The motivated hypothalamus

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Final physiological regulation of eating resides in the hypothalamus. There signals from the periphery (e.g., leptin, insulin, glucose) activate and inhibit circuits that drive ingestive behavior. Thus leptin and insulin act on neurons in the arcuate nucleus. Leptin inhibits neurons that coexpress neuropeptide Y (NPY) and agouti-related peptide (AGRP) and also activates proopiomelanocortin (POMC) neurons whose transmitter is the POMC-derived α-melanocyte stimulating hormone (α-MSH). As expected, POMC neurons are anorexigenic (their activation reduces ingestive behaviors), whereas the NPY/AGRP neurons are orexigenic (2, 6). Most arcuate nucleus POMC neurons also express cocaine- and amphetamine-related transcript (CART). All these neurons project to other regions of the hypothalamus, including the paraventricular nucleus and, importantly, the lateral hypothalamic area, where further signal processing occurs (6). In the lateral hypothalamus are found populations of neurons expressing melanin concentrating hormone (MCH) and orexins A and B, all peptides that have been demonstrated to be orexigenic. These are pathways that respond to alterations in body energy stores (circulating glucose levels, body fat content) and are quite specific (e.g., 10).

It is an everyday observation that humans and other animals show distinct food preferences. Consumption of different foods is heavily influenced by such preferences (e.g., 9), indicating food intake can be motivated by factors, such as taste, other than body energy stores. The preferred foods are considered to provide “rewards” and to engage reward, or motivational, circuitry in the brain. Reward circuitry is localized to the limbic system and is well known to affect ingestive behavior (e.g., 3). More than two decades ago, Mogenson et al. (5) proposed that the nucleus accumbens is an important motor output site for the limbic system, a proposal that has been abundantly confirmed (e.g., 1, 8). There is direct and indirect, bidirectional communication between nucleus accumbens, in particular the shell region, and relevant regions of the hypothalamus. Inhibition of neurons in the accumbens shell by injection of the inhibitory neurotransmitter GABA results in strong activation of neurons in several areas, including the paraventricular nucleus of the hypothalamus and, particularly, the lateral hypothalamic area (4, 7).

The elegant and lucid study by Zheng et al. (11) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology exemplifies regulatory and integrative physiology and extends the previous studies of the role of nucleus accumbens in food intake. The authors used double labeling to identify which neurons in hypothalamus exhibit altered activation state after injection of a GABA agonist (muscimol) into the accumbens shell. Activation states were assessed by c-Fos immunoreactivity, and neurons were identified by antibodies directed against specific transmitters. In the lateral hypothalamus, a higher fraction of orexin, but not MCH, neurons were double labeled after muscimol injection; in the arcuate nucleus, double labeling of CART neurons was reduced, whereas double labeling of NPY neurons was probably increased. Because muscimol injection induced Fos expression in many other hypothalamic neurons of unknown phenotype, the authors point out that this is only the first step in tracking the activation patterns that occur in response to motivated feeding.

REFERENCES