Orexins: neuropeptides for all seasons and functions

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THE NEUROPEPTIDES OREXIN (ORX) A AND B WERE FIRST IDENTIFIED by a screen for novel hypothalamic homeostatic regulatory peptides (15). Because of the substantial homology in amino acid sequences with secretin, they were named hypocretins by one group (9). Because they stimulated food intake, they were called ORXs by another (42). While the relatively small number of ORX-expressing neurons are localized specifically within the lateral hypothalamus (LH), their G protein-coupled receptors [ORX1R (Hcrtr1) and ORX2R (Hcrtr2)] (42) and presumptive target neuronal populations are widely distributed throughout the nervous system in a variety of cortical, limbic, hippocampal, thalamic, brain stem monoamine neuron-containing, and spinal cord areas (8, 32, 39, 52, 53). This broad distribution of potential anatomical targets made it obvious from the beginning that these neurons were involved in much more than just the simple act of eating. In fact, ORX neurons exemplify the way in which a few thousand neurons can modulate many complex behaviors and physiological functions. A review of their targets suggests that ORX neurons can regulate ingestion by activation of pathways that stimulate the drive to eat (hunger); produce behavioral arousal; increase motor and supporting cardiovascular systems required to seek, procure, and ingest food; and autonomic and neuroendocrine systems required to digest, assimilate, and store ingested nutrients and generate satiety signals required for termination of individual meals (8, 19, 20, 24, 35, 53).

Although they undoubtedly receive inputs from higher cortical centers relating to the cognitive and motivational aspects of ingestion, ORX neurons have a critical reciprocal feedback loop with hypothalamic arcuate nucleus anabolic neuropeptide Y/agouti-related peptide (NPY/AgRP) and catabolic proopiomelanocortin neurons. The interaction with NPY/AgRP neurons appears to be important for modulation of feeding (10, 33, 41, 54, 58), but these feedback loops also provide the anatomical substrate for the control of the ingestive, neuroendocrine, autonomic, and thermogenic components of energy homeostasis (2, 4, 12, 14, 21). As opposed to most orexigenic peptides, the feeding stimulatory effects of ORX are most pronounced during the light phase when rodents are satiated and largely inactive (20, 24, 59). Thus the ORX system may be maximally activated during the dark phase when normal feeding occurs and therefore is not amenable to further exogenous stimulation. This fits with the idea that ORX, like NPY, may have a major role in arousal and the motoric and autonomic activation required to seek and procure food rather than providing the primary motivational forces needed to initiate feeding (43). However, ORX is also likely to be involved in the motivational aspects of hunger because ORX injections into the nucleus accumbens shell, a brain area involved in reward behavior, stimulate both feeding and motor activity (49). Melanin-concentrating hormone (MCH) neurons are the other important group of orexigenic LH neurons. They have projections that largely overlap those of ORX neurons (11, 51). Because MCH neurons express ORX receptors (2), local release of ORX onto MCH neurons or the focal injection of ORX into the LH probably stimulates feeding by a combined effect on both sets of neurons with engagement of the full range of behavioral and physiological systems required for the expression of ingestive behavior.

There is some dispute as to how responsive ORX neurons are to changes in the nutritional status of the organism. This is due to conflicting studies regarding their responses to fasting and exogenously administered leptin. Thus ORX neurons do increase their expression of ORX mRNA and immunoreactive protein after short-term fasts and insulin-induced reductions in glucose but not after prolonged fasting, streptozotocin-induced diabetes, voluntary overconsumption of palatable foods, or hypoglycemia when food is available (6, 31, 50). On the other hand, there is good evidence that ORX neurons are true glucosensing neurons, i.e., neurons that alter their firing rate when ambient glucose levels change. They are prototypic glucose-inhibited neurons that are activated by low- and inhibited by high-glucose levels (5, 34, 45). Interestingly, although ORX and MCH are both orexigenes and have largely overlapping targets, MCH neurons have the opposite response to changes in ambient glucose levels. They are typical glucose-excited neurons that are activated by high- and inhibited by low-ambient glucose levels (5). In addition to responding to glucose, ORX neurons also express Lepr-b, the signaling form of the leptin receptor (18, 22). Leptin inhibits the increase in ORX expression that occurs during short-term fasting (31). Paradoxically, although ORX expression is not altered by long-term fasting, leptin administration increases its expression in chronically fasted mice (50). Collectively, such studies suggest that ORX neurons may be involved in the short-term regulation of food intake, especially during states of low glucose availability (3, 6, 16, 44, 50).

The discovery of ORX and MCH neurons in the LH supported the dual-center hypothesis for the control of ingestion in which the LH is the feeding center and the ventromedial hypothalamus is the satiety center (47). This hypothesis was based on the effects of large hypothalamic lesions that had marked effects on feeding and body weight. These profound effects mistakenly led to the conclusion that the hypothalamus was the almost sole controller of energy homeostasis. However, several sets of findings amassed over many years have finally led us away from this hypothalamicentric view. First, studies demonstrated that the neural pathways controlling this homeostasis are not only redundant but enormously plastic as befits a system so critical to the survival of the organism. Thus although large lesions of the LH decrease and ventromedial hypothalamic lesions markedly increase food intake and adi-
A new homeostatic balance that is reasonably well defended (23). This fact strongly suggested that the hypothalamic centers were neither critical nor did they act alone to control energy homeostasis. The discovery of glucosensing neurons clustered in groups throughout the brain provided a mechanism by which the brain could monitor the metabolic status of the body (1, 37). It also led to the realization that such a sensing function was widely distributed rather than being concentrated solely in the hypothalamus as would have been predicted by the dual center hypothesis (29). The final nail in the coffin of the dual center hypothesis was the demonstration that many of these same widely distributed glucosensing neurons also regulated their membrane potential, firing rate, transmitter and peptide release, and gene transcription by sensing a number of metabolic substrates, peptides, and hormones relating to the metabolic status and energy stores of the body (29, 38, 40, 46, 55, 56, 60). Thus the terms metabolic sensors or nutrient sensors are currently used to describe such neurons that are arrayed in a distributed network throughout the brain (29). ORX neurons are likely to be such metabolic sensors that participate in a wide variety of functions critical to the regulation of energy homeostasis.

With this thought in mind, the current studies of Teske et al. (48) are particularly relevant because they address the issue of how ORX activates motor activity as well as feeding. Rather than focusing on why individuals become obese, they have examined the way in which some individuals are able to remain lean when the fat content and caloric density of their diet is increased. Several of these same authors previously showed that lean humans have elevated levels of spontaneous physical activity (SPA) that is associated with increased nonexercise activity thermogenesis (30). In the present studies, they used rats selectively bred to develop diet-induced obesity (DIO) or to be diet resistant (DR) (26, 28) to test the hypothesis that obesity resistance would be associated with a genetically determined, ORX-mediated increase in SPA. They found that DR rats did indeed have higher levels of baseline SPA than DIO rats before they were exposed to a calorically dense diet. Importantly, they found that injecting ORXA into the LH produced equivalent increases in food intake in DIO and DR rats but evoked a greater increase in motor activity in DR than in DIO rats. This enhanced ORX-mediated motor activation was associated with an age-dependent elevation of LH ORX1 and/or ORX2 receptor expression in DR vs. DIO rats. Interestingly, the DR rats were not only more active under basal conditions and after LH ORXA injections than the DIO rats, but they also were more active than the outbred Sprague-Dawley strain from which the DIO and DR rats were originally selectively bred (26). The fact that ORXAs injections increased both feeding and SPA in DR rats may account for the observation that chronic central infusion of ORX in other rat strains increases daytime food intake without significantly affecting body weight gain (59). On the other hand, ablation of ORX neurons produces mice that are narcoleptic or hypophagic but obese, suggesting that their obesity might be, in part, due to reduced levels of activity (17).

As pointed out by the authors, DIO rats have many preexisting features that would allow them to eat beyond their metabolic needs and store calories as fat when energy-dense food was readily available. Not only do they have reduced SPA and running activity but they are also centrally leptin and insulin resistant before they become obese (7, 25, 27). Because obesity is associated with a number of comorbidities, it is usual to think of obesity as being abnormal, whereas lean individuals are considered to be normal. Whereas the hyperactivity in lean individuals might provide a competitive advantage for finding food located in distant locations, the increased energy required for such activity might negate any resultant gains in energy obtained as it appears to do during chronic ORX infusions (59). On the other hand, a reduced level of SPA and the ability to eat beyond one’s metabolic needs because of a reduced sensitivity to the anorectic effects of leptin and insulin would confer a competitive advantage with the approach of winter or when food was otherwise in short supply. In fact, the obesity-prone individual who carries such a thrifty genotype may be the best suited to the hunter-gatherer and subsistence agricultural societies of our forbears (36). It is only recently in the last 30 years that the abundant supply of calorically dense, highly palatable foods available at low energetic cost have produced an additive risk of dying from type 2 diabetes mellitus, hypertension, cardiovascular disease, and stroke in such individuals (13). Until recently, even this apparent disadvantage was unlikely to reduce the thrifty gene pool, since most of these comorbidities occur at older ages, after these genes have already been transmitted to the next generation. However, we are now in the midst of an epidemic of childhood obesity that carries with it all of the same risks seen in older individuals. Such risks clearly threaten the ability of obese children to pass on whatever genes might predispose them to develop obesity and type 2 diabetes (57). Thus the present studies of Teske et al. (48), which help us to understand the workings of the neural systems underlying obesity resistance, are of increasingly critical importance if we are to develop strategies to combat the rise of childhood and adult obesity. Also, these studies provide additional support for the prediction that ORX neurons should participate in the regulation a huge array of behaviors and physiological functions involved in the regulation of energy homeostasis.

REFERENCES