Modulation of IL-10 signaling in persistent human infection certainly needs consideration as a possible antiviral strategy. Interestingly, the current therapy for HCV—interferon-alpha and ribavirin—among other things downmodulates IL-10 secretion in APCs (ref. 11) and T cells (ref. 12). The immunoregulatory roles of IL-10 and its receptors as well as PD-1 and its ligands need to be considered in future clinical trials in humans. However, the good news from the two new mouse studies is that IL-10 receptor blockade did not lead to major immune-mediated pathology.

Viruses make excellent immunologists. And so the current findings on IL-10 and PD-1 emerge from the convergence between virology and the study of autoimmunity and tolerance. There has been a long history of trying to link viruses to the pathogenesis of autoimmune disease; however, it now looks like the reverse process, linking mechanisms of tolerance to the pathogenesis of virus infections, might be a particularly exciting area in future.


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# Keeping the fat off with nesfatin

Martin G Myers Jr

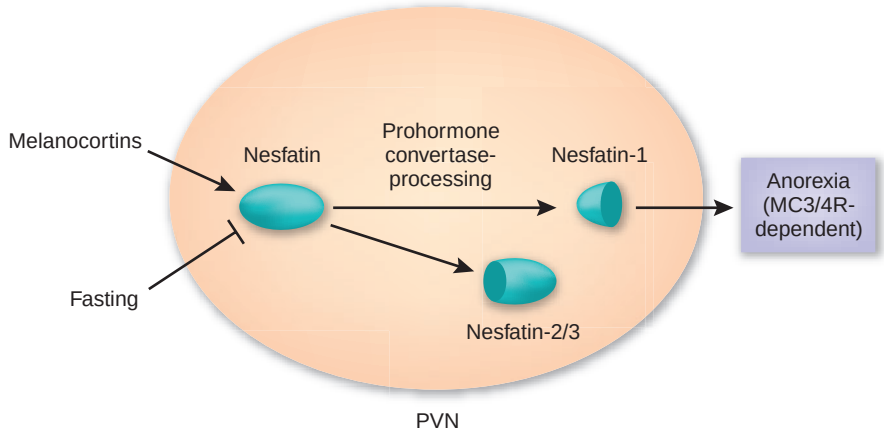
**A newly described neuropeptide, nesfatin-1, acts in the brain to suppress appetite.**

Some of the components of brain circuits that control feeding have come to light over the last several years, including an extensive list of hormones and compounds that decrease feeding when injected into the brain. Yet only a subset of these substances are physiologically relevant and can lend insight into the brain processes that control appetite—moreover, precious few mediate meaningful long-term changes in body weight. Our understanding of how brain circuitry controls appetite remains sparse[1–3].

In a recent issue of *Nature*, Oh-I *et al.* define a physiologic role in the suppression of appetite for a novel brain-expressed peptide, nesfatin-1, which is derived from the previously described protein nucleobindin-2 (NUCB2, a.k.a. NEFA) (refs. 4,5 and **Fig. 1**). Although lengthier studies will be necessary, modulation of nesfatin-1 levels in the brain alters feeding and body weight for over one week without apparent loss of efficacy.

The investigators discovered that the secreted protein NUCB2 is expressed in areas of the hypothalamus that are prominently involved in appetite regulation, prompting them to examine a potential role for this molecule in feeding. Indeed, the authors showed that injection of NUCB2 directly into the brain of rats promotes anorexia (decreased appetite)—and that the injection of antibodies to NUCB2 (anti-NUCB2) to neutralize endogenous NUCB2 in the rat central nervous system (CNS) potently stimulates feeding. These observations implicate NUCB2 in the neuronal pathways that suppress appetite.

Whereas the injection of many peptides into the brain may nonspecifically decrease appetite by making the animal feel sick, the authors show that this is not the case for NUCB2. Indeed, fasting suppressed NUCB2 expression specifically in a region of the hypothalamus known to have an important role in anorexia—the paraventricular nucleus (PVN). The PVN compiles a variety of inputs that regulate feeding to generate an integrated signal of hunger or satiety that is then passed on to other regions of the brain. One of the major pathways that modulates the appetite-regulating function of the PVN is the melanocortin system, in which melanocortin peptides (such as α-melanocyte-stimulating hormone,




Kim Caesar

**Figure 1** Regulation and function of nesfatin in the control of feeding. Nesfatin is a prohormone that is cleaved by prohormone convertases to an $NH_2$-terminal nesfatin-1 peptide and to nesfatin-2/3. Whereas nesfatin-2/3 have no effect on feeding, nesfatin-1 suppresses eating in a manner that requires functional melanocortin receptors (MC3/4R). Although there are no data to confirm the actual site of nesfatin-mediated satiety, the nutritional regulation of nesfatin is restricted to the paraventricular nucleus of the hypothalamus (PVN), where its expression is suppressed by fasting and enhanced by the action of melanocortins (a signal of satiety). The PVN is also a major site of MC3/4R receptor expression and action in the suppression of feeding.

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α-MSH) derived from the arcuate nucleus of the hypothalamus activate the melanocortin-3 and melanocortin-4 receptors (MC3/4R) in the PVN to promote anorexia in response to meals and sufficient body energy stores[1,2,6]. Melanocortin action increases the expression of NUCB2 in the PVN. Thus, not only does NUCB2 mediate anorexia, but its expression in the PVN is regulated in a manner that is consistent with a role in the physiologic regulation of appetite.

The authors also note that NUCB2 contains multiple potential sites for processing by prohormone convertases proteases that specifically cleave secreted precursor proteins into smaller active peptides[7]. Indeed, NUCB2 is coexpressed with multiple prohormone convertases in the hypothalamus. Moreover, the action of prohormone convertase on NUCB2 releases an $NH_2$-terminal fragment—nesfatin-1—that is present in the CNS, is regulated by fasting in the PVN, and possesses all of the anorectic activity of NUCB2.

Neither the COOH-terminal NUCB2 fragments (nesfatin-2/3) nor a mutant NUCB2 precursor that is resistant to prohormone convertase—dependent processing retains any effect on feeding—suggesting that nesfatin-1 must be cleaved from intact NUCB2 in order to suppress feeding. Thus, nesfatin-1 is a novel peptide product of NUCB2, and it is this peptide that mediates the anorexic action of NUCB2 in the CNS.

Unfortunately, there are few clues detailing the mechanism of nesfatin-1 action. NUCB2 was initially defined as a potential leucine zipper– and 'EF hand'–containing protein of unknown function that is expressed in lymphoblastic cells[5]. Subsequent experiments have defined the ability of the EF hands to complex calcium and have suggested a role for the leucine zipper motifs in complex formation with heterologous proteins[8–10]. The protein is localized within the endoplasmic reticulum (ER) and Golgi and is secreted from cultured cells[8,11]. Recent studies have also suggested that the EF hand and leucine zipper region may be involved in complex formation with tumor necrosis factor receptor-1 (TNFR1) and other proteins within the secretory pathway and on the cell surface[8]. All of these attributes of NUCB2 are mediated by motifs found within nesfatin-2/3, however[4]. Thus, prior knowledge regarding NUCB2 sheds little light on the mechanism of nesfatin-1 action.

What we do know is that the action of nesfatin-1 is blocked by MC3/4R antagonists and that nesfatin-1 itself does not directly activate melanocortin receptor–dependent signaling in cultured cells[4]. If we are to assume that nesfatin-1 produced within the PVN (where its expression is regulated by feeding and by melanocortin action) mediates its anorexic actions, one way of synthesizing these results is that nesfatin-1 could be expressed in melanocortin-responsive PVN neurons. In these neurons, nesfatin-1 could act locally to potentiate the action of melanocortins on MC3/4R signaling. Alternatively, nesfatin-1 could act trans-synaptically in a manner that requires coordinate output by other melanocortin-dependent signals. Clearly, other possibilities exist as well.

Certainly, we cannot rule out the possibility that the anorectic action of nesfatin-1 is mediated by some area or areas other than the PVN. NUCB2 is also expressed in the arcuate nucleus and the lateral hypothalamic area—both regions of the brain that modulate feeding[1,2]. Going forward, it will be crucial to understand the site and mechanism of action for the anorectic signal mediated by nesfatin-1. Identifying a receptor or nonclassical binding partner for nesfatin-1 will be an important first step in this journey.


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