Aspects of the neuroendocrine regulation of body weight homeostasis

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NEUROENDOCRINE EFFECTS OF LEPTIN

Body weight homeostasis is maintained via a complex series of interrelationships between the Central Nervous System (CNS) and peripheral tissues. These interactions comprise mainly the autonomic nervous and the endocrine systems. Leptin is a hormone that is synthesized and secreted by white adipose tissue. Once in the blood, it is transported into the CNS where, following binding to its specific long form hypothalamic receptor, it acts as a satiety factor. At the hypothalamic level, leptin regulates the levels of several neuropeptides which, themselves, exert effects on both food intake and intermediary metabolism [14, 15, 20]. Although leptin has been discovered several years ago [29], many questions remain concerning several facets of its action. As summarized below, we have studied some of the central effects of leptin on glucose metabolism, on uncoupling proteins, on thyroid hormones, as well as on serotonin transporters within the cerebral cortex.

Hormono-metabolic effects of leptin

Upon using euglycemic-hyperinsulinemic clamps associated with the labeled 2-deoxy glucose technique, we have observed that the intracerebroventricular (i.c.v.) infusion of leptin for 4 days in normal rats resulted in increased skeletal muscle glucose metabolism, while glucose uptake by white adipose tissue was decreased [5]. These leptin effects were due to the actual reduction of food intake, as they could be mimicked, in control animals infused with a vehicle, by reducing their food consumption to the same degree as that produced by leptin administration (pair-feeding). In contrast, leptin maintained, or increased the expression of uncoupling proteins (UCPs) at the same level as that of ad libitum fed vehicle-infused controls, whereas the diminution of food intake imposed to the pair-fed control group resulted in marked decreases in the expression of these proteins [5].

We have observed that four day of intravenous, or of i.c.v. leptin infusion produced similar effects on both glucose metabolism and insulin sensitivity, as well as on the expression of UCPs [5, 17].

The experiments together allow to conclude that: 1) leptin, via centrally-elicited mechanisms, modulates tissue glucose metabolism differentially in different tissues, and up-regulates the expression of peripheral uncoupling proteins; 2) leptin produces its effects either via the actual decrease in food intake (as is the case of glucose metabolism), or via pathways unrelated to food intake (case of UCPs).

Effects of leptin on thyroid hormones

It is known that thyroid hormones modulate the expression and activity of uncoupling proteins, of skeletal muscle UCP3, in particular [8, 9, 13]. We have hypothesized that leptin, acting centrally, could influence UCP3 expression by acting on thyroid hormones.

Three groups of rats were studied: ad libitum fed control rats i.c.v. infused with the vehicle; rats i.c.v. infused with leptin for 6 days; control rats pair-fed to the amount of food consumed by the leptin group and i.c.v. infused with the vehicle. We observed that food restriction (pair-feeding) resulted in a marked decrease in the expression of muscle UCP3 compared to that of ad libitum fed control animals [4]. The central infusion of leptin decreased food intake as expected, an effect that was, however, accompanied by the maintenance of UCP3 expression at the level observed in ad libitum fed controls. Concomitantly, plasma levels of T3 and T4 were decreased in pair-fed controls, while only those of T4 were lowered by the leptin infusion, T3 levels remaining at the levels measured in ad libitum fed controls [4]. To determine whether leptin has a role in the conversion of T4 to T3, the effect of chronic i.c.v. infu-
sion of leptin in normal rats on the activity of hepatic deiodinase type 1 was investigated. We observed that the deiodinase activity was increased by central leptin administration compared to pair-fed control rats [4]. It is therefore conceivable that central leptin may upregulate UCP3 expression by favoring T4 conversion into T3. In agreement with such a concept, we observed that leptin was completely ineffective on UCP3 expression, when administered to hypothyroid rats [4].

Thus, it may be concluded that thyroid hormones appear to modulate some of the effects of leptin, notably that on muscle UCP3 expression, thus playing a role in the regulation of the leptin-elicited energy dissipating mechanisms.

Effects of leptin on serotonin transporters in the cerebral cortex

The central serotoninergic system is implicated in many physiological processes such as the control of food intake and energy balance [10]. We have studied the effect of four day i.c.v. infusion of leptin in normal rats on the number of cerebral cortex serotonin transporters, and on the expression of the gene coding for these transporters in the raphe nuclei. We observed that leptin reduced the number of these transporters, without influencing their synthesis [3]. This leptin effect was unrelated to leptin-induced decrease in food intake, as it was not observed in pair-fed vehicle-infused controls [3]. These data indicate the existence of interrelationships between leptin and the central serotoninergic system. This could be of importance, as serotonin transporters are the target of several psycho-stimulants or anti-depressive drugs.

NEUROENDOCRINE EFFECTS OF NEUROPEPTIDE Y (NPY)

NPY is one of the hypothalamic targets of leptin [14, 15, 20]. When acutely administered i.c.v. in normal rats, NPY markedly increases food intake [11, 12]. Leptin decreases hypothalamic NPY synthesis, thereby partly exerting its satiety effect [20, 21]. In most animal models of rodent obesity, hypothalamic NPY levels are higher than normal [1, 2], hence obesity. To study the hormono-metabolic effects of NPY, we have infused the peptide centrally for seven days in normal rats. Chronic NPY infusion resulted in marked increases in food intake, body weight and white adipose tissue mass [27, 28]. Concomitantly, NPY-infused animals became hyperinsulinemic, hypercorticos-teronemic and hyperleptinemic [18, 27, 28], these abnormalities persisting as long as the NPY infusion was pursued [23]. In NPY-infused rats, the adipose tissue insul sensitivity was increased, while that of all squeletal muscles was decreased [27, 28]. It is worthwhile noticing that all these NPY-elicited hormono-metabolic changes are the mirror image of those brought about by leptin, as described above [14, 15]. Additionally, the central effects of NPY required the presence of glucocorticoids, as they failed to occur when NPY was i.c.v. infused to adrenalectomized rats [19]. As the central infusion of dexamethasone plus NPY restored the full effects of the neuropeptide [26], it is suggested that glucocorticoids exert a “permissive” effect on the development of obesity by acting within the CNS.

EFFECTS OF GLUCOCORTICOIDS IN THE NEUROENDOCRINE CONTROL OF METABOLISM

Given the likely importance of glucocorticoids in NPY-induced obesity, we have studied the effects of glucocorticoids per se on body weight homeostasis by i.c.v. infusing these hormones in normal rats. Such a central glucocorticoid administration resulted in increased food intake, body weight, plasma insulin and leptin levels relative to controls [25]. These changes were the likely result of central glucocorticoids increasing the levels of NPY, while decreasing those of CRH [25]. Of note was the observation that when glucocorticoids were administered peripherally, instead of centrally, a decrease in food intake and body weight occurred [25]. This could be the result of peripheral glucocorticoids stimulating adipose tissue leptin secretion, as initially reported [6].

In recent experiments, we have observed that the i.c.v. glucocorticoid infusion in normal rats produced a decreased rate of overall glucose disappearance and, specifically, a decreased peripheral glucose utilization by the muscle mass (Cusin et al., submitted for publication). Based upon the previous observations that genetically preobese pups, as well as overtly obese fa/fa rats are characterized by hyperinsulinemia that is largely due to an increased activity of the parasympathetic nervous system [7, 16, 22], additional experiments with dexamethasone were performed to determine a possible involvement of the parasympathetic nervous system in the dexamethasone-elicited effects. I.c.v. dexamethasone infusion was therefore carried out in both sham-operated (controls) and vagotomized animals. It was of interest to observe that, in vagotomized rats, food intake and body weight remained normal relative to controls, and that no insulin resistance developed, in contrast to the effects of central dexamethasone in normal rats (Cusin et al., submitted for publication).

In other studies, we observed that the actual thinning effect of leptin was inhibited by glucocorticoids [24]. Thus, a given dose of leptin i.c.v. injected in intact normal rats decreased food intake and body weight, but
Aspects of the neuroendocrine regulation of body weight

this leptin effect was much more pronounced when leptin was administered to adrenalectomized rats, to be progressively inhibited by the superimposed supplementation of adrenalectomized animals with dexamethasone [24].

These results together suggest that central glucocorticoids favor food intake and body weight gain, as well as the establishment of an obesity syndrome associated with insulin resistance. The obesity syndrome induced by central glucocorticoids appears to involve the activation of the parasympathetic nervous system. These observations could be of relevance for human obesity, given the reports showing the impact of stressful situations on body weight gain.

Abbreviations : CNS, Central Nervous System ; NPY, Neuropeptide Y ; POMC, Proopiomelanocortin ; α-MSH, α-Melanocyte-Stimulating Hormone ; CART, Cocaine-and Amphetamine-Regulated Transcript ; ANS, Autonomic Nervous System.

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