J. Biosci., Vol. 18, Number 2, June 1993, pp 161-173. © Printed in India.

Brown adipose tissue: from thermal physiology to bioenergetics

PAUL TRAYHURN
Division of Biochemical Sciences, Rowett Research Institute, Bucksburn, Aberdeen AB2 9SB, Scotland, UK

MS received 6 August 1992; revised 25 January 1993

Abstract. Brown adipose tissue is an organ in mammals specialized for the generation of heat. The tissue plays an important role in thermoregulatory heat production (non-shivering thermogenesis), and in nutritional energetics (through the process of diet-induced thermogenesis). Much of the current interest in brown adipose tissue has been catalysed by the postulate (1970's) that a reduced capacity for thermogenesis underlies the development of obesity. Heat is generated in brown fat by a controlled uncoupling of oxidative phosphorylation, a process regulated by a tissue-specific mitochondrial uncoupling protein, M_r 32-33,000. The immunological identification of uncoupling protein is now used as a biochemical criterion for distinguishing brown fat from white adipose tissue. The gene coding for uncoupling protein has been cloned in several species, and a number of factors regulating the expression of the gene, as well as the amount and activity of the protein itself, have been documented. In addition to its direct role in heat production, brown adipose tissue has some notable general metabolic properties, such as in the conversion of thyroxine to triiodothyronine. An overview of the biology of brown adipose tissue is presented in this article, with an emphasis on some recent developments.

Keywords. Brown adipose tissue; thermogenesis; heat; uncoupling protein.

1. Introduction

The past 15 years has seen a considerable growth of interest in the biology of a specialized form of adipose tissue, namely brown adipose tissue (BAT) or brown fat. Traditionally, BAT has been associated with thermoregulation through its role in the generation of heat by *non-shivering thermogenesis",* the tissue is prominent in hibernators, the newborn of many mammalian species, and in adult rodents adapted to the cold (Cannon and Nedergaard 1985; Himms-Hagen 1986; Nedergaard *et al* 1986). The more recent focus on BAT has come primarily from the recognition that the tissue also plays a significant role in nutritional energetics, especially in *diet-induced thermogenesis* (Rothwell and Stock 1986). A large number of studies have indicated, in particular, that impaired thermogenesis in BAT is important in the aetiology of obesity in rodent models (Trayhurn 1986; Himms Hagen 1989).

This article presents a short overview of the biology of brown fat, with some emphasis on recent developments. Our current understanding of the tissue is the result of an intensive application of concepts and techniques derived from a wide range of biological disciplines—from molecular biology through to whole-animal physiology and nutrition. For a detailed description of specific areas, the reader is referred to several recent reviews (Cannon and Nedergaard 1985; Trayhurn and Nicholls 1986; Himms-Hagen 1989; Ricquier *et al* 1991; Klaus *et al* 1991); because of limitations of space, these and other review articles are quoted, where appropriate.

2. Mechanism of heat production in brown adipose tissue

All metabolic reactions generate heat, as a reflection of thermodynamic inefficiency. Heat is therefore a normal by-product of metabolism. In BAT, however, heat is the *primary* product, the generation of which is the central function of the tissue. The extensive interest in brown fat reflects the fact that it is the sole tissue in mammals specialized for heat production. BAT is extensively vascularized, exhibiting a very high rate of blood flow during peak thermogenesis. Indeed, up to one-third of the cardiac output may be directed to the tissue in rats adapted to the cold (Foster and Frydman 1978; Foster 1986), enabling heat to be rapidly transferred to the body core. The high blood flow also ensures that the substrates (including oxygen) required to fuel thermogenesis are provided at rates appropriate to the major demands of the tissue.

Heat is generated in BAT through a unique (apparently) proton translocation mechanism located in the mitochondrial inner membrane (Nicholls and Locke 1984; Nicholls *et al* 1986). This acts as a proton 'short-circuit' across the membrane such that the proton gradient which is usually generated during respiration is dissipated as heat rather than being linked to the synthesis of ATP (see figure 1). The proton translocation of BAT mitochondria is regulated by a specific 'uncoupling protein' (also termed 'thermogenic) in the inner membrane (Cannon and Nedergaard 1985; Nicholls *et al* 1986). Uncoupling protein (UCP), M_r 32-33,000, is subject to acute regulation such that the proton translocation of the mitochoadria, and thus the heat produced, varies according to the physiological requirements for thermogene sis.

The concentration of UCP in the mitochondria changes in response to chronic alterations in the requirements for thermogenesis, and this is a key mechanism for altering the capacity for thermogenesis in BAT. UCP increases, for example, in the cold and decreases in the warm (Trayhurn *et al* 1987). Prolonged exposure to a thermogenic stimulus also results in an increase in the total amount of UCP in BAT through an increase in the mitochondrial content of the tissue (mitochondrio genesis). In general, parallel changes occur in the mitochondrial content of BAT and the specific mitochondrial concentration of UCP. Acutely, as indicated above, activation of pre-existing UCP occurs, and this is often reflected in what is described as an 'unmasking of guanosine 5'-biphosphate (GDP) binding sites' on he protein, mitochondrial GDP binding being a widely used assay for assessing the thermogenic activity of the tissue *in vitro* (Trayhurn and Milner 1989). There are, therefore, three distinct mechanisms for altering thermogenesis in BAT.

Free fatty acids (or possibly acyl CoA's) provide the intracellular signal for the activation of the proton conductance pathway, through an interaction with UCP (Nichols *et al* 1986). Thus fatty acids play a dual role, as both primary fuel and Signal for the activation of thermogenesis. The initial event in the stimulation of thermogenesis is the release of noradrenaline from the sympathetic nerves which extensively innervate BAT˙ The tissue contains a novel â$_3$ −adrenoceptor (Arch *et al* 1984; Arch 1989), to which noradrenaline binds, and this leads, through a cascade of events, to the activation of hormone-sensitive lipase with the stimulation of lipolysis (figure 1).

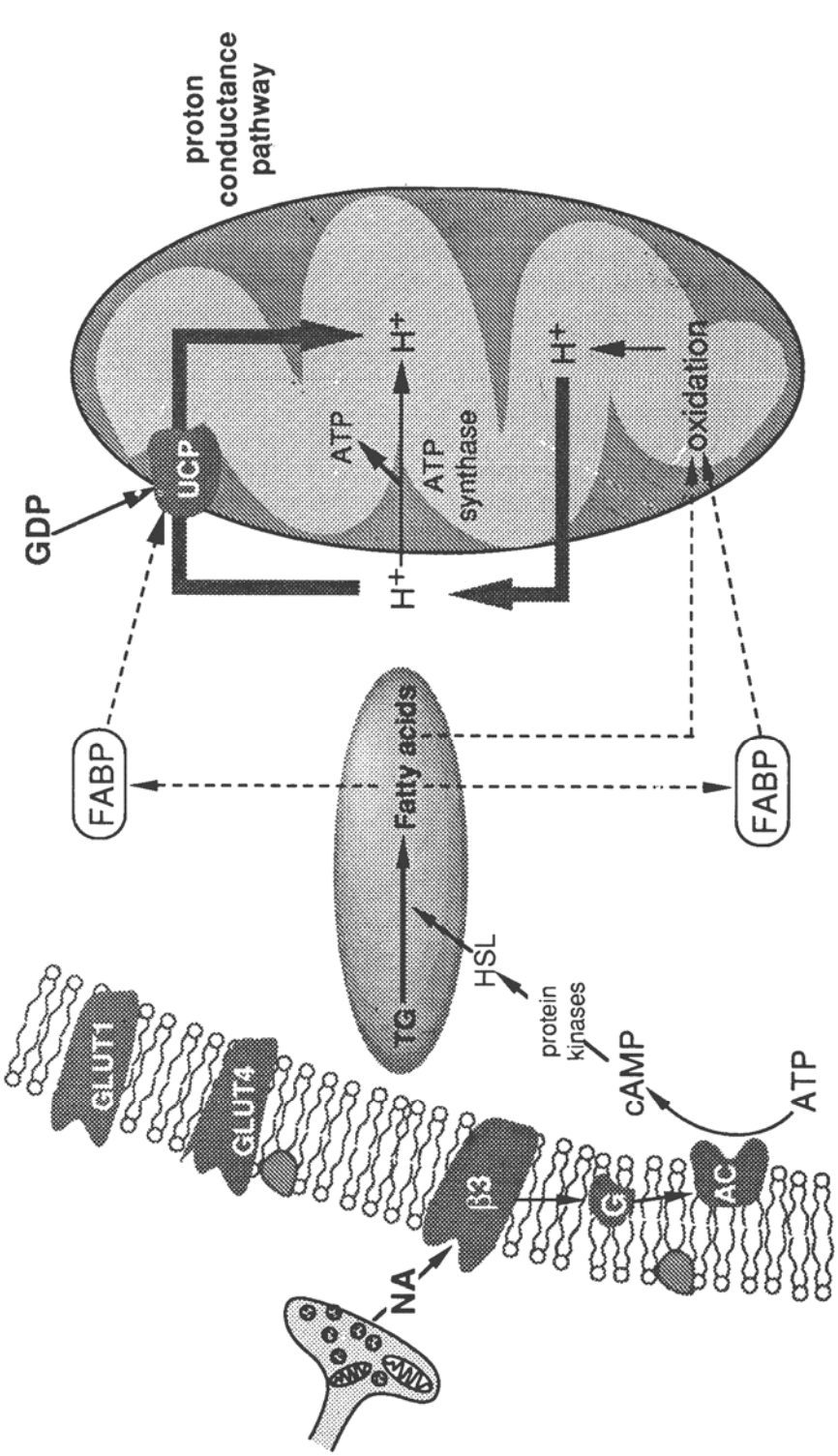

Figure 1. A schematic representation of the mechanism of thermogenesis in brown adipose tissue. NA, Noradrenaline, β_3, β_3-adrenoceptor; G, G-binding proteins; AC, adenyl cyclase; HSL, hormone-sensitive lipase; TG, triacylglycerols; FABP, fatty acid binding protein; GDP, guanosine biphosphate; UCP, uncoupling protein.

3. Structure of the brown adipocyte: distinction between brown and white adipose tissue

The two types of adipose tissue are unified by their ability to store large quant-ities of triacylglycerol, as lipid droplets. Functionally, however, they play quite different roles in energy metabolism — white fat is the primary organ of energy storage for the body, while BAT utilizes its triacylglycerols to generate heat. In its normal form, white adipose tissue has a single large droplet (described as 'unilocular') with up to 85% of the weight of the tissue as triacylglycerol, the cytoplasm being sparse with relatively few mitochondria. In the classic form of brown fat, some 30–50% of the tissue weight is triacylglycerol and this is arranged in multiple lipid droplets ('multilocular'). In contrast to white adipose tissue, the cytoplasm in BAT is extensive and contains large numbers of mitochondria with a well-developed cristae structure (see Nechad 1986).

Although in their traditional forms BAT and white fat can be readily distinguished histologically, there can be considerable overlap in gross appearance between the less extreme forms of the two tissues. Thus, for example, BAT in obese animals has a reduced mitochondrial content and the tissue is 'unilocular', while in cold-exposed animals white adipose tissue may become 'multilocular' with the mitochondria more evident (Loncar *et al* 1988a, b). The key feature differentiating the two tissues is at the biochemical level — in the presence in BAT of UCP and the proton conductance pathway (Cannon and Nedergaard 1985; Klaus *et al* 1991; Ricquier *et al* 1991). BAT can therefore be distinguished by the identification of UCP using immunological procedures, an approach now widely employed to assess the species and age distribution of the tissue (see below).

An alternative approach to the identification of BAT is the detection of the mRNA for UCP (by Northern blotting), although in this case it is necessary to assume that the mRNA is actually transcribed, and that sufficient of the protein is synthesized to have the appropriate physiological effect. Mitochondrial GDP binding has also been used to identify BAT, but this does not provide sufficient specificity in that mitochondria from most tissues will, to some extent, bind [^{3}H] purine nucleotides.

The degree to which BAT and white fat are quite distinct tissues, or part of a continuous spectrum of adipose tissues, remains uncertain. In ruminants, there is a rapid loss of UCP and its mRNA from adipose tissues over the early days, or weeks, of postnatal life, and this implies a transition of white fat to BAT (Casteilla *et al* 1987, 1989; Soppela *et al* 1991). Similarly, the re-appearance of UCP and its mRNA in dogs treated with ß-agonists, is indicative of a re-conversion of white fat to brown (Champigny *et al* 1991). Immunocytochemistry is required to determine whether individual adipocytes undergo a reversible transition between 'brown' and 'white' forms, or whether there is a recruitment process from a pool of defined (committed) precursor cells within a given adipose tissue depot.

4. Structure and molecular biology of uncoupling protein

UCP is a member of the family of mitochondrial carriers, and there is considerable homology between it and both the ADP/ATP translocase and the mitochondrial phosphate carrier (Klingenberg 1990). UCP consists of a single polypeptide chain

with 306 amino acids. In terms of secondary structure, the protein contains ~ 50 % α-helix, ~30% *β*-sheet, and 7% *β*-turn. Several models have been proposed for the organization of UCP within the inner mitochondrial membrane. The models are similar in suggesting that there are six hydrophobic transmembrane α-helices, although the most recent model has proposed that the hydrophobic segment nearest to the C-terminal end of the molecule does not completely span the membrane (Klaus *et al* 1991). There appear to be two hydrophilic loops on the matrix side of the membrane, with three hydrophilic loops and the C-terminal region of the molecule on the cytosolic side (Klaus *et al* 1991). The region of the protein responsible for the translocation of protons may be located close to the N-terminal end of the molecule.

Some of the most important recent developments in the study of BAT have come from the application of molecular biology, and this has of course focussed on UCP. The gene coding for the protein has been cloned and sequenced in several species — rats, mice, rabbits, cattle and humans (see Ricquier *et al* 1991; Klaus *et al* 1991). Heterogeneity between species in the sequence of the UCP gene is very evident; comparison of the derived amino acid sequences suggests, however, that there is considerable species homology in the primary structure of the protein itself (Klaus *et al* 1991). A central issue is the basis for the tissue-specific expression of the UCP gene. This question is under active investigation, and the regulatory elements (promoter sequences) that allow hormonal responsiveness are being explored. The transcription unit of the UCP gene contains 6 exons, and in rats and humans is close to 9 kbases in size (Ricquier *et al* 1991).

The availability of cDNA's for UCP has provided a tool for the detection and measurement of the mRNA for the protein, so that factors (environmental, nutritional, hormonal) which affect UCP gene transcription can be examined. Acute cold exposure has been shown, for example, to induce a striking increase in the level of UCP mRNA (Bouillaud *et al* 1984; Ricquier *et al* 1991), as the first event underlying the production of more of the protein. UCP mRNA is also increased during overfeeding with a cafeteria diet, and in response to *β*-agonists (Bouillaud *et al* 1984). On the other hand, fasting (at least in the short-term) and streptozotocin-induced diabetes result in a fall in the level of UCP mRNA (Champigny and Ricquier 1990; Brander *et al* 1993). It is evident that physiologically the UCP gene is transcriptionally regulated by noradrenaline from the sympathetic nervous system, and that T_3 also plays a role (Bianco *et al* 1988).

Large, or full length, rat cDNA's for UCP do not appear to hybridize readily with UCP mRNA from widely different species (*e.g.* cattle, humans), reflecting the heterogeneity between species in the sequence of the gene. One relatively substantive region of 27 bases is, however, identical in rats and cattle, and shows only a single base change in mice, rabbits and humans (Brander *et al* 1993). This highly conserved region contains a preponderance of guanine and cytosine (*i.e.* the bases which form triple hydrogen bonds) and the complementary sequence has been recently synthesized as a 27-mer oligonucleotide (3'-TGGAAGGGCGACCTGTGGCGGTTTCAG-5') to provide a simple probe for studying the expression of the UCP gene across a wide range of species (Brander *et al* 1993). Using this probe we have been able to detect the mRNA for UCP, and thus the expression of the UCP gene, in species as diverse as laboratory rodents, pipistrelle bats, and newborn ruminants such as goats and red deer (Brander *et al* 1993).

5. Elevated thermogenesis in brown adipose tissue

The classical function of BAT is to generate heat for thermoregulatory purposes. Consequently, much is known about the response of the tissue to exposure of animals to cold. Acutely, as noted above, the proton translocation of the mitochondrial inner membrane is increased through the activation of pre-existing UCP. Chronic exposure to cold induces, however, a constellation of changes in BAT. These include an increase in cell number in the tissue, an increase in the mitochondrial content, and an increase in the specific mitochondrial concentration of UCP (see Himms-Hagen 1986, 1989; Trayhurn *et al* 1987). The net effect of these changes is to greatly augment the *capacity* for thermogenesis, and this is driven principally by increased stimulation from the sympathetic system (Himms-Hagen 1986). Other metabolic processes, such as the provision of substrates, change in parallel.

The effects on BAT of overfeeding with a variable and palatable 'cafeteria' diet consisting of human food items has also been extensively studied (Rothwell and Stock 1986). Such a diet leads to a stimulation of 'diet-induced thermogenesis', a process that provides a counter-regulatory mechanism in the control of whole-body energy balance such that energy expenditure is increased on overfeeding and energy storage (as lipid) reduced. Both the thermogenic activity and capacity of BAT are increased in young animals (rats, mice) fed a cafeteria diet (Rothwell and Stock 1986). Thus, as animals with cold exposure — with which there are many parallels – mitochondrial GDP binding, mitochondrial content, and the specific mitochondrial concentration of UCP are each augmented (together with other measures linked to the activity of the tissue). Again, such changes are the result of an increase in the sympathetic stimulation to BAT (Rothwell and Stock 1986).

Additional situations in which the thermogenic activity of BAT is augmented include the arousal from hibernation (Milner *et al* 1989), fever, and the cachectic state associated with cancer (see Himms-Hagen 1989). Such changes have important correlates on a whole-body basis in that the capacity for non-shivering thermogenesis and the overall rate of energy expenditure may be increased.

6. Functional atrophy of brown adipose tissue

There are a number of situations which lead to a functional atrophy of BAT. The most widely studied is that related to obesity, and the activity of the tissue has been investigated in a range of different types of obese animal (Himms-Hagen 1989). In general, it is evident that there is a relative atrophy of the tissue in obesity, with a reduction in mitochondrial GDP binding, mitochondrial content and the concentration of UCP (see Himms-Hagen 1989). The decrease in GDP binding is an early event, the other changes following later. The decrease in thermogenic activity and capacity in BAT in obese animals contributes substantially to the positive energy balance which leads to the obese state.

Fasting also results in a major atrophy of BAT, with a substantial fall in both the specific mitochondrial concentration and total tissue content of UCP. Such changes are reversed by refeeding, but this needs to be prolonged in order for their to be a full restoration of thermogenic capacity (Trayhurn and Jennings 1988). Lactation leads to a similar functional atrophy of BAT as that in fasting, and the lactation-

induced changes are largely reversed following the weaning of the pups (Trayhurn 1989). The decline in thermogenesis occurring in lactation is thought to reduce the energy costs of milk production through a reduction in the non-lactational component of maternal energy expenditure (Trayhurn 1989). Equally, energy expenditure is reduced by the atrophy of BAT occurring during fasting.

In the same way that the activation of thermogenesis results from sympathetic stimulation, functional atrophy of BAT is attributable to a fall in sympathetic tone (see Himms-Hagen 1989). Regulation of the tissue is also, however, dependent on other factors, such as insulin and glucocorticoids. This is clearly illustrated in relation to the effects of experimentally-induced diabetes. A major atrophy of BAT occurs in animals made diabetic with streptozotocin, there being a substantial fall in the amount of UCP (Geloen and Trayhurn 1990a). The protein, and therefore thermogenic capacity, is restored in a dose-dependent manner by the long-term infusion of insulin from implanted osmotic minipumps (Geloen and Trayhurn 1990a). Studies in which the sympathetic innervation of BAT was surgically cut suggest that insulin regulates the amount of UCP in the tissue through an interaction with the sympathetic nervous system (Geloen and Trayhurn 1990b).

Insulin may also regulate the expression of the gene coding for UCP. In preliminary studies we have observed that the level of UCP mRNA is greatly reduced in BAT of streptozotocin-diabetic animals (Brander *et al* 1993).

7. General metabolic role of brown adipose tissue

In addition to the direct generation of heat, BAT has several general metabolic properties of key importance. In physiological terms these are, of course, linked to the primary thermogenic function of the tissue.

BAT has a high capacity for the *de novo* synthesis of fatty acids when an animal is fed a high carbohydrate/low fat diet, which varies according to the long-term acclimation temperature, the lower the temperature the greater being the rate of lipogenesis (Trayhurn 1981). In a cold-acclimated mouse, for example, BAT may be responsible for approximately one-third of whole-body lipogenesis — a contribution that is considerably greater than that of the liver (Trayhurn 1981). Thus, under defined conditions BAT is a very major site of the conversion of carbohydrate to lipid. The high rate of lipogenesis in BAT is a reflection of the requirement for fatty acids as the primary fuel for thermogenesis. Fatty acids can also be obtained from the circulation, either directly or in the form of triacylglycerols. A high lipoprotein lipase activity is present in the tissue, enabling circulating triacylglycerols to be utilized to provide fatty acids without *de novo* synthesis (Carneheim *et al* 1984).

BAT has a high rate of glucose uptake, glucose being the primary substrate for lipogenesis in the tissue; glucose is not, however, a major direct substrate for thermogenesis (Cawthorne 1989). Glucose uptake into BAT is stimulated by both insulin and noradrenaline from the sympathetic nervous system (Cawthorne 1989), and occurs primarily through the presence of the insulin-sensitive facilitative glucose transporter—GLUT4 (James *et al* 1989). GLUT4 is found exclusively in those tissues in which glucose uptake is stimulated by insulin (skeletal muscle, heart and the adipose tissues). Euglycaemic clamp studies indicate that BAT is particularly sensitive to insulin, the stimulation of glucose uptake being considerably greater than in other tissues (Ferre *et al* 1986). BAT may therefore provide a particularly

valuable model system for investigating the mechanism of insulin action.

A fatty acid-binding protein *(Mr* 14,800) has recently been isolated and characterized from BAT (Dutta-Roy *et al* 1992). The fatty acid-binding proteins are a family of low molecular weight proteins that are widely distributed in tissues, and which are believed to play an important role in the intracellular transport and metabolism of fatty acids and associated ligands (Kaikaus *et al* 1990). Given the high flux of fatty acids in BAT, resulting from their importance both as a fuel and as an intracellular signal for the activation of proton translocation, fatty acid-binding protein may play a key role in the regulation of thermogenesis (figure 1). In newborn lambs (which have a high capacity for non-shivering thermogenesis) fatty acid-binding protein amounts to several per cent of the total cytosolic protein—a higher concentration than that of a similar protein in the liver (Dutta-Roy *et al* 1991).

A key area in which the metabolism of BAT is of particular interest is that relating to thyroid hormone. In rats, the tissue contains a high activity of the type II iodothyronine 5'-deiodinase enzyme (Silva and Larsen 1983) that catalyses the conversion of thyroxine (T_4) to the biologically active thyroid hormone, triiodothyronine (T_3). This enzyme is stimulated by the sympathetic nervous system, and cold exposure overnight leads to a substantial increase in the activity in BAT through synthesis of the protein (Silva and Larsen 1983; Himms-Hagen 1989). It has been suggested that brown fat may provide T3 for utilization by other tissues (Fernandez *et al* 1987), but the primary site of action of the T3 is BAT itself, where the hormone is implicated in the control of the transcription of the UCP gene (Bianco *et al* 1988).

High iodothyronine 5'-deiodinase activity is also found in the perirenal BAT of newborn ruminants (lambs, cattle, goats), but in these species the type I form appears to predominate (Giralt *et al* 1989; Wu *et al* 1991; Nicol *et al* 1992). The activity, and thus the capacity to generate T_3, declines markedly during the rapid transition of BAT to white adipose tissue over the first weeks of postnatal life in ruminants (Giralt *et al* 1989; Wu *et al* 1991; Nicol *et al* 1992). The basis for the marked species differences in the type of iodothyronine 5'-deiodinase present in BAT is not clear. However, it is likely that when the type I form occurs, BAT may make a significant contribution to the provision of circulating T_3.

Recent work has demonstrated that the type I iodothyronine 5'-deiodinase is a selenium-containing enzyme, and disorders of thyroid hormone metabolism occur in selenium deficiency — as in Keshan's disease in man and degenerative myopathies in agricultural animals (see Arthur 1991). Perhaps somewhat surprisingly, the type II enzyme does not contain selenium. Nonetheless, feeding rats a selenium-deficient diet leads to a reduction in the activity of the type II iodothyronine 5'-deiodinase in brown fat and other tissues, and the cold-induced increase in the activity of the enzyme in BAT is greatly impaired (Arthur *et al* 1991). Overall these observations suggest that selenium deficiency may have important implications for the generation of thermoregulatory heat, particularly in newborn agricultural animals where perinatal survival may be severely compromised in regions where the feedstuffs are selenium-deficient.

8. Species distribution

The majority of studies on BAT have been conducted on small laboratory rodents,

particularly in work focussed on the role of the tissue in the regulation of energy balance. However, the limited type of animal that has been employed has raised concern over the general applicability of the concepts that have evolved. From a general biological point of view it is, of course, important to know the species distribution of BAT. This is of particular interest from an evolutionary perspective in that systems specialized for the generation of heat are required by homeotherms, though not by poikilotherms. There are, nonetheless, special circumstances where an ability to generate heat for a thermal function is evident in poikilotherms; an example is in the warming of the flight muscle in bumble bees, enabling flight to occur at low ambient temperatures (Newsholme and Crabtree 1976).

Until recently, brown fat was diagnosed in different species, and distinguished from white adipose tissue, on the basis of histological appearance. However, since this is now recognised to be an unsatisfactory and potentially misleading approach to identifying BAT, as discussed earlier, recent studies have focussed on the immunological identification of UCP as providing the critical criteria for the tissue. The most effective way of identifying UCP is by immunoblotting (or Western blotting), since this ensures that immunoreactivity occurs at the molecular weight appropriate to the protein. Immunoblotting has now been applied to a variety of mammalian species, ranging from rodents to ungulates through to primates such as man. Table 1 shows the species in which UCP has been identified. In some cases, such as ruminants (cattle, sheep, goats, reindeer) UCP and hence BAT, is present only for a restricted period over the first few days or weeks of postnatal life—presumably because for thermal reasons the tissue is required only for the initial period after birth.

Table 1. Species distribution of BAT.

Laboratory:
Mouse—Rat—Guinea pig—Rabbit
Hibernators:
Hamsters (Golden, European, Turkish)—Ground squirrels (Richardson's, Columbian, 13-lined)—Pipistrelle bat—Edible dormouse
Other rodents:
Djungarian hamster—Wood lemming—Wood mouse—Orkney vole
Domesticated*:
Dog—Sheep—Cattle—Reindeer (Caribou)—Red deer—Goat
Primates:
Monkeys (Rhesus, Cynomologus, Macaca)—Humans (newborn and adult)

Based on the immunological identification of uncoupling protein in an adipose tissue.

* Present only in the neonate/young.

As more animals are examined, and UCP identified, species and situations where the tissue is *absent* take on increasing significance. Among mammals, the domesticated pig is the sole species reported where UCP has not been found (Trayhurn *et al* 1989). We have also been unable to identify the protein in several avian species adapted to the sub-arctic winter (Saarela *et al* 1991); current evidence would suggest that BAT is restricted to mammals.

9. Brown adipose tissue in man

Studies demonstrating an impairment of BAT activity in obese rodents rapidly led to consideration of the possibility that low rates of thermogenesis in the tissue may be involved in the development of human obesity (Himms-Hagen 1979). UCP has been isolated from adipose tissue of human neonates, and the protein has also been detected in adult humans (Lean 1989). Furthermore, the gene coding for UCP in humans has been cloned, and partially sequenced (Cassard *et al* 1990). Thus BAT is present in man and studies in patients with phaeochromocytoma indicate that a major activation of the tissue can take place in adults, given the appropriate (catecholaminergic) stimulus (Lean 1989).

Despite the data from experimental animals, it now seems highly improbable that impaired thermogenesis in BAT is implicated in the aetiology of human obesity. This does not, however, preclude the possibility that the disorder can be treated by therapeutic agents targeted to BAT, particularly in view of the activation of the tissue that occurs with phaeochromocytoma. In principle, any mechanism for stimulating energy expenditure provides a therapeutic route for obesity, providing that the activation is substantial and that it occurs without detrimental cardiovascular effects. The position is analogous to that of dieting in that given a substantial reduction in intake, weight will inevitably be lost — *irrespective of whether excessive consumption is the critical aetiological factor.*

The presence of a novel *ß*3-adrenoceptor in BAT has provided a clear theoretical route for the development of anti-obesity agents which specifically stimulate the tissue without provoking a major cardiovascular response. However, in practice this approach has yet to lead to an effective therapy.

10. Coda—achievements of research on brown adipose tissue

Although it is now evident that BAT does not represent the 'philosophers stone' in terms of the aetiology of obesity in man, the achievements of studies on the biology of the tissue over the past 15 years are nonetheless considerable. These achievements particularly include the elucidation of the unique bioenergetics of BAT mitochondria, and the demonstration that in small mammals the tissue plays an important role in the regulation of energy balance. The identification of a novel *ß* -adrenoceptor, and the recognition of BAT as an important site in the generation of T_3 from T_4—and in the conversion of carbohydrate to lipid —are also of considerable importance. In addition, BAT has served as an important model system for investigating both environmental. effects and the neural (sympathetic) regulation of peripheral metabolism—down to the level of the expression of individual genes.

Acknowledgements

I am grateful for the assistance of my colleagues at the Rowett Research Institute, Aberdeen.

References

Arch J R S 1989 The brown adipocyte *ß*-adrenoceptor; *Proc. Nutr. Soc.* **48** 215–223

Arch J R S, Ainsworth A T, Cawthorne M A, Piercy V, Sennitt M V, Thody V E, Wilson C and Wilson S 1984 Atypical *ß*-adrenoceptor on brown adipocytes as target for anti-obesity drugs; *Nature* (*London*) **309** 163–165

Arthur J R 1991 The role of selenium in thyroid hormone metabolism; *Can. J. Physiol Pharmacol.* **69** 1648–1652

Arthur J R, Nicol F, Beckett G J and Trayhurn P 1991 Impairment of iodothyronine 5'-deiodinase activity in brown adipose tissue and its acute stimulation by cold in selenium deficiency; *Can. J. Physiol. Pharmacol.* **69** 782–785

Bianco A C, Sheng X and Silva J E 1988 Triiodothyronine amplifies norepinephrine stimulation of uncoupling protein gene transcription by a mechanism not requiring protein synthesis; *J. Biol. Chem.* **263** 18168–18175

Bouillaud F, Ricquier D, Mory G and Thibault J 1984 Increased level of mRNA for the uncoupling protein in brown adipose tissue of rats during thermogenesis induced by cold exposure or norepinephrine infusion; *J. Biol. Chem.* **259** 11583–11586

Brander F, Keith J S and Trayhurn P 1993 A 27-mer oligonucleotide probe for the detection and measurement of the mRNA for uncoupling protein in brown adipose tissue of different species; *Comp Biochem. Physiol.* **B104** 125–131

Cannon B and Nedergaard J 1985 The biochemistry of an ineficient tissue: brown adipose tissue; *Essays Biochem.* **20** 110-164

Carneheim C, Nedergaard J and Cannon B 1984 ß-adrenergic stimulation of lipoprotein lipase in rat brown adipose tissue during acclimation to cold; *Am. J. Physiol.* **246** E327-E333

Cassard A-M, Bouillaud F, Mattei M-G, Hentz E, Raimbault S, Thomas M and Ricquier D 1990 Human uncoupling protein gene — structure, comparison with rat gene, and assignment to the long arm of chromosome-4; *J. Cell Biochem.* **43** 255-264

Casteilla L, Champigny O, Bouillaud F, Robelin J and Ricquier D 1989 Sequential changes in the expression of mitochondrial protein mRNA during the development of brown adipose tissue in bovine and ovine species. Sudden occurrence of uncoupling protein mRNA during embryogenesis and its disappearance after birth; *Biochem. J.* **257** 665-671

Casteilla L, Forest C, Robelin J, Ricquier D, Lombet A and Ailhaud G 1987 Characterization of mitochondrial-uncoupling protein in bovine fetus and newborn calf; *Am. J. Physiol.* **252** E627–E636

Cawthorne M A 1989 Does brown adipose tissue have a role to play in glucose homeostasis? *Proc. Nutr. Soc.* **48** 207-214

Champigny O and Ricquier D 1990 Effects of fasting and refeeding on the level of uncoupling protein messenger RNA in rat brown adipose tissue—evidence for diet-induced and cold-induced responses; *J. Nutr.* **120** 1730-1736

Champigny O, Ricquier D, Blondel O, Mayers R M, Briscoe M G and Holloway B R 1991 β_3-adrenergic receptor stimulation restores message and expression of brown-fat mitochondrial uncoupling protein in adult dogs; *Proc. Natl. Acad. Sci. USA* **88** 10774-10777

Dutta-Roy A K, Huang Y and Trayhurn P 1992 Fatty acid-binding protein (FABP) in rat brown adipose tissue; in *Obesity in Europe 1991* (eds) G Ailhaud, B Guy-Grand, M Lafontan and D Ricquier (Paris: John Libbey) pp 293-296

Dutta-Roy A K, Huang Y and Trayhurn P 1991 Fatty acid-binding protein in brown adipose tissue of the newborn lamb; *Proc. Nutr. Soc.* **50** 211A

Fernandez J A, Mampel T, Villarroya F and Iglesias R 1987 Direct assessment of brown adipose tissue as a site of systemic tri-iodothyronine production in the rat; *Biochem. J.* **243** 281-284

Ferre P, Burnol A F, Leturque A, Terretaz J, Penicaud L, Jeanrenaud B and Girard J 1986 Glucose utilization in vivo and insulin-sensitivity of rat brown adipose tissue in various physiological and pathological conditions; *Biochem. J.* **233** 249-252

Foster D O 1986 Quantitative role of brown adipose tissue in thermogenesis; in Brown *adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 31-51

Foster D O and Frydman M L 1978 Nonshivering thermogenesis in the rat. II. Measurements of blood flow with microspheres point to brown adipose tissue as the dominant site of the calorigenesis induced by noradrenaline; *Can J. Physiol. Pharmocol.* **56** 110-122

Geloen A and Trayhurn P 1990a Regulation of the level of uncoupling protein in brown adipose tissue by insulin; *Am. J. Physiol.* **258** R418-R424

Geloen A and Trayhurn P 1990b Regulation of the level of uncoupling protein in brown adipose tissue by insulin requires the mediation of the sympathetic nervous system; *FEBS Lett.* **267** 265-267

Giralt M, Casteilla L, Vinas O, Mampel T, Iglesias R, Robelin J and Villarroya F 1989 Iodothyronine 5'-deiodinase activity as an early event of prenatal brown-fat differentiation in bovine development; *Biochem. J.* **259** 555-559

Himms-Hagen J 1979 Obesity may be due to a malfunctioning of brown fat; *Can. Med. Assoc. J.***121** 1361-1364

Himms-Hagen J 1986 Brown adipose tissue and cold-acclimation; in *Brown adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 214-268

Himms-Hagen J 1989 Brown adipose tissue thermogenesis and obesity; *Prog. Lipid Res.* **28** 67-115

James D E, Strube M and Mueckler M 1989 Molecular cloning and characterization of an insulin regulatable glucose transporter; *Nature (London)* **338** 83-87

Kaikaus R M, Bass N M and Ockner R K 1990 Functions of fatty acid binding proteins; *Experientia* **46** 617-630

Klaus S, Casteilla L, Bouillaud F and Ricquier D 1991 The uncoupling protein UCP —a membraneous mitochondrial ion carrier exclusively expressed in brown adipose tissue; *Int. J. Biochem.* **23** 791-801

Klingenberg M 1990 Mechanism and evolution of the uncoupling protein of brown adipose tissue; *Trends Biochem. Sci.* **15** 108-112

Lean M E J 1989 Brown adipose tissue in humans; *Proc. Nutr. Soc.* **48** 243-256

Loncar D, Afzelius B A and Cannon B 1988a Epididymal white adipose tissue after cold stress in rats. I Nonmitochondrial changes; *J. Ultrastruct. Mol. Struct. Res.* **101** 109-122

Loncar D, Afzelius B A and Cannon B 1988b Epididymal white adipose tissue after cold stress in rats. II. Mitochondrial changes; *J. Ultrastruct. Mol. Struct. Res.* **101** 199-209

Milner R E, Wang L and Trayhurn P 1989 Brown fat thermogenesis during hibernation and arousal in Richardson' s ground squirrel; *Am. J. Physiol.* **256** R42-R48

Nechad M 1986 Structure and development of brown adipose tissue; in *Brown adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 1-30

Nedergaard J, Connolly E and Cannon B 1986 Brown adipose tissue in the mammalian neonate; in *Brown adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 152-213

Newsholme E A and Crabtree B 1976 Substrate cycles in metabolic regulation and in heat generation: *Biochem. Soc. Symp.* **41** 61-109

Nicol F, Lefranc H, Arthur J R and Trayhurn P 1992 Types I and II iodothyronine 5'-deiodinase activities in perirenal brown adipose tissue of neonatal goats; *Biochem. Soc. Trans.* **20** 336S

Nicholls D G and Locke R M 1984 Thermogenic mechanisms in brown fat; *Physiol Rev.* **64** 1-64

Nicholls D G, Cunningham S A and Rial E 1986 The bioenergetic mechanisms of brown adipose tissue thermogenesis; in *Brown adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 52-85

Ricquier D, Casteilla L and Bouillaud F 1991 Molecular studies of the uncoupling protein; *FASEB J.* **5** 2237-2242

Rothwell N J and Stock M J 1986 Brown adipose tissue and diet-induced thermogenesis; in *Brown adipose tissue* (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 269-298

Saarela S, Keith J S, Hohtola E and Trayhurn P 1991 Is the mammalian brown fat specific mitochondrial uncoupling protein present in adipose tissues of birds?; *Comp. Biochem. Physiol.* **B100** 45-49

Shinohara Y Shima A, Kamida M and Terada H 1991 Uncoupling protein is expressed in liver mitochondria of cold-exposed and newborn rats; *FEBS Lett* **293** 173-174

Silva J E and Larsen P R 1983 Adrenergic activation of triiodothyronine production in brown adipose tissue; *Nature (London)* **305** 712-713

Soppela P, Nieminen M, Saarela S, Keith J S' Morrison J N' Macfarlane FandTrayhurn P 1991Brown fat-specific uncoupling protein in adipose tissues of newborn reindeer; *Am. J. Physiol.* **260** R1229-R1234

Trayhurn P 1981 Fatty acid synthesis in mouse brown adipose tissue: the influence of environmental temperature on the proportion of whole-body synthesis in brown adipose tissue and the liver; *Biochim. Biophys. Acta* **664** 549-560

Trayhurn P 1986 Brown adipoe tissue and energy balance; in *Brown adipose* tissue (eds) P Trayhurn and D G Nicholls (London: Edward Arnold) pp 299-338

Trayhurn P 1989 Thermogenesis and the energetics of pregnancy and lactation; *Can. J. Physiol. Pharmacol.* **67** 370-375

Trayhurn P and Jennings G 1988 Nonshivering thermogenesis and the thermogenic capacity of brown fat in fasted and/or refed mice; *Am. J. Physiol.* **254** R11-R16

Trayhurn P and Milner R E 1989 A commentary on the interpretation of in vitro biochemical measures of brown adipose tissue thermogenesis; *Can. J. Physiol Pharmacol.* **67** 811-819

Trayhurn P and Nicholls D G 1986 *Brown adipose tissue* (London: Edward Arnold) pp 1-374

Trayhurn P. Ashwell M, Jennings G, Richard D and Stirling D M 1987 Effect of warm or cold exposure on GDP binding and uncoupling protein in rat brown fat; *Am. J. Physiol.* **252** E237-E243

Trayhurn P, Temple N J and Van Aerde J 1989 Evidence from immunoblotting studies on uncoupling protein that brown adipose tissue is not present in the domestic pig; *Can J. Physiol. Pharmacol.* **67** 1480-1485

Wu S Y, Kim J K, Chopra I J, Murata Y and Fisher D A 1991 Postnatal changes in lambs of two pathways for thyroxine 5'-monodeiodination in brown adipose tissue; *Am. J. Physiol.* **261** E257-E261