Control of white and brown adipose tissues by the autonomic nervous system

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Interest in the neural regulation of the adipose tissues has increased considerably in recent years. In the case of brown adipose tissue (BAT) this reflects the development of the concept that the tissue is important in the regulation of energy balance. The substantial innervation of BAT has been recognized, however, for some considerable time (see Barnard *et al.* 1980). In the present paper we have set out to briefly summarize current views on the role of the autonomic nervous system, in practice the sympathetic system, in the control of both white adipose tissue (WAT) and BAT. The regulatory effects of the sympathetic system on these two tissues can be considered in terms of acute effects on the central metabolic pathways, and chronic effects relating to the growth and development of the tissues.

The main emphasis of this review is on BAT, reflecting the more restricted picture of the role of the sympathetic system in the regulation of WAT.

The distinction between WAT and BAT

Before discussing the effects of the autonomic system in detail, it is appropriate to consider the properties of the two forms of adipose tissue and their distinctive features. The fundamental feature of the adipose tissues is, of course, their ability to store large quantities of lipid in the form of one or more triacylglycerol droplets. The two tissues have, however, quite different roles in energy metabolism. WAT is the main long-term energy store, providing substrates (fatty acids) for utilization in other tissues. In contrast, the primary function of BAT is to produce heat, either for thermoregulation or in relation to the regulation of energy balance. The triacylglycerol stored in BAT is therefore used directly by the tissue, although it may also provide a rapidly mobilized source of fatty acids in certain acute situations (Nedergaard & Lindberg, 1979).

There is some debate as to whether WAT or BAT are two quite distinct tissues, or whether they represent the extreme ends of a continuous spectrum of adipose tissues, which are interconvertible (Ashwell, 1985). Whichever proves correct, it is apparent that BAT varies considerably in the extent to which it is thermogenic, and this is part of the argument for a continuous spectrum. The present paper will

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Table 1. *The major features distinguishing white and brown adipose tissues**

	White	Brown
Primary function	Energy storage	Thermogenesis
Anatomical distribution	Extensive	Restricted
Fat droplet	Unilocular	Multilocular
Ultrastructure	Restricted number of mitochondria with few cristae	Large numbers of mitochondria with well-developed cristae
Vasculature	Relatively sparse	Extensive
Sympathetic innervation	Relatively sparse (mainly to blood vessels)	Extensive (to both blood vessels and adipocytes)
Fatty acids	Exported	Largely oxidized in situ
Mitochondria	Coupled	Regulated uncoupling
Uncoupling protein	Absent	Present (up to 15% of mitochondrial protein)
Responses to cold	Slight	Very extensive changes

*Adapted from Ashwell (1985).

focus on the classic forms of the two tissues (e.g. epididymal WAT and interscapular BAT).

Table 1 lists some of the major features which differentiate the adipose tissues. Traditionally, at the histological level, WAT is described as 'unilocular' in the sense that the triacylglycerol is present in a single droplet, while BAT is considered to have a 'multilocular' arrangement of the stored lipid, i.e. there are multiple fat droplets. In addition, BAT has large numbers of mitochondria with a well-developed cristae structure, while the numbers of mitochondria are limited in WAT (see Slavin, 1985). These distinctions are not absolute, however, in that a unilocular structure is evident in BAT, and the numbers of mitochondria reduced, when the rates of thermogenesis are low (Nechad, 1986).

The central distinguishing feature between WAT and BAT is at the biochemical level, in the presence of a thermogenic proton conductance pathway in BAT mitochondria. This pathway is characterized by an uncoupling protein of 32 000 Mr relative molecular mass (Nicholls & Locke, 1984), which appears to be diagnostic of BAT (Cannon *et al.* 1982; Cannon & Nedergaard, 1985). The protein is not present in WAT, or more strictly is below the level of detection of the immunological procedures developed for its assay (Cannon *et al.* 1982; Lean *et al.* 1983; Ricquier *et al.* 1983).

Innervation of the adipose tissues

WAT depots are found in a large number of sites in the body, both subcutaneously and internally, while BAT is more restricted in its distribution. Both tissues are innervated by the sympathetic system, but there is little evidence for an important parasympathetic innervation in either tissue (Barnard *et al.* 1980;

Fredholm, 1985). Parasympathetic influences on thermogenesis have, however, been described (Rothwell *et al.* 1981). The degree of sympathetic innervation and the level of vascularization are relatively sparse in WAT, compared with BAT, and this is a further feature differentiating the tissues. The sympathetic innervation to WAT was originally thought to be associated with the blood vessels alone, but some direct innervation of the white adipocytes is now recognized (see Slavin, 1985). BAT has a clear dual innervation, in that there are sympathetic nerve endings on both the blood vessels and each adipocyte (Barnard *et al.* 1980; Nechad, 1986).

The concentration of noradrenaline in WAT, which is an indication of the extent of the sympathetic innervation, is of the order of 40 ng/g tissue (Fredholm, 1985). This compares with the considerably greater concentration of 1000 ng/g, or more, in BAT or the heart (Barnard *et al.* 1980).

Adrenoceptors in WAT and BAT

WAT is generally considered to have mainly β_1-adrenoceptors on the plasma membrane, although α_2-receptors appear to predominate in hamster and human WAT, with an antilipolytic action (see Vernon & Clegg, 1985). β_1-adrenoceptors (Bukowiecki *et al.* 1978), or a mixed β_1/β_2 population (Rothwell *et al.* 1985), have been described in BAT. Other evidence, however, suggests that the β-adrenoceptor in both tissues is of a novel subtype, i.e. neither β_1 nor β_2 (Arch *et al.* 1984*a*,*b*). Although originally described in the rat, it is now apparent that the novel subtype may occur in other species, at least for BAT (J. R. S. Arch, personal communication). Thermogenesis is primarily a β-adrenoceptor-activated process, but BAT also contains α_1-adrenoceptors, which mediate a series of events in the tissue, including a stimulation in phosphatidylinositol metabolism and the mobilization of intracellular Ca^{2+} (Cannon & Nedergaard 1985). Cholinergic receptors have not been described in either tissue.

The presence of a new β-adrenoceptor subtype creates considerable potential for the pharmacological manipulation of the adipose tissues, particularly in relation to the treatment of obesity.

Lipolysis in WAT

The main metabolic pathways in WAT relate to the synthesis and breakdown of triacylglycerol. Fatty acids may be derived either from the circulation, or from *de novo* synthesis, particularly from glucose. The main effect of catecholamines on WAT is to stimulate lipolysis through the activation of hormone-sensitive lipase, via a cyclic AMP-dependent system (see Belfrage, 1985). Sympathetic stimulation of the vasculature in WAT leads to vasoconstriction, by an α-adrenoceptor-mediated mechanism, while an increase in the activity of the direct sympathetic innervation to the white adipocytes will stimulate lipolysis (see Vernon & Clegg, 1985).

Apart from a stimulation of lipolysis through the activation of the sympathetic innervation of the adipocyte, lipolysis in WAT may be stimulated by circulating

catecholamines produced from the adrenals. The relative importance of circulating catecholamines and locally secreted noradrenaline to the stimulation of lipolysis in WAT has not been clearly established. The success of the white adipocyte preparation for in vitro studies has tended to obscure the importance of sympathetic innervation in the control of lipolysis in WAT, while focusing on the role of adrenaline. Indeed, these preparations may also have led to an over-emphasis on the role of other hormonal factors, such as ACTH, growth hormone, and glucagon, in the regulation of lipolysis (Hales *et al.* 1978).

Three basic observations underlie the view that the sympathetic system does play an important role in the regulation of lipolysis in WAT in vivo: denervation leads to an increase in lipid mass; electrical stimulation of the nerves to WAT results in the release of fatty acids; and the abolition (pharmacologically) of sympathetic activity inhibits the normal mobilization of lipids (see Hales *et al.* 1978). Little work has been done on directly measuring sympathetic activity in WAT, reflecting the technical problems associated with the low noradrenaline content of the tissue. It is therefore difficult to define the relative importance of the sympathetic system in lipolysis in WAT in different situations. It seems likely, however, that in situations such as severe exercise, stress and cold exposure, the direct sympathetic stimulation of WAT is the main mechanism for increasing the rate of lipolysis (Hales *et al.* 1978). On the other hand, the gradual increase in lipid mobilization occurring during starvation is unlikely to be due to the activity of the sympathetic system. In other tissues, fasting is associated with a reduction in sympathetic activity (Young & Landsberg, 1977).

Acute effects of noradrenaline on BAT

The central mechanism for thermogenesis in BAT is the mitochondrial proton conductance pathway, elucidated by Nicholls and his group (Nicholls & Locke, 1984). This pathway produces a proton short-circuit across the inner mitochondrial membrane, resulting in a controlled uncoupling of respiration from the synthesis of ATP. The proton conductance of BAT mitochondria is regulated by a 32 000 Mr uncoupling protein which is located in the inner membrane. Long-term adaptive changes in the concentration of uncoupling protein, induced by a thermogenic stimulus to the animal (e.g. cold, overfeeding), lead to alterations in the capacity of the proton conductance pathway (Himms-Hagen, 1986).

Noradrenaline is the main mediator of thermogenesis in BAT and has been shown to have a number of effects on the tissue (Table 2). Sympathetic stimulation leads to an initial vasoconstriction in BAT, by an α-adrenoceptor-mediated mechanism, followed by vasodilation (Foster, 1986). The latter may result from increases in the local concentration of a vasodilator. The central and best-documented effects of noradrenaline on the brown adipocyte are the stimulation of lipolysis and the activation of the proton conductance pathway (see Nicholls & Locke, 1984). These two processes appear to be directly linked in that fatty acids are now considered to be the main signal leading to an increase in mitochondrial proton conductance (Nicholls *et al.* 1986).

Table 2. *Summary of the main effects of noradrenaline on brown adipose tissue*

Acute effects	
Lipolysis	Stimulated
Glucose uptake	Stimulated
Lipoprotein lipase	Stimulated
Pyruvate dehydrogenase	Converted to active form
5′-Deiodinase	Stimulated
Proton conductance pathway	Stimulated
Chronic effects	
Mitochondrial mass	Increased
Specific mitochondrial concentration of uncoupling protein	Increased
No. of cells	Increased?

Sympathetic stimulation leads additionally to an increase in the supply of substrate to BAT. In contrast to WAT, lipoprotein lipase in BAT is stimulated by noradrenaline, resulting in an increased uptake of fatty acids by the adipocyte (Carneheim *et al.* 1984). Studies with 2-deoxyglucose suggest that glucose uptake is also stimulated by noradrenaline (Cooney *et al.* 1985). The extra glucose appears to be oxidized, rather than converted to lipid, since the conversion of pyruvate dehydrogenase from the inactive to the active form is stimulated by noradrenaline, without any effect on the activity of acetyl-CoA carboxylase (*EC* 6.4.1.2) (Gibbons *et al.* 1985). Noradrenaline has now been reported to similarly increase pyruvate dehydrogenase activity in WAT (Kilgour & Vernon, 1986).

A further important enzyme under sympathetic control in BAT is 5′-deiodinase, which converts thyroxine to 3,5,3′-triiodothyronine (Silva & Larsen, 1983).

Sympathetic activity in BAT

The activity of the sympathetic nervous system in a tissue can be assessed by noradrenaline turnover studies (see Landsberg & Young, 1983). A number of such studies have been made on BAT in a variety of physiological and pathophysiological states (Table 3). Cold exposure and voluntary overfeeding lead

Table 3. *Summary of the main physiological and pathophysiological conditions in which sympathetic activity in brown adipose tissue is altered*

	Sympathetic activity	Thermogenesis
Cold	Increased	Increased
Overfeeding	Increased	Increased
Fasting	Decreased	Decreased
Lactation	Decreased	Decreased
Streptozotocin-induced diabetes	Decreased	Decreased
Obesity	Decreased	Decreased
Administration of corticosteroids	Decreased	Decreased
Administration of insulin	Increased	Increased

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Table 4. *Sympathetic activity in brown adipose tissue in different types of obese animal*

	Sympathetic activity	Thermogenesis
Obese (*ob/ob*) mouse	Decreased	Decreased
Zucker (*fa/fa*) rat	Decreased	Decreased
Rats with lesions of the ventromedial hypothalamus	Decreased	Decreased
Monosodium glutamate-lesioned mouse	Decreased	Decreased
KK mouse	Decreased	—
High-fat-fed golden hamster	Decreased	Increased

to increases in sympathetic activity in BAT, resulting in increased thermogenesis (Himms-Hagen, 1985, 1986). In contrast, sympathetic activity in the tissue is reduced on fasting (Young & Landsberg, 1977), and in situations such as lactation (Trayhurn & Wusteman, 1987), streptozotocin-induced diabetes (Yoshida *et al.* 1985) and obesity (see Romsos, 1985). In each of these conditions a decrease in thermogenesis in BAT follows the reduction in sympathetic activity.

Sympathetic activity has been shown to be decreased in several different types of obese animal (Table 4). Only in the golden hamster fed on a high-fat diet is there a dissociation between sympathetic activity and thermogenesis in BAT (Hamilton *et al.* 1986). Explanations for this unexpected observation include an increase in the sensitivity to noradrenaline in the brown adipocyte of the fat-fed hamster, and the possibility that the sympathetic system plays a much less central role in the stimulation of thermogenesis in this hibernating species than in other rodents.

The most comprehensive studies on sympathetic activity in obese animals have been performed on the *ob/ob* mouse and the Zucker rat (see Romsos, 1985): both show low activity under normal conditions, together with an impairment in the response to diet. Acute exposure to cold, however, elicits a normal activation of the sympathetic system (Romsos, 1985). A chronic state of understimulation from the sympathetic system leads to a long-term atrophy of BAT. Studies on the effects of adrenalectomy in the Zucker rat and the *ob/ob* mouse have indicated that the low level of thermogenesis in BAT in obesity relates to a glucocorticoid-induced suppression of sympathetic activity (Vander Tuig *et al.* 1984; York *et al.* 1985).

Corticosteroids appear to have a general inhibitory effect on the sympathetic system in BAT (York *et al.* 1985). Insulin, on the other hand, stimulates sympathetic activity (Rothwell *et al.* 1983). The effect of other hormones has not been reported, but it seems likely that the sympathetic innervation to BAT will be subject to modulation by a variety of factors. In addition to effects on the sympathetic system, hormonal influences on thermogenesis may be expressed directly on the brown adipocyte. Insulin, for example, has several important direct effects on BAT, including the stimulation both of glucose uptake and lipogenesis (McCormack & Denton, 1977; Cooney *et al.* 1985).

Chronic effects of the sympathetic system on the growth and development of the adipose tissues

Chronic cold-exposure or overfeeding on a palatable diet lead to a major hypertrophy of BAT, involving increases in the number of brown adipocytes and the number of mitochrondia per cell, as well as a specific increase in the activity of the proton conductance pathway (see Cannon & Nedergaard, 1985; Himms-Hagen, 1986). Following recent work by Mory *et al.* (1984), where rats were constantly infused with noradrenaline from implanted osmotic minipumps, the sympathetic system has been clearly established as having a central role in the hypertrophy of BAT. The thermogenic capacity of the tissue is greatly increased by noradrenaline infusion, involving increases in both mitochondrial mass and the specific mitochondrial concentration of uncoupling protein (Table 2). The importance of the sympathetic system in the growth and development of BAT is also underlined by a number of other studies, particularly those involving an implanted phaeochromocytoma and the chronic administration of long-acting β-agonists (see Arch *et al.* 1984*b*; Himms-Hagen, 1985).

Any effects of chronic sympathetic stimulation on WAT are much less clear than with BAT. However, in view of the increased turnover of triacylglycerol that occurs in cold-adapted animals (Trayhurn, 1981), it is likely that the maintenance of high lipolytic rates will relate to prolonged sympathetic stimulation.

Conclusions

It is evident from what has been discussed in this brief overview that the sympathetic nervous system plays a dominant role in the regulation of thermogenesis in BAT, with important implications for the regulation of energy balance. The sympathetic system also appears to be the major factor in the growth and development of the tissue in response to a chronic thermogenic stimulus. Other factors which influence the activity of BAT may operate by modulating the activity of the sympathetic system, such as is the case with corticosteroids, although direct hormonal effects on BAT also occur (e.g. with insulin). The importance of the sympathetic system, relative to that of circulating hormones, in the regulation of lipolysis in WAT is less clear. Investigation of the sympathetic activity of WAT, together with the factors influencing the sympathetic system in the tissue in different physiological and pathological conditions, is an important area for further study. Insight into the basis for regional differences in the metabolic activity of WAT may well emerge from such studies.

REFERENCES

Arch, J. R. S., Ainsworth, A. T., Cawthorne, M. A., Piercy, V., Sennitt, M. V., Thody, V. E., Wilson, C. & Wilson, S. (1984*a*). *Nature* **309**, 163–165.

Arch, J. R. S., Ainsworth, A. T., Ellis, R. D. M., Piercy, V., Thody, V. E., Thurlby, P. L., Wilson, C., Wilson, S. & Young, P. (1984*b*). *International Journal of Obesity* **8**, Suppl. 1, 1–11.

Ashwell, M. (1985). In *Metabolic Complications of Human Obesities*, pp. 265–274 [J. Vague, P. Björntorp, B., Guy-Grand, M., Rebuffé-Scrive and P. Vague, editors]. Amsterdam: Elsevier.

Barnard, T., Mory, G. & Nechad, M. (1980). In *Biogenic Amines in Development*, pp. 391–439 [H. Parvez and S. Parvez, editors]. Amsterdam: Elsevier/North Holland Biomedical Press.
Belfrage, P. (1985). In *New Perspectives in Adipose Tissue: Structure, Function and Development*, pp. 121–144 [A. Cryer and R. L. R. Van, editors]. London: Butterworths.
Bukowiecki, L., Follea, N., Vallieres, J. & LeBlanc, J. (1978). *European Journal of Biochemistry* **92**, 189–196.
Cannon, B., Hedin, A. & Nedergaard, J. (1982). *FEBS Letters* **150**, 129–132.
Cannon, B. & Nedergaard, J. (1985). *Essays in Biochemistry* **20**, 110–164.
Carneheim, C., Nedergaard, J. & Cannon, B. (1984). *American Journal of Physiology* **246**, E327–E333.
Cooney, G. J., Caterson, I. D. & Newsholme, E. A. (1985). *FEBS Letters* **188**, 257–261.
Foster, D. O. (1986). In *Brown Adipose Tissue* [P. Trayhurn and D. G. Nicholls, editors]. London: Edward Arnold (In the Press).
Fredholm, B. B. (1985). In *New Perspectives in Adipose Tissue: Structure, Function and Development*, pp. 45–64 [A. Cryer and R. L. R. Van, editors]. London: Butterworths.
Gibbons, J. M., Denton, R. M. & McCormack, J. G. (1985). *Biochemical Journal* **228**, 751–755.
Hales, C. N., Luzio, J. P. & Siddle, K. (1978). *Biochemical Society Symposium* **43**, 97–135.
Hamilton, J. M., Mason, P. W., McElroy, J. F. & Wade, G. N. (1986). *American Journal of Physiology* **250**, R389–R395.
Himms-Hagen, J. (1985). *Annual Review of Nutrition* **5**, 69–94.
Himms-Hagen, J. (1986). In *Brown Adipose Tissue* [P. Trayhurn and D. G. Nicholls, editors]. London: Edward Arnold (In the Press).
Kilgour, E. & Vernon, R. G. (1986). *Proceedings of the Nutrition Society* **45**, 76A.
Landsberg, L. & Young, J. B. (1983). In *Mammalian Thermogenesis*, pp. 99–140 [L. Girardier and M. J. Stock, editors]. London: Chapman & Hall.
Lean, M. E. J., Branch, W. J., James, W. P. T., Jennings, G. & Ashwell, M. (1983). *Bioscience Reports* **3**, 61–71.
McCormack, J. G. & Denton, R. M. (1977). *Biochemical Journal* **166**, 627–630.
Mory, G., Bouillaud, F., Combes-George, M. & Ricquier, D. (1984). *FEBS Letters* **166**, 393–396.
Nechad, M. (1986). In *Brown Adipose Tissue* [P. Trayhurn and D. G. Nicholls, editors]. London: Edward Arnold (In the Press).
Nedergaard, J. & Lindberg, O. (1979). *European Journal of Biochemistry* **95**, 139–145.
Nicholls, D. G. & Locke, R. M. (1984). *Physiological Reviews* **64**, 1–64.
Nicholls, D. G., Cunningham, S. & Wiesinger, H. (1986). *Biochemical Society Transactions* **14**, 223–225.
Ricquier, D., Barlet, J.-P., Garel, J.-M., Combes-George, M. & Dubois, M. P. (1983). *Biochemical Journal* **210**, 859–866.
Romsos, D. R. (1985). *International Journal of Obesity* **9**, Suppl. 2, 55–62.
Rothwell, N. J., Saville, M. E. & Stock, M. J. (1981). *Pflügers Archiv* **392**, 172–177.
Rothwell, N. J., Saville, M. E. & Stock, M. J. (1983). *American Journal of Physiology* **245**, E160–E165.
Rothwell, N. J., Stock, M. J. & Sudera, D. K. (1985). *American Journal of Physiology* **248**, E397–E402.
Silva, J. E. & Larsen, P. R. (1983). *Nature* **305**, 712–713.
Slavin, B. G. (1985). In *New Perspectives in Adipose Tissue: Structure, Function and Development*, pp. 23–43 [A. Cryer and R. L. R. Van, editors]. London: Butterworths.
Trayhurn, P. (1981). *Biochimica et Biophysica Acta* **664**, 549–560.
Trayhurn, P. & Wusteman, M. C. (1987). *Proceedings of the Nutrition Society* **46** (In the Press).
Vander Tuig, J. G., Ohshima, K., Yoshida, T., Romsos, D. R. & Bray, G. A. (1984). *Life Sciences* **34**, 1423–1432.
Vernon, R. G. & Clegg, R. A. (1985). In *New Perspectives in Adipose Tissue: Structure, Function and Development*, pp. 65–86 [A. Cryer and R. L. R. Van, editors]. London: Butterworths.
York, D. A., Marchington, D., Holt, S. J. & Allars, J. (1985). *American Journal of Physiology* **249**, E299–E305.
Yoshida, T., Nishioka, H., Nakamura, Y. & Kondo, M. (1985). *Diabetologia* **28**, 692–696.
Young, J. B. & Landsberg, (1977). *Science* **196**, 1473–1475.

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