Metabolic sensing and regulation by the hypothalamus

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This issue of the American Journal of Physiology-Endocrinology and Metabolism contains the first three in a series of review articles dealing with metabolic sensing in the hypothalamus and the regulation of physiological processes. The convergence of molecular genetic techniques with intracellular signaling and neuroanatomical approaches in recent years has revealed mechanisms of hypothalamic regulation and physiology not previously possible utilizing any one of these methodologies alone. Building upon insights made possible by recent studies, the series examines the mechanisms by which hypothalamic centers sense the metabolic state and thereby regulate energy balance, glycemic control, reproduction, and other neuroendocrine and autonomic end points. Each of these reviews is written by a leader in this field of inquiry, in collaboration with up-and-coming young investigators.

Drs. Jens Brüning, Eva Rother, and A. Christine König discuss the substantial recent work regarding hypothalamic insulin and leptin action in the regulation of glucose and nutrient partitioning in the liver and other peripheral tissues. In particular, this analysis extends the early work of Dr. Brüning, which revealed the metabolic and reproductive function of insulin receptors in the central nervous system. Subsequent work has elucidated the role for the phosphatidylinositol 3'-kinase (PI3K) pathway in the regulation of ATP-sensitive potassium (K<sub>ATP</sub>) channels and the control of membrane potential in the function of the “classic” proopiomelanocortin (POMC) and neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons in the arcuate nucleus of the hypothalamus (ARC). Specifically, stimulation of PI3K activates K<sub>ATP</sub> channels to hyperpolarize these neurons, with important consequences for the regulation of hepatic nutrient handling and glucose homeostasis.

Drs. Tamas Horvath and Qian Gao trace the overlapping and divergent functions of leptin and estrogen in the hypothalamus: both modulate reproductive function and each participates in the regulation of energy homeostasis (although the hormones are clearly produced and regulated by different mechanisms). In addition to examining the hypothalamic functions of leptin and estrogen, the authors focus on the regulation of the latent transcription factor STAT3 by these hormones and discuss how STAT3 mediates common and distinct responses to these hormones in the regulation of energy balance and the hypothalamic control of reproduction.

The review by Drs. Joel Elmquist, Carol Elias, and Jennifer Hill also deals with the metabolic control of reproduction, but at the level of the neural substrate (as opposed to the intracellular signaling pathways) by which metabolic signals such as leptin mediate permissive effects upon the neuroendocrine reproductive axis. This timely review examines recent findings suggesting important roles for NPY, as well as neuronal populations outside of the ARC, in the regulation of reproduction by metabolic and nutritional cues from the periphery. Additionally, the likely role for kisspeptin in the regulation of neuroendocrine reproductive function features prominently in this discussion.

Overall, these reviews exemplify the kind of exciting research and important insights that have been generated recently into the metabolic regulation of hypothalamic processes and the role of metabolic sensing in the hypothalamus in the regulation of metabolic and endocrine physiology.