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# Integration in the PVN: another piece of the puzzle

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THE PARAVENTRICULAR NUCLEUS (PVN) of the hypothalamus is a major integratory region in the hypothalamus that helps maintain homeostasis. Functionally, the PVN is involved in regulation of food intake, responses to stress, modulating metabolic rate, thermoregulation, and regulation of cardiovascular function and the autonomic nervous system (2, 4, 7, 14, 30, 34, 40). It is unique in that in contains primarily estrogen receptor β-receptors that regulate transcripts for vasopressin and oxytocin and also affect the function of preautonomic neurons (24, 35). The PVN influences neuroendocrine function and the production and secretion of substances such as vasopressin, thyrotropin-releasing hormone (TRH), orexin, corticotropin-releasing factor (CRF), and oxytocin (6, 12, 21). The PVN communicates with other hypothalamic nuclei such as the dorsal medial nucleus, the arcuate nucleus, and the caudal hypothalamus (1, 8, 13, 26). It receives inputs, either directly or indirectly, from rostral brain regions, including the limbic system and amygdala, and caudal brain stem regions such as the nucleus tractus solitarius (A2 region), A5 region of the pons, the rostral ventrolateral medulla (RVLM), and locus ceruleus (17, 20, 30, 35–38). Outputs to autonomic regions that modulate sympathetic nervous system and cardiovascular function have been extensively described (10, 27, 35, 39, 40, 42). In contrast, less research has focused on the role of the PVN in control of breathing.

Early research into the role of the hypothalamus on ventilation by Redgate (29) indicated that depression of hypothalamic function by injection of thiopental or hypothalamic lesions also depressed ventilation in anesthetized adult cats. In 1974, Kastella and colleagues (16) showed that respiratory-related neurons in the anterior hypothalamus of cats existed adjacent to areas that receive baroreceptor and chemoreceptor input. These investigators suggested that respiratory and cardiovascular integration occurred in this portion of the hypothalamus in a similar manner to that described in the brain stem. In 1997, Yeh and coworkers (41) demonstrated that the PVN influences respiratory timing and activity in urethane-anesthetized Wistar rats that were vagotomized and ventilated. Diaphragmatic electromyographic ($D_{EMG}$) activity was used to determine ventilatory output. Bilateral microinjection of glutamate into the PVN stimulated frequency of breathing and $D_{EMG}$ peak activity. Concomitantly, arterial blood pressure also increased. By microinjection of 4% Fluorogold into the phrenic nucleus, Yeh and coworkers (41) showed that there were direct connections between the PVN and phrenic motoneurons and the diaphragm and indirect connections between the PVN and brain stem bulbospinal neurons. Subsequently, Schlenker and colleagues (32) reported that unilateral microinjection of bicuculline, a γ-aminobutyric acid $(GABA)_A$ receptor antagonist, into the PVN of conscious rats increased mean arterial pressure (MAP), breathing frequency, the volume of a breath, heart rate, and oxygen consumption for up to 10 min following injection. Elegant studies by Mack and coworkers (21) demonstrated that oxytocin neurons in the PVN were involved in neuronal modulation of breathing by projecting to the RVLM pre-Bötzinger complex neurons and to phrenic motoneurons. Later the same year, Kc and coworkers (17) reported that PVN vasopressin-containing neurons innervate respiratory-related medullary and spinal cord areas and affect control of breathing in air and in response to hypercapnia (18). Thus these studies established the substrates for PVN perturbations affecting control of breathing, metabolic rate, and cardiovascular function in rats.

The PVN is also implicated in increased blood pressures in response to carotid body stimulation. Kubo and coworkers (19) noted that microinjection of the nonselective amino acid receptor kynurenate, the non-*N*-methyl-D-aspartate (NMDA) receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione, the NMDA receptor antagonist 2-amino-5-phosphonovalerate, and α-adrenergic receptor antagonists inhibited the pressor response to direct injection of an inorganic phosphate solution into the vasculature that bathes the carotid body. More recently, Olivan and coworkers (25) determined that bilateral lesions of the PVN prevented chemoreflex activation by KCN in awake rats. These experiments clearly indicated that the PVN is involved in modulating the cardiovascular pressor responses to peripheral chemoreceptor stimulation.

In this issue of the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, Reddy et al. (Ref. 28, see p. R789) investigated not only the pressor, but also the sympathoexcitatory and respiratory, responses to KCN in anesthetized rats. By comparing cardiopulmonary responses to stimulation of central chemoreceptors by 10% $CO_2$, the investigators elucidated the selectivity of the PVN in chemoreceptor responses. This methodical study used microinjection of 2% lidocaine into the PVN of anesthetized rats to reversibly demonstrate that KCN stimulation of the carotid body causing increased renal sympathetic nerve activity (RSNA), MAP, and phrenic nerve activity (PNA) was dependent, in part, on the PVN. After lidocaine treatment, the increases of RSNA, MAP, and PNA in response to KCN were attenuated. Anatomical controls verified the specificity of PVN involvement. To determine whether peripheral chemoreceptive stimulation of the carotid body was necessary to elicit PVN stimulation, the carotid sinus nerve was cut, attenuating the effects of KCN stimulation. To investigate the role of $GABA_A$ receptors in KCN-mediated stimulation, muscimol, the $GABA_A$ receptor agonist, and bicuculline methiodide, the $GABA_A$ receptor antagonist, were microinjected into the PVN. Muscimol inhibited and bicuculline augmented the cardiopulmonary and sympathoexcitatory responses to KCN. Finally, lidocaine microinjection into the PVN did not affect the physiological responses to inhaled 10% $CO_2$, indicating that the PVN is not necessary for modulating cardiopulmonary and RSNA responses to hypercapnia.

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As in all good studies, questions arise as a result of the findings. These include further elucidation of what are the neural pathways and neurotransmitters involved in the physiological responses to peripheral chemoreceptor stimulation. Because there are a large number of neurotransmitters in specific subnuclei of the PVN, excitatory candidates may include oxytocin, vasopressin, leptin, ANG II (possibly acting on ANG I receptors), TRH, CRF, and NMDA among others (8, 9, 11, 12, 20, 33, 34, 42). Another question may include what other hypothalamic nuclei are involved in chemoreflex responses. For example, the caudal hypothalamus and the arcuate nucleus affect control of breathing and cardiovascular function (3, 15). Studies using Fos protein as a marker of neuronal excitation indicate that a number of hypothalamic nuclei including the PVN, arcuate nucleus, dorsomedial hypothalamic nucleus, and posterior hypothalamic nucleus respond to exposure to hypoxia and to hypercapnia (3, 18). What are the functional roles of these other nuclei in peripheral and centrally mediated physiological responses? Would similar findings occur in conscious rats? Are there sex differences in these responses (31)? Finally, what is the role of these nuclei in pathological conditions such as congestive heart failure, sleep apnea (and its metabolic and cardiovascular consequences), and genetic disorders such as Prader-Willi syndrome that affect PVN function (10, 22, 23)? Unlike extensive studies of brain stem nuclei, fewer investigations of cardiopulmonary and autonomic function in hypothalamic regions have been conducted. This study raises the level of the bar in how these future studies will be conducted.

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