

### Corticosteroid inhibition of thermogenesis in obese animals

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The wide range of animal models that have been used for the study of obesity may be classified into four major types according to the origin of that obesity, i.e. genetic, dietary, endocrine or that following hypothalamic damage (Bray & York, 1979). The ability to prevent the further development of obesity by adrenalectomy is a common feature between these models (Hausberger & Hausberger, 1960; Mook *et al.* 1972; Bray, 1982; Bruce *et al.* 1982; Holt *et al.* 1983; Marchington *et al.* 1983, 1986; Rothwell *et al.* 1984; Saito & Bray, 1984; Saito *et al.* 1985; Debons *et al.* 1986; Freedman *et al.* 1986; Tokunaga *et al.* 1989). Bruce *et al.* (1982) were the first group to report this effect, in rats developing obesity after electrolytic lesions to the ventromedial hypothalamus. While the effect of adrenal status is most pronounced in the obesities, subsequent observations have shown a similar role of the adrenal in the control of energy balance in lean animals.

Brown adipose tissue (BAT) thermogenesis is thought to play an important role in the control of energy balance in the rodent species, in addition to its accepted role in the maintenance of body temperature during exposure to cold environments (Rothwell & Stock, 1984). Part of the evidence for this has been the demonstration of impaired diet-related BAT function in the obesities, and the coincident restoration of normal energetic efficiency and normal BAT function after adrenalectomy (Trayhurn & James, 1978; Marchington *et al.* 1983, 1986; Rohner-Jeanrenaud *et al.* 1983; Knehans & Romsos, 1984; Allars *et al.* 1987). These relations can be illustrated by studies on the obese Zucker (*falfa*) rat. BAT mitochondrial GDP binding of *falfa* rats, an index of mitochondrial thermogenic activity, is reduced from an early age in the preobese *falfa* rat (Bazin *et al.* 1984; Holt *et al.* 1984). After weaning, the BAT progressively develops the appearance of an hypoactive tissue as mitochondrial content, GDP binding and uncoupling protein (UCP) concentration are reduced, while triacylglycerol deposits increase (Holt *et al.* 1983; Triandafillou & Himms-Hagen, 1983; Bazin *et al.* 1984; Allars *et al.* 1987). Adrenalectomy rapidly restores both the morphological appearance and the function of the tissue to normal; mitochondrial content, GDP binding and UCP concentration increasing to levels observed in lean rats. Replacement of adrenalectomized *falfa* rats with glucocorticoids, but not aldosterone, reverses all these effects of adrenalectomy and restores the development of obesity (Holt *et al.* 1983; Freedman *et al.* 1985, 1986). The obesity of the *falfa* rat has been attributed, in part at least, to the impairment in the normal metabolic response to feeding (Rothwell *et al.* 1983, 1984). Thus, the acute increase in oxygen consumption that follows a meal is impaired in the *falfa* rat, as are the chronic responses to giving extra sucrose, or cafeteria, high-fat and low-protein diets (Holt *et al.* 1983; Triandafillou & Himms-Hagen, 1983; Allars *et al.* 1987). Both the acute and chronic responses are corrected after adrenalectomy. Likewise, the adaptive changes in BAT function that normally occur on overfeeding are greatly attenuated in obese *falfa* rats, but are restored after adrenalectomy (Holt *et al.* 1983; Marchington *et al.* 1983; Rothwell *et al.* 1984).

Similar changes to those described previously have also been reported in other forms of genetic obesity, in particular in the obese (*ob/ob*) and diabetic (*db/db*) mice, and in the obesity resulting from hypothalamic damage (Cox & Powley, 1977; Trayhurn, 1979;

Rohner-Jeanrenaud *et al.* 1983; Saito & Bray, 1984; Hogan *et al.* 1985; Smith & Romsos, 1985). In addition, it is now clear that adrenal status also affects BAT function and energetic efficiency in lean rats (Rothwell & Stock, 1984; Rothwell *et al.* 1984). The effect is most clearly demonstrated in the old cafeteria-fed rat in which the age-dependent loss of adaptive response to the diet is prevented by adrenalectomy (Rothwell *et al.* 1984). The effect of adrenalectomy may be limited to animals fed on diets in which carbohydrate provides the major energy component, and may only be partial when very-high-fat diets are provided (Smith & Romsos, 1985; Bray *et al.* 1989).

Glucocorticoids are required for normal BAT non-shivering thermogenesis (Fellenz *et al.* 1982), yet these same hormones appear to inhibit BAT diet-related thermogenesis. Such evidence suggests that BAT *per se* is not the primary site of glucocorticoids in controlling BAT function, a suggestion which is supported by the reports of normal BAT response to noradrenaline stimulation in obese rats where diet-related (Holt *et al.* 1984) but not cold-related BAT thermogenesis is impaired. Some impairment in the sympathetic drive to BAT, as measured by tissue noradrenaline turnover, has been demonstrated in all animal models of obesity that have been studied (Van der Tuig *et al.* 1982; Nijjima *et al.* 1984; Yoshimatsu *et al.* 1984; Romsos, 1985; Bray *et al.* 1989). Indeed, the normal response to cold acclimation in the obese rat and the absence of response to dietary stimuli correlate with the effects of these stimuli on sympathetic activity. Likewise, the restoration of BAT responses to dietary signals after adrenalectomy of *falfa* rats and *ob/ob* mice has been associated with increased sympathetic drive to BAT (Van der Tuig *et al.* 1984; York *et al.* 1985). Recently, we (Holt & York, 1989a) have been able to confirm the reduction in sympathetic drive to BAT of obese rats by direct measurement of the electrical activity of the nerves innervating the interscapular BAT pad. Cannon & Nedergaard (1986) have postulated that the  $\alpha_1$ -adrenergic pathway has an important role in BAT hyperplasia and growth, probably through effects on the thyroxine 5'-deiodinase (EC 3.8.1.4) enzyme. This hypothesis is supported by our observations (Raasmaja & York, 1988) in obese rats that  $\alpha_1$ -adrenergic receptor density on brown adipocytes was reduced, but restored to normal levels by either adrenalectomy or cold acclimation, but not dietary stimuli. Thus, it would appear that the increase in sympathetic drive to BAT that results from the removal of glucocorticoid initiates a complex series of responses that leads to the restoration of normal morphological appearance and function of the tissue.

Changes in circulating glucocorticoid levels initiate reciprocal effects in pituitary adrenocorticotrophic hormone (ACTH) secretion and hypothalamic corticotrophin-releasing factor (CRF) production. It is then pertinent to ask which, if any, of these hormones or neuropeptides is responsible for the described effects of adrenal status on sympathetic drive to BAT. Any potential role for ACTH may be discounted for two reasons: first, hypophysectomy has a similar effect to adrenalectomy in preventing obesity (Powley & Morton, 1976), while second, corticosterone replacement to hypophysectomized obese rats restores the defects in BAT function, food intake and energetic efficiency (Holt *et al.* 1988a). Thus, attention has been directed towards understanding the possible role of glucocorticoid-CRF interaction in the control of obesity, and in particular in the control of sympathetic activity to BAT. The demonstration that a single injection of a glucocorticoid into the lateral ventricle of adrenalectomized gold-thioglucose-obese mice would temporarily restore weight gain and excess food intake (Debons *et al.* 1986) is suggestive of a central effect of glucocorticoids. CRF is widely distributed in the brain and has been identified in a number of hypothalamic centres known to function in the control of energy balance (Brown *et al.* 1982). CRF given intracerebroventricularly (icv), either acutely or chronically, suppresses food intake (Levine *et al.* 1983; Arase *et al.* 1988), enhances sympathetic activity (Brown &

Fisher, 1985; Arase *et al.* 1988) and depresses parasympathetic activity (Tache & Gunion, 1985). A lack of CRF function would provide an attractive hypothesis to explain the defects in a number of obese models and the restoration of normal energetic efficiency and BAT function after adrenalectomy. We have recently shown that CRF given icv will increase the firing rate of sympathetic nerves innervating the interscapular BAT pad in a dose-dependent manner in both lean and obese (*falga*) rats, but that the maximal response to CRF remains substantially reduced in the obese rat (York *et al.* 1988; Holt & York 1989b). Thus, CRF alone appears to be unable to mimic the effects of adrenalectomy, and the possibility must be considered that other neuropeptides, whose secretion is sensitive to glucocorticoid removal, are involved. Chronic infusions of CRF given icv into obese rats will, however, prevent further weight gain and reduce insulin levels (York *et al.* 1988). However, the question remains as to whether impaired CRF activity can be implicated in the development of obesity, or whether adrenalectomy, through its stimulation of CRF and other neuropeptide secretion, may provide a compensatory mechanism which can override the defective control of energy balance.

Glucocorticoids regulate the response of the sympathetic nervous system to diet-related signals, and this effect appears to be most prominent in animals fed on high-carbohydrate diets (Smith & Romsos, 1985). Several independent lines of evidence now suggest an interaction between glucocorticoids and carbohydrate-related aspects of energy balance. Liebowitz *et al.* (1985) have demonstrated the presence of a glucocorticoid-dependent  $\alpha_1$ -adrenergic system for carbohydrate feeding in the paraventricular nucleus (PVN) of rats. The PVN is also the site of CRF-containing neurons which control ACTH secretion from the pituitary (Sawchenko *et al.* 1984). However, it is unlikely that the PVN is the major site for any glucocorticoid control of diet-related thermogenesis, since it has not been possible to demonstrate any functional connection between the PVN and sympathetic nerves innervating BAT (Holt *et al.* 1988b), and since the obesity observed after lesions of the PVN is also prevented by adrenalectomy (Tokunaga *et al.* 1988). Likewise, the ventromedial hypothalamus is unlikely to be the site of action of glucocorticoids or CRF in controlling energy balance, since the effect of adrenalectomy is still observed in obesity resulting from damage to this region (Bruce *et al.* 1982).

2-Deoxy-D-glucose (2-DOG) is a glucoprivic agent which has multiple actions in the central nervous system. Among these are the stimulation of feeding and the suppression of sympathetic drive to BAT, both effects of which are absent in the obese (*falga*) rat but are restored after adrenalectomy (Ikeda *et al.* 1980; Allars & York, 1986; York *et al.* 1988). Conversely, glucocorticoids will suppress these effects of 2-DOG in lean rats. Finally we have shown (Holt & York, 1989a; York *et al.* 1988) that obese (*falga*) rats have an attenuated sympathetic response to acute injections of glucose into the third ventricle, consistent with their impaired response to changes in dietary intake. Thus, we may propose the hypothesis that the glucocorticoid or CRF actions may be on the lateral hypothalamus (LH). Lesions of the LH stimulate sympathetic activity (Yoshida *et al.* 1983). Furthermore, the activity of glucose-sensitive cells in this region is inhibited by glucose (Oomura, 1983). A glucocorticoid inhibition (CRF stimulation) of such cells might provide the mechanism underlying the effects of glucocorticoid status on sympathetic responses, as outlined in Fig. 1.

While the site of, and mechanism through which, glucocorticoids affect BAT function are still unknown, it is clear that (1) the glucocorticoid effects are mediated through changes in the sympathetic drive to the tissue, (2) the effect is specific to diet-related sympathetic activity and is mediated centrally, and (3) changes in CRF production or activity, or both, may play an important role in mediating the response to alterations in glucocorticoid status.

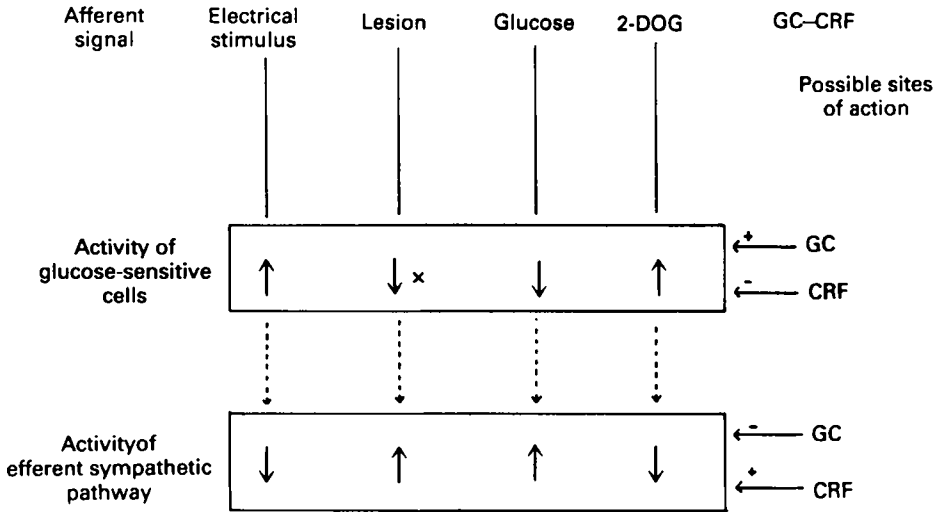


Fig. 1. Hypothetical sites of action of glucocorticoid (GC) in regulating diet-related sympathetic activity. The hypothesis envisages that reduced activity of glucose-sensitive cells in the lateral hypothalamus leads to the removal of an inhibitory influence and stimulation of the efferent sympathetic pathway. Glucocorticoids are envisaged as either activating cells at the lateral hypothalamic level or inhibiting the sympathetic pathway efferently. ↑, Increased activity; ↓, decreased activity; ×, activity abolished; -, inhibitory; +, stimulatory. CRF, corticotrophin-releasing hormone; 2-DOG, 2-deoxy-D-glucose.

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