Hindbrain energy status controls hypothalamic metabolic and neuropeptide signals. Focus on “Hindbrain lactostasis regulates hypothalamic AMPK activity and hypothalamic metabolic neurotransmitter mRNA and protein responses to hypoglycemia”

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Submitted 19 February 2014; accepted in final form 19 February 2014

THE CENTRAL NERVOUS SYSTEM detects correlates of reduced energy availability and activates circuits that trigger compensatory responses that collectively restore energy balance. The seminal experiments of Claude Bernard and Walter Cannon defined concepts underlying the regulatory physiology of energy balance, an area that continues to attract investigators interested in addressing a range of important unresolved questions. Those questions include: 1) which correlates of energy availability are detected, 2) what unique molecular elements define the neurons and glia that detect energy status signals, 3) where are these cellular detectors located within the brain, 4) what circuits connect the detectors to various effector pathways, and 5) where are the commands resulting in the execution of compensatory response generated? The paper by Gujar and colleagues (2a) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology is noteworthy as it addresses several of these questions and further it investigates the organization of the regulatory system itself. The authors ask: what is the relationship between two anatomically distinct sites of energy status detection that affect function, and do they operate autonomously or do they interact?

Gujar et al. (2a) investigated the neuropeptide-expressing neurons of the arcuate, paraventricular, and lateral hypothalamus (LH) and the catecholamine-expressing A2 neurons of the nucleus tractus solitarius (NTS) in the dorsal medulla. Hindbrain neurons and astrocytes are energy status sensitive (1, 8–12) and express a variety of molecular features [e.g., (2, 4, 7 cf. (6)] linked to metabolic state detection. By contrast, the functional contributions of hypothalamic energy status-sensitive neurons have been pursued longer and more intensely in this regard giving rise to the common perspective that the hypothalamus singularly mediates this functional role. For this reason, the authors’ conclusion that the metabolic status of hindbrain A2 neurons (conveyed to the forebrain via rostral projections) controls the metabolic readout of hypothalamic neurons and their neuropeptide gene/protein expression is most intriguing.

In a rodent model, Gujar and colleagues reduced energy availability globally (using systemic insulin treatment) or locally in the hindbrain (via fourth ventricle delivery of the monocarboxylate inhibitor of lactate transport). To assess the metabolic impact of these treatments, phosphorylated adenosine monophosphate kinase (pAMPK), a readout of energy status (3, 5), was measured in NTS A2 and in the aforementioned hypothalamic neurons. Also assessed were hypothalamic neuropeptide gene and protein expression, a variety of plasma hormones, and feeding behavior.

Two experiments were designed to determine whether altering the energy status of hindbrain neurons control hypothalamic pAMPK levels and neuropeptide gene and protein levels. In the first experiment, lactate delivery confined to the hindbrain reversed the effects of insulin on pAMPK activity in A2 neurons and, importantly, also reversed the insulin-induced effects on pAMPK levels in arcuate LH neurons, on arcuate neuropeptide Y (NPY) mRNA and protein levels, and LH orexin protein levels. In the second experiment, the effects of a hindbrain-administered monocarboxylate inhibitor (which induced an energy deficit) on A2 and hypothalamic neuronal pAMPK activity and hypothalamic neuropeptide effects were measured under two conditions. In one condition, connectivity between hindbrain A2 neurons and the hypothalamus was intact, and in the other, rats were treated with neurotoxin 6-hydroxydopamine (6-OHDA) to destroy A2 catecholamine neurons and their axonal projections to hypothalamic neurons. In rats with normal hindbrain-hypothalamic connectivity, the monocarboxylate inhibitor elevated pAMPK levels in A2 neurons and, importantly, also elevated pAMPK levels in arcuate NPY and LH orexin neurons and attenuated them in arcuate pro-opiomelanocortin (POMC) neurons. Markedly reducing hindbrain-hypothalamic catecholamine connectivity attenuated or completely eliminated the hypothalamic effects.

Collectively, these data support a novel view, one might call it a “bottom-up” view, of the organization of neural systems that contribute to energy status detection and maintenance and challenge the prevailing view that the hypothalamus is the primary center for metabolic detection. These ideas about the relationship between different neural populations of metabolic detectors are exciting and are likely to prompt future research.

GRANTS
This paper was supported by National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-21397.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


