Orexins and anorexins: thoughts for food

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The hypothalamus has been recognized for a long time as a pivotal structure in the regulation of appetite. It moved even more center stage when the adipocyte-derived hormone leptin was found to exert effects on the ventrobasal area of the hypothalamus, notably the arcuate nucleus. Based on anatomical experiments, this region of the brain has been suspected for a long time of mediating satiety, since its destruction results in hyperphagia and obesity. In contrast, destruction of lateral hypothalamic areas results in underfeeding, suggesting that they might harbor appetite stimulating neurons. Indeed, besides the anorectic effects of leptin, several neuropeptides were shown to exhibit appetite stimulatory properties, such as neuropeptide Y (NPY) and melanin-concentrating hormone (MCH), the former being expressed in the arcuate nucleus, and the latter in the lateral hypothalamus (1). Sakurai et al. (2) have now identified the orexins, small peptides expressed in the lateral hypothalamus, which also result in the stimulation of feeding.

The authors initially set out to identify novel cerebral ligands for several orphan G protein-coupled cell surface receptors. To this aim, dozens of cell lines stably expressing such orphan receptors were established, and HPLC-separated brain fractions were tested for their potential to increase cytoplasmic calcium levels. Using this functional assay, coupled to chromatographic separation techniques, the investigators were able to isolate a novel neuropeptide, subsequently termed orexin, which can be processed into two different peptides of 33 and 28 amino acids (orexin-A and -B respectively). The characterization of the orexin receptor gene (OX1R) from the recombinant cell line used for the screening process revealed a protein with 20–25% sequence identity to NPY, thyrotropin-releasing hormone and cholecystokinin receptors. A second putative receptor gene was identified based on sequence homology (OX2R). Both receptors bind and are activated by orexins at nanomolar concentrations, with the OX1R being selective for orexin-A. Serendipitously, the same neuropeptides have been cloned independently by De Lecea et al. (3), who named them ‘hypocretins’. However, at that point the function of these novel peptides remained still elusive. Examination of the tissue distribution of orexins and their receptors revealed the presence of pre-pro-orexin mRNA and protein in the lateral and posterior hypothalamus. However, no signal was present in the periventricular hypothalamus (PVH), ventromedial hypothalamus (VMH) or the arcuate nucleus. Consistent with the suspected role of the lateral hypothalamus as an appetite-stimulating center, intraventricular administration of orexins resulted in an over 10-fold increase in food intake 1 h after injection, an effect which persisted for 4 h. In keeping with the notion of the appetite-promoting activity of the orexins, their precursor mRNA levels were upregulated over 2-fold after a 48 h fast.

How then, do the orexin- and MCH-producing neurons sense the metabolic status of the organism? Two general hypotheses can be proposed: (i) The neurons in the lateral hypothalamus directly sense certain metabolites, such as glucose. Since this area contains glucose-sensitive neurons, it is at least plausible that they are involved in the regulation of orexin secretion. (ii) Endocrine or paracrine signals regulate the release of orexogenic factors. Several afferent projections into the lateral hypothalamic area have been proposed, among them neurons responding to the appetite-suppressing α-melanocyte-stimulating hormone.

While little is known about the afferent pathways to the lateral hypothalamus, Elmquist et al. (4) have further elucidated the neuronal wiring among the hypothalamic nuclei involved in the inhibitory action of leptin on appetite stimulation. These investigators utilized a labeling technique, whereby afferent neurons to the PVH were visualized by retrograde labeling (cholera toxin B), and neuronal activation was assessed by an increase in Fos protein, both detected by double-label immunohistochemistry. This approach allowed the identification of neurons projecting into the PVH which are activated directly by leptin. The authors demonstrated that some neurons within the dorsomedial hypothalamus, and to the lesser degree in the VMH, are activated by leptin and project directly or indirectly, respectively, into the PVH. In contrast, the arcuate nucleus (and thereby NPY) is thought to be inhibited by leptin. These leptin-responsive hypothalamic nuclei, besides their projections into the PVH resulting in altered neuroendocrine and sympathetic output, are known to be involved in the regulation of insulin secretion and circadian rhythmicity. Hence, this model might potentially account for the modulatory actions of leptin (and hence nutritional status) on these parameters.

These papers illustrate that the unraveling of complex behavioral patterns, such as feeding and appetite, is approachable with current experimental tools. However, in order to assess the relative importance of these putative pathways in vivo, ingeniously engineered
transgenic animal models with regulatable and region-
specific changes in these neuropeptides and their
receptors will be required.

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