Signalling in body-weight homeostasis: neuroendocrine efferent signals

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Whilst a number of neuroendocrine afferent signals are implicated in body-weight homeostasis, the major efferent pathway is the sympathetic nervous system (SNS), which affects both energy expenditure and substrate utilization. Thyroid hormones and their interactions with the SNS may also have a role to play. Some of the variability in resting energy expenditure can be explained by differences in SNS activity, and β-blockade can reduce energy expenditure and diet-induced thermogenesis in Caucasians. Excess energy intake leads to SNS activation and increased diet-induced thermogenesis. A relationship has also been demonstrated between spontaneous physical activity and SNS activity. In many animal models the SNS activates brown adipose tissue thermogenesis, hence increasing diet-induced thermogenesis and dissipating excess energy as heat. This effect is mediated via β_3-adrenoceptors and activation of an uncoupling protein unique to brown adipose tissue. Homologous proteins have been identified in human tissues and may play a role in human energy expenditure. How the SNS is implicated in this process is unclear at present. β_3-Adrenoceptor polymorphism has been associated both with lower resting energy expenditure in some populations and with reduced autonomic nervous system activity. SNS effects on substrate cycling may also play a role. In the development of obesity the effects of the SNS in promoting lipolysis and fat oxidation are likely to be at least as important as its effects on thermogenesis. β-Blockade has relatively small effects on energy expenditure, but more pronounced effects on reducing lipid oxidation, so tending to favour fat storage and weight gain. Low lipid oxidation is a risk factor for weight gain, and there is some evidence that low basal sympathetic nerve activity in muscle is associated with this process. Overall, the relationship between SNS activity and obesity is complex, with evidence of low SNS activity occurring in some, but not all, studies.

Sympathetic nervous system: Obesity: Energy expenditure

The major neuroendocrine efferent pathway implicated in body-weight homeostasis is the sympathetic nervous system (SNS). It has long been known that circulating catecholamines can stimulate energy expenditure (EE) in human subjects (Cori & Buchwald, 1930). Evidence that the SNS is involved in body-weight regulation was provided by studies demonstrating reduced noradrenaline turnover during fasting in rats (Landsberg & Young, 1978). The SNS impacts on body weight via effects on both EE and on substrate utilization, and may also be involved in the regulation of leptin production (Trayhurn *et al*. 1995). β_3-Agonists reduce leptin gene expression in rats and may suppress food intake by this mechanism (Li *et al*. 1997). Reciprocally, leptin can activate the SNS (Haynes *et al*. 1997; Friedman & Halaas, 1998). The metabolic effects of the SNS are mediated by the sympathetic innervation of skeletal muscle and adipose tissue. The present review will centre mainly on the putative role of the SNS in the development and maintenance of obesity, although it seems likely that body-weight regulatory mechanisms evolved mainly to protect against the effects of starvation and do not function as well in preventing obesity.

Assessment of sympathetic nervous system activity

The SNS may contribute to the regulation of all aspects of EE, i.e. resting EE (REE), diet-induced thermogenesis (DIT) and spontaneous physical activity (Fig. 1). In reviewing the role of the SNS in controlling thermogenesis it is important to note how SNS activity has been assessed (Young & Macdonald, 1992; Macdonald, 1995). Techniques providing estimates of basal SNS activity include 24 h urinary excretion of noradrenaline, plasma noradrenaline concentrations, plasma noradrenaline

Abbreviations: DIT, diet-induced thermogenesis; EE, energy expenditure; MSNA, sympathetic nerve activity in muscle; REE, resting energy expenditure; SNS, sympathetic nervous system; UCP, uncoupling protein.

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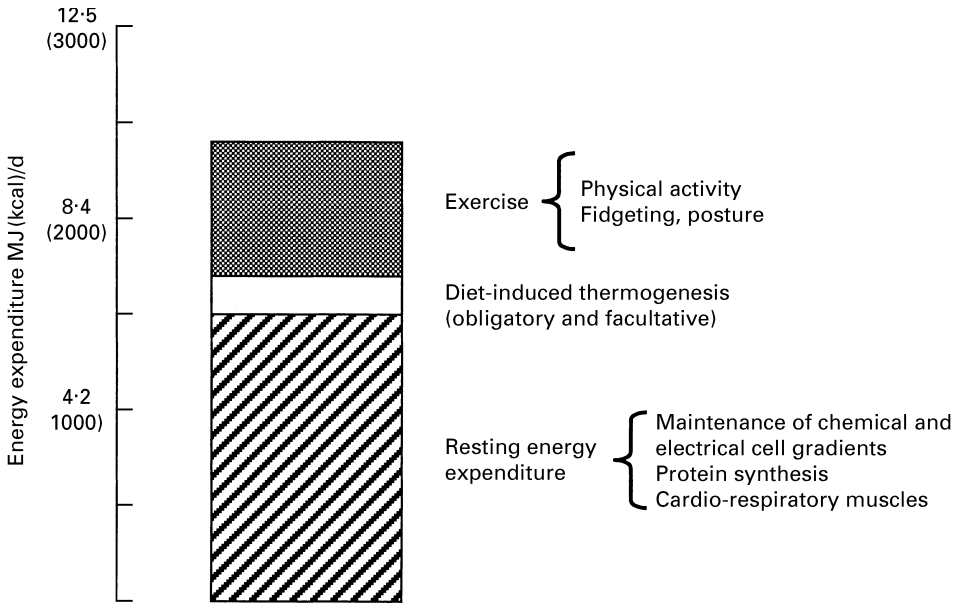

Fig. 1. Components of energy expenditure.

kinetics, and more recently the use of muscle sympathetic nerve firing rates. The latter technique is particularly useful in assessing acute responses of the SNS to diet and exercise. However, it should be noted that within many tissues the direct effects of the SNS are mostly on the vasculature, leading to secondary effects on metabolism, and that the sympathetic nerve activity of muscle (MSNA) is predominantly related to blood flow and blood pressure control.

In interpreting differences in SNS activity between normal-weight and over- and underweight subjects it is not always clear whether the differences seen are causal, or are secondary to the changed nutritional state. It is also important to distinguish between established steady-state alterations and acute changes during weight loss, or weight gain. Several groups have therefore studied obese patients after weight loss (post-obese) to see whether differences remain. In addition, although reduced SNS activity has been proposed to contribute to the development of obesity, body fat itself may be a major determinant of SNS activity. BMI is positively correlated with 24 h urinary noradrenaline excretion (Troisi *et al*. 1991), and some obese subjects are characterized by higher rates of sympathetic nerve discharge (Scherrer *et al*. 1994; Spraul *et al*. 1994). Indeed, heightened sympathetic activity has been proposed to be secondary to obesity and accompanying insulin resistance (Landsberg, 1986), and to be part of the metabolic syndrome leading to increased cardiovascular risk (Reaven *et al*. 1996). However, other work using autonomic function tests of heart rate and blood pressure has described depressions in both SNS and parasympathetic activity to be weakly associated with increasing percentages of body fat (Peterson *et al*. 1988). It was proposed that these alterations might be important in the aetiology of obesity. Thus, mode of assessment of the SNS is important. Finally, there is considerable evidence that the SNS is activated in a discrete fashion, with selective activation of specific tissues or systems (Muntzel *et al*. 1994), so that data obtained on sympathetic activity to one tissue (e.g. skeletal muscle) cannot be extrapolated to whole-body effects.

Measures of SNS activity on their own provide only some of the material needed to assess the role of the SNS in EE and substrate utilization. The other information required is tissue responsiveness to a given level of SNS activity. Responses to exogenous infusions of noradrenaline and adrenaline have been used to assess this aspect of the SNS. In reviewing the results and conclusions from these studies, great subject heterogeneity is readily apparent (Connacher *et al*. 1988). This heterogeneity can be attributed to differences in subject age, antecedent diet, blood pressure, gender, physical activity and body fat distribution, but may also be partly explained by the demonstration of polymorphisms in adrenergic receptors (see p. 401). In future studies using catecholamine infusions it will be important to categorize subjects according to their adrenoceptor status.

Energy expenditure and the sympathetic nervous system

Fig. 2 shows possible roles for the SNS in EE. A number of studies using varying methodologies have shown that some of the variability in REE can be explained by differences in measures of SNS activity. 24 h Urinary noradrenaline excretion was found to correlate with total 24 h EE, independent of body size and body composition (Saad *et al*. 1991). The same group was able to demonstrate similar correlations between SNS activity and total 24 h EE using MSNA (Spraul *et al*. 1993) and ^{3}H-labelled noradrenaline turnover (Christin *et al*. 1993). Plasma noradrenaline concentration has also been shown to be a significant, but weak (1·1 %), determinant of 24 h EE and sleeping EE (Toubro *et al*. 1996); thus, low sympathetic activity may contribute to low EE and predispose to weight gain.

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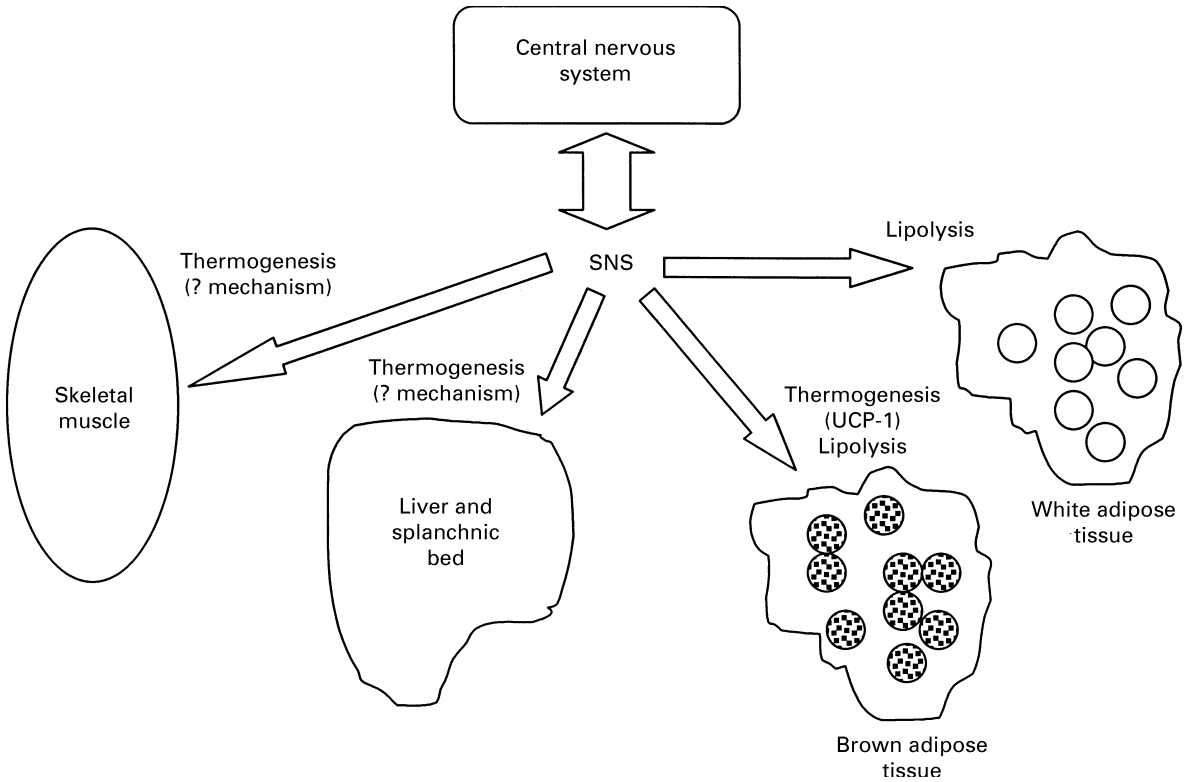

Fig. 2. Possible roles for the sympathetic nervous system (SNS) in energy expenditure. UCP-1, uncoupling protein-1.

It has proved difficult to demonstrate the involvement of the SNS in the regulation of REE. Whilst adrenoceptor blockade would be predicted to reduce EE if basal sympathetic tone was important in modulating REE, the effects seen have been small and not widely reproduced. Several investigators have examined the effects of β-adrenoceptor blockade on REE, with oral β-blockade causing a fall in REE (Welle *et al.* 1991), but intravenous β-blockade failing to mimic this effect (Vernet *et al.* 1987). Other evidence put forward in support of a role for sympathetic tone in REE is the observation that chronic oral β-blockade leads to weight gain (Rossner *et al.* 1990). However, the weight gain in this setting is small and is more likely to be due to the effects of β-blockade on fat mobilization and utilization than on effects on thermogenesis.

Several groups have examined whether REE is reduced in post-obese subjects. The hypothesis being that a low REE would predispose to weight regain, and indeed might be causal in their obesity. A recent meta-analysis of these studies (Astrup *et al.* 1999) found that in about 15 % of subjects, REE corrected for fat-free mass and fat mass was indeed lower than that found in controls. Perhaps in these subjects alterations of the SNS or other processes involved in the regulation of EE may account for a low REE and a high risk of weight regain. However, the total number of formerly-obese subjects studied was small despite the use of meta-analysis (*n* 124), the differences in REE from controls were small (3 %) and some controls also had a low REE. Indeed, in a commentary on this meta-analysis (Hill & Wyatt, 1999) it was concluded that the data were more in support of the view that a low REE was not a likely cause of relapse in most formerly-obese subjects.

Many studies have looked at the relationship between DIT, the increment in metabolic rate over REE following a meal, and indices of SNS activity. A large part of DIT can be accounted for by the energy costs of nutrient storage (obligatory thermogenesis), but a proportion of total DIT may be regulated by the SNS (facultative thermogenesis; Acheson *et al.* 1984). Schwartz *et al.* (1987, 1990*a*) demonstrated that the rise in plasma noradrenaline after a meal was correlated with the rise in EE. This group was also able to demonstrate that reducing central SNS outflow by systemic administration of the α_2-adrenoceptor agonist clonidine decreased the thermogenic response to a test meal (Schwartz *et al.* 1988). DIT can also be reduced by peripheral blockade of the SNS using β-blockade (Astrup *et al.* 1989), with the major site of this effect being skeletal muscle.

There has been some interest in the role of the parasympathetic nervous system in the regulation of EE, particularly with regard to DIT. Muscarinic blockade of the parasympathetic nervous system with atropine reduces the thermic response to a mixed meal (Nacht *et al.* 1987). However, the influence of atropine in slowing gastric emptying may account for this effect. When intravenous glucose was given, atropine infusion did not alter glucose-induced thermogenesis (Schneeberger *et al.* 1991). Indeed, apart from the data derived from cardiac autonomic function and percentage body fat (Peterson *et al.* 1988), there is little evidence that the parasympathetic nervous system is involved in the regulation of EE in human subjects.

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In common with other studies investigating impaired thermogenesis in obese subjects there is conflicting data as to whether or not DIT is reduced in the obese. Many obese subjects have low DIT associated with reductions in indices of SNS activation (Astrup *et al*. 1990; Spraul *et al*. 1994), which is not apparent some other obese subjects, in particular Pima Indians (Kush *et al*. 1986). Furthermore, it is unclear whether impaired DIT is related to the obese state, with obesity-associated insulin resistance leading to a reduction in both DIT and SNS activation. Some studies show that reduced SNS activity persists after weight loss (Astrup *et al*. 1990; Jequier, 1990), but other studies show that DIT normalizes (Bukkens *et al*. 1991; Webber *et al*. 1994*a*).

Longer-term excess energy consumption may lead to SNS activation, as assessed by raised noradrenaline turnover found when normal-weight volunteers are overfed (O'Dea *et al*. 1982). In contrast, underfeeding leads to reductions in noradrenaline turnover (O'Dea *et al*. 1982; Schwartz *et al*. 1990*b*). However, the relationship between SNS activity and thermogenesis may not be causal, as β-blockade did not reduce the elevated REE found in subjects overfed for 20 d (Welle & Campbell, 1983; Welle *et al*. 1989). One possible explanation for these conflicting findings is the suggestion that variation in diet composition accounts for some of the heterogeneity in the responses of the SNS. Increased proportions of carbohydrate in the diet, especially sucrose, have been shown to stimulate thermogenesis and SNS activity (as assessed by plasma catecholamine concentrations; Raben *et al*. 1997).

Whilst a number of alterations in the SNS have been described in obesity and in response to overnutrition, there has also been interest in the relationship between starvation and malnutrition and SNS activity. Underfeeding reduces noradrenaline turnover (O'Dea *et al*. 1982), suggesting that SNS activity is reduced, but tissue responsiveness to catecholamines may be increased, as demonstrated by enhanced thermogenic (Webber *et al*. 1995) and lipolytic (Jensen *et al*. 1987) responses to infused adrenaline. This alteration in adrenoceptor sensitivity favours mobilization of lipid and its utilization as an energy substrate during fasting. Chronic undernutrition, on the other hand, may be accompanied by reduced thermogenic responses to catecholamines (Kurpad *et al*. 1989). It has been suggested that early nutrition may affect the development of the SNS, and hence have enduring effects on its responses (Young & Morrison, 1998). The SNS innervation of white adipose tissue may also influence adipocyte differentiation and proliferation, giving rise to longer-term effects on lipolytic capacity (Bartness & Bamshad, 1998).

The decline in physical activity of the population has been linked clearly to the increasing prevalence of obesity in the UK (Prentice & Jebb, 1995). Interestingly, a relationship between spontaneous physical activity and noradrenaline turnover, independent of body size and composition, has been described (Christin *et al*. 1993). This relationship was present in both Caucasians and Pima Indians. The unanswered question is whether greater spontaneous physical activity results in increased SNS activity, or whether the primary change is in enhanced SNS activity leading to greater fidgeting and higher muscle tone in some subjects. One recent study has suggested that susceptibility to weight gain may be partly accounted for by changes in what was termed non-exercise activity thermogenesis (representing fidgeting and posture; Levine *et al*. 1999). When normal-weight subjects were overfed by 4·2 MJ (1000 kcal)/d in excess of weight maintenance requirements, variation in the increase in non-exercise activity thermogenesis accounted for 10-fold differences in fat storage (Levine *et al*. 1999).

On reviewing many of the studies of obesity and metabolism it has been proposed that the US Pima Indian population in particular may have a defect in the SNS regulation of metabolism. Whereas many Caucasians studied show a clear relationship between MSNA and REE, no such correlation was found in Pima Indians (Spraul *et al*. 1993). Likewise, β-blockade with propranolol failed to reduce REE in Pima Indians (Saad *et al*. 1991). Finally, fasting MSNA correlates positively with body fat in Caucasians, but not in Pima Indians (Spraul *et al*. 1994). Thus, although studies with Pima Indians may reveal that a defective SNS has a role to play in their high prevalence of obesity, it is less clear whether these data throw light on the involvement of the SNS in obesity in other populations (Macdonald, 1995). Indeed, more recently doubt has been cast on the hypothesis that the Pima Indians have a 'thrifty genotype' (presumed in part to act via alterations of the SNS) which renders them susceptible to obesity when exposed to an affluent lifestyle. A group of Mexican Pima Indians were identified who live a traditional lifestyle and remain lean compared with their US counterparts. These Mexican Pima Indians showed no difference in resting metabolic rate, corrected for fat-free mass, from that measured in non-Pima Mexicans (Fox *et al*. 1998). This finding suggests that changes in energy metabolism (and therefore also in SNS activity) observed in the US Pima Indians are secondary to the obese state and not causal.

Uncoupling proteins, substrate cycling and sympathetic activity

In many animal models it has been clearly shown that the SNS activates brown adipose tissue thermogenesis, and by this means DIT is increased and excess energy dissipated as heat (Himms-Hagen, 1990). This effect is mediated via β_3-adrenoceptors and activation of an uncoupling protein (UCP) unique to brown adipose tissue (UCP-1). During fasting SNS activity falls, as does UCP-1 expression. In mice the main role of UCP-1 would appear to be in thermoregulation, with UCP-1 'knockout' mice being unable to keep warm in the cold, but not becoming obese (Enerback *et al*. 1997).

UCP homologous with those found in mice have since been identified in human tissues, with UCP-2 widely expressed (Fleury *et al*. 1997) and UCP-3 mainly restricted to skeletal muscle (Boss *et al*. 1997). In rats UCP-3 levels are increased by treatment with β_3-agonists (Gong *et al*. 1997), suggesting that at least some of the thermogenic effects of SNS activation are mediated by UCP. UCP-3 expression may play a role in human EE, with one study in Pima Indians showing a correlation between sleeping metabolic rate and expression of the long form of UCP-3

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RNA in skeletal muscle (Schrauwen *et al*. 1999). However, the involvement of the SNS in this process is unclear at present. This work needs to be replicated in other populations, with measures of SNS activity being made.

Interestingly, when mice were bred which could not synthesize adrenaline or noradrenaline (by inactivating the gene coding for dopamine β-hydroxylase) they also did not become obese, despite being unable to induce brown adipose tissue thermogenesis (Thomas & Palmiter, 1997). This finding suggests that although the SNS is a major regulator of EE, there are other pathways which may normally be redundant that can play an important role. However, this 'knockout' mouse model does not simply remove SNS efferent actions from the equation, but will also have widespread consequences on central signalling processes. Interpretation of the data is therefore not straightforward.

In addition to the regulation of UCP, the SNS may also have effects on substrate cycling which can influence EE (Newsholme, 1980). In patients with severe burns REE is greatly elevated, as are plasma catecholamine concentrations and rates of triacylglycerol–fatty acid cycling (Wolfe *et al*. 1987). Intravenous β-blockade with propranolol can reduce these elevated rates of substrate cycling (Wolfe *et al*. 1987), although no concurrent measures of EE are available from this study.

Substrate utilization and the sympathetic nervous system

In the development of obesity SNS effects on promoting lipolysis and fat oxidation are likely to be at least as important as effects on thermogenesis (Tremblay, 1992). Lower rates of fat oxidation, as indicated by higher RQ, have been shown to predict weight gain (Zurlo *et al*. 1990). Whilst β-blockade has relatively small effects on EE, it has much more pronounced effects on reducing lipid oxidation, which would tend to favour fat storage and weight gain (Acheson *et al*. 1988; Buemann *et al*. 1992). There is some evidence that low basal MSNA is associated with low rates of lipid oxidation (Snitker *et al*. 1998). The response of obese subjects to exogenous infusions of catecholamines has also been proposed to favour fat storage over fat oxidation. Fatty acid oxidation is either impaired in the obese in response to adrenaline infusion (Connacher *et al*. 1991), or falls in comparison with normal-weight controls (Webber *et al*. 1994*b*).

Interestingly, UCP-3 expression appears to increase with fasting (Gong *et al*. 1997). This finding is perhaps counter-intuitive, as the fall in EE during fasting might be expected to be accompanied by reduced UCP expression as an energy-sparing mechanism (UCP-1 behaving in this fashion). Elevation of non-esterified fatty acid concentrations mimics this effect on UCP-3 expression in rat skeletal muscle (Weigle *et al*. 1998). Changes in UCP-3 with fasting may therefore be important in fat mobilization and utilization as an energy substrate rather than in fuel economy.

Adrenoceptors and obesity

The clear evidence that the SNS has a major role in EE has led to the search for candidate genes for obesity amongst those coding for adrenoceptors. Most work so far has centred on the β_2- and β_3-adrenoceptors. There is evidence that both β_1- and β_2-adrenoceptors are involved in skeletal muscle thermogenesis in human subjects (for review, see Blaak *et al*. 1993). However, the β_3-adrenoceptor has been the subject of most attention, having a clear role in brown adipose tissue lipolysis and thermogenesis in animals. Both β_1- and β_2-adrenoceptors mediate lipolysis in white adipose tissue, whilst α_2-adrenoceptor activation inhibits lipolysis. Overall effects on lipolysis may depend on the relative proportions of β- and α_2-adrenoceptors on adipocytes.

In 1995 three research groups identified a miss-sense mutation in codon 64 of the gene for the β_3-adrenoceptor, with a replacement of tryptophan by arginine (Trp64Arg; Clement *et al*. 1995; Walston *et al*. 1995; Widen *et al*. 1995). In some populations an increased BMI has been found in carriers of this mutation, and variation in REE has also been associated with this polymorphism, but in many other studies these findings have not been replicated (for review, see Arner & Hoffstedt, 1999). Heterogeneity of the obese state and the presence or absence of other associated complications such as hypertension and diabetes may account for these conflicting findings. In addition, interactions with other putative candidate genes for obesity may be important. A recent study showed that in obese subjects with both the Trp64Arg mutation in the β_3-adrenoceptor gene and a mutation in the UCP-1 gene, weight gain after a very-low-energy diet was more rapid than in those subjects with only one or neither of these mutations (Fogelholm *et al*. 1998). The β_3-adrenoceptor Trp64Arg polymorphism has also been associated with reduced autonomic nervous system activity (Shihara *et al*. 1999).

β_2-adrenoceptor polymorphism has also been proposed to have a role to play in body-weight regulation, the β_2-adrenoceptor being the main adrenoceptor in human white adipose tissue which mediates lipolysis. A strong correlation between obesity and the Gln27Glu polymorphism has been demonstrated (Large *et al*. 1997), and more recently this polymorphism was specifically associated with obesity in patients who were physically inactive (Meirhaeghe *et al*. 1999). Another mutation, Arg16Gly, was associated with greater weight loss in response to a low-energy diet and exercise regimen in Japanese women (Sakane *et al*. 1999). Altered functioning of adrenoceptors caused by genetic polymorphisms may predispose to weight gain.

Thyroid hormones and energy expenditure

Thyroid hormones, in particular tri-iodothyronine, also appear to be involved in body-weight homeostasis. Pathological reductions and increases in thyroid hormones have marked effects on REE (Kyle, 1950). Even within the normal physiological range there is evidence that tri-iodothyronine concentrations can account for some of the variability in REE (Astrup *et al*. 1992; Toubro *et al*. 1996). In addition, a low REE in post-obese women may be accounted for by low tri-iodothyronine concentrations (Astrup *et al*. 1996). There is substantial evidence of interactions between thyroid hormone status and adrenergic receptors in animals (Bilezikian & Loeb, 1983), although

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this work has not always been replicated *in vivo* in human subjects (Johnson *et al*. 1995).

Conclusions

Overall, the relationship between SNS activity and obesity is complex. There are alterations in SNS activity associated with changes in body weight, and these alterations may be modified by factors including adrenoceptor polymorphisms and diet. In some groups and individuals altered SNS activity is likely to play a major part in the development and maintenance of the obese state. Further research will need to focus on how a greater understanding of the interplay between the SNS and body weight can lead to improved strategies for prevention of weight gain and the treatment of obesity.

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