MINIREVIEW

Role of Brown Adipose Tissue Thermogenesis in Control of Thermoregulatory Feeding in Rats: A New Hypothesis That Links Thermostatic and Glucostatic Hypotheses for Control of Food Intake (43847A)

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Abstract. **The hypothesis proposed in this review provides a novel view of both the control of feeding and the function of brown adipose tissue (BAT) thermogenesis. It takes into account the episodic nature of feeding in rats allowed free access to food and the necessity for episodic events in the controlling systems which govern initiation and termination of feeding. A feeding episode is proposed to occur during an episode of increased sympathetic nervous system activity that stimulates BAT thermogenesis and increases body temperature. Two different aspects of stimulated BAT metabolism, namely increased uptake of glucose and increased heat production, evoke initiation and termination of feeding, respectively. Initiation is mediated by a transient dip in blood glucose concentration caused by stimulated glucose utilization in BAT. Feeding continues while both BAT and core temperature continue to rise. Termination is induced by the high level of core temperature brought about by the episode of stimulated BAT thermogenesis. The time between initiation and termination determines the size of the meal and depends on the balance between BAT thermogenesis and heat loss, and thus on ambient temperature. The underlying cause of the episodic stimulation of sympathetic nervous system activity is a decline in core temperature to a level recognized by the hypothalamus as needing a burst of increased heat production. Thus, BAT thermogenesis is important in control of meal size, relating it to thermoregulatory needs. When this function is lost, as in many obese animal models of obesity, the animal loses its ability to remain in energy balance by precisely adjusting its intake in relation to environmental temperature and meal size increases. The hypothesis also predicts that an increase in endogenous heat production that is not due to BAT thermogenesis will prevent the matching of intake to increased expenditure via thermoregulatory feeding. This is seen, for example, in the shivering rat during the early stage of acclimation to cold. Feeding is viewed as the outcome of a thermoregulatory event. Rats do not eat to warm up; they start to eat after they have started to warm up and stop eating once they have warmed up. The phenomenon is termed *thermoregulatory feeding,* to distinguish it from feeding initiated by other stimuli.** [P.S.E.B.M. 1995, Vol 208]

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Background

Despite over a century of extensive research there is still no clear understanding of the physiological mechanisms that regulate the intake of food in mammals. The existence of numerous hypotheses for control of food intake in rats attests both to the complexity of the subject and to our lack of a clear understanding of the phenomenon. Such hypotheses tend to concentrate upon relatively narrow aspects of the subject, for example, the glucostatic, lipostatic, and thermostatic hypotheses. Bray (1–4) proposed a broader hypothesis of a reciprocal relationship between food intake and sympathetic nervous system activity, low sympathetic nervous system activity being associated with hyperphagia and obesity. However, his hypothesis fails to account for the slow but substantial physiological increase in food intake that accompanies the large increase in sympathetic nervous system activity in the rat acclimating to cold. This review presents a new hypothesis that brings together certain elements of the glucostatic and thermostatic hypotheses and provides a novel insight into a hitherto unsuspected relationship between food intake and sympathetic nervous system activity and thermogenesis. It links food intake with the *pulsatile* or *episodic* nature of numerous metabolic and neuroendocrine events, including sympathetic nervous system activity. It also proposes a role for brown adipose tissue (BAT) thermogenesis in the control of timing of both the initiation and the termination of feeding.

Feeding Patterns in Rats. It should be emphasized at the outset that laboratory rats do not eat continuously. Rats living in a constant environment with temperature up to 10°C below thermoneutrality (29°–30°C), regular periods of light and dark, and continuous access to a monotonous food supply spontaneously eat between 9 and 12 discrete meals per day, mostly during the dark phase (5–7). The meals are separated by nonfeeding periods. Usually, the amount of food ingested per day depends on the size of the meals rather than their frequency. When rats increase their overall food intake (e.g., in such physiological or pathological conditions as acclimation to cold or genetic or hypothalamic obesity), they usually do so, not by increasing the meal frequency, which may even be reduced, but by increasing the size of individual meals (8).

Any hypothesis about control of food intake must take into account factors that make the rat start eating and those that make it stop. Meal initiation is usually considered to be a result of a metabolic deficiency (expressed as hunger) that occurs after a nonfeeding interval, the length of which is related to the size of the previous meal (9). On the other hand, meal termination (due to satiety) occurs long before most of a meal has been digested and absorbed. It is usually thought to be controlled by signals arising from the intestine. Control of initiation is thought to be independent of control of termination (3, 9).

Events Occurring Before and During Meals. A train of events, that at first sight might seem unrelated, are found on closer scrutiny to be linked to the intermittent episodes of feeding. These events are as follows (evidence for their occurrence is detailed below): (i) fluctuations of body temperature of approximately 1°C. Eating begins shortly after the temperature starts to rise and stops when the temperature reaches its peak; (ii) an increase in intensity of stimulation of BAT via its sympathetic innervation induces a sharp increase in its rate of thermogenesis with production of sufficient heat to raise body temperature; (iii) the sudden increase in metabolic activity of BAT provokes an influx of glucose from the circulation into the BAT, with an attendant fall in blood glucose concentration; (iv) as the hypoglycemia reaches its lowest level, continued high intensity of sympathetic nervous system activity evokes countermeasures in liver that restore the blood glucose concentration to its previous level; (v) by a direct or indirect action on the brain, the fall in blood glucose concentration induces the rat to start eating; (vi) as the high rate of thermogenesis in BAT persists during the meal, the body temperature continues to rise to reach a peak at which counterregulatory measures come into play to prevent hyperthermia. The rat stops eating. Sympathetic stimulation of BAT ceases. Body temperature starts to fall.

It is the purpose of this review to examine the way that these events are linked throughout the cyclic episodes of feeding and to show how they can serve as the basis for a hypothesis of thermoregulatory control of eating.

Thermostatic and Glucostatic Feeding Hypotheses. In his thermostatic hypothesis for control of food intake, Brobeck (10) initially proposed that "animals eat to keep warm and stop eating to prevent hyperthermia." He later modified this proposal to "animals stop eating to stay cool" (11). His hypothesis emphasized the close relationship between control of energy expenditure for thermoregulation and control of energy intake by feeding. On the other hand, Mayer (12) in his glucostatic hypothesis for control of food intake, proposed that a decreased availability of glucose at a specific sensing site plays a role in the initiation of feeding.

Proposed Thermoregulatory Feeding Hypothesis. In this review, I propose the following new hypothesis: thermogenesis induced by accentuated sympathetic nervous system stimulation of BAT is responsible both for the preprandial fall in glucose concentration that signals meal initiation and for the prandial rise in core temperature that, on reaching its peak, signals

meal termination. This intense BAT thermogenesis is brought on by a burst of activity in its sympathetic nerve supply. Feeding is here viewed as the outcome of a thermoregulatory event. Rats do not eat to warm up: they start to eat after they have started to warm up and stop eating once they have warmed up. I call this phenomenon *thermoregulatory feeding*, to distinguish it from feeding initiated by other stimuli. The sequence of events is illustrated diagrammatically in Figure 1.

Thermostatic Events and Sequelae

Core Temperature Rises Before a Meal. Recent studies of feeding in rats living under the conditions outlined above have shown that cyclic oscillations in core (liver) temperature occur 9–12 times per day, varying by about 0.5°C above and below an average level; this average level is considerably higher in the dark than in the light phase (17, 18). Eating begins some time *after* the start of the rising phase of a temperature oscillation. Older studies also sometimes detected a rise in abdominal temperature before a meal, in parallel with a rise in brain temperature (see Fig. 4 in Ref. 19). However, these older studies described the increase in brain temperature as coincident with or occurring shortly after the onset of feeding (19–21). The reason for this is probably that the measuring procedures then in use were unable to assess very precisely minute by minute temperature changes. The older studies agreed, however, that the increase in temperature was not due to the actual metabolism of the food itself, since it occurred long before any food ingested could have entered any metabolic pathways

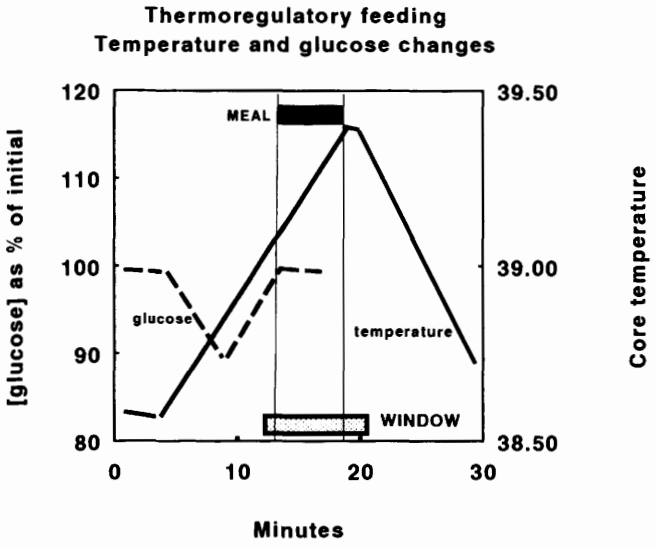

Figure 1. Diagrammatic representation of the sequence of events during thermoregulatory feeding. The diagram is based upon data for the time course in core temperature changes in De Vries *et al.*, 1993 (17), and for the time course in changes in blood glucose concentration in Campfield *et al.*, 1985, Campfield and Smith, 1986, and Campfield, 1990 (14, 15, 16). See text for further explanation.

and because it was unrelated to the energy density of the food (19, 21).

Meal Termination is Induced by a High Core Temperature. A recent study has shown that, during the dark phase, feeding terminates when liver temperature reaches 39.3°C (17). A previous study also identified 39.3°C as the brain temperature at which feeding ceases (21). Skin temperature likewise increases as the temperature rises. This indicates that both heat production and heat loss mechanisms are activated (17). Skin temperature continues to rise after the core temperature starts to fall, so that heat loss is prolonged beyond the period of enhanced heat production. Recognition of the elevated core temperature by sensors in liver can signal neurally mediated inhibition of feeding. Evidence for this includes the inhibition of feeding by external heat applied to the liver (22), the loss of this inhibition in rats with subdiaphragmatic denervation of the liver (23), and the demonstration of thermosensitive afferent fibers in the hepatic branch of the vagus nerve (24). However, sensing of elevated brain temperature by temperature-sensitive neurons in the hypothalamus (25) cannot be excluded from a role in the signaling mechanism for meal termination.

Source of the Increased Heat Production Is Suggested to Be BAT. In the studies described above, although liver and brain temperatures have been emphasized, there is, in fact, no evidence that the warming is due to increased thermogenesis in either the liver or the brain. During the feeding episode, liver temperature is usually lower than portal vein temperature (18) and brain temperature is usually lower than arterial blood temperature (19). These temperature differences suggest that much of the heat is actually being produced elsewhere. Moreover, cyclic oscillations in temperature occur not only in liver and brain but in all internal organs, including interscapular BAT, where the highest temperature has been recorded (26). Measurements of blood flow through interscapular BAT during the rising and falling phases of oscillations in core temperature show a 200-fold greater flow during the rising phase than during the falling phase (26). The difference is equivalent to that seen when norepinephrine is infused into rats (27). Perirenal BAT temperature and blood flow have not been measured directly, but both the close proximity of this BAT depot to the liver and its marked capacity to respond to norepinephrine with an increase in blood flow (27) suggest that its capacity to contribute to the increase in core temperature might be substantial. The rise in liver temperature, imputed to liver thermogenesis in some studies (17, 18), can probably be attributed to a warming of the liver as a consequence principally of perirenal BAT thermogenesis.

Oscillations in Sympathetic Nervous System Activity May Trigger BAT Thermogenesis During

Warming. If the warming phase of a thermoregulatory feeding episode is due to BAT thermogenesis, then it must be induced by an increase in sympathetic nervous system activity. Cyclic oscillations in sympathetic nervous system activity do, in fact, occur in rats (28), with about the same frequency as the oscillations in body temperature and the episodes of feeding, but their relationship to feeding has not been studied.

The episodic nature of meals is here proposed to be directly related to the pulsatile nature of sympathetic nervous system activity, initiating increases in BAT thermogenesis, which increase core temperature. Episodes of thermoregulatory feeding are proposed to occur during episodes of increased sympathetic nervous system activity. Thus, feeding can be directly related to increased sympathetic nervous system activity.[2]

Could cyclic oscillations in sympathetic nervous system activity and in thermogenesis in BAT be reflected in overall energy expenditure? Evidence has existed for some time for an increase in metabolic rate coincident with rises in brain and abdominal temperatures and with feeding episodes (19, 29–31). This is consistent with recent work that has shown that metabolic rates of intact rats, when corrected for energy expenditure for movement and for resting energy expenditure, show approximately nine cyclic episodes of "supplementary" heat production, by nonshivering thermogenesis (32). The cyclic episodes of nonshivering thermogenesis have been seen in rats living at 21°C and are presumably associated with oscillations in sympathetic nervous system activity, in core temperature, and in thermogenesis in BAT (32). They continue during food deprivation (33). They are not detectable in rats living at thermoneutrality (32).

Thermostatic Termination of Thermoregulatory Feeding. The following conclusions and suggestions about an episode of thermoregulatory feeding are based upon the studies discussed above: (i) eating is the culmination of a thermoregulatory process. Rats warm up before eating. Eating does not initiate the warming process; (ii) warming is initiated by increased sympathetic nervous system activity, which stimulates thermogenesis in BAT, particularly in abdominal depots of BAT; (iii) feeding is a late event during the rising phase of core temperature. It is terminated by the sensing of an elevated temperature in liver and transmission of the information centrally by afferent sensory nerves in the hepatic branch of the vagus; perhaps also by sensing of the elevated temperature in the brain itself; (iv) energy expenditure during thermoregulatory feeding episodes is of sufficient magnitude to be detected as oscillations in energy expenditure in intact rats; and (v) the trigger for the cyclic increases in sympathetic nervous system activity is unknown, but could well be the decline in core temperature.

The initiation of feeding during the rising phase of core temperature is not explained by any of the above. In order to relate initiation of feeding to the pulsatile increase in sympathetic nervous system activity and in BAT thermogenesis another aspect of BAT metabolism must be invoked, namely, its large capacity to use glucose when stimulated.

Glucostatic Events and Sequelae

Blood Glucose Concentration Decreases Transiently Before Feeding. A transient decline in blood glucose concentration has frequently been observed immediately before meal initiation and has been proposed as causative in this initiation (9, 13–16). While the onset of a meal can sometimes be mimicked by the administration of a stimulus to insulin secretion (34) and a pulse of insulin secretion can sometimes be detected before the decline in blood glucose concentration (16), evidence that pulsatile insulin secretion is directly responsible for meal initiation is lacking. An important question remains: What is the usual physiological stimulus to the decline in blood glucose concentration before a meal?

Comparison of the time course of the rise in core temperature before a meal (17) with the time course of the decline in blood glucose concentration before a meal (14, 15) shows that the rise in temperature precedes the decline in glucose concentration (Fig. 1). This suggests that increased thermogenesis, which raises the core temperature, results in accelerated glucose utilization of sufficient magnitude to reduce its concentration in the blood.

BAT Uses More Glucose When Thermogenesis Is Stimulated. Sympathetic stimulation induces a very large increase in the utilization of glucose by BAT (35, 36). Stimulation of thermogenesis in BAT increases utilization of glucose, not as a fuel for thermogenesis, but as a cytosolic resource for ATP generation when generation of ATP by mitochondrial oxidative phosphorylation is compromised by the uncoupled state of the mitochondria (37–40). Stimulation of utilization of glucose by BAT is mediated by its sympathetic innervation and involves activation of glucose transporters located in the plasma membrane (41–48) but does not depend on an action of insulin to induce translocation of glucose transporters. The glucose taken up is largely converted to lactate and exported (39, 40). I suggest that glucose utilization by BAT is greatly increased at the start of the rise in core temperature when thermogenesis is stimulated and

[2] Reported measurements of average sympathetic nervous system activity have usually been made by assessing turnover of norepinephrine over periods of 12 to 24 hours. However, they give no clear view of the true ultradian fluctuations in activity. It remains to be shown whether an increase in sympathetic nervous system activity is expressed as more pulses, larger pulses, or both more and larger pulses.

that the withdrawal of glucose from the blood is sufficiently rapid to lower its concentration.

Increased Hepatic Glucose Output Restores Glucose Concentration in Blood to its Previous Level. Swiftly, counterregulatory processes in the liver reverse the decline in blood glucose. These processes include glycogenolysis and gluconeogenesis, the latter using lactate exported from BAT (part of the BAT-liver cycle [37, 39, 40]) (Fig. 2). Increased hepatic glycogenolysis, associated with activation of glycogen phosphorylase, has long been a puzzling "consequence" of food ingestion (49, 50). Here, it is seen as one of the two counterregulatory processes that restore blood glucose to its previous level when thermoregulatory requirements dictate that glucose will be used by BAT. These processes are mediated by increased sympathetic nervous system activity in BAT and liver alike (see Fig. 2 for a modified BAT-liver cycle applicable to thermoregulatory feeding). Transient increases in blood free fatty acid (FFA) and glycerol concentrations occur at the time at which blood glucose reaches its lowest level (51), most probably because of increased export from the BAT of some of the FFA released in stimulated lipolysis. These FFA are probably oxidized in the liver to provide the ATP needed to drive gluconeogenesis (39, 40) (Fig. 2).

Initiation of Thermoregulatory Feeding. Since, as proposed above, the increased thermogenesis during the rising phase of core temperature occurs in BAT, it follows that this must be accompanied by increased utilization of glucose by BAT. It is, therefore, proposed that sympathetic-mediated activation of BAT thermogenesis results in increased glucose utilization to the extent that glucose concentration in the blood declines. This lowering of blood glucose is sensed by central receptors, presumably in the hypothalamus, or possibly by peripheral receptors in the liver, as a signal for initiation of feeding. Cyclic oscillations in secretion of norepinephrine in the hypothalamus (52, 53) and of NPY in the PVN (54, 55) have been demonstrated, and it is here suggested that cyclic oscillations in release of neurotransmitters involved in initiating food intake occur in association with feeding episodes.

Role of Stimulated BAT Thermogenesis in Control of Thermoregulatory Feeding: A Summary of the Hypothesis

Stimulated BAT thermogenesis is proposed to provide signals for both initiation and termination of thermoregulatory feeding episodes (meals). Oscillations in multiple linked systems, roughly 9–12 per day,

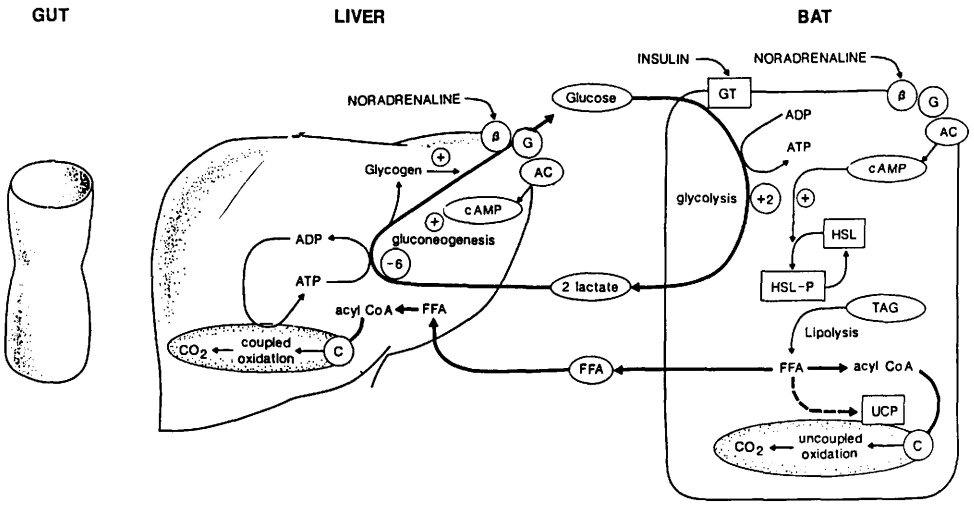

Figure 2. The BAT-liver cycle for glucose metabolism during the increase in core temperature in thermoregulatory feeding episodes in rats. Activation of the sympathetic nervous system results in release of noradrenaline from nerve endings in BAT. Noradrenaline stimulates thermogenesis in BAT via interaction with a β-adrenergic receptor, activation of adenylate cyclase and cyclic AMP (cAMP)-mediated activation (⊕) of hormone-sensitive lipase (HSL) by phosphorylation (HSL-P). The resulting increase in rate of lipolysis increases concentration of intracellular fatty acids (FFA) which serves both as signal for operation of the uncoupling protein (UCP) (dotted arrow) and as fuel for the increased rate of uncoupled mitochondrial oxidations (solid arrow). Accentuated thermogenesis also markedly augments entry of glucose into the brown adipocyte via glucose transporters (GT) located in the plasma membrane. The glucose is metabolized via glycolysis, providing ATP (+2 per glucose) for vital cell functions which might otherwise be compromised by the reduced ATP production in oxidative phosphorylation. The glucose is converted almost quantitatively to lactate which is exported from the BAT. Liver takes up the lactate and reconverts it to glucose in gluconeogenesis, which is also stimulated (⊕) by noradrenaline released from nerve ending in the liver via adenylate cyclase activation and an increase in cAMP level. At the same time, the increase in cAMP level stimulates glycogenolysis (⊕), thereby augmenting further the release of glucose from the liver. The liver uses 6 ATP to synthesize glucose from lactate; these ATP are obtained by oxidizing in liver mitochondria some of the FFA released from BAT. It is here proposed that stimulated glucose utilization by BAT results in a decline in blood glucose concentration, which is then reversed by the stimulated increase in glucose output by the liver. See text for further discussion and references. Figure 2 is adapted from figures in Himms-Hagen, 1990 and 1992 (39, 40), where the metabolic processes are discussed in more detail.

provide the following sequence of events during a single feeding episode (Fig. 1):

1. Low core (or perhaps hypothalamic) temperature provides a signal for selective activation of the sympathetic nervous system to increase heat production in BAT.

2. Norepinephrine stimulates thermogenesis in BAT; core temperature starts to rise.

3. Increased glucose utilization by stimulated BAT causes a decline in blood glucose concentration. Lactate is produced from the glucose by glycolysis and exported.

4. In liver, counterregulatory increases in gluconeogenesis (using lactate exported from BAT) and in glycogenolysis increase glucose output and raise the low blood glucose level back to normal. Both are stimulated by norepinephrine liberated from sympathetic nerve endings in the liver. Liver derives the energy for gluconeogenesis from oxidation of FFA released from BAT.

5. Decline in blood glucose concentration is recognized by the hypothalamus as a signal for the initiation of feeding (glucoprivic feeding). Pulses of release of one or more orexigenic neurotransmitters occur. Feeding starts.

6. Continued stimulation of BAT thermogenesis eventually raises core and brain temperature to about 39.3°C. Temperature sensors in liver transmit signals via afferent nerves in the vagus to the brain. Temperature sensors in the brain may also generate signals. Signals result in both termination of feeding and cessation of stimulation of sympathetic innervation to BAT (thermostatic termination of feeding). BAT temperature starts to decline.

7. Core temperature then gradually declines until the next episode of temperature elevation begins. The thermic effect of the food ingested, due to its metabolic processing and related to its composition, will delay the fall in body temperature, resulting in the known correlation of inter-meal interval to the size of the preceding meal.

Perspectives

BAT Thermogenesis in Thermal Balance and in Energy Balance. The role of BAT thermogenesis in thermoregulatory feeding is here proposed to be 2-fold. First, it triggers initiation of feeding by reducing blood glucose concentration during the early stage of stimulated thermogenesis. Second, it triggers termination of feeding by virtue of the elevated core temperature it eventually induces. The existence of two separate controlling systems, one for meal initiation and another for meal termination, has already been proposed (9). In the present hypothesis, the two are also seen to be separate, via blood glucose sensing for initiation and via temperature sensing for termination, but nonetheless linked in that both trace their origin to the same process, namely, stimulation of thermogenesis in BAT.

The hypothesis proposed in this review provides a novel view of the control of feeding which invokes a function of BAT thermogenesis. BAT thermogenesis is usually viewed as primarily providing the heat for maintenance of body temperature (cold-induced nonshivering thermogenesis) and secondarily providing a means for wasting excess ingested food energy (diet-induced thermogenesis). The hypothesis put forward here provides a role for BAT thermogenesis in control of meal size, relating energy intake to environmental temperature (i.e., in control of both energy and thermal balance).

In the hierarchical structure of regulatory neural mechanisms that influence food intake, thermoregulatory feeding, as defined in this review, is probably one of the most fundamental, since it underlies the matching of energy intake to energy requirement for maintenance of body temperature. In thermal balance, body temperature is stringently regulated within fairly narrow limits by both heat production and heat loss mechanisms (56). In contrast, in energy balance, the size of the energy stores is probably not specifically controlled, but is determined by regulation of energy intake on the one hand and of energy expenditure for thermogenesis and other purposes on the other (56). Since energy expenditure for BAT thermogenesis during episodes of thermoregulatory feeding is fairly small compared with total energy expenditure (it can be calculated to be about 7% of the total in a a rat living at 21°C from data in Ref. 32), in order to meet overall energy requirements, there must be an amplification factor of roughly 15 built into thermoregulatory feeding (i.e., the rat on average eats 15 times more than it expends during episodic warming).

Central control of BAT thermogenesis involves the ventromedial hypothalamus (VMH), which exerts both a stimulatory influence on the sympathetic nerves that innervate the brown adipocytes and, via the lateral hypothalamus, a restraining influence on BAT thermogenesis (57). The latter is mediated by restriction of blood flow to prevent overheating of BAT (57). One would therefore expect both these regions of the hypothalamus to be involved in control of thermoregulatory feeding via their influence on BAT thermogenesis.

Obviously, the fundamental controlling mechanisms involved in thermoregulatory feeding can be overridden by other mechanisms at different levels of the hierarchy. The powerful drive that certain centers in the hypothalamus can exert to induce feeding could, if not appropriately restrained, overcome the finely tuned control of thermoregulatory feeding. For example, suppose the secretion of an orexigenic neuropeptide,

such as NPY, at an appropriate site were pulsatile and exaggerated. This would not only induce eating, but would also suppress BAT thermogenesis (58) and thereby induce atrophy of BAT (59–61). Meal initiation in response to glucose utilization by stimulated BAT would be supplanted by meal initiation in response to the pulsatile increase in NPY release. The rise in core temperature from BAT thermogenesis would be less rapid, meal termination would be delayed, and meals would become larger. There is, indeed, evidence that NPY release in the paraventricular nucleus of the hypothalamus increases meal size (62) and attenuates satiety (63), and that secretion of NPY is a physiological signal for feeding (64). Perhaps there is normally a reciprocal balance between central control of peripheral nervous stimulation of BAT thermogenesis and central NPY-induced suppression of sympathetic stimulation of BAT thermogenesis, which, if upset, could result in hyperphagia with larger meals.

Thermoregulatory Feeding in States of Altered Energy Balance. To what extent might changes in thermoregulatory feeding be involved in physiological or pathological states of altered energy balance? The capacity for BAT thermogenesis is known to be increased in association with leanness in both the hyperphagic cold-acclimated rat and the hypophagic lateral hypothalamic (LH)-lesioned rat. Conversely, the capacity for BAT thermogenesis is decreased in association with hyperphagia and obesity in the genetically obese fa/fa rat, in the ventromedial hypothalamic (VMH)-lesioned rat and in the transgenic mouse with ablation of BAT. The following speculative discussion illustrates the way in which the thermoregulatory feeding hypothesis might provide new insight into each of these different states of altered energy balance. In particular, it can provide insight into why either reduction or elevation of sympathetic nervous system activity could be associated with hyperphagia under different circumstances and suggests new experimental approaches to the study of the control of feeding.

The cold-acclimated rat. Acute exposure to cold (4°C) induces an immediate increase in energy expenditure. This is not immediately balanced by an increase in energy intake. Food intake does increase slowly, requiring 7–10 days to reach a new maximum level, roughly double that of the rat living at usual laboratory temperatures (24°–26°C) (5, 65). The increase in food intake is entirely due to an increase in meal size, meal frequency declining somewhat (5, 8), and the increase in meal size likewise takes about 8 days to develop (5). In fully acclimated animals, meal size is inversely related to environmental temperature (5, 8). Thus, during the early stage of acclimation to cold, the rat remains in negative energy balance for several days. Acclimation to cold is known to be accompanied by a large increase in sympathetic nervous system activity, but evidence that the cold-acclimated rat retains ultradian fluctuations is lacking. The present discussion assumes that these fluctuations are retained.

How can the slowness of the adaptive increase in food intake be related to the mechanism proposed above for thermoregulatory feeding? The relation requires taking into account two major phenomena that occur during the initial days of acclimation to cold (38, 66): (i) shivering thermogenesis by skeletal muscle, which is the major initial thermogenic process that contributes to the immediate increase in energy expenditure (67, see Fig. 5 in Ref. 68). This common mammalian acute response to cold appears to be unable to invoke a corresponding immediate compensatory increase in energy intake; and (ii) a coordinated growth of BAT that substantially increases the capacity of the rat for BAT thermogenesis (nonshivering thermogenesis) (66). This process takes up to two weeks to fully develop (69, see Fig. 3 in Ref. 68) and, as it occurs, there is a reciprocal decline in the magnitude of shivering thermogenesis (67). I suggest that only when the capacity of the rat for BAT thermogenesis is sufficiently enhanced can the rat cease shivering and allow itself to experience the progressively larger fall in core temperature needed to initiate thermoregulatory feeding. Warming during the episodes of heating is slow, because the large capacity for BAT thermogenesis is offset by the more rapid heat loss due to the low environmental temperature. This slowness of warming allows a greater time to elapse between initiation and termination of feeding; hence the eating of larger meals. Since both the enhanced capacity for BAT thermogenesis and the rapid rate of heat loss are directly related to environmental temperature, the balance between them provides a direct link between environmental temperature and the size of a meal.

When the cold-acclimated rat returns to a warm environment, meal size decreases immediately (5). The rapidity of this change is probably due to the large capacity to warm up during thermoregulatory feeding, which remains high because the large capacity for BAT thermogenesis is no longer being offset by heat loss, which is reduced because of the warmer environmental temperature. The time available for feeding between initiation and termination of the meal is small. If the cold-acclimated rat is removed from the cold environment for 6–10 days, then returned to the cold environment, its food intake increases immediately (65). The slow adaptation that occurred the first time the rat experienced the cold is not required because cold-acclimated rats retain a large capacity for thermogenesis in BAT during a brief period in a warm environment, and do not need to shiver when reexposed to cold. Thermoregulatory feeding with large meal sizes is therefore resumed right away.

The genetically obese fa/fa rat. In the hyperphagic fa/fa fatty rat, an increase in meal size (70, 71) is associated with reduced sympathetic nervous system activity and with atrophied BAT. BAT of the fa/fa rat has a poor capacity to use glucose in response either to norepinephrine or to insulin (72–74) and is therefore unlikely to generate the required signal for initiation of food intake during thermoregulatory feeding. The atrophied BAT is also unlikely to generate rapidly the high temperature needed to terminate feeding. Indeed, the oscillations in BAT temperature appear blunted in the fa/fa rat (75). It is unfortunate that for the fa/fa rat little information is available about pulsatile release of one or more appropriate neurotransmitters in the hypothalamus or about ultradian fluctuations in sympathetic nervous system activity. However, the limited studies reported would seem to justify some speculation about the abnormality in its control of feeding. There is considerable evidence for an increased NPY release in the hypothalamus of the fa/fa rat (76, 77), including its suprachiasmatic nucleus, a known site for regulation of circadian rhythms (78). The change is not primary, since it is not observed in young fa/fa rats before the development of the obesity (76, 77) but occurs only after suppression of thermogenesis in BAT, a very early abnormality in the fa/fa rat (79). An increase in the size of pulses of NPY release should induce not only the hyperphagia but also the suppression of BAT thermogenesis and thereby atrophy of the BAT (58–61). Because of the atrophy of its BAT, the fa/fa rat lacks the normal ability to warm up during a feeding episode; its meal size is quite large (weak termination signal). This is quite different from the situation in the cold-acclimated rat discussed above where the hyperphagia and increased meal size are associated with reduced secretion of NPY in the PVN (80), so that feeding is probably almost entirely thermoregulatory. The fa/fa rat is unable to increase its food intake any further when acclimated to cold (81), but whether cold-acclimation enables the fa/fa rat to acquire a more normal control of meal size (i.e., by BAT thermogenesis during thermoregulatory feeding) is not known.

The rat with a ventromedial hypothalamic lesion. In the VMH-lesioned rat, meal size increases but frequency remains unchanged. There is loss of circadian variation, so that meal size remains high during the light phase (82). BAT is atrophied, probably secondary to attenuated stimulation of its sympathetic innervation (38). As in the fa/fa rat, meal termination would be expected to be delayed. This delay could lead to ingestion of larger meals. Atrophy of BAT, with a low capacity for thermogenesis, would imply also a reduced capacity of the BAT to use glucose. In fact, in the VMH-lesioned rat, meal initiation occurs sooner than normal in the train of events during a feeding episode, often at the start of or during a decline in blood glucose concentration (83). Thus, meal initiation must be due to factors other than increased utilization of glucose by BAT, possibly to overactivity of central neurotransmitters that promote feeding (e.g., NPY or norepinephrine).

The rat with a lateral hypothalamic lesion. In contrast to the VMH-lesioned rat, the rat that has recovered from a lateral hypothalamic lesion eats very small and very frequent meals primarily during the dark phase, nibbling constantly rather than eating discrete meals (84). The highly active BAT in the LH-lesioned rat (37, 38, 57) presumably leads to meal termination quite soon after meal initiation. The LH-lesioned rat has been shown to increase its food intake when adapted to cold (85). Whether it does so by acquiring a more normal meal pattern is not known.

The mouse with genetic ablation of BAT. In a recently discovered animal model of obesity in which BAT is virtually absent, namely the transgenic mouse with genetic ablation of BAT, marked hyperphagia develops (86), supporting the link proposed here between BAT thermogenesis and control of food intake.

Conclusions

The hypothesis proposed in this review provides a novel view of both the control of feeding and the function of BAT thermogenesis. It emphasizes the episodic nature of feeding and the necessity for episodic events in the controlling systems which govern both initiation and termination of feeding. A feeding episode is suggested to occur during an episode of increased sympathetic nervous system activity that stimulates BAT thermogenesis. Two different aspects of stimulated BAT metabolism, namely increased uptake of glucose and increased heat production, evoke initiation and termination of feeding, respectively. BAT thermogenesis is seen to be important in the control of meal size, relating it to environmental temperature (i.e., in control of energy balance). When this function is lost, as in the obese animals discussed above, other cruder mechanisms take over and the animal loses its ability to remain in energy balance by precisely adjusting its intake in relation to environmental temperature.

The hypothesis predicts that an increase in endogenous heat production that is not due to sympathetic stimulation of BAT thermogenesis will prevent the matching of intake to increased expenditure via thermoregulatory feeding. This is seen, for example, in the shivering rat during the early stage of acclimation to cold (see above) and in the rat infused with a thermogenlic β_3-adrenergic agonist to produce a sustained increase in BAT thermogenesis (87). In neither of these examples does intake rise to match the increase in expenditure.

The hypothesis reveals many gaps in our knowl-

edge. Ultradian fluctuations in sympathetic nervous system activity, in BAT thermogenesis, in core temperature, and in glucose and lactate concentrations in blood need to be studied in both normal animals and in animals in with disturbed patterns of food intake, such as the cold-acclimated rat, the genetic or hypothalamic obese rat, the lean LH-lesioned rat, and the rat living at thermoneutrality. Ultradian fluctuations in release of neurotransmitters in specific regions of the hypothalamus need to be studied and correlated with feeding episodes. Studies that measure in conscious, unrestrained rats, living at a specified temperature, all the different aspects of episodic feeding discussed above will be required for the elaboration of a complete picture of the control of thermoregulatory feeding.

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