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REVIEW

Sympathetic control of white adipose tissue in lean and obese humans

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Abstract

Aim: To induce lipolysis, catecholamines could reach the adipocyte via the blood stream after being released from the adrenal medulla or, alternatively, via neuronal release in the vicinity of the fat cell. Sympatho-neuronal effects on fat tissue lipolysis have been demonstrated in experimental animal models. However, the role of sympathetic nerves in the control of lipolysis in human white adipose tissue, which is sparsely innervated, has not been clarified.

Conclusion: The present review summarizes evidence for a direct neuronal influence on lipolysis in humans.

Keywords adipose tissue, human, lipolysis, obesity, sympathetic.

Physiological importance of sympathetic activity for energy balance

The regulation of lipolysis, which determines body fat mass and body weight, depends on the balance between hormonal and sympathetic mechanisms. Lipolysis is predominantely inhibited by insulin while it is promoted by catecholaminergic influences. Endocrine and sympathetic mechanisms affect each other in the regulation of fat mass, and are coordinated in the central nervous system as well as through adaptation of postreceptor signalling. Body weight regulating hormones such as insulin, leptin, corticotropin releasing hormone, melanocyte stimulating hormone and cortisol regulate food intake via hypothalamic appetite centres, but may also affect energy dissipation through activation or suppression of sympathetic nerve activity. Thus, sympathetic activity to effector organs of metabolism is a key factor for maintenance of body weight.

Several studies have tried to evaluate the importance of sympathetic activity for the regulation of energy expenditure in humans. Sympathetic β-adrenergic stimulation evokes an increase in metabolic rate which induces thermogenesis under fasting conditions (Staten *et al.* 1987, Simonsen *et al.* 1992, Blaak *et al.* 1993). Furthermore, sympathetic activation is largely responsible for the facultative component of the thermic effect of acute energy intake in humans and can be reduced by β-blockade (Acheson *et al.* 1984, DeFronzo *et al.* 1984). These studies focussed on the thermogenic effects of increased sympathetic activity. Whether the resting metabolic rate is also regulated by the sympathetic nervous system is a matter of longstanding debate (Acheson *et al.* 1984, DeFronzo *et al.* 1984, Seaton *et al.* 1984, Ravussin *et al.* 1985, Astrup *et al.* 1989, Christin *et al.* 1989, Welle *et al.* 1991). However, a recent thoroughly conducted study suggests that β-adrenergic blockade effectively reduces the resting metabolic rate in lean human adults (Monroe *et al.* 2001). This finding could have important clinical implications because the administration of β-blocking substances or drugs which inhibit sympathetic tone, such as clonidine (Schwartz *et al.* 1988), could reduce the metabolic rate to an extent which increases body weight. So far, this has not been examined prospectively but there is evidence that chronic β-blocking treatment increases body weight (Rossner *et al.* 1990, Sharma *et al.* 2001). It should be underlined that these studies relied on systemic stimulation or inhibition of sympathetic effector organs by

catecholamines or β-blocking substances, rending them unable to distinguish between sympathetic effects on glucose or fat metabolism. Hence, they cannot specifically address the importance of sympathetic activity for regulation of body fat mass. However, evidence that polymorphisms of β_2- and β_3-adrenoceptors coincide with obesity may also argue in favour of catecholamine-induced lipolysis being important for fat mass regulation (Clement *et al.* 1995, Large *et al.* 1997).

Catecholamine-induced lipolysis

Noradrenaline and adrenaline activate lipolysis via β_1-, β_2- and β_3-adrenoceptors and these neurotransmitters are the most important lipolytic substances *in vivo* (Lafontan & Berlan 1993). However, catecholamines also stimulate α_2-adrenoceptors on the fat cell which inhibit lipolysis. The coexistence of different adrenoceptors which increase or decrease the rate of lipolysis in isolated fat cells raises the question of their functional coordination *in vivo*. Experiments aiming to stimulate sympathetic activity by physiological manoeuvres like exercise (Arner *et al.* 1990) or mental stress (Hagstrom-Toft *et al.* 1993, Karlsson *et al.* 1997) have demonstrated an increased lipolysis *in vivo*, arguing for a predominance of β-adrenoceptor- mediated lipolysis under physiological conditions and against the assumption that α-adrenergic inhibition plays an important role in the regulation of lipolysis *in vivo*. Interestingly, catecholaminergic lipolysis differs between intact fat tissue and isolated fat cells. This difference may depend on endocrine and paracrine mechanisms which are not present in fat cell cultures, underlining the importance of *in vivo* experiments.

The lipolytic effects of catecholamines may also depend on the type of fat tissue being examined. The rate of lipolysis has been reported to be low in the subcutaneous femoral/gluteal region, intermediate in the subcutaneous abdominal region and high in the visceral (i.e. omental) region (Mauriège *et al.* 1987, Jansson *et al.* 1990, Mauriège *et al.* 1991, 1995, Arner 1995, Morrison 1999). These regional variations in lipolysis may be explained by site variations in the lipolytic and antilipolytic activity of adrenoceptors, and in addition by endocrine and paracrine factors. Antilipolytic insulin receptors, α_2-receptors and adenosine receptors have been reported to be most active in subcutaneous fat cells. However, part of the variation could also be explained by a regional differentiation of sympathetic outflow to fat tissue. Studies in rats have demonstrated differences in sympathetic control of metabolic and cardiovascular function in the splanchnic region (Morrison 1999, 2001), and a recent study has provided evidence for a somatotophic organisation of central control over the selective innervation of subcutaneous vs. intra-abdominal fat by both the sympathetic and parasympathetic branches of the autonomic nervous system (Kreier *et al.* 2002).

Sympathetic function in obesity

The fact that the sympathetic system undoubtedly plays an important role in the regulation of fat metabolism has lead several investigators to study sympathetic function in human obesity. Several branches of the sympathetic system show altered activity in obese subjects. Changes in heart rate variability (Karason *et al.* 1999), plasma catecholamine concentrations (Young & Macdonald 1992), pupillary latency period (Peterson *et al.* 1988) and sympathetic nerve activity to the muscle vascular bed (Spraul *et al.* 1993, Scherrer *et al.* 1994, Grassi *et al.* 1995, Somers 1999) have been described. Studies on muscle sympathetic nerve activity (MSNA) are of interest for the question whether changes in sympathetic activity could be involved in a disturbed energy balance, resulting in weight gain. Basal MSNA correlates with resting energy expenditure in Caucasian population (Spraul *et al.* 1993) and the respiratory quotient, which is high during low lipolytic activity, is inversely correlated with MSNA (Snitker *et al.* 1998). Given that muscle lipolysis may be important for energy expenditure, these results suggest that a low sympathetically mediated energy expenditure could be a risk factor for body-weight gain (Ravussin *et al.* 1988, Ravussin 1995). The fact that several studies have reported an increased MSNA in obese subjects (Scherrer *et al.* 1994, Grassi *et al.* 1995) and that total body noradrenaline spillover is similar in lean and obese subjects (Rumantir *et al.* 1999) seems at odds with this notion, but it is conceivable that an initially low sympathetic activity results in fat accumulation which in turn augments sympathetic outflow through compensatory endocrine mechanisms. One such compensatory mechanism could be increased leptin release from larger fat depots, an endocrine signal known to increase sympathetic activity via hypothalamic mechanisms in rats (Haynes *et al.* 1997, 1999). Glucocorticoid effects may also be involved (Grassi *et al.* 2001), i.a. via suppression of corticotropin releasing hormone (a sympathoexcitatory substance with obvious anorexigenic properties) and/or increased neuropeptide Y release (a sympathoinhibitory substance with orexigenic properties). Apart from the above-mentioned and other possible endocrine mechanisms, it should be stressed that sympathoexcitation may be an unspecific secondary consequence of obesity. For instance, the obstructive sleep apnea syndrome commonly observed in obese subjects may contribute substantially to the augmentation of MSNA (Narkiewicz *et al.* 1998). Finally, when discussing the role of sympathetic activity in the control

of fat and body mass, it must be recognized that the findings of unaltered total body noradrenaline spillover and increased MSNA in obesity do not unequivocally exclude the possibility that a selective reduction in sympathetic discharge to fat depots could contribute to an accumulation of fat mass and weight gain in general.

Neural control of white adipose tissue

Although subcutaneous fat tissue is the most important energy store of the body, the question whether this tissue receives metabolically relevant neural input in humans remains to be resolved. Animal experiments have shown that stimulation of sympathetic nerves to white adipose tissue (WAT) increases lipolysis *in vitro* (Corell 1963) and *in vivo* (Rosell 1966), despite the sparse innervation of WAT (Slavin & Ballard 1978). This innervation has recently be characterized and labelled by retrograde tracers, which allow the localization of central nervous structures governing sympathetic outflow to the WAT (Bamshad *et al.* 1998, Bartness & Bamshad 1998). Denervation of WAT increases fat pad mass and fat cell number in Siberian hamsters (Youngstrom & Bartness 1998), suggesting that the neural input to fat tissue not only repesents a lipolytic but also an antitrophic factor.

In humans, the route of sympathetic innervation of WAT has not been described and its role in inducing fat tissue lipolysis has not been determined. Global measures of sympathetic activity such as determination of plasma catecholamine concentrations, or recordings of activity in specific sympathetic branches like the MSNA, are unlikely to reflect sympathetic metabolic signals to the subcutaneous fat tissue. WAT is in all probability only a minor contributor to total body catecholamine spillover, and specific determination of WAT catecholamine spillover is not possible, as a single arterial supply and venous drainage cannot be defined in humans. Lacking direct methods to determine sympathetic outflow to WAT, studies have tried to assess the role of sympathetic innervation in induction of subcutaneous lipolysis in subjects with interrupted sympathetic outflow following a high spinal cord injury. These studies suggest that sympathetic innervation has no clear effect on the basal lipolytic rate of fat tissue (Karlsson *et al.* 1995) but induces lipolysis under conditions of sympathoexcitation (Karlsson *et al.* 1997). Although these studies suggest a role of sympathetic neurones in the regulation of subcutaneous lipolysis, at least under stimulated conditions, they were not able to define the exact route of sympathetic innervation to WAT.

Lipolytic effects of intraneural electrical stimulation in humans

Intraneural electrical stimulation has previously been used to study sympathetic control of cutaneous vaso- and sudo-motor function (Wallin & Elam 1997). We have recently developed a model aiming to study sympathetic control of subcutaneous lipolysis, involving intraneural electrical stimulation of the lateral femoral cutaneous nerve (supplying a large skin area with a thick subcutaneous fat layer) and monitoring of lipolysis through measurement of interstitial glycerol release via microdialysis catheters placed within the innervation zone of the stimulated nerve fascicle (Fig. 1). To exclude systemic effects of the (painful) intraneural stimulation, the glycerol release of the stimulated area was compared with the local glycerol release in a corresponding area on the contralateral unstimulated leg. Regional blood flow was monitored bilaterally with laser doppler flowmetry. The intraneural electrode was used for recording, to characterize the pattern of sympathetic discharge in the lateral femoral cutaneous nerve compared with more distal recordings of skin sympathetic nerve activity in the median and peroneal nerve (Fig. 2; Dodt *et al.* 1999), and subsequently for electrical stimulation of nerve fascicles supplying the region drained by the microdialysis catheters (Dodt *et al.* 1999, 2000).

In a group of seven healthy lean women, 10 min of unilateral intraneural stimulation elicited a $22 \pm 8\%$ increase ($P < 0.05$) in glycerol levels in the stimulated region, while no change was observed in the corresponding area of the contralateral leg (Fig. 3). However, in order to reach an appropriate intraneural site,

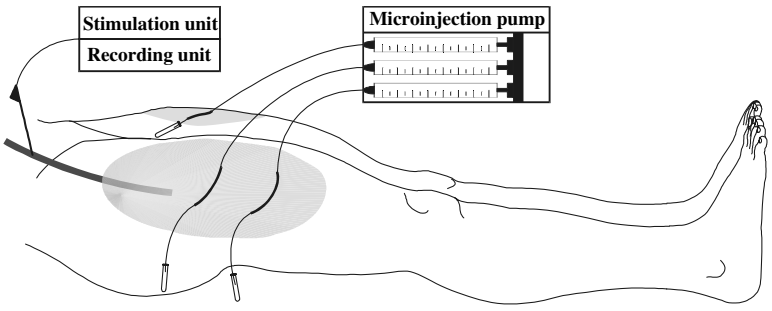

Figure 1 Experimental setup: after a suitable stimulation/recording site within the lateral cutaneous nerve had been established, two microdialysis probes were inserted in the receptive field and one additional control probe in a corresponding area on the contralateral leg. From Dodt *et al.* 1999.

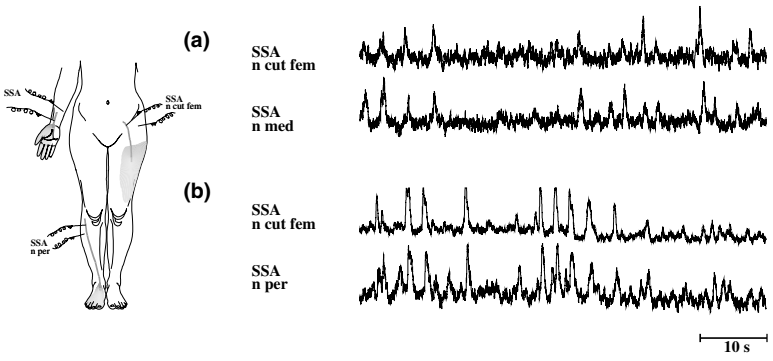

Figure 2 Simultaneous recordings of skin sympathetic nerve activity (SSA) in the lateral cutaneous femoral nerve and the median nerve (subject A), and the lateral cutaneous femoral nerve and the superficial peroneal nerve (subject B). No specific 'lipomotor activity' could be discerned in the mean voltage neurogram of the lateral cutaneous femoral nerve. From Dodt *et al.* 1999.

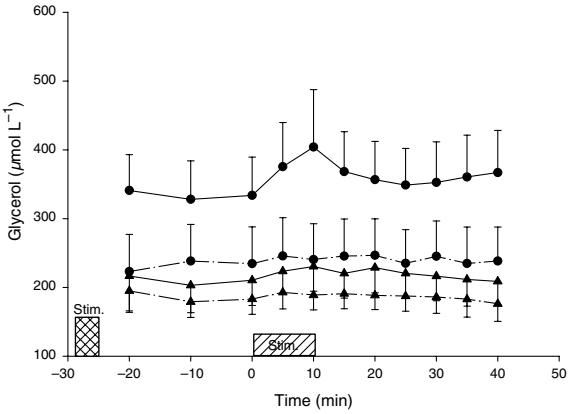

Figure 3 Interstitial glycerol levels in the innervation territory of the lateral cutaneous femoral nerve in seven lean (circles) and seven obese (triangles) subjects (mean ± SEM). The solid lines represent the levels in the innervation area of the stimulated lateral cutaneous femoral nerve while the broken lines represents the levels in the contralateral unstimulated area. Prior to the insertion of the microdialysis probes, the nerve was localized using transcutaneous and intraneural stimulation (cross-hatched box). After an equilibration period of 45 min and a baseline period of 30 min, the lateral cutaneous femoral nerve was again stimulated for 10 min (hatched box). Stimulation significantly enhanced glycerol release in lean subjects, while lipolysis was not significantly affected in the obese group (weight × time interaction: $P < 0.05$). From Dodt *et al.* 2000.

the experimental procedure involved shortlasting transcutaneous and intraneural stimulation of the nerve prior to the standardized stimulation period. Although shortlasting, this initial unstandardized stimulation had a strong lipolytic effect *per se* (47 ± 13% higher glycerol levels in the stimulated vs. unstimulated area before the standardized 10 min stimulation, $P < 0.05$). Thus, neural stimulation elicited an overall increase in glycerol levels by 72 ± 17%. This glycerol increase was not explained by changes in regional blood flow, which did not differ between the two legs (Dodt *et al.* 1999). In a group of seven obese female subjects (Dodt *et al.* 2000), the same intraneural stimulation protocol produced no significant change in subcutaneous lipolysis (Fig. 3). These *in vivo* results suggest that human obesity is characterized by a profound unresponsiveness of the subcutaneous adipose tissue to neurally induced lipolysis.

The reason for this blunted lipolytic response in obese subjects remains to be elucidated. A lipolytic resistance to neural stimulation could be the result of a dysfunction of β-adrenoceptors on lipocytes and/or of the hormone-sensitive lipase (Langin *et al.* 1996). β-Adrenoceptor dysfunction has been suggested to cause obesity by several studies (Lacasa *et al.* 1984, Lönnqvist *et al.* 1992, Reynisdottir *et al.* 1994a,b, Clement *et al.* 1995, Large *et al.* 1997). However, because of the presence of spare adrenoreceptors, such receptor defects should result in reduced β-adrenergic sensitivity without alteration of the lipolytic capacity (Lacasa *et al.* 1984, Arner *et al.* 1988). Hence, our results in obese subjects are more likely be attributed to a post-receptor defect.

The importance of receptor and post-receptor defects for the pathogenesis of obesity was suggested in an interesting *in vivo* study on obese children using adrenaline infusion (Bougnères *et al.* 1997). Our recent studies using *in situ* stimulation of a cutaneous nerve and measurement of glycerol release within its innervation territory may support the concept of a reduction of adrenergically mediated lipolysis in obesity. Other neurally released substances apart from catecholamines could, however, also be involved in the regulation of lipolysis in obesity. For example, neuropeptide Y which inhibits lipolysis (Fain & Shepherd 1979) may modulate the catecholamine effect. Whether changes in the release of this or other neuromodulators is relevant for the lipolytic resistance in obesity remains to be elucidated.

Obesity is characterized by an increase in number and size of fat cells (Bertrand *et al.* 1978, Bougnères *et al.* 1997). It is conceivable that a disproportional increase in fat cell mass in relation to efferent sympathetic nerve fibres and/or blood vessels may serve as an explanation for the present results. To our knowledge, it has not

been established whether sympathetic nerve fibres proliferate during the development of obesity or remain constant in size, thus leading to a relatively less-innervated adipose tissue in obesity. A decreased blood flow in subcutaneous fat tissue has been described in the abdominal, but not in the femoral, region of obese subjects (Knittle *et al.* 1979). However, a reduced blood flow would have induced an increase in interstitial glycerol levels and thus can also not explain the present results (Jansson *et al.* 1992).

Our *in vivo* experiments in obese female subjects, showing a reduced local lipolytic response to intraneural stimulation, are compatible with the theory that a diminished lipolytic response to sympathetic activation may be a pathogenetic factor in the development of obesity and may impede weight reduction. However, the impact of blunted responses to neural activation should be related to the reduced antilipolytic effect of insulin (Jansson *et al.* 1992) and the altered lipoprotein lipase activity (Jensen *et al.* 1997) prevailing in obesity. Furthermore, prospective studies in pre- and post-obese subjects have to be performed.

Conclusion

Total body lipolysis is directly proportional to total body fat mass. Consequently, obese subjects show a higher total body lipolysis than lean subjects simply because they have a larger fat mass, whereas lean and obese do not differ in relative lipolysis per kilogram fat mass (Jansson *et al.* 1992). In contrast, isolated fat cells from obese subjects show an increased basal lipolysis, a reduced antilipolytic response to insulin and also a reduced response to β-adrenoceptor stimulation. The discrepancies between *in vivo* and *in vitro* findings concerning human lipolysis must be resolved before the role of the sympathetic nervous system in the regulation of human fat tissue mass and adipocyte cellular size can be fully clarified. Our recent studies, combining intraneural electrical stimulation of human cutaneous nerve fascicles supplying WAT on the thigh with microdialytic evaluation of glycerol release within the territory innervated by the stimulated nerve fascicle, clearly demonstrate that lipolysis can be neurally induced, and that this neural effect can be blunted in obese subjects. This technique provides a human *in vivo* model for further studies of neural control of lipolysis in health and disease.

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