Commentary

MOLECULAR METABOLISM

Central leptin and autonomic regulation: A melanocortin business

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The regulation of energy homeostasis is precisely controlled by the central nervous system (CNS) [1,2]. Some key areas such as the hypothalamus and the brainstem receive signals on energy and nutritional status transmitted from the periphery, for example leptin, insulin, ghrelin, thyroid hormones, and gonadal steroids, among others. The information from those signals is integrated in the CNS and modulates different aspects of the energy balance such food intake, energy expenditure (EE), and peripheral metabolism, as well as other physiological processes, including cardiovascular and hemodynamic functions, for example blood pressure [1,2]. This fine-tuned control is mainly exerted by two complementary and non-exclusive drivers: the endocrine system and the autonomic nervous system (ANS) (see Figure 1). The ANS innervates several peripheral organs/tissues, including brown and white adipose tissue (BAT and WAT), liver, pancreas, gut, kidney, adrenal glands, and skeletal muscle. The ANS consists of two branches, the sympathetic (SNS) and parasympathetic (PSNS) nervous system. Traditionally, the SNS has been associated with catabolic responses and the PSNS with anabolic responses [1,2]. Under some physiological circumstances both the SNS and PSNS can be activated or inhibited at the same time, but typically when one is activated the other is inhibited [1,2]. The adipose tissue is innervated by the SNS, whereas PSNS innervation of some fat depots is still controversial [2–4]. The liver and pancreas are innervated by splanchnic sympathetic and vagal parasympathetic nerves [5,6]; skeletal muscle also receives both sympathetic and parasympathetic innervation [7].

Even though the anatomical basis of the autonomic control of peripheral tissues is well established [1,2], the central molecular mechanism and, particularly, the molecular networks controlling the differential activation and/or inhibition of the SNS and the PSNS on metabolic organs/tissues remain elusive. In this issue of *Molecular Metabolism*, Rahmouni and colleagues add new knowledge that helps to understand how the adipocyte-derived hormone leptin modulates the periphery through the ANS. By using a combination of physiological, anatomical, viral trans-neuronal tracing, electrophysiological, and conditional genetic ablation methods, the authors show that the two-key cell populations within the arcuate nucleus of the hypothalamus (ARC), namely proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons, modulate the ANS in a very specific fashion, mediating different effects of leptin [8]. Specifically, they generated mice lacking leptin receptor (LepR) in either POMC or AgRP neurons of the ARC by crossing $LepR^{fl/fl}$ mice with either $POMC^{Cre}$ mice or $AgRP^{Cre}$ mice. Interestingly, the strains differed in their ability to regulate the SNS and the PSNS nerves subserving several peripheral targets. Notably, the observed effects in terms of sympathetic or parasympathetic nerve activation (SNA or PSNA) correlated with the metabolic phenotype of the animals. For example, the leptin-evoked sympathoexcitatory action of BAT was diminished in both $POMC^{Cre}/LepR^{fl/fl}$ and $AgRP^{Cre}/LepR^{fl/fl}$ mice, which was coherent with the obese phenotype exhibited by both models [8]. Quite the opposite, the sympathetic effect of central leptin on WAT was dependent on AgRP but not POMC neurons. Next, they analyzed the effect of LerR deletion on hepatic, lumbar, splanchnic, renal and adrenal SNA and PSNA. Their results showed that both POMC and AgRP neurons contribute to the leptin-elicited increase in hepatic PSNA (but not SNA, which depends only on AgRP neurons) and that leptin-induced increase in lumbar, splanchnic and renal (but no adrenal) SNA is mediated by POMC (but not AgRP) neurons (see Figure 1). Finally, they investigated the implication of proopiomelanocortin (PI3K) signaling on the sympathetic renal effects of leptin, since it is known that modulation of this kinase in the hypothalamus mediates the effects of leptin on kidney but not BAT, hind limbs, or the adrenal glands [9]. Therefore, they generated conditional knockout mice lacking the catalytic p110α or p110β subunits of PI3K in POMC neurons of the ARC. $POMC^{Cre}/p110\alpha^{fl/fl}$ (but not $POMC^{Cre}/p110\beta^{fl/fl}$) displayed a decreased SNA response to leptin, indicating that p110α is the isoform necessary for mediating that effect [8].

The importance of these findings is that they show for the first time that POMC and AgRP neurons are differentially implicated in mediating the effects of leptin on autonomic nerve activity subserving various tissues and organs. This is of relevance for several reasons. POMC and AgRP neurons are known to differentially regulate energy balance. The central melanocortin system modulates energy homeostasis through the anorectic actions of the agonist α-melanocyte stimulating hormone (α-MSH, which is a POMC cleavage product) and the endogenous orexigenic melanocortin receptor antagonist AgRP [2,10]. Five melanocortin receptors have been identified: MC1R-MC5R. The feeding-related effects of both α-MSH and AgRP are mediated via MC3R and MC4R. Circulating hormones such as leptin, insulin, ghrelin, thyroid hormones and gonadal steroids act on POMC neurons providing

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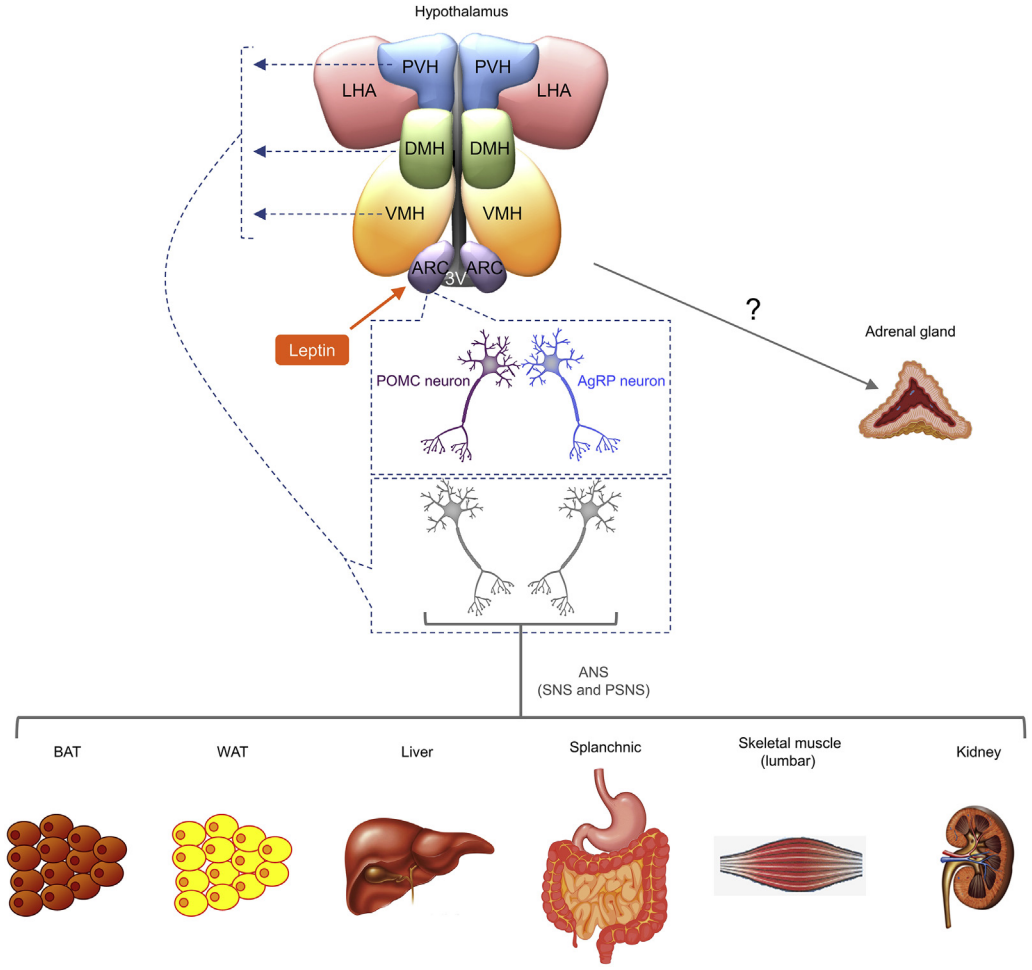

Figure 1: Central leptin modulates the autonomic nervous system through POMC and AgRP neurons in the ARC. Central leptin acts in the hypothalamus to modulate the autonomic nervous system (ANS) activity innervating several organs and tissues A recent manuscript from *Rahmouni and colleagues* has demonstrated that proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus (ARC) differentially modulate the two branches of the ANS, namely the sympathetic (SNS) and parasympathetic (PSNS) nervous system subserving brown and white adipose tissue (BAT and WAT), liver, gut, lumbar skeletal muscle and kidney. ARC neurons evoke those effects by modulating pre-autonomic sympathetic and parasympathetic neurons in other nuclei, such as the paraventricular (PVH), the dorsomedial (DMH) and the ventromedial (VMH). The leptin-evoked effect on the sympathetic innervation of adrenal gland is independent of POMC and AgRP neurons.

information on energy status from the periphery. For example, leptin increases the activity of anorectic POMC neurons, increasing its gene expression and the secretion of α-MSH, and decreases the release of AgRP, leading to anorexia. Moreover, POMC and AgRP neurons mutually inhibit each other [10]. The effects of POMC and AgRP neurons on BAT have been extensively studied and confirmed by Rahmouni and colleagues; both neuronal populations are important for the regulation of thermogenesis [2,8]. However, the fact that only AgRP neurons mediate leptin's effects on inguinal WAT by increasing the SNA indicates that leptin-evoked lipolysis and browning of white fat [1,2] are likely independent of POMC neurons. A similar rationale can be applied to the central leptin effect on hepatic metabolism [1,2]. On the other hand, the effect of leptin on lumbar, splanchnic, and renal SNA, which is relevant for the modulation of blood pressure, seems to be dependent on POMC neurons. Whether this divergent regulation is specific for leptin or whether it also applies to other hormonal signals is of interest and will require further investigation. The relevance of this specific regulation in the context of human disease is also intriguing. Patients with leptin, POMC, and MCR4R deficiency exhibit obesity and impaired peripheral metabolic regulation [1,2,10]; therefore, it is plausible that in addition to the hyperphagia and decreased energy expenditure, those phenotypes could be related to differential autonomic-mediated actions of POMC and AgRP neurons on specific organs. Consequently, it will be essential to have a deeper understanding of the molecular mechanisms modulating the divergent effect of both ARC populations on the ANS to better understand obesity and to develop more efficient and rational therapies. The work of Rahmouni and colleagues has laid the foundation for this new knowledge.

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