A tasty morsel: the role of the dorsal vagal complex in the regulation of food intake and swallowing. Focus on “BDNF/TrkB signaling interacts with GABAergic system to inhibit rhythmic swallowing in the rat,” by Bariohay et al.

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ENERGY BALANCE DEPENDS on the regulation of two central circuits that control feeding behavior. On one hand, the central nervous system (CNS) must coordinate and integrate appetite, food-seeking behavior, and thermoregulation. On the other hand, signals relating to satiety (e.g., from the gut) and overall energy balance must be transduced in the periphery and feedback to the CNS. Traditional models of feeding control viewed the hypothalamus as the command center (11). According to this view, stimulation of the lateral hypothalamus (i.e., feeding center) results in voracious eating, whereas stimulation of the ventromedial nuclei of the hypothalamus elicits nutritional satisfaction (i.e., satiety center). In contrast, the caudal brain stem is viewed as the seat of motor and premotor networks for ingestive behavior and as the primary relay station for the integration of signals from the periphery with projections to the hypothalamus. In this framework, caudal brain stem networks are not autonomous but are subject to descending modulation arising from hypothalamic sources (8).

Bariohay et al. (2) add to a growing body of literature that challenges the “hegemony of the hypothalamus” and supports the caudal brain stem as a second autonomic integrator of food intake regulation. The first line of evidence in support of this view is provided us by experiments in chronically instrumented rats that demonstrated coordinated behavioral responses to gustatory and visceral afferent stimuli following complete high mesencephalic transection (7). Based on these observations, it appeared that the caudal brain stem contains at least some of the normal control mechanisms of hunger and satiation previously assigned exclusively to hypothalamic-forebrain structures (8). Second, recent research into neuropeptides and, in particular, the role of peptides and neurohormones in regulating feeding behavior reveals that the caudal brain stem, like the hypothalamus, contains an abundance of leptin and insulin receptors, glucose sensing mechanisms, and neuropeptide mediators relevant to energy balance (8). Moreover, leptin, the circulating molecule for the regulation of food intake and body weight regulation, acts directly within the dorsal vagal complex (DVC) (6), underscoring the notion that ingestion may be controlled at more caudal levels of the mammalian brain (8, 9). Of particular relevance for this commentary, the neurotrophic brain-derived neurotrophic factor (BDNF) has recently been found to cause anorexia and weight loss following infusion into the DVC of the adult rat (1).

The DVC

The caudal brain stem plays a crucial role in ingestive behaviors, as it contains all the motoneurons that participate swallowing, as well as chewing, suckling, and licking. The generation of these ingestive patterns depends upon organized inputs from premotor neurons located in the DVC. The DVC comprises the nucleus tractus solitarius (NTS), the area postrema, and the dorsal motor nucleus of the vagus nerve. The subnuclei of the NTS are of particular interest as the site(s) of integration of peripheral signals with the motoneurons that drive swallowing. Thus, neurons in the interstitial and intermediate subnuclei of NTS receive dense projections from mechanoreceptors in the upper digestive tract (via afferents in V, IX, and X) and, in turn, send viscerotopic projections to pharyngeal and laryngeal motoneurons in the nucleus ambiguous and to facial, trigeminal, and hypoglossal motoneuron pools. Importantly, the NTS is the site of integration of signals related to satiety, such as CCK, emitted when food enters the lower gastrointestinal tract. Remarkably, endogenous BDNF content in the DVC declines after 48 h of fasting and increases following refeeding. Moreover, systemic treatments with leptin and CCK increase BDNF content initially in the DVC and, in the case of CCK, subsequently in the hypothalamus (9). On the basis of these observations, it seems that BDNF is a downstream effector of leptin and CCK and an important signaling pathway whereby the DVC controls food intake.

Bariohay et al. (2) draw our attention once again to the role played by extrahypothalamic networks in the control of energy balance and reveal a (potentially) surprising role for the neurotrophin BDNF and its high-affinity receptor tropomyosin-related kinase B in food intake and body weight control at the level of the DVC. Using a carefully conceived experimental preparation, the authors provide the first evidence of inhibition of the motor component of feeding i.e., the swallowing reflex, following microinjection of BDNF into the DVC of anesthetized, spontaneously breathing rats. Remarkably, the effects of BDNF on swallowing are potentiated by coinjection of GABA, an effect that is nicely reversed when BDNF was coinjected with the GABA_A receptor antagonist bicuculline. Thus, GABAergic neurotransmission appears to be an important downstream effector through which BDNF inhibits swallowing.

But are the effects of BDNF, when administered into the NTS, evoked secondarily to stimulation of vagal afferents or does BDNF act directly to change the GABA receptivity of NTS premotoneurons involved in swallowing? Here, Bariohay et al. (2) embark on a second line of inquiry and explore the notion that inhibition of the swallowing reflex involves
activity-dependent plasticity of DVC neuronal networks (3, 5). It has been shown that DVC circuits involved in gastro-intestinal motility undergo some degree of plasticity, depending upon inputs they receive (12). And, at the cellular level, repetitive stimulation of afferent fibers leads to short- or long-term depression of excitatory synapses in the NTS, whereas inhibitory inputs are potentiated (10, 13). Accordingly, the authors explore the effects of sustained stimulation of the superior laryngeal nerve afferents on endogenous BDNF protein in the DVC and hypothalamus and show that BDNF content within the DVC declines after superior laryngeal nerve stimulation, allowing the eating sequence to continue.

The study conducted by Bariohay et al. (2), of course, raises a good many more questions than it answers. In particular, one wonders what effect more natural stimuli, i.e., an initial fasting period followed by unlimited access to food and continuous eating might exert on BDNF levels, and, by extension, what other the sources exist for BDNF and what range of stimuli elicits its release and/or synthesis. Nevertheless, this work is important because it highlights the role that brain stem structures play in the complex control of ingestive behaviors and satiety, which will ultimately enhance our understanding of eating disorders. Moreover, it underscores the danger that can arise when the nervous system is arbitrarily divided into “upper,” “lower,” “peripheral,” and “central” components, when, in fact, there is just one nervous system as so eloquently stated by Blessing in his monograph (4).

REFERENCES