph, 1980; Booth, 1980). Recent data of McHugh & Moran (1978) showed that in the monkey there is a highly responsive 'caloric meter' in the stomach or upper intestine. Deutsch *et al.* (1978) also believe that the stomach is a principal site for assessing energy intake.

The intestines may be a second site for regulation of food intake. Intestinal distention and intestinal hormones are known to modulate the rate of gastric emptying. Motilin, a recently identified and characterized intestinal hormone, is involved in the periodic surges of gastrointestinal peristalsis. Secretion of intestinal hormones or the absorption of nutrients may also serve as signals for energy ingestion which can, in a negative feedback loop, suppress further feeding. Infusion of glucagon into the hepatic-portal vein suppresses feeding in the rabbit (Martin & Novin, 1977). Whether such signals operate directly through peripheral concentrations of hormones or nutrients or both or through effects on the liver and, in turn, the vagus nerve, is at present uncertain.

The lacteals provide a route by which some digested nutrients can enter the circulation without passing through the liver. Triglycerides composed of long chain fatty acids enter the venous circulation as chylomicrons by this route. The quantity of energy entering the general circulation is that fraction of the dietary intake which was composed of long chain fatty acids. The fact that diets containing large quantities of fat are associated with the development of obesity in experimental animals (Schemmel *et al.* 1970) suggests that short-circuiting of energy around the liver to the general circulation may diminish the 'sensing' of this energy that would occur if it flowed through the liver (Bray *et al.* 1980).

Dietary obesity

It is now well recognized that dietary obesity can be produced by at least three mechanisms. The first of these, described previously, is to feed animals a high-fat diet. The second is to offer a sucrose solution in addition to a normal diet (Kanarek & Hirsch, 1977). The third is to provide animals with a variety of snack foods in addition to their regular diet (Sclafani & Gorman, 1977; Rothwell & Stock, 1979). In each instance the animal fails to compensate for the novel foods or change in fat content by adjusting energy intake to maintain energy balance. Recent studies have indicated that the use of fructose in the drinking solution is not associated with the same maladaptive sequence as when sucrose, maltose or glucose are used (Teague, Kanarek *et al.* 1981). With fructose in the drinking solution, the increase in body fat and the increase in brown adipose tissue is no different than in animals drinking tap water. In contrast, animals having access to solutions of maltose, sucrose or glucose have an increase in body fat and an increase in brown adipose tissue. We will return to discuss the interpretation of this change in brown adipose tissue later.

The substitution of medium chain triglyceride, that is, triglyceride containing fatty acids of eight or ten carbons for long chain triglyceride, blunts the effect of a high-fat diet in the induction of obesity (Bray *et al.* 1980). Indeed, even the Osborne Mendel rat, which usually develops obesity readily on a high-fat diet, does not do so when this high-fat diet is composed of medium chain triglyceride. The fact that absorption of medium chain triglyceride is through the liver whereas that for long chain triglyceride circumvents the liver as chylomicrons provides additional information for an important role of the liver in sensing energy.

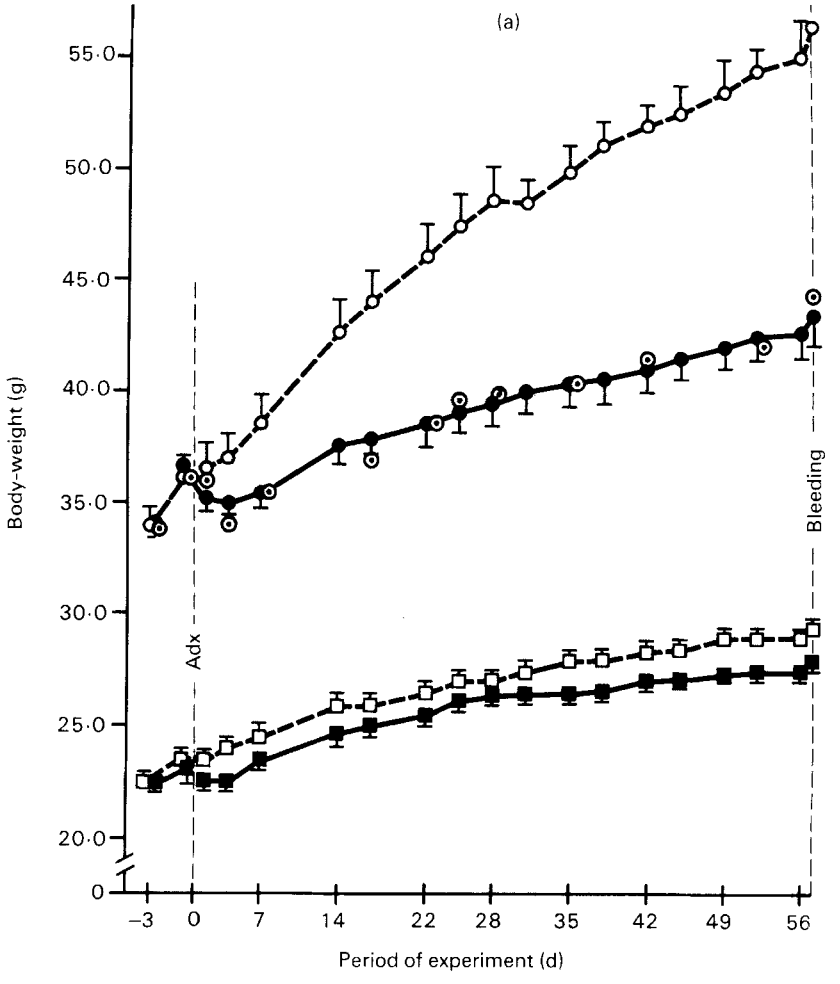
The possibility that acetoacetate or β-hydroxybutyrate may be involved in regulating energy intake needs careful evaluation (Davis *et al.* 1981). Recent results from our laboratory suggest that animals which are susceptible to fat-induced dietary obesity may have quantitatively different mechanisms for sensing circulating ketone levels. We have found that brain uptake of ketones is higher in the animals which fail to become obese when eating diets containing long chain triglyceride, and shows a greater response during feeding of high-fat diet (Teague, Lee *et al.* 1981). It is thus conceivable that one mechanism for sensing circulating energy stores derived from fats may be the adaptive response of the blood-brain barrier to the transport of ketone.

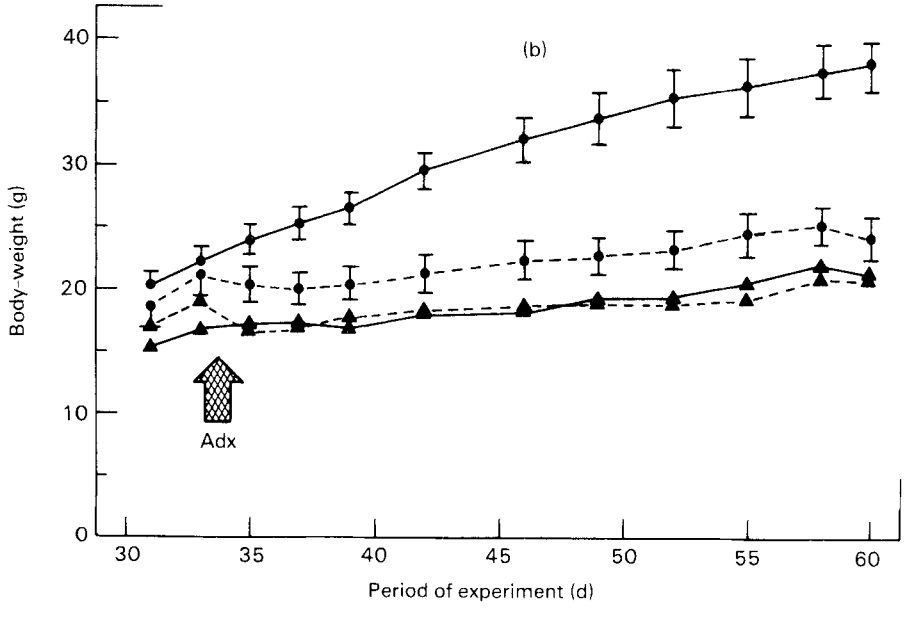
Other signals generated by the digestion or absorption or both of food may also participate in producing satiety. CCK, a peptide released from the gut, has been suggested by Smith and his colleagues (Smith & Gibbs, 1979) to be one such signal. CCK is effective in reducing food intake when injected into animals prior to or just after the initiation of a meal. CCK will also produce a small but statistically significant reduction in food intake of human subjects (Kissileff *et al.* 1981). Thus, CCK and possibly other, as yet to be identified, gastric or intestinal peptides may be important signals for the presence or quantity or both of food that is being ingested (Nishizawa & Bray, 1980).

The circulating pool of energy has two principal routes of disposal. The first is triglyceride, which is stored in adipose tissue. The second is to other tissues and brown fat which use the circulating nutrients as energy sources for metabolic and mechanical work (James & Trayhurn, 1981). The control of triglyceride storage and breakdown is complex. As noted earlier, the cephalic phase and subsequent absorption of nutrients are associated with release of GIP (gastrointestinal inhibitory polypeptide, also known as the glucose insulin polypeptide) which enhances insulin secretion. Insulin, by increasing glucose entry into cells, stimulates lipogenesis in adipose tissue and liver, and plays a primary role in the uptake and storage of fuel in fat cells and liver. When energy is no longer being rapidly absorbed and processed, insulin levels fall, and the lipolytic process, which is inhibited by insulin, increases. Further acceleration of lipolysis can be produced by the sympathetic nervous system, by growth hormone, by increased blood flow and possibly by adrenal cortical steroids.

Neurohumoral and hormonal mechanisms for regulating the mobilization of free fatty acids and glycerol may be deranged in the induction of experimental forms of obesity. The syndrome of hypothalamic hyperphagia can be prevented or reversed by vagotomy. Vagotomy, however, does not reverse the genetic obesity of the fatty rat (Opsahl & Powley, 1974). A second mechanism which will reverse hypothalamic obesity is the addition of a bitter tasting substance like quinine to the diet of animals with this syndrome. The effective treatments for hypothalamic hyperphagia are summarized along with other effective treatments for experimental models of obesity in Table 1.

In contrast to the animal with hypothalamic obesity, animals with genetic obesity appear to depend upon the function of the endocrine system.





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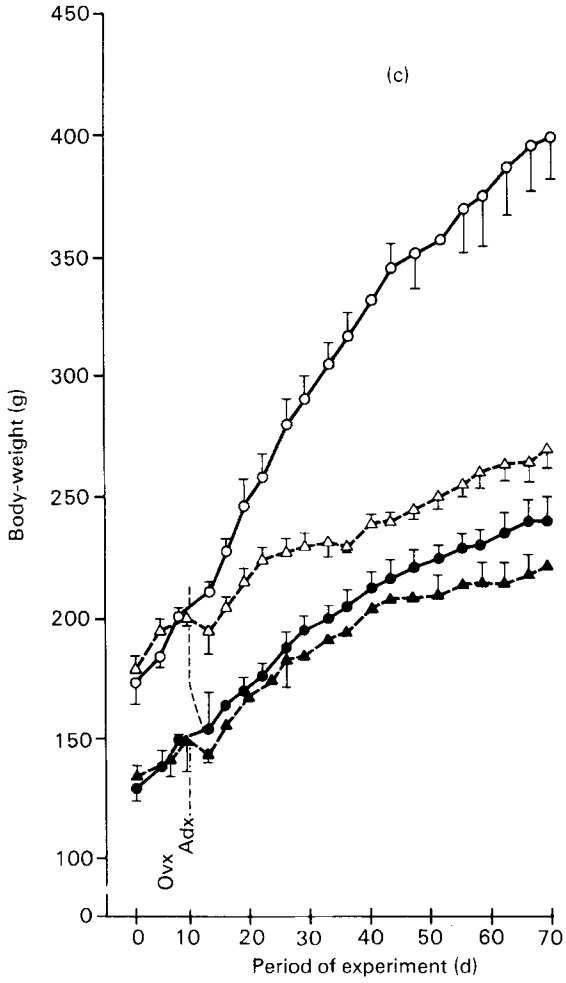

Fig. 5. The effect of adrenalectomy on the body-weight of three types of genetically obese and lean animals. (a) In the obese mouse (*ob/ob*). (○– – –○) Obese sham operated controls, (●——●) obese adrenalectomized, (⊙) obese sham operated pair-fed controls, (□– – –□) lean sham operated controls, (■——■) lean adrenalectomized. (b) In the diabetes mouse (*db/db*). (●——●) Obese sham operated controls, (●– – –●) obese adrenalectomized, (▲——▲) lean sham operated controls, (▲– – –▲) lean adrenalectomized. (c) In the fatty (Zucker) rat (*fa/fa*). (○——○) Obese sham operated controls, (△– – –△) obese adrenalectomized, (●——●) lean sham operated controls, (▲– – –▲) lean adrenalectomized. In all three types the removal of the adrenals reduced food intake and arrested the further progression of the obesity (Yukimura & Bray, 1978*a*,*b*; Shimomura & Bray, 1981). Mean values with standard errors represented by vertical bars. Adx, adrenalectomy or sham operation.

Adrenalectomy will prevent the appearance or arrest the progress in all three forms of recessively inherited obesity (Bray & York, 1979). This is shown in Fig. 5 and summarized in Table 1.

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Table 1. *An approach to treatments for obesity based on etiology and mechanisms*

Types of obesity	Mechanism	Treatment
Hypothalamic	Autonomic hypothesis	Vagotomy
	Hyperinsulinemia	Quinine in diet
Endocrine:		
Hypercorticism	↑ Corticosteroids	Adrenalectomy
Hyperinsulinism	↑ Insulin	Lower insulin
Ovariectomy	Progesterone/E_2 imbalance	Adrenalectomy
Nutritional:		
High-fat diet	?	Medium chain triglyceride diet
Oral sucrose solution	?	Remove sucrose
Genetic:		
Recessive	?	Adrenalectomy
Dominant	?	Dehydroepiandrosterone

The mechanisms involved in the storage and utilization of energy in adipose tissue represent important control points for the disturbances in energy balance which produced obesity or anorexia or both.

Energy expenditure

Energy expenditure is depicted in the two lower boxes of Fig. 2. One box shows brown fat, which produces heat, primarily in the form of uncoupled oxidation, and all other metabolic tissues whose energy output is measured as both heat production and mechanical work. Energy expenditure, expressed in relation to body-weight or surface area, is highest in infancy and gradually declines with ageing (Bray, 1976). Increasing ambient temperature, which reduces the requirements for heat production, is associated with a reduction in food intake. When goats are placed in a high environmental temperature, rectal temperature rises and food intake declines. The levels of physical activity also influence intake. In occupations with heavy physical requirements, food intake increases. Similarly, cold exposure increases energy intake, whereas sedentary occupations may produce some reduction (Bray, 1980).

An important role for brown adipose tissue in control of energy expenditure has been proposed recently by several laboratories (Himms-Hagen, 1979; Rothwell & Stock, 1979). This tissue appears to be hypofunctional in genetically obese animals (Trayhurn & James, 1980). It is under control of the sympathetic nervous system but whether the defect in the genetically obese mouse is the result of impaired sympathetic function or impaired tissue response to catecholamines remains to be established. Brown fat is known to hypertrophy under a variety of conditions of overeating in experimental animals (Teague, Lee *et al.* 1981) and may serve as a site for dissipation of excess energy under certain circumstances. Recently Glick *et al.* (1981) have proposed that brown adipose tissue may also play an important role in the dissipation of heat after eating a meal, which is known as specific dynamic effect or diet induced thermogensis.

The possibility of differing levels of metabolic efficiency in other tissues has also been proposed and may involve such mechanisms as futile cycles (Newsholme,

1978), alterations in activity of the sodium pump (York *et al.* 1978; Bray, Kral *et al.* 1981) and alterations in protein turnover (Trostler *et al.* 1979). The relative contributions of disturbances in energy expenditure to the over-all problems of energy balance observed with obesity and anorexia remain to be established (Garrow, 1978), but it is clear that the disturbances on the side of energy output may be the most effective site for the new treatments for both conditions.

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