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The sympathetic nervous system in white adipose tissue regulation

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Sympathetic stimulation has long been recognized to mobilise fatty acids from white adipose tissue. However, it is now apparent that adipose tissue is not only concerned with energy storage as fat, but is a major endocrine and secretory organ. This change has resulted from the identification of leptin as a hormone of energy balance secreted by white adipose tissue. The sympathetic system is a key regulator of leptin production in white fat. Sympathomimetic amines, cold exposure or fasting (which lead to sympathetic stimulation of white fat), decrease *ob* gene expression in the tissue and leptin production. On the other hand, sympathetic blockade often increases circulating leptin and *ob* gene expression, and it is postulated that the sympathetic system has a tonic inhibitory action on leptin synthesis. In rodents this action is through stimulation of β3-adrenoceptors. The adrenal medulla (as opposed to the direct sympathetic innervation) has been thought to play only a minor role in the catecholaminergic regulation of white adipose tissue. However, in rodents responses of the leptin system to adrenergic blockade vary with the method used. Changes in leptin and *ob* gene expression are considerably less using methods of blockade that only effect the terminal adrenergic innervation, rather than medullary secretions as well. Stimulation of the leptin system increases sympathetic activity and hence metabolic activity in many tissues. As well as leptin, other (but not all) secretions from white adipose tissue are subject to sympathetic regulation. In obesity the sympathetic sensitivity of adipose tissue is reduced and this factor may underlie the dysregulation of leptin production and other adipose tissue secretions.

Sympathetic nervous system: White adipose tissue: Leptin production: β-Adrenoceptors: Obesity

The present short review considers the role of the sympathetic nervous system in the regulation of white adipose tissue (WAT). From the early studies of Cannon (1929) came the concept of the sympathetic nervous system and the adrenal medulla being present to prepare the animal for 'fight or flight' by raising blood glucose, mobilising fatty acids from adipose tissue, increasing heart rate, redistributing blood flow and elevating metabolic rate. Cannon (1929) thought that the adrenal medulla was more important than the sympathetic innervation. However, it has become accepted that as far as the mobilisation of fat is concerned, the direct sympathetic innervation of adipose tissue is more important than the adrenals. Briefly, the evidence can be summarised as being that sympathetic denervation leads to an increase in adipose tissue weight relative to the non-denervated pad; nerve stimulation results in fatty acid release, and sympathetic or ganglionic blockade inhibits the mobilisation of lipid (Gilgen *et al*. 1962; Rebuffé-Scrive, 1991), while adrenal demedullation is not effective.

Adipose tissue has thus been regarded as an organ for energy storage as fat, with the sympathetic nervous system being the major regulator of fat mobilisation to provide homeostasis of energy supply. Although adipose tissue secretions such as adipsin and tumour necrosis factor α (TNF-α) predate the discovery of leptin, the cloning of the *ob* gene (Zhang *et al*. 1994) and the finding that leptin, the resulting hormone, secreted primarily from WAT, decreased food intake and increased energy expenditure, has shown that adipose tissue is a major endocrine organ. Other protein factors and cytokines from WAT, which act both locally or systemically, have also been identified (Mohamed-Ali *et al*. 1998). The present brief review will seek to show the importance of the sympathetic nervous system in the regulation of the metabolic and secretory functions of adipose tissue, and will suggest that there is some evidence for the involvement of the adrenal medulla in the responses.

Abbreviations: BAT, brown adipose tissue; 6OHD, 6-hydroxydopamine; αMPT, α-methyl-*p*-tyrosine; TNF, tumour necrosis factor; UCP, uncoupling protein; WAT, white adipose tissue.

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Sympathetic activity in fat relative to other tissues

Changes in sympathetic activation in individual tissues are often studied by examining the rate of noradrenaline turnover within the tissue. In most tissues a decrease in turnover is associated with fasting (Young & Lansberg, 1977), while an increase occurs in cold exposure or overfeeding, as energy expenditure increases either to counteract the cold or the excess energy intake. As expected, noradrenaline turnover increases in WAT in cold-exposed rodents (Garofalo *et al*. 1996), but also in fasted rodents (Migliorini *et al*. 1997). There is, therefore, elevated (not decreased) sympathetic activity and raised fatty acid mobilisation from WAT in fasting as well as in cold exposure.

These responses are thought to primarily involve the direct sympathetic innervation. This theory is based on the experimental evidence detailed earlier, and also on our understanding of the excitation of adrenergic receptors and the known levels of circulating catecholamines. The β3-adrenoceptor is the predominant β-subtype in adipose tissue of rodents (although not in man) and has a decreased affinity for adrenaline relative to that exhibited by β1- or β2-adrenoceptors, and for noradrenaline an affinity less than that of β1-adrenoceptors but greater than that of β2-adrenoceptors (Tate *et al*. 1991). The β3-receptor is, therefore, more likely to be stimulated by the high noradrenaline concentrations that will be found in the immediate vicinity of the terminal adrenergic nerve fibre (Fig. 1) than by catecholamines derived from the circulation (Giacobino, 1996). Normally, circulating adrenaline levels (derived entirely from the adrenal medulla) are lower (Kopin, 1989) than the level of noradrenaline (derived mainly from sympathetic overspill), and may not be high enough to be physiologically important in comparison with the direct sympathetic innervation. However, circulating adrenaline levels may be raised at times of stress if blood glucose falls (e.g. fasting, cold exposure), and may then contribute to the sympathetic response in adipose tissue (Young *et al*. 1984). Further indications that adrenaline may be involved will be shown when the effects of different methods of sympathetic blockade are considered. However, circulating adrenaline is likely to be more important in man, due to the decreased sensitivity of human adipose tissue to β3-adrenoceptor stimulation (Arch & Wilson, 1996) and the greater importance of β2-receptors, which are more sensitive to adrenaline. Thus, adrenaline and noradrenaline are equally potent in increasing glycerol secretion from adipose tissue in human subjects (Hjemdahl & Linde, 1983); β3-adrenoceptors have been estimated to be only 20 % of the total population of β-adrenoceptors in human WAT, and although stimulation of β3-adrenoceptors can be demonstrated, effects of isoprenaline are mediated exclusively by β1- and β2-receptors (Tavernier *et al*. 1996).

One final consideration is that WAT also contains α1- and α2-receptors (Lafontan & Berlan, 1993). The α2-adrenoceptors like β3-receptors are G-protein coupled, but decrease rather than increase adenyl cyclase levels. α2-Receptor stimulation may therefore be expected to have the reverse effects to β3-receptor stimulation. For lipolysis, stimulation of α2- and β3-receptors have been suggested to

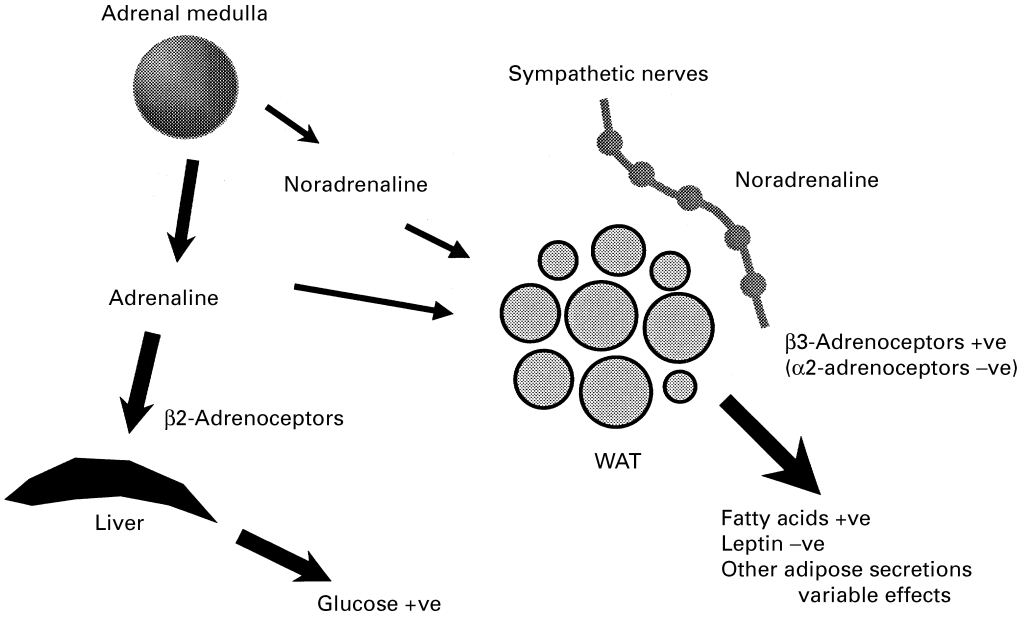

Fig. 1. Sympathetic regulation of white adipose tissue (WAT): Sympathetic regulation is provided by high concentrations of noradrenaline released from sympathetic nerves and stimulating β3-adrenoceptors (also inhibitory α2-receptors) in rodent WAT. Stimulation of β3-adrenoceptors leads to the mobilisation of fatty acids, as an energy source for other tissues, but inhibits the secretion of the hormone leptin, and has variable effects on a number of tissue factors and cytokines. The adrenal medulla secretes mainly adrenaline into the circulation, an important function of which is to raise blood glucose by stimulating liver β2-receptors. Circulating adrenaline levels are often not high enough to affect WAT β3-receptors, but sufficient adrenaline may be secreted when stimulated by a fall in plasma glucose, particularly in man where β2-adrenoceptors are more important in adipose tissue. +ve, stimulation; –ve, inhibition.

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have an interplay, with α2-receptors predominating and decreasing lipolysis at low concentrations of catecholamines, while β3-receptors are more important at higher concentrations (Lafontan & Berlan, 1993). α1-Adrenoceptors are less abundant and may not be involved in lipolysis, but their stimulation increases glycolysis, and hence lactate production (Faintrenie & Geloen, 1996). There are differences in receptor sensitivity between depots and with obesity in man. Thus, omental fat in obese human subjects has increased β3-receptor and decreased α2-receptor effects on lipolysis compared with subcutaneous fat (Richelsen *et al*. 1991; Hoffstedt *et al*. 1997). The possible interplay of α- and β-adrenoceptor effects and differences between depots in relation to obesity merits further consideration in relation to the sympathetic regulation of leptin, and other adipose tissue secretions as well.

Short-term regulation of leptin production

Although *ob* gene expression in WAT and leptin levels are related to adiposity, leptin as well as some other adipose tissue secretions are subject to short-term regulation. The present review will aim to show that the sympathetic system is a key regulatory system. Other factors that regulate leptin production have been reviewed by Trayhurn & Beattie (2001). Acute treatment with catecholamines in both experimental animal and human studies reduce circulating leptin. This process occurs via β3-adrenoceptors in rodents, as selective β3 agonists (BRL 35153A, CL31643 etc.) suppress leptin gene expression and decrease leptin levels (Moinat *et al*. 1995; Trayhurn *et al*. 1996). In human subjects, although there is some evidence that β3-receptors may be involved in fatty acid mobilisation from WAT (Enocksson *et al*. 1995), the sympathetic regulation of WAT is likely to be mainly through β1- and β2-receptors (Sennitt *et al*. 1998). Second, fasting leads to a rapid profound fall in *ob* gene expression, which is rapidly reversible and therefore not related to any change in body adiposity, in both experimental animal and human studies (Trayhurn *et al*. 1995*b*; Boden *et al*. 1996). Third, cold exposure leads to increased noradrenaline turnover and hence sympathetic stimulation, an increased metabolic rate and mobilisation of fatty acids in order to maintain body temperature and a rapid decrease in leptin gene expression and plasma leptin levels (Trayhurn *et al*. 1995*a*; Bing *et al*. 1997), and are rapidly reversed on rewarming; again indicating a key role for leptin in nutritional regulation rather than reflecting changes in adiposity.

Another way of elucidating the importance of the sympathetic nervous system in leptin production is by the use of adrenergic blockade and is considered in detail elsewhere. Briefly, sympathetic blockade can give evidence of the tonic regulation of leptin production (Trayhurn & Beattie, 2001), but studies have been limited by the lack of effective β3-adrenoceptor blockers. Sympathetic blockade can be achieved by using α-methyl-*p*-tyrosine (αMPT), an inhibitor of tyrosine hydroxylase, to inhibit catecholamine synthesis (Young & Lansberg, 1977) in peripheral sympathetic nerves and in the adrenal medulla. The action of αMPT will be considered in some detail because of the contrast in the extent of its effects compared with those of 6-hydroxydopamine (6OHD). Administration of αMPT provides an effective block of all sympathetic effects and leads to an increase in leptin level of up to 8-fold within 8–10 h in lean mice; αMPT more than reversed the fall in leptin level and *ob* mRNA in response to a 24 h fast (Rayner *et al*. 1998). These effects must be contrasted with those of 6OHD, which chemically sympathectomises the peripheral sympathetic innervation without affecting brain adrenergic systems or the adrenal medulla. During fasting 6OHD raises leptin levels, but to a lesser extent than αMPT (Sivitz *et al*. 1999). Levels of *ob* gene mRNA increased in brown adipose tissue (BAT) in this study, although not in WAT, suggesting that the change in leptin in response to 6OHD may represent an increased output from BAT. In recent experiments we have been unable to increase leptin levels or *ob* gene expression in WAT in fasted mice by sympathetic blockade with 6OHD. In these mice fasting surprisingly raised plasma noradrenaline levels up to 4-fold. This rise was inhibited by 6OHD, suggesting effective sympathetic neurone blockade. The differential effects of 6OHD relative to αMPT may relate to continued adrenaline secretion. However, despite the profound effects of some forms of sympathetic blockade, sympathetic knockout mice (unable to synthesise dopamine β-hydroxylase; Thomas & Palmiter, 1997) are surprisingly non-obese, with a raised metabolic rate. Uncoupling protein (UCP) 1 but not UCP2 mRNA levels are raised but, as expected, animals are cold intolerant. Understanding sympathetic regulation of WAT and its relationships with other regulatory systems still has some way to go.

Sympathetic innervation

Although sympathetic nerve fibres are known to follow the blood vessels to WAT, a key question has been whether there is direct sympathetic innervation of the white adipocytes, rather than transmitter spillover from the sympathetic innervation of the blood supply (Bartness & Bamshad, 1998) or sympathetic changes in tissue permeability. Nerve fibres in close apposition with adipocytes (Cinti, 1999) have been demonstrated and is comprehensively covered in another review from the present symposium (Cinti, 2001). Functional sympathetic nerves regulating lipolysis have also been shown (Gilgen *et al*. 1962; Rebuffé-Scrive, 1991). The sympathetic pathways involved have been identified by retrograde tracing of pseudorabies virus, injected into inguinal and epididymal WAT pads in hamsters and rats. The sympathetic pathway was traced back through the intermediolateral cell group to the central autonomic nucleus of the spinal cord; in the brain stem pseudorabies virus-labelled cells were seen in a number of areas, including the solitary tract, which is known to be involved in the control of voluntary food intake (and which contains leptin receptors; Mercer *et al*. 1998). In the hypothalamus prominent pseudorabies virus labelling was seen in the paraventricular nucleus, which is known to be involved in sympathetic responses (e.g. paraventricular nucleus stimulation induces sympathetically-mediated lipolysis; Bartness & Bamshad, 1998). However, little labelling was evident in the ventromedial hypothalamus, even though this region has long been associated with sympathetic effects (e.g. leptin injection into ventromedial hypothalamus (Satoh *et al*.

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1999) leads to an increase in circulating catecholamines). Finally, sympathetic connections are also seen in the suprachiasmatic nucleus, which is known to be concerned with the initiation and regulation of circadian rhythms, and may relate to the circadian variation in leptin levels. Clearly, there is a functional sympathetic innervation from the areas of the brain that are involved in the regulation of energy balance. Finally, there is evidence of leptin-sensitive afferent pathways from sympathetic tissues (Niijima, 1998), and the importance of afferent sympathetic pathways from adipose tissue will need to be evaluated.

The sympathetics and energy expenditure in white adipose tissue compared with other tissues

As well as decreasing food intake, leptin increases energy expenditure (Campfield *et al*. 1995; Pellymounter *et al*. 1995) through the sympathetic system. The evidence for sympathetic feedback to adipose tissue following leptin secretion will be considered (Fig. 2). Leptin (intracerebroventricular or into the ventromedial hypothalamus) has been shown to increase circulating adrenaline and noradrenaline levels (i.e. stimulate both sympathetic nerves and the adrenal medulla; Satoh *et al*. 1999), although another report has suggested that this increase is primarily brought about by an increase in sympathetic nerve activity (Haque *et al*. 1999). In rodents these effects on energy expenditure involve the sympathetic stimulation of UCP1 activity in BAT (Scarpace *et al*. 1997) and are prevented by sympathetic denervation of BAT (Scarpace & Matheny, 1998). Leptin has been shown to increase noradrenaline turnover in BAT (Collins *et al*. 1996); it increases sympathetic nerve activity to the kidney, adrenals and the hindlimb (Dunbar *et al*. 1997; Haynes *et al*. 1997) and glucose uptake in heart, BAT and striated muscle (Minokoshi *et al*. 1999), but not in WAT. Leptin has also been shown to increase glucose turnover in the liver and decrease hepatic glycogen content (Kamora *et al*. 1997), suggesting the involvement of adrenaline in the responses. Although sympathetic effects following leptin administration have been demonstrated in many tissues, there has been less evidence of a closed feedback loop changing energy metabolism in WAT. Leptin does increase UCP2 and UCP3 gene expression in this tissue (Zhou *et al*. 1997; Liu *et al*. 1998; Scarpace *et al*. 1998). However, sympathetic stimulation of WAT has yielded varying effects on UCP gene expression in WAT. β3-Adrenoceptor agonists increased UCP2 and UCP3 mRNA in the rat (Emilsson *et al*. 1998), although other groups have reported no change in UCP2 and UCP3 gene expression (Savontaus *et al*. 1998; Gomez-Ambrosi *et al*. 1999). Sympathetic stimulation by cold exposure (16 h) did not change UCP2 mRNA in WAT in the rat (Fleury *et al*. 1997), although this period of cold exposure may have been insufficient. Fasting increases UCP2 and UCP3 mRNA in WAT (although UCP3 gene expression is low in WAT) in both mouse and rat (Boss *et al*. 1997, 1998; Ricquier & Bouillaud, 2000). This effect may be unrelated to the sympathetic stimulation, as consistently mRNA levels for UCP2 and UCP3 in WAT and muscle are increased at times of increased fatty acid metabolism (high-fat diets, obesity, fasting), suggesting that these UCP may have a role in the regulation of fatty acid metabolism (Boss *et al*. 1998). In summary, although leptin alters UCP2 and UCP3 gene expression, the role of UCP2 and UCP3 in the sympathetic stimulation of energy metabolism in WAT through UCP is not completely established.

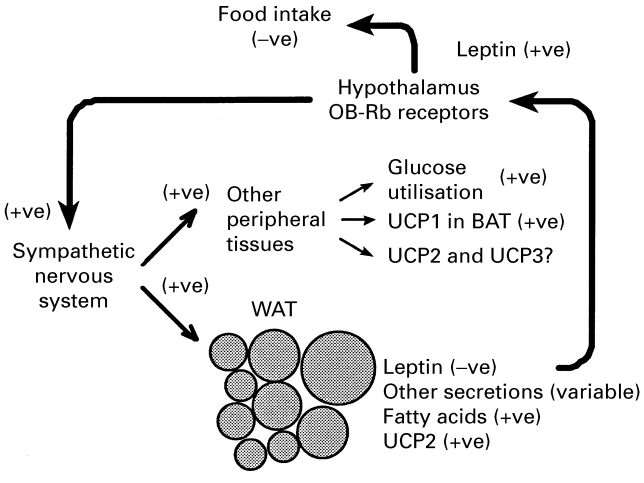

Fig. 2. Negative feedback to white adipose tissue (WAT) through the sympathetic nervous system: Leptin stimulates the hypothalamic OB-Rb splice variant of the leptin receptors to decrease food intake and increase sympathetic activity, principally through sympathetic nerves and their transmitter noradrenaline. Sympathetic stimulation increases glucose utilization, increases heat production through uncoupling protein (UCP) 1 in brown adipose tissue (BAT) and possibly through UCP2 and 3 in other tissues (e.g. muscle and WAT). Sympathetic stimulation provides negative feedback to WAT to limit leptin production. +ve, stimulation; –ve, inhibition.

Cyclic nature of leptin production

Leptin levels do not increase immediately with feeding in the manner that many other hormones do. Overfeeding has been shown to raise leptin levels (Kolaczynski *et al*. 1996). This effect is unlikely to be related to the increased sympathetic activity induced by overfeeding (Lansberg & Young, 1978), which may be expected to decrease circulating leptin. In man and rodents leptin levels peak at night and fall to a nadir the next morning (Sinha *et al*. 1996; Licinio *et al*. 1997). Much of this diurnal pattern is entrained to the meal pattern (Schoeller *et al*. 1997) and peaks before the maxima in the adrenocorticotrophic hormone and cortisol rhythms in human subjects (Licinio *et al*. 1997). In rats too the diurnal variation in leptin does not relate to the corticosteroid cycle (Ahima *et al*. 1996).

As well as a diurnal cycle of leptin secretion, an ultradian rhythm in the level of plasma leptin has been detected. In human subjects different pulse frequencies have been detected, depending on the frequency of sampling. At the most frequent sampling, there were thirty-two peaks over 24 h with a mean cycle duration of 32·8 min (Licinio *et al*. 1997), and it has been suggested that this frequency relates best to the frequency of fluctuation of catecholamine levels in plasma rather than to the intrinsic frequencies of secretion of insulin or corticosteroids (Himms-Hagen, 1999). It is possible that the sympathetic system exerts a tonic

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inhibition of leptin synthesis rather than merely switching off leptin production in response to an emergency; this tonic control may well be pulsatile as well.

The sympathetic regulation of other secretions from white adipose tissue

A detailed consideration of other secretions from adipose tissue is given in a companion review (Trayhurn & Beattie, 2001). The sympathetic regulation of many adipose tissue secretions is less well documented than that for leptin. Lipoprotein lipase, which is secreted from adipose tissue and leads to the lipolysis of circulating triacylglycerol before entry into adipose tissue, is clearly down regulated by the sympathetics; levels and gene expression in adipose tissue are decreased by sympathomimetic amines (Deshaies *et al*. 1993), fasting (Picard *et al*. 2000), or cold exposure (Bertin *et al*. 1985). There is direct evidence for the sympathetic regulation of plasminogen activator inhibitor-1 and angiotensinogen in WAT. Plasminogen activator inhibitor-1 inhibits the activation of plasminogen to plasmin, and hence inhibits the breakdown of fibrin. Plasminogen activator inhibitor-1 levels in WAT are raised in obesity, and catecholamines are inhibitory in rodents (Gottschling-Zeller *et al*. 1999; Halleux *et al*. 1999). Adipose tissue is second only to the liver in the production of angiotensinogen (Jones *et al*. 1997). Fasting increases angiotensinogen gene expression in adipose tissue, while having no effect on its expression in the liver (Frederich *et al*. 1992). Angiotensinogen mRNA in WAT is also down regulated by β-adrenergic stimulation (Jones *et al*. 1997). Surprisingly, angiotensinogen mRNA levels vary in different animal models of obesity, angiotensinogen mRNA in WAT being increased in *ob/ob* mice (Frederich *et al*. 1992) but reduced in *fa/fa* rats (Jones *et al*. 1997). In human subjects, angiotensinogen levels are raised in obesity (Faloia *et al*. 2000) and have been linked with the hypertension sometimes found. Among pro-inflammatory cytokines, interleukin-6 is increased by β-adrenergic stimulation in human subjects and in isolated adipocytes (Mohamed-Ali *et al*. 2000). TNF-α is increased on adrenergic stimulation (Orban *et al*. 1999). TNF-α is interesting in that it is known to regulate other adipose tissue secretions such as leptin and plasminogen activator inhibitor-1 (Samad *et al*. 1999), so that there is a possibility of indirect TNF-α-mediated sympathetic regulation. TNF-α is also able to down regulate β-receptors and adrenergic function in adipocytes (Berkowitz *et al*. 1998), indicating the complexity of the modulation of sympathetic regulation in this tissue. The metallothionein gene has recently been shown to be expressed in adipose tissue. Metallothionein gene expression is not altered by fasting, but is increased by a β3-agonist (Trayhurn *et al*. 2000). Recently, two new secretions from adipose tissue have been documented. Fasting-induced adipose tissue factor, a target for peroxisome proliferator-activated receptor α, is increased on fasting (Kersten *et al*. 2000), while resistin, which increases with high-fat feeding and decreases insulin sensitivity, is decreased in fasting (Steppan *et al*. 2001). Although fasting is a useful means of perturbing the sympathetic system, it has other metabolic effects, such as reducing insulin secretion and increasing glucocorticoid secretion. Other factors are known to be secreted from adipose tissue, but are not at present known to be sympathetically regulated. Examples are retinol-binding protein (Montague *et al*. 1998) which is involved in the transport of retinoids, and adiponectin which is a collagen-like plasma protein that has an inhibitory effect on the proliferation of vascular smooth muscle cells and is the product of the adipose tissue-specific and most abundant gene transcript, apM1. Its plasma levels are decreased in obesity (Arita *et al*. 1999).

Sympathetic control in obesity

Obese rodents (*fa/fa, ob/ob, db/db* mutants) and human subjects have decreased responsiveness to sympathetic stimulation and have down regulated β-adrenoceptors in WAT (Muzzin *et al*. 1991; Collins *et al*. 1994, 1997, 1999; Breslow *et al*. 1997). This effect is manifested by both decreased fatty acid mobilisation and decreased responsiveness of the leptin system to sympathetic stimulation (fasting (Trayhurn *et al*. 1995*b*; Hardie *et al*. 1996), sympathomimetic amines or αMPT (Rayner *et al*. 1998)). The decreased β3-receptor sensitivity may in turn be associated with the decreased leptin sensitivity or absence of leptin. Thus, in *ob/ob* mice leptin treatment increases β3-adrenoceptor expression (Breslow *et al*. 1997).

Obesity is sometimes associated with hypertension in human subjects (Rumantir *et al*. 1999) and in some rodent models of obesity (e.g. *fa/fa* rats (Carlson *et al*. 2000) but not *ob/ob* mice). The hypertension often seen in obesity has been linked with increased sympathetic tone and with increased noradrenaline spillover from the kidneys and heart (Dunbar *et al*. 1997; Haynes *et al*. 1997). While sympathetic activity to, or responsiveness of, WAT itself may be decreased, it is possible that sympathetic activity to other organs may be increased to raise their metabolic rate as part of an attempted homeostatic regulation of the increased energy accretion, but may result also in an increase in blood pressure (Dunbar *et al*. 1997). This effect may link with the actions of leptin in increasing glucose and fat metabolism, which have been already mentioned.

An overview of the role of the sympathetic system in the regulation of adipose tissue secretion

The sympathetics (the system for 'fight or flight') inhibit a number of adipose tissue secretions. This action is best exemplified by leptin, the hormone of plenty that stimulates haematopoiesis, angiogenesis and reproductive function, and acts as a growth factor and as a metabolic regulator; functions that are necessary for long-term survival rather than short-term survival. The altered levels of many of these secretions in obesity may relate to the decreased sympathetic regulation as well as the increased fat mass, and they are likely to contribute to the increased morbidity and mortality of obesity. It is therefore important to understand the extent and importance of sympathetic actions.

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