Interactions between the melanocortin system and the hypothalamo-pituitary-thyroid axis

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Abstract

Recent studies of transgenic mice and humans have provided compelling evidence for the importance of the hypothalamic melanocortin system in the regulation of energy balance. Energy homeostasis is a balance between food intake (energy input) and energy expenditure. The melanocortin system regulates feeding via effects of the endogenous agonist, α-melanocyte stimulating hormone (α-MSH) and the endogenous antagonist agouti-related protein (AgRP) on melanocortin 3 and 4 receptors (MC3-Rs and MC4-Rs). It has been demonstrated that the melanocortin system interacts with the hypothalamo-pituitary-thyroid (HPT) axis. Thyroid hormones influence metabolism and hence energy expenditure. Therefore, an interaction between the HPT axis and the melanocortin system would allow control of both sides of the energy balance equation, by the regulation of both energy input and energy expenditure. Here we will discuss the evidence demonstrating interactions between the melanocortin system and the HPT axis.

1. Introduction

There is growing evidence that the central melanocortin system is important in the regulation of energy balance through co-ordinated actions on both food intake and energy expenditure [58]. Within this system, agouti-related protein (AgRP), the endogenous antagonist at melanocortin 3 and 4 receptors (MC3- and MC4-Rs), stimulates feeding [50;53], whereas alpha-melanocyte stimulating hormone (α-MSH), the endogenous ligand for these receptors, reduces food intake. The α-MSH precursor, pro-opiomelanocortin (POMC), is expressed in a population of arcuate neurons distinct from those expressing AgRP.

Energy homeostasis is a balance between food intake (energy input) and energy expenditure [22]. The hypothalamo-pituitary-thyroid (HPT) axis produces the thyroid hormones tri-iodothyronine (T3) and thyroxine (T4), which stimulate energy expenditure, largely via increased thermogenesis [59]. Therefore, the HPT axis plays a key role in the regulation of energy homeostasis. Whilst initial studies of the role of the melanocortin system in the regulation of energy homeostasis concentrated largely on the control of food intake, more recent studies have also shown an interaction between the melanocortin system and the HPT axis. Such an interaction would allow control of both sides of the energy balance equation, by the regulation of both energy input and energy expenditure. Here we will discuss the evidence demonstrating interactions between the melanocortin system and the HPT axis.

2. The HPT axis

The hypothalamic tri-peptide, thyrotrophin-releasing hormone (TRH), is essential for the normal biosynthesis and release of thyroid stimulating hormone (TSH) from the anterior pituitary and in turn, thyroid hormones from the thyroid gland [65]. Although TRH neurons are located in a number of hypothalamic nuclei [38], the hypophysiotrophic TRH neurons which project to the median eminence to regulate anterior pituitary TSH release are confined to the medial and periventricular parvocellular regions of the PVN [29]. TRH is released from these hypophysiotrophic neurons into the hypophyseal portal circulation to regulate the release of TSH from the anterior pituitary. TSH stimulates the thyroid gland to synthesise and release the thyroid hormones T4 and the biologically more active T3. The major pathway for the production of T3 is via 5'-deiodination of the outer ring of T4 by deiodinase enzymes which accounts for the majority of circulating T3 [68]. When plasma thyroid hormone

concentrations fall, such as in primary hypothyroidism, TRH biosynthesis and secretion are up-regulated in hypophysiotrophic TRH neurons, thus increasing TSH release from thyrotrophs in the anterior pituitary [63].

3. The HPT axis and starvation

It has been well characterised that in states of negative energy balance, such as prolonged fasting, regulation of the HPT axis is altered, as manifested by low plasma T3, and T4, with a low or inappropriately normal TSH and a reduction in TRH biosynthesis and secretion [1,5,9,15,16,25,27,33,51,64]. This central hypothyroidism following starvation may be an important adaptive response, by reducing thermogenesis and hence, reducing the obligatory use of energy stores [21]. Present evidence indicates that this adaptation to starvation is achieved through a reduction in PVN TRH, demonstrating that a central mechanism contributes to this physiological adaptive response. Starvation specifically down-regulates TRH mRNA expression in the PVN where hypophysiotrophic TRH neurons are located [5]. This effect of starvation is specific to the PVN, since adjacent non-hypophysiotrophic TRH neurons in the lateral hypothalamus are unaffected by fasting [40].

4. Leptin and the HPT axis

Following the discovery of the adipocyte-derived hormone leptin by Friedman *et al* in 1994 [69], subsequent studies over the last decade support a role for leptin as a negative feedback signal from the periphery to the central nervous system (CNS) to regulate energy homeostasis (for reviews see [17], 44 ,58]. In addition to its role in regulating body weight, leptin signals to the CNS the transition from the fed to fasted state (for review see [70]).

In rodents, peripheral administration of leptin during a forty-eight hour fast substantially blunts the observed fasting-induced fall in plasma T4 [1 40]. Leptin appears to be acting at the level of the hypothalamus, since exogenous leptin abrogates the fasting-induced suppression of pro-TRH mRNA [40]. Regulation of the HPT axis by leptin may be direct through the long form of its receptor Ob-R, which is present on a subset of TRH neurons in the PVN or indirect, via its actions on the arcuate nucleus [26, 49]. In support of a direct role, leptin directly activates the TRH promoter *in vitro* [26] and *in vivo* [24] via the signal transducer and activator of transcription 3 (STAT 3) signalling pathway. However, because there is a high concentration of Ob-Rs in the arcuate nucleus [3] and chemical ablation of the arcuate nucleus abolishes the effect of fasting and leptin administration on the HPT axis [41], leptin may also indirectly regulate the HPT axis via the arcuate nucleus.

5. The melanocortin system and the HPT axis

Leptin activates POMC gene expression in the arcuate nucleus [46 62] making POMC-derived α-MSH a candidate for mediating the indirect regulation of TRH expression by leptin. Several rodent studies using double-labelling immunocytochemistry show that the melanocortin system is well positioned to interact with the HPT axis. Arcuate α-MSH neurons send monosynaptic projections to the soma and first-order dendrites of TRH neurons in the parvocellular division of PVN, the site of hypophysiotrophic TRH neurons [19]. In addition, AgRP is also contained in axon terminals heavily innervating TRH neurons in the PVN [42]. In fact, all TRH neurons receiving contacts from α-MSH containing fibres are also innervated by axons containing AgRP [19]. These findings have been replicated in

humans, with the demonstration that α-MSH- and AgRP-containing neurons within the infundibular nucleus, the human equivalent of the rodent arcuate nucleus, are in close juxtaposition to PVN TRH neurons [45]. Since both α-MSH and AgRP signal through the MC4-R, the finding that approximately half of TRH neurons in the medial parvocellular PVN express the MC4-R [26] provides further morphological evidence to support a role for the melanocortin system in the response of the HPT axis to altered energy states.

Recent *in vitro* and *in vivo* studies provide further support for this hypothesis. Intracerebroventricular (ICV) infusion of α-MSH in fasted rats completely restores pro-TRH mRNA levels in the PVN to normal fed levels [19]. Arcuate AgRP mRNA expression in the same group of rats remained elevated despite α-MSH administration, indicating that this positive effect of exogenous α-MSH on PVN pro-TRH mRNA is not due to an inhibition of AgRP gene expression [19]. However, in the same study, plasma thyroid hormones were only restored to 50% of fed levels by ICV α-MSH. This is in contrast to the effects of exogenous leptin administration during fasting, which restores both pro-TRH mRNA in the PVN and plasma thyroid hormones to fed levels [40]. Therefore, it appears that α-MSH mediates only some of the regulatory effects of leptin on the HPT axis. Consistent with a stimulatory effect of α-MSH on the HPT axis, a single ICV injection of α-MSH in fasted rats increases plasma TSH and stimulates TRH release from hypothalamic explants [32].

The MC4-R, like the other MC-Rs, signals by increasing levels of intracellular cyclic AMP (cAMP) [66]. This in turn activates protein kinase A and hence, phosphorylates cAMP response element binding protein (CREB), to induce the transcription of genes

containing a cAMP response element (CRE) [14]. Human, rat and murine TRH promoters have a conserved element that bears close homology to a canonical CRE [39]. *In vitro* studies in a heterologous cell system demonstrate that α-MSH signalling through MC4-Rs activates the TRH promoter via phosphorylation and binding of CREB [26]. This was recapitulated *in vivo* where ICV injection of α-MSH increased phosphorylated CREB in TRH neurons within the anterior, medial and periventricular parvocellular subdivisions of the PVN [56].

Conversely, CNS infusion of AgRP to *ad libitum* fed rats produces central hypothyroidism, with reduced plasma thyroid hormones, inappropriately normal or decreased TSH and suppressed PVN pro-TRH mRNA expression [20, 60]. However, CNS administration of AgRP did not affect type 2 deiodinase activity in brown adipose tissue (BAT), a major effector organ for thyroid hormones in regulating thermogenesis [20]. This finding, together with a marked reduction in pro-TRH mRNA expression in the PVN, suggests that AgRP acts centrally, via TRH suppression within the PVN, rather than peripherally to reduce circulating thyroid hormones. In support of this, AgRP inhibits TRH release *in vitro* from hypothalamic explants [32]. Furthermore, AgRP [32] and the synthetic MC4-R antagonist SHU9119 [49] inhibit leptin-induced hypothalamic TRH release *in vitro*.

Together, these data provide support a role for α-MSH and AgRP mediating the effects of leptin on the HPT axis via central melanocortin receptors. Further work is needed to establish whether additional peripheral hormones regulating energy balance can also influence the HPT axis via the melanocortin system. Although both MC3- and MC4-Rs are abundant in the hypothalamus [47, 52], it remains unclear which

receptor is the key regulator of energy balance. The obesity phenotype of the MC4-R null mouse strongly supports a role for this receptor in obese states [28]. Transgenic mice lacking the MC3-R have not clarified the role of the MC3-R to the same extent [7, 13]. Similarly, since α-MSH [57] and AgRP [50] bind to both MC3- and MC4-Rs, studies of the interactions between the melanocortin system and the HPT axis are unable to establish which receptor subtype(s) is involved. An *in vitro* study using selective MC3- and MC4-R ligands has suggested differential roles for the MC3- and MC4-Rs in the regulation of hypothalamic TRH release [31]. However, to date, only the MC4-R has been found to be expressed on TRH neurons [26]. Therefore, the exact role of the MC3- and MC4-R in the regulation of the HPT axis needs further clarification.

6. Thermogenesis, thyroid hormones and the melanocortin system

Thermogenesis involves the production of heat to maintain body temperature in cold environments. Thermogenic mechanisms are classified as either obligatory or adaptive. Obligatory thermogenesis represents the energy dissipated as heat in the many energetic transformations inherent to life. Diet-induced thermogenesis is a form of adaptive thermogenesis and describes the marked increase in heat production which serves to reduce or prevent the development of obesity [55]. In small mammals, including the human neonate, the main site of adaptive thermogenesis is BAT. The remarkable thermogenic capacity of BAT is due to its unique ability to uncouple phosphorylation in a controlled manner, allowing it to dissipate energy as heat [55].

The primary molecule involved in adaptive thermogenesis in BAT is uncoupling protein (UCP-1), which is organised in the inner membrane of BAT mitochondria and uncouples proton entry from ATP synthesis [34, 48]. UCP-1 is exclusive to BAT where it is regulated by the sympathetic nervous system and peripheral hormonal factors including thyroid hormones [30]. Both cold exposure [4] and hyperphagia [12] are associated with an increase in BAT UCP-1 levels. Intracellular conversion of T4 to T3 by type 2 deiodinase is essential for the typical cold-induced increase in BAT UCP protein [6]. However diet-induced thermogenesis may not be associated with altered BAT type 2 deiodinase activity [35]. Nevertheless, thyroid hormones do potentiate diet-induced thermogenesis [54].

In addition to its role in regulating food intake, the central melanocortin system may regulate thermogenesis in BAT and hence, energy expenditure. A single ICV injection of α-MSH increases BAT temperature and BAT sympathetic nerve activity, whereas conversely, these are decreased by AgRP [67]. Similarly, prolonged ICV administration of the synthetic MC4-R antagonist HS014 suppresses BAT UCP-1 mRNA levels [2], yet chronic peripheral injection of the MC4-R agonist MTII is associated with an increase [10].

In support of these findings, MC4-R null mice are unable to increase oxygen consumption, a marker of energy expenditure, in response to high-fat diet suggesting that the MC4-R is necessary for diet-induced thermogenesis [8]. Similarly, MC4-R null mice are also unable to increase activity-based energy expenditure, shown to make an important contribution to energy balance [43], following increases in dietary fat [8].

Regulation of adaptive thermogenesis by the melanocortin system may be achieved, at least in part, via the HPT axis. In rodents, chronic AgRP injection increases BAT weight due to increased adiposity, but reduces BAT UCP-I protein and plasma TSH [60]. Interestingly, these effects are independent of food intake. Similarly, chronic ICV administration of AgRP over the same period reduces oxygen consumption as a marker of energy expenditure, associated with blunted BAT thermogenic capacity [61]. Therefore, inhibition of the HPT axis by AgRP may down-regulate BAT UCP-I levels, hence reducing adaptive thermogenesis and ultimately, energy expenditure.

7. The HPT axis in models of an abnormal melanocortin system

A number of transgenic murine models of abnormal melanocortin signalling have provided considerable support for the importance of the melanocortin system in regulating energy balance. However, to date, detailed analyses of the HPT axis in these models are limited. MC3-R deficient mice have normal plasma T4 levels [7, 13], although plasma thyroid hormones in either MC4-R-null [28] or AgRP over-expressing [23, 50] have not been described. In a recent study, transgenic mice lacking all POMC-derived peptides had reduced plasma T4 [11], consistent with a stimulatory effect of POMC-derived peptides such as α-MSH on the HPT axis.

In humans, MC4-R mutations are the commonest monogenic form of obesity [18]. Although the majority of individuals with MC4-R deficiency have plasma T4 and TSH levels within the normal range, a small number have an elevation in plasma TSH [18]. Since the normal range for plasma T4 is wide, this does not exclude abnormalities in the HPT axis of these individuals, particularly under circumstances

such as fasting which may functionally challenge the HPT axis. Humans deficient in POMC are hyperphagic and obese, with red hair [36]. In the original study describing these individuals, it was assumed that their HPT axis was normal due to normal plasma T4 [36]. However, a recent, more detailed analysis of these subjects shows that in fact POMC-deficient humans have normal plasma T3 and T4 levels, with elevated plasma TSH which can be suppressed to within the normal range with T4 supplementation [37]. The mechanism responsible for these abnormalities remains under investigation, but does provide further support for stimulatory effects of melanocortin peptides such as α-MSH on the HPT axis.

8. Conclusions

The role of the melanocortin system is well established in the regulation of food intake. However, it is becoming increasingly clear that there is an additional important role for the melanocortin system in the regulation of energy expenditure, at least in part, due to interactions with the HPT axis. Anatomically, POMC and AgRP neurons are poised to regulate hypophysiotrophic neurons in the PVN. Growing evidence supports a stimulatory role for α-MSH on the HPT axis, whilst AgRP is inhibitory. The interaction between the HPT axis and the melanocortin system is shown schematically in Figure 1. In states of negative energy balance, associated with an increase in AgRP, valuable energy stores would be conserved by both an increase in food intake and a reduction in energy expenditure, in part due to suppression of the HPT axis. Conversely, in times of nutritional abundance, an associated increase in α-MSH would serve to signal both a reduction in food intake and also an increase in energy expenditure by up-regulating the HPT axis. These alterations in energy expenditure as well as food intake may be important adaptive responses in

maintaining energy homeostasis. Although the adiposity signal leptin is likely to also have direct effects on the HPT axis, it seems likely that some of these effects may be mediated indirectly via the melanocortin system. However, further work is needed to establish whether the melanocortin system regulates the HPT axis independently of leptin and this remains a fascinating area for further investigation.

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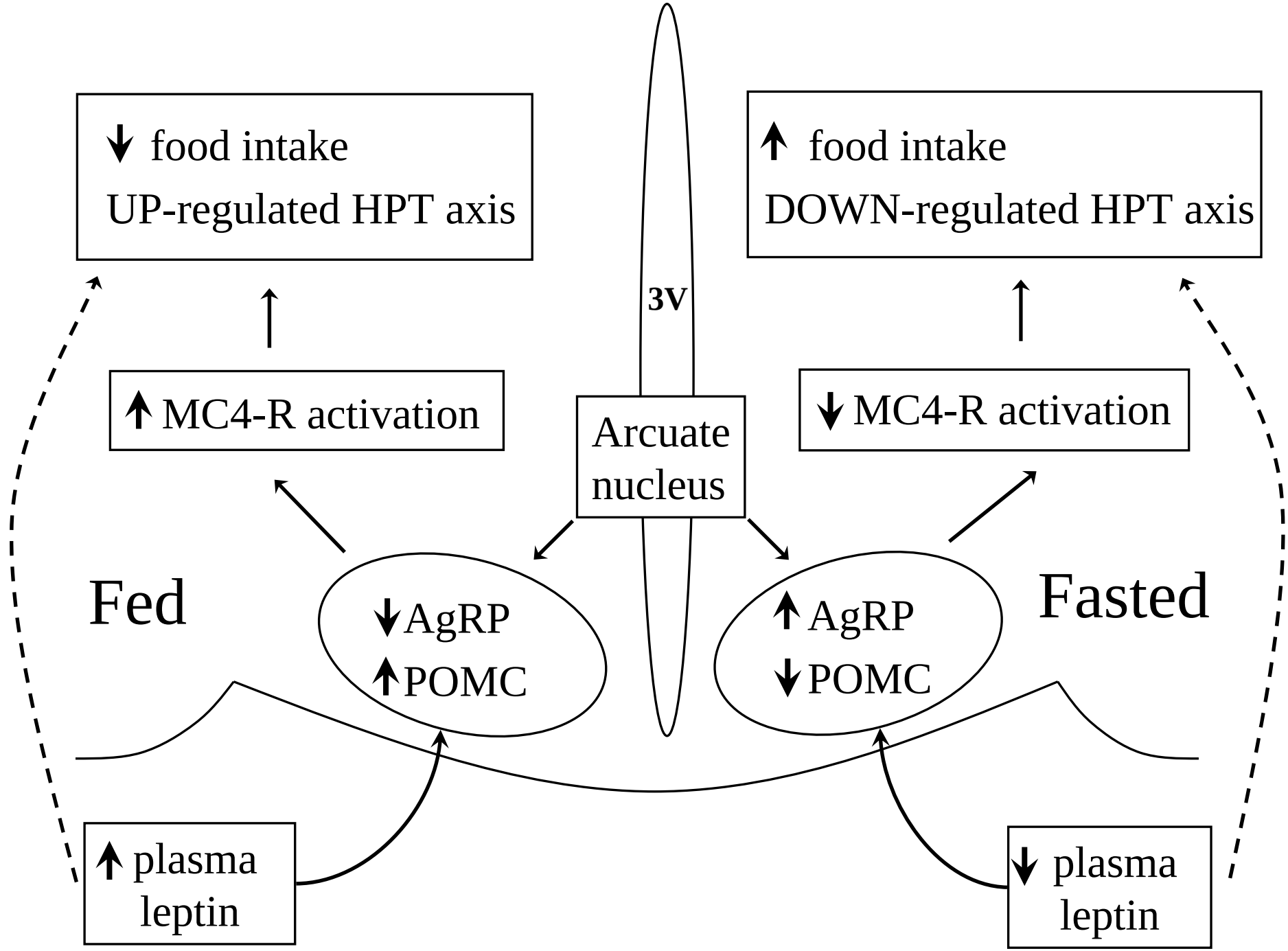
Figure legend

Figure 1

A hypothetical model of the interactions between the melanocortin system and the HPT axis in fed and fasted animals. In the fed state (shown on the right), an elevation in circulating leptin promotes high POMC and low AgRP mRNA levels in the arcuate nucleus, with subsequent increased MC4-R activation. This is associated with a reduction in food intake and an increase in the activity of the HPT axis, stimulating energy expenditure. In the fasted state (shown on the left), circulating leptin falls, leading to a reduction in POMC and an increase in AgRP mRNA expression in the arcuate nucleus. In this state of negative energy balance, increased AgRP stimulates food intake and inhibits the HPT axis, reducing energy expenditure. Although the melanocortin system may mediate some of the effects of leptin on the HPT axis, leptin also has direct effects on the TRH neurons in the hypothalamic PVN (shown by dashed arrows).


↓ food intake
UP-regulated HPT axis
↑ food intake
DOWN-regulated HPT axis
3V
↑ MC4-R activation
Arcuate nucleus
↓ MC4-R activation
Fed
↓AgRP
↑POMC
↑AgRP
↓POMC
Fasted
↑ plasma leptin
↓ plasma leptin

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