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BROWN ADIPOSE TISSUE METABOLISM AND THERMOGENESIS

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INTRODUCTION

History

Although the thermogenic function of brown adipose tissue (BAT) has been known for over 20 years, until recently studies on this tissue have been largely limited to work of physiologists interested in animals living at low temperatures or hibernating and of biochemists interested in the peculiarities of its mitochondrial function. Six years ago it was realized that the energy expended for thermogenesis in BAT can contribute substantially to total energy expenditure, that thermogenesis in BAT occurs not only in response to cold but also in response to eating, and that BAT thermogenesis does not occur normally in some obese animals. This has led to an expansion of research on BAT, principally by nutritionists and by clinicians interested in the regulation of energy balance.

Literature Surveyed

The number of publications in this field is increasing so rapidly that it is impossible in the available space to cite all of those appearing in the last three years. Of necessity the list of references is largely limited to the most recent or comprehensive papers. Several reviews are available for further information in specific areas. The comprehensive book on BAT edited by Lindberg (96) is currently being updated (editors, D. G. Nicholls and P. Trayhurn). A book on mammalian thermogenesis, edited by Girardier & Stock (48), contains a large amount of recent information in this area. Extensive reviews are available on the mechanisms of BAT thermogenesis (115, 116), on brown adipocyte metabolism and its control (24, 25, 46, 113), on control of growth of BAT (9, 25, 121), on diet-induced thermogenesis (134, 139, 143), on dietary regulation of the sympathetic nervous system (88), on brown adipose tissue function in relation to obesity (59, 63, 64, 66), on brown adipose tissue in the newborn (27, 28) and on cold-induced nonshivering thermogenesis in BAT (40, 62). A more detailed review on the same range of topics as the present one is also available (66). A survey of BAT metabolism and obesity will soon be available in ***Clinics in Endocrinology and Metabolism*** (see 121). Proceedings of recent symposia

on regulation of energy expenditure, on drugs and novel approaches to obesity (see 100, 172) and on thermal physiology (see 41) contain more information in this area.

Categories of Thermogenesis

Brown adipose tissue thermogenesis is classified as a component of facultative thermogenesis, i.e. a process that may or may not be switched on, depending on need and on the capabilities and characteristics of the animal in question (60). In this, it resembles shivering thermogenesis in skeletal muscle. Both processes are under central and peripheral neural control, sympathetic in the case of BAT, somatic motor in the case of skeletal muscle. Both are somewhat elusive processes to study, particularly biochemically, since they may or may not be switched on according to the experimental conditions and even when switched on in vivo cannot be expected to survive in isolated tissue preparations. They are to be contrasted with obligatory thermogenesis, which occurs in all organs of the body as an essential product of the reactions necessary to maintain life and which in most mammals is responsible for the maintenance of a temperature above that of the surroundings. Obligatory thermogenesis is controlled primarily by thyroid hormones (49, 60) and usually persists in isolated tissue preparations.

THERMOGENESIS IN BROWN ADIPOSE TISSUE

Brown Adipose Tissue

MORPHOLOGY The cells of BAT are usually multilocular (contain several drops of stored triacylglycerol) and characteristically are packed with many large mitochondria (25, 96, 113). When the cells are thermogenically inactive they become filled with lipid and may superficially resemble white adipose tissue cells (25). BAT cells are innervated directly by sympathetic nerves (9) and connected to each other by gap junctions (153), which may provide electrical coupling between them (46, 47). BAT deposits also include mast cells (106) and numerous other cell types (25).

BAT deposits are located in specific interscapular, subscapular, axillary, and intercostal regions and also lie along the major blood vessels of abdomen and thorax. Small BAT deposits were also identified recently in large white adipose tissue deposits (191). Thus, BAT cells may have a wider distribution than has hitherto been supposed. The amount of BAT varies with the species, the stage of development, and, since BAT grows when stimulated and regresses when quiescent (see the section on trophic responses), with the prior nutritional and environmental experience. Many, but not all, species have abundant BAT when newborn [rats, mice, guinea pigs, and humans do, hamsters do not (27,

28)] and in some species adults retain large amounts whereas in other species they do not. BAT has an extensive vasculature and is capable of extremely high rates of blood flow when stimulated (40).

MECHANISMS OF THERMOGENESIS BAT mitochondria have a unique proton conductance mechanism that permits them to become reversibly uncoupled (115, 116) and thus to oxidize both endogenous and exogenous substrates at an extremely high rate independent of the need to phosphorylate ADP. This mechanism is controlled by the intracellular concentration of fatty acids (24, 115, 116), generated principally by the breakdown of endogenous triacylglycerol. The mechanism involves a specific protein (molecular weight 32,000) that has one binding site for purine nucleotide per dimer on the outer surface of the inner mitochondrial membrane. Variously known as thermogenin (26), uncoupling protein (7, 90, 120), nucleotide binding protein (95), or simply the 32,000(-M_r) protein (115, 116) this protein has now been isolated (95) and an immunoassay for it developed (26, 90, 120). Immunological studies show that the protein is unique to BAT mitochondria. Reconstitution experiments suggest that other membrane components may also be involved in the thermogenic mechanism (18). The protein will be referred to in this review as the uncoupling protein (UCP).

OTHER METABOLIC PATHWAYS Numerous other metabolic events follow the interaction of noradrenaline, released from the sympathetic nerve supply, with one or more types of receptor on the cell surface (see the section below on receptors). These events include depolarization of the plasma membrane, stimulation of several plasma membrane activities (adenylate cyclase, Na,K-ATPase, phosphatidylinositol hydrolysis, possibly also T_4 5'-deiodinase), accumulation of cyclic AMP, activation of one or more protein kinases, activation of triacylglycerol lipase, acceleration of lipolysis, and increased fatty acid oxidation (15, 24, 25, 46, 113, 115, 116, 162, 164). Some of these events provide a direct link between noradrenaline and the mitochondrial thermogenic mechanism, mediated, as noted above, by fatty acids. Others are presumably involved in the trophic response (see the section on trophic responses). The function of some of these events is not yet clear.

In addition to metabolizing endogenous triacylglycerol, BAT can also use exogenous triacylglycerol and glucose for thermogenesis as well as for maintenance and replenishment of its endogenous lipid stores. The activity of BAT lipoprotein lipase increases very rapidly in response to acute sympathetic stimulation (29, 53). The rate of lipogenesis is often stimulated simultaneously with that of fatty acid oxidation and thermogenesis (99). Thus, glucose can serve as a thermogenic substrate when it is abundantly available, e.g. after a meal when insulin is secreted (99). Thermogenesis can also occur without stimulated lipogenesis, the two being regulated independently.

TROPHIC RESPONSES BAT grows when it is stimulated by prolonged and intense activation of its sympathetic nerve supply (9). This growth involves the division of precursor endothelial cells, with a consequent hyperplasia of the tissue (24, 25). Both total protein and mitochondrial mass increase to an extent that may parallel or exceed the hyperplasia. The increase may even occur without hyperplasia, depending on the intensity of the stimulation and possibly on other factors. The capacity of BAT for such nonmitochondrial processes as glycolysis and lipogenesis can also be selectively regulated (31, 99). An increase in the concentration of gap junctions is also usually seen when BAT grows (153). Mitochondrial adaptations include a selective increase in the concentration of the UCP and a change in phospholipid fatty acid composition. The former can be detected within 3–4 hours of acute exposure to cold (112, 121) and is associated with an increase in the amount of mRNA specific for this protein (19, 43, 123). Work with mRNA derived from BAT and cell-free protein-synthesizing systems is currently providing information about regulation of the synthesis of the UCP and of its incorporation into mitochondria (19, 43, 121, 123). Elucidation of the functions of the numerous protein kinases of BAT, some dependent on cyclic AMP or cyclic GMP and some independent of these compounds, will also be required for a fuller understanding of both thermogenic and trophic responses of BAT (164). Studies with cultured (107, 108, 111) or transplanted (109) BAT should provide insight into the nature and roles of trophic factors that interact with BAT.

The trophic response of BAT varies both quantitatively and qualitatively with the nature of the external stimulus, with the age and perhaps sex of the animal, with the diet, and with the species and genetic background of the experimental subject. Some of this variation may be attributed to differences in the activity of the sympathetic nervous system but some may also be due to variations in the BAT itself and in its control by other factors.

MEASUREMENT OF THERMOGENESIS AND AMOUNT OF BAT The only quantitative method for assessment of BAT thermogenesis in intact animals is measurement of its blood flow, with radioactive microspheres, and of the A-V difference in oxygen tension across the various BAT deposits (40). This approach is technically difficult, not readily applicable to all the deposits of BAT in the body, and not applicable at all to human studies. Indirect measures include the assessment of the increase in metabolic rate in response to noradrenaline, most of which occurs in BAT in the rat, or of the catecholamine-induced increase in BAT temperature or changes in surface temperature. These measures are however, far from quantitative.

Several in vitro methods have been used to give a qualitative index of thermogenic state of BAT in the intact animal. These include measurements of respiration in tissue fragments (50), of activity of Na,K-ATPase in homogen-

ates (139), and of GDP binding by mitochondria isolated from BAT (60, 61). That none of these is quantitative or completely reliable might be expected for a process that requires the continuing presence of noradrenaline for its persistence in the intact animal. The most used method measures the binding of GDP to mitochondria. Binding is low in mitochondria from quiescent BAT and is rapidly increased (within an hour) when the tissue is acutely stimulated by activation of its sympathetic nerves or by administration of noradrenaline (20, 22, 35). This increase is associated with ultrastructural changes in the isolated mitochondria, is rapidly reversible (61), and does not require protein synthesis (35). The changes in GDP binding are attributed to the unmasking and remasking of binding sites on the UCP in the mitochondrial membrane (60, 61), an interpretation reinforced by the direct measurement of the amount of protein present and the extent to which added nucleotide binds to it (7). The rapidity of changes measured, for example in 20 minutes during arousal of mice from torpor (65), the occurrence of diurnal variation (148), and the rapidity of masking after cessation of an infusion of noradrenaline (61) all point to the persistence in isolated mitochondria of a change in the intact tissue that is associated with the state of thermogenic activation and not directly with the concentration of the UCP. Unmasking and masking do not appear to occur in mitochondria isolated from hamster BAT (174) and some workers do not detect it even in rats (112, 114), possibly because of subtle differences in their isolation procedure that permit unmasking to occur in vitro. Unmasking is known to be produced in vitro by preincubation of mitochondria at a reduced pH (165).

Some measurements of the amount of BAT present in an animal may be inaccurate because of difficulty in recognizing the tissue visually, particularly when it is replete with lipid and white in appearance. The wet weight of BAT is a useless measure of metabolic capacity, serving only as a very rough index of the amount of lipid stored in the tissue. Measurement of total protein, DNA, or a mitochondrial marker enzyme, such as cytochrome oxidase, provides a better index of the amount, but not of the activity, of the tissue. The recent development of an immunoassay for the UCP provides a more specific means of identifying BAT. Since the concentration of this protein in BAT varies according to the extent to which the tissue is stimulated (see the section on trophic responses), measurement of the amount of the UCP is a good index of the potential thermogenic capacity of BAT, but not of its actual thermogenic activity. Whether this potential is expressed depends (*a*) on whether the sympathetic nervous system is functional and appropriately controlled, and (*b*) on the responsiveness of the tissue. Assessment of the former requires the measurement of noradrenaline turnover in BAT (88), another useful index of the potential thermogenic activity of BAT.

Neural Control of BAT Thermogenesis and Trophic Responses

CENTRAL NERVOUS CONTROL Central nervous mechanisms that control BAT are those that act via its sympathetic nerve supply. They are integrated with those that control thermoregulation, with those that control energy balance, and, in certain hibernators, with those that control responsiveness to photoperiod (62). An interaction with the neural control of blood pressure also occurs (161).

Activation of BAT thermogenesis by stimulation of the ventromedial region of the hypothalamus (137), on the one hand, and the lack of diet-induced activation of BAT thermogenesis (32, 72, 73, 124, 149) and of noradrenaline turnover in BAT (194) in animals with a variety of hypothalamic lesions, on the other hand, both point to an important role for the hypothalamus in the control of BAT thermogenesis. The ventromedial region of the hypothalamus of the rat is, however, not required for cold-induced BAT thermogenesis (32, 69, 72, 158) and alternative controlling pathways must also be involved. A lower brain stem center that exerts a thermogenic drive on BAT (144) is presumably normally inhibited by higher centers.

Receptors that relay signals for BAT thermogenesis must include temperature receptors in the skin, the preoptic region of the hypothalamus and possibly also the spinal cord (see 62), insulin receptors, probably in the hypothalamus (88, 128), and other receptors, as yet unknown, that relay information about dietary lipid and about dietary protein levels. The cephalic phase of food ingestion may also invoke BAT thermogenesis via insulin receptors.

PERIPHERAL SYMPATHETIC NERVOUS CONTROL Thermogenic and trophic responses of BAT are primarily controlled by its sympathetic innervation (9, 24, 25, 121). A modulatory role for the serotonin-containing mast cells in the regulation of noradrenaline release has also been suggested (106, 121).

Innervation The sympathetic nerves to interscapular BAT of the rat arise via the medial and inferior cervical ganglia and the first three thoracic ganglia (159). The neural pathways between these nerves and the higher brain centers are unknown. Innervation of other BAT deposits is not known. No parasympathetic innervation of BAT has been detected (23). The direct thermogenic action of noradrenaline on BAT cells is very well established (24, 113) and can account for the thermogenic response of the tissue to nerve stimulation. The electrical coupling between individual BAT cells in deposits in the intact animal also serves to propagate the effect of sympathetic stimulation (46, 47). Other hormones, particularly thyroid and adrenal cortical hormones, can modulate BAT thermogenesis either by influencing the responsiveness of the tissue to noradrenaline or by influencing the central mechanisms that control the activity of the sympathetic innervation of BAT (see the sections on thyroid hormone and glucocorticoids).

The trophic response of BAT to sympathetic stimulation is also thought to be mediated by noradrenaline and perhaps by other factors also (9, 66, 121). Early experiments in which animals were treated chronically with noradrenaline failed to produce the entire spectrum of trophic changes seen in BAT of cold-acclimated animals, particularly the increased concentration of UCP (35). Moreover, initial studies of rats adapted to eating a cafeteria diet indicated a trophic response of BAT without an increase in concentration of the UCP (139). Implantation of two types of noradrenaline-secreting pheochromocytoma in rats produced changes similar to those in cold-acclimated rats in the one case but not in the other (122). All these findings pointed to another substance in addition to noradrenaline mediating the cold-induced mitochondrial changes. However, more recent work using the more sensitive immunoassay for the UCP has, in fact, demonstrated an increase in UCP in BAT mitochondria of cafeteria-fed rats (114). Moreover, the chronic administration of noradrenaline in close proximity to interscapular BAT by implanted pumps (105, 121) or the chronic administration of long-acting sympathomimetics (192) can induce a BAT hypertrophy that is accompanied by an increased mitochondrial concentration of the UCP. Thus, although the participation of other factors in the trophic response cannot be excluded, it seems likely that, except in hamsters (see the section on photoperiod and thermogenesis), the intensity and duration of sympathetic stimulation alone can influence the type of trophic response seen.

Receptors Adrenoceptors on BAT cells that are involved in the thermogenic response include both α- and β-subtypes. Both types are required for a maximum response in vivo (41, 42). Adrenoceptors must also be present on blood vessels and nerve endings but have not been characterized. On the basis of the relative potencies of a series of sympathomimetic agonists and antagonists on thermogenesis in BAT cells, on adenylate cyclase in BAT, and for binding to BAT membranes, the β-adrenergic receptor was originally identified as a β_1-subtype (24). Recent studies with more selective β_1- and β_2-adrenoceptor agonists and antagonists indicate the presence of a mixed population of β_1- and β_2-adrenoceptors (143, 165). Another suggestion, based on actions of newer catecholamine analogs, is that a third type of β-adrenoceptor is present on BAT cells (2, 3). The concentration of β-adrenoceptors is down-regulated by chronic stimulation by noradrenaline, as in cold-acclimated animals (24, 25, 168, 169) and these receptors appear to become uncoupled from the adenylate cyclase complex during cold acclimation (110, 167–169).

α_1-Adrenergic receptors participate in noradrenaline-induced turnover of phosphatidylinositol (103, 104), in gating of calcium channels (30), in initial electrical changes in the plasma membrane (47, 75), in stimulation of Na,K-ATPase (139), and in stimulation of T_4 5'-deiodinase (162). The exact function

of these changes is not yet clear and they play a relatively minor role in the thermogenic response of isolated cells to noradrenaline (103, 152). They may be more important in the intact animal, in which, for example, electrical coupling between cells (46, 47) and availability of T_4 as substrate for the 5'-deiodinase might potentiate the thermogenic action of a limited amount of noradrenaline. Such potentiation of the thermogenic action of the β-agonist, isopropylnoradrenaline, by an agonist acting on α_1-adrenoceptors has been seen in vivo (41, 42). In contrast to β-adrenoceptors, α_1-adrenoceptors appear to be up-regulated when the tissue is chronically stimulated (118, 119).

α_2-Adrenergic receptors are present in BAT of some species and may mediate inhibition of adenylate cyclase (37, 152, 166) and control of cyclic GMP levels (164). Their functional significance is not understood.

Endocrine Control of BAT Thermogenesis and Trophic Responses

THYROID HORMONE Thyroid hormone is required for the thermogenic response of BAT to noradrenaline (60). Thus, the response of BAT to cold-exposure (175) and to nerve stimulation (157) is lacking in hypothyroid rats. That only permissive amounts of thyroxine are sufficient for normal thermogenic and trophic responses of BAT in thyroidectomized rats indicates that thyroid hormone does not exert a directive role in these changes (175). Moreover, provision of excess exogenous thyroid hormone may result in suppression of BAT thermogenic function in intact animals (175) and does not induce BAT hypertrophy, other than that due to an accumulation of lipid (131, 175). The activity of Na,K-ATPase, often considered a target for thyroid hormone in other organs may or may not be modified in BAT by thyroid status (85, 131).

The well-known complex interaction between thyroid status and the activity and actions of the sympathetic nervous system (see 60, 66) is further complicated by the recent demonstration that BAT synthesizes T_3 from T_4 (92, 163) and that the 5'-deiodinase that catalyzes this conversion is stimulated by noradrenaline (162). If endogenously made T_3 should be the primary determinant of the responsiveness of BAT to noradrenaline (and this is not yet established), then the sympathetic nervous system would control the thyroid-dependent responsiveness of BAT to its own action on thermogenesis and growth. If T_4 deiodination in BAT is partly also responsible for the delivery of T_3 into blood (163), then the coincident changes in BAT thermogenesis and in T_3 level in the blood that frequently occur, as in cold-acclimated animals, in cafeteria-fed animals, and in fasting animals (see 92) may be reflections of the same event, namely, stimulation of BAT by noradrenaline. Indeed, chronic stimulation of BAT thermogenesis by administration of noradrenaline is associated with an increase in the level of T_3 in the blood (125).

GLUCOCORTICOIDS Excessive amounts of glucocorticoids suppress BAT thermogenesis in mice (45) and in rats (74), probably by a central action to suppress diet-induced thermogenesis, since cold-induced BAT thermogenesis is not prevented (45). Diet-induced thermogenesis in BAT can occur in the absence of glucocorticoids (74) and it may be presumed that the thermogenic response of BAT to noradrenaline does not require these hormones, in contrast to most other metabolic effects of catecholamines on other organs. Moreover, normal thermogenic and trophic responses of BAT occur in hypophysectomized rats maintained on no more than permissive amounts of T_4 and corticosterone (39) or with no therapy (89), which indicates again only a limited role for directive actions of glucocorticoids on BAT. The failure of adrenalectomized rats to survive acute cold-exposure may be due to a failure of catecholamine-induced substrate mobilization in tissues other than BAT (66).

Glucocorticoid receptors are present in BAT (38). Their role is unknown but may be in the control of some enzyme activities or unrelated functions such as their antiinflammatory action.

An effect of glucocorticoids to suppress peripheral conversion of T_4 to T_3 (98), not yet demonstrated for BAT, may well be due not to a direct action of these hormones but to an indirect effect that reduces sympathetic nervous activity, and thus due to lesser peripheral stimulation of the 5'-deiodinase by noradrenaline. Adrenalectomy results in an increased level of T_3 in blood (74).

INSULIN Two distinct roles of insulin in control of BAT are a direct action to modulate its glucose metabolism and a central action to regulate its sympathetic nervous activity. Insulin promotes glucose utilization and lipogenesis in BAT (99, 113) and is required for both cold- and diet-induced thermogenesis in BAT (132). BAT thermogenesis is suppressed in insulin-deficient diabetic rats (156) and in insulin-resistant diabetic mice, such as the ob/ob mouse (70) and the db/db mouse (52). Insulin is required for the trophic response of BAT (132) and BAT of diabetic animals atrophies (156, 160). The occurrence of BAT hyperplasia in cafeteria-fed rats has been correlated with the maintenance of normal glucose tolerance and presumably normal insulin sensitivity (33). The loss with aging of the hyperplastic component of the trophic response to cafeteria feeding may be associated with the development of insulin resistance in older animals (140).

The simultaneous insulin-dependent stimulation of lipogenesis and of thermogenesis by sympathetic stimulation suggests an obligatory link between these two processes (31). Thermogenesis is not, however, always linked to lipogenesis, since the latter is suppressed in animals fed high-fat diets whereas the former is promoted (101, 145, 179).

Insulin is not apparently involved in the regulation of lipoprotein lipase activity of BAT (29, 53), in contrast to its regulatory role in white adipose

tissue. Rather, this enzyme is regulated by sympathetic nervous activity (29, 53). Only minor and variable changes occur in the activity of this enzyme in BAT in response to feeding and fasting (44, 117) and a suppression has been observed in sucrose-fed rats (54).

GLUCAGON A thermogenic and trophic action of glucagon has been proposed to influence the response of BAT to cold acclimation (87). It must, however, be borne in mind that glucagon administration in vivo results in the liberation of catecholamines, which may participate in the trophic responses observed, and that high concentrations of this hormone are required for a direct thermogenic action on BAT cells in vitro. The correlations, however, between glucagon levels and BAT responses during cold acclimation suggests that some regulatory role may be assigned to glucagon in this situation. Any role of glucagon in responses of BAT to diet appears unlikely.

PITUITARY HORMONES Because hypophysectomized rats can exhibit normal thermogenic and trophic BAT responses in the cold (39, 89), any major role of direct regulation by pituitary hormones of BAT can be excluded. Their role in regulation of thyroid and adrenal cortical function would, of course, be important for normal BAT function.

SEX HORMONES Receptors for estradiol are present in BAT of both female and male rats (55) and for progesterone in female rats only (56). The role of these receptors is not known. No change in BAT dry weight occurs in ovariectomized rats treated with either or both hormones (80). Sex differences in BAT thermogenesis and trophic responses have not been studied systematically. In one strain of rats (brown Norway) females respond better than males, whereas the reverse is true of another strain (Lewis) (T.-C. Yang and J. Himms-Hagen, unpublished results). Thus, no generalization is possible Lactation is associated with suppression of BAT thermogenesis (171–173) and lowering of UCP concentration (8). The mechanism of this suppression is unclear, but may well be due to a central reduction in sympathetic nervous activity rather than to any direct hormonal action on BAT itself.

MELATONIN In species that are sensitive to photoperiod, such as the hamster, a pineal-dependent hypertrophy of BAT occurs in response to a short photoperiod (11, 183). Chronic administration of melatonin promotes a trophic response of BAT in hamsters (11, 183) but not in rats (121). The mechanism of action of melatonin is not understood. Its effect to cause simultaneous gonadal regression appears to be exerted centrally. The pineal gland is not required for cold- or diet-induced growth of BAT in hamsters (176, 177) and these responses are presumably mediated by the sympathetic nervous system (see the section on photoperiod and thermogenesis).

BROWN ADIPOSE TISSUE AND THERMOGENESIS IN NORMAL ANIMALS

Cold-Induced Nonshivering Thermogenesis

First described some thirty years ago (see 40, 62, 66), cold-induced nonshivering thermogenesis (NST) was demonstrated to occur almost exclusively in BAT only six years ago (40). NST in BAT is of particular importance in thermoregulation in a number of rodent species when they are newborn or adapted to living at low temperatures. It can account for as much as 40–50% of total energy expenditure in the rat living at 4°C (62) and in the mouse living at 22°C (171).

One would expect NST in BAT to be suppressed in animals that hibernate or enter daily periods of torpor, presumably by suppression of sympathetic nervous activity in the tissue. Marked activation of BAT thermogenesis has been observed during daily arousal from torpor of the food-restricted mouse (65) and during arousal of the hibernating bat. Some human populations (Australian Aborigines, Kalahari Bushmen) resemble the laboratory mouse in entering daily periods of shallow torpor when their food supply is restricted. Whether their rewarming also involves BAT is unknown.

Control of NST is by the sympathetic nervous system, with responses to peripheral and central temperature receptors being integrated in the central nervous system (62). Prolonged exposure to cold results in a trophic response of BAT (see the section on trophic responses) that results in a large increase in the capacity of the animal for NST. In all studies of BAT, whether they involve cold acclimation or not, it is most important to recognize that any animal maintained at a temperature below thermoneutrality (i.e. below about 28°C for the rat or 32–34°C for the mouse) will have BAT that exhibits a thermogenic and trophic state that has arisen because of chronic stimulation of NST in BAT.

Diet-Induced Thermogenesis

The existence of diet-induced thermogenesis (DIT) was first suspected some 80 years ago and it has been studied sporadically since that time (134, 139, 143). Once the crucial role of BAT in NST had been defined (40) it was soon recognized to have a similar role in DIT, likewise under sympathetic control (134, 139, 143). An increased blood flow in BAT is seen in association with DIT (133) and can even be detected after a single meal (51).

DIT is frequently studied in animals fed a "cafeteria" or "supermarket" diet, composed of a rotating menu of palatable items designed to induce them to overeat (139, 143). Several problems are inherent in the use of such a diet, including the variability in composition from one laboratory to another, the interindividual variability in the composition of the diet selected, and the difficulty in measuring food intake. Moreover, inclusion of salty foods may

complicate the outcome, since provision of sodium chloride in the diet can itself promote a trophic response of BAT, apparently without simultaneous thermogenic activation (21). The adaptive response to such a diet also depends on the species, age, sex, and genetic background of the animal being studied as well as on the composition and amount of food being eaten, the environmental temperature, the prior nutritional state of the animal, and even the time of year and conditions in the animal house, such as lighting (126, 138, 139, 148). Variation between strains of rat (126) is seen at its extreme in the genetically obese fa/fa rat in which DIT is defective [see the section on fatty rats (fa/fa)]. It is little wonder, given the large number of ways in which cafeteria feeding experiments can be designed (choice of species, strain, age, sex, previous nutrition, previous temperature acclimation, temperature during the experiment, lighting conditions and time of day the animal is studied in relation to the diurnal rhythm of feeding, selection of cafeteria foods, time of day and number of times per day the food is offered, handling of the animal before it is killed, method of assessment of BAT thermogenesis and amount) and the paucity of information about such design in many published papers that some workers have failed to detect the phenomenon of DIT (4, 5, 10) and that there is so much controversy on this subject (57, 142).

Both dietary carbohydrate and dietary lipid stimulate sympathetic nervous system activity (154, 182, 190) and DIT in BAT (127, 141, 147). However, a diet deficient in protein also stimulates sympathetic nervous activity (81) and DIT (146) in BAT and it is sometimes difficult, given the nature of the cafeteria diet, to decide which change in diet composition and/or amount is responsible for observed changes in BAT.

Nevertheless, the chronic increase in sympathetic stimulation engendered by a cafeteria diet or a protein deficient diet results in a trophic response of BAT that resembles but is generally smaller than that seen in cold-acclimated animals (112, 114, 139). Thus, the capacity for DIT of the animal adapted to eating a cafeteria diet increases because of the trophic response of its BAT, and energy balance studies indicate that much of the extra energy intake of the cafeteria-fed rat may be dissipated as DIT (126, 136, 139). As might be expected for two types of adaptation that both produce BAT growth, acclimation to cold results in a greater capacity for DIT and adaptation to a cafeteria diet results in a greater capacity for NST.

Food-Restriction and Thermogenesis

Different species regulate their BAT differently in response to the availability of a limited amount of food. In rats, fasting reduces the activity of the sympathetic nervous system in BAT (190) while prolonged food restriction reduces the size and thermogenic activity of BAT (130, 135), the growth of BAT during acclimation to cold (79), and the capacity of the rat for a thermo-

genic response to noradrenaline (130, 135). The reduced size of BAT probably also contributes to the high metabolic efficiency of animals during refeeding after food restriction (130). The adaptation is a logical one to expect in a situation in which it is to the advantage of the animal to conserve energy. In contrast, the mouse reacts to food restriction by becoming torpid early each morning (77, 184) and BAT thermogenesis is suppressed during torpor (65). Energy conservation in this case is achieved by reduced energy expenditure in all organs of the body, including BAT, because of their low temperature. At least once daily the food-restricted mouse arouses spontaneously from torpor; it will also arouse when disturbed. During arousal, BAT thermogenesis is stimulated, presumably as a result of sympathetic activation (65). BAT of the mouse does not atrophy during food restriction, indeed it may even show a trophic response, probably because the trophic effect of the daily stimulation during arousal outweighs the atrophic effect of reduced stimulation during torpor.

Photoperiod and Thermogenesis

Seasonal breeders regulate growth of their BAT not only in relation to diet and to temperature but also in relation to photoperiod, by a mechanism mediated primarily by melatonin secreted by the pineal gland (11, 183). Relatively little is known about the control of trophic and thermogenic responses of hamster BAT (see the section on melatonin) but this control apparently differs from that seen in rats and mice. Hamsters, the only example of this group studied to any appreciable extent, grow more BAT when cold adapted, a process not accompanied by hyperplasia (67) but including mitochondrial adaptations, notably an increase in the concentration of the UCP (67, 174, 176, 177). Short photoperiod likewise promotes BAT growth (11, 176, 177, 183), apparently without the mitochondrial adaptations seen during cold acclimation (176, 177). In rats, in contrast, short photoperiod has no effect on BAT (86).

Hamsters fed a palatable diet do not change their energy intake but do grow more BAT and acquire an increased capacity for a thermogenic response to noradrenaline (11, 176, 177, 183). Paradoxically, the metabolic efficiency of the fat-fed hamster decreases and it becomes more obese. Its hypertrophied BAT is not thermogenically active in that there is no increase in GDP binding (176, 177) (although it must be borne in mind that this measurement possibly may not reflect the thermogenic state of hamster BAT mitochondria) (see the section on measurement of thermogenesis and amount of BAT). How BAT grows and yet does not function thermogenically in the hamster is not understood. Control of trophic responses in BAT of hamsters may not even be mediated by noradrenaline since chronic administration of noradrenaline does not produce a trophic response in hamsters (176, 177) as it does in rats (see the section on trophic responses). Since denervation induces tissue regression (177), it can be concluded that the sympathetic nerves are involved. A trophic

factor other than noradrenaline and melatonin may be involved in the control of BAT growth in hamsters.

BROWN ADIPOSE TISSUE AND THERMOGENESIS IN OBESE ANIMALS

Recent reviews provide a background to BAT and thermogenesis in obese animals (59, 63, 64, 66); only selected examples and more recent information are discussed here. The concept that defective DIT and/or NST in BAT can contribute to obesity (58, 63, 64) has led to a large amount of work on BAT function in a variety of obese animals. In all, one or another type of defective control of BAT thermogenic and/or trophic responses has been detected. In none has a primary defect in BAT been found. Current research on the role of the suppressive action on BAT thermogenesis of glucocorticoids (see the section on glucocorticoids) has been prompted by the almost uniform effect of adrenalectomy to ameliorate their obesity. Only for the fa/fa rat has it so far been elucidated that an abnormal sensitivity to a suppressive effect of glucocorticoids may result in defective DIT in BAT (see the section on fatty rats). Considerably more information about the role of glucocorticoids in the defective functioning of BAT in the other types of obese animal can be expected to appear soon.

Hypothalamic Obesity

GOLDTHIOGLUCOSE-LESIONED MICE The goldthioglucose (GTG)-obese mouse is characterized by a high metabolic efficiency which, together with hyperphagia, produces its obesity. It has relatively inactive BAT and fails to activate either BAT thermogenesis (72) or sympathetic nervous activity in its BAT (194) when on a cafeteria diet. A normal activation of BAT thermogenesis and growth occurs in the cold-acclimated GTG-obese mouse (72) and a normal regulation of body temperature in the cold. Thermoregulation at a lower body temperature than normal does occur during the night and early morning in the restricted-fed GTG-obese mouse (J. Himms-Hagen, unpublished results), and this must also contribute to its high metabolic efficiency.

Thus, the defect in the GTG-obese mouse lies in the lack of control of diet-sensitivity of the sympathetic nervous system. The site of the defect is probably in the ventromedial region of the hypothalamus. Since adrenalectomy ameliorates the obesity of the GTG-obese mouse (34), yet this animal does not usually have excessively high levels of corticosterone in its blood (150), the central sensitivity to the suppressive action of glucocorticoids may normally be antagonized at the level of the ventromedial hypothalamus, an antagonism lacking in the GTG-obese mouse.

MEDIAL HYPOTHALAMIC-LESIONED RATS Medial hypothalamic lesions of various types are associated with inactive BAT (69, 158), that does not respond thermogenically when the rat eats a cafeteria diet (32, 73, 149). The low sympathetic nervous activity in BAT (180) suggests a lack of diet-induced activation. Cold-induced thermogenic and trophic responses of BAT occur normally (32, 69, 73, 158). The effect of the lesion is thus similar to that in the GTG-obese mouse (see above). As in the GTG-obese mouse, adrenalectomy alleviates the obesity (82).

Genetic Obesity

FATTY RATS (FA/FA) The BAT of the young fatty rat does not respond thermogenically to diet, either long-term (74, 178) or short-term feeding of a single meal (97, 127, 129, 141, 188). The defect is apparent at a very early age (13, 188). Cold-induced thermogenesis and trophic responses of BAT can occur normally (74, 178) and this rat is able to become cold acclimated and to increase its capacity for NST in the normal way (4, 16). The response to administered noradrenaline is normal (16, 127) and increases after acclimation to cold (16, 127, 141). Probably because of the chronic lack of trophic stimulation of the tissue, BAT tends to atrophy in older fa/fa rats and comes to resemble white adipose tissue in its appearance and lack of thermogenic capacity (93, 94). Its normal lipoprotein lipase activity (76), in contrast to the elevated activity in white adipose tissue, indicates that it is not, in fact, converted to white adipose tissue, but is simply degenerated and ultimately denervated BAT that has a reduced responsiveness to catecholamines (93, 102, 185) and little UCP (6).

Adrenalectomy of the fa/fa rat restores the responsiveness of its BAT to diet (74, 97) and raises the reduced level of T_3 in its blood (97, 188). Yet the fa/fa rat does not have excessively elevated levels of corticosterone in its blood (97, 188). Rather, its defect appears to lie in a genetically determined excessive sensitivity, possibly of its hypothalamus, to the suppressive effect of corticosterone on BAT thermogenesis (74). The detection of a gene dosage effect of the abnormal fa gene on the thermogenic state of BAT and on the T_3 level in the blood of heterozygotes (188) indicates that these changes are close to the genetic defect. There are abnormalities in hypothalamic chemistry in the fa/fa rat (see 59) but their relationship to the postulated hypothalamic defect is not understood.

OBESE MICE (OB/OB) The high metabolic efficiency of the ob/ob mouse is associated with BAT that is thermogenically inactive (12, 70, 71, 155) with little UCP (6) and usually poorly responsive to noradrenaline (12, 14, 15, 155, 170). The reduced sympathetic nervous activity in BAT (83, 84, 189, 193) appears to result in these secondary atrophic changes in BAT. Treatments that

increase sympathetic nervous activity in BAT, such as acclimation to mild cold (84, 193) and feeding a cafeteria diet (68), improve BAT function (68, 70), presumably because of the trophic effect of the increased sympathetic activity. It has been postulated that the reduced sympathetic nervous activity in BAT of the ob/ob mouse leads to a relatively hypothyroid state of the tissue, which in turn results in refractoriness to noradrenaline (65, 68, see the section on thyroid hormone). Provision of extra thyroid hormone also improves BAT function in the ob/ob mouse (71) without any change in sympathetic nervous activity (85). Adrenalectomy increases sympathetic nervous activity in BAT of the ob/ob mouse (181), ameliorates its obesity (151), and presumably also improves the defective functioning of its BAT.

The basic defect in the ob/ob mouse probably lies in a centrally determined excessively high propensity for entry into torpor, i.e. for thermoregulation at a lower than normal body temperature, even in the fed state (see the section on food-restriction and thermogenesis). The ob/ob mouse appears to sense itself to be starving and becomes torpid, even in the presence of an adequate food supply (65, 184). The unusual cold intolerance of the ob/ob mouse, long known as a remarkable characteristic of this animal, has previously been attributed to a failure of NST in its BAT (59, 63, 170). However, a more likely explanation is the entry of the mouse into irreversible torpor after a variable period during which it does thermoregulate in the cold (68). Even normal food-restricted mice have their BAT in a quiescent state when they are torpid (65); presumably sympathetic nervous activity in BAT is low under these conditions. Daily arousal from torpor has a thermogenic and trophic effect on their BAT. The ob/ob mouse, when fed a restricted amount of food once a day experiences episodes of profound torpor (about 5–6°C below normal body temperature) but arouses daily before feeding (65). Such a regime also improves the defective functioning of its BAT, probably as a result of the trophic effect of the daily thermogenic activation during arousal.

The defect in control of torpor in the ob/ob mouse is postulated to be in the hypothalamus and associated with the known abnormal hypothalamic ultrastructure and biochemistry (see 62). It may also be associated with the high levels of corticosterone in the blood (150) and/or an abnormally central high sensitivity to the suppressive effect of corticosterone. The defect may lie in the sensing of dietary carbohydrate, usually mediated by insulin (see the section on central nervous control), and be associated with the insulin resistance of the ob/ob mouse. The ob/ob mouse is indeed able to sense a diet high in fat (15, 68) and to respond by increasing sympathetic nervous activity and thermogenesis in its BAT (68); it does not become torpid under these conditions and its BAT function improves (15, 68).

It is worth noting that the literature on the ob/ob mouse is replete with contradictory and inexplicable observations, which because of space limitations are not reviewed in detail here. These probably arise from the extremely

variable phenotypic expression of the genetic defect secondary to variations in housing, handling, and treatment of the animals. Variables that influence the thermogenic state of BAT in the ob/ob mouse include environmental temperature, diet availability and composition, time of day diet is provided, noise, and other disturbances permitting or preventing torpor (including numbers and types of mice in each cage), lighting conditions and the time of day the mouse is studied in relation to lights on. Since handling or a change in environment promotes arousal from torpor, which necessitates thermogenic activation of BAT, it is extremely difficult to study the animal in the state in which it spontaneously spends most of its life in the animal house.

PHARMACOLOGY OF BROWN ADIPOSE TISSUE THERMOGENESIS

The idea that defective thermogenesis might contribute to human obesity (78) and evidence that defective BAT thermogenesis can contribute to animal obesity (58) have led to attempts to develop thermogenic drugs that might be useful in the treatment or prevention of human obesity. Numerous such compounds are currently being studied, but relatively little information has so far appeared in the literature. Of the various pharmacological approaches to the promotion of BAT thermogenesis (165, 186) the most common has been the search for sympathomimetic agents with a heightened selectivity for BAT. Several such agents appear to promote thermogenesis and fat loss in obese animals and to stimulate BAT (1–3, 36, 100, 187, 192). This research area is one that can be expected to evolve and to generate a considerable literature in the near future.

BROWN ADIPOSE TISSUE AND THERMOGENESIS IN HUMANS

The possible role of BAT thermogenesis in human energy balance is reviewed in more detail elsewhere (64). The principal problem in assigning a quantitative role to BAT is our current inability to assess the amount and thermogenic activity of BAT other than by destructive techniques (see the section on measurement of thermogenesis and amount of BAT). The recent use of immunocytochemical techniques conclusively demonstrated the presence of BAT in man (17, 91), reinforcing previous conclusions based on histological methods. However, even quantitation by this means would provide only a measure of thermogenic potential and not actual thermogenic activity at any particular time. Assessment of thermogenic activity in a quantitative manner must await the development of new experimental approaches.

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