Metabolic acidosis inhibits hypothalamic warm-sensitive receptors: a potential causative factor in heat stroke

THE PREOPTIC AREA and anterior hypothalamus (POAH) is regarded as the primary site for thermoreception in the mammalian brain. Peripheral thermal afferents synapse on temperature-sensitive neurons in the POAH. The POAH, in particular, contains a high concentration of warm-sensitive neurons, which are proposed to activate heat-loss responses while inhibiting heat-production. Accordingly, electrical stimulation or localized warming of the POAH decreases core temperature, whereas lesioning or localized cooling of the POAH increases core temperature (2, 3).

Core body temperature is maintained constant around a “set point” by the neural control and integration of various physiological reflexes (autonomic, endocrine, cardiorespiratory, and motor) and behavioral responses. Because of the number of organ systems utilized to maintain body temperature, and the variety of autonomic and behavioral functions that are regulated by the hypothalamus, it is not surprising that thermosensitive neurons in the hypothalamus are sensitive to multiple types of stimuli, including hyperosmolarity, hyperglycemia, sex steroids (4), and, as reported in this issue of the Journal of Applied Physiology, cellular acidosis (11).

Wright and Boulant (11) have tested and proven the hypothesis that warm-sensitive neurons in the POAH are inhibited by hypercapnic acidosis. Conversely, temperature-insensitive neurons are unresponsive to hypercapnic acidosis. The significance of this finding is twofold. First, the authors have clarified a discrepancy in the literature regarding the effects of hypercapnia on thermosensitive neurons (6, 9); as reported here, under in vitro conditions, the primary effect of hypercapnic acidosis is to reduce activity of warm-sensitive neurons in the POAH. Second, this finding supports the new hypothesis that inhibition of warm-sensitive neurons in the POAH during cellular acidosis may disrupt normal heat loss mechanisms. This, in turn, could contribute to thermoregulatory dysfunction that causes core hyperthermia during respiratory acidosis (8).

Molecular CO2 or hypercapnia per se is not the critical stimulus, however. The authors (11) have shown that the inhibitory effect of hypercapnic acidosis on warm-sensitive neurons occurs by a mechanism that is dependent on extracellular pH (pHc). This conclusion was based on their findings that the inhibitory effect of hypercapnic acidosis (↑PCO2, ↓pHc, unchanged HCO3−) on firing rate was mimicked by isocapnic acidosis (unchanged PCO2, ↓pHc, ↓HCO3−) but not isohydric hypercapnia (↑PCO2, unchanged pHc, ↑HCO3−). All three acid-base manipulations would have likely caused a significant decrease in intracellular pH (pHi) (7). Thus it seems likely that decreased pHc is the critical stimulus causing inhibition of neuronal activity.

Given the importance of pH in the inhibitory mechanism they have reported, it is tempting to speculate that metabolic acidosis (i.e., isocapnic acidosis: unchanged PCO2, ↓pHc, ↓HCO3−, ↓pHi) may be an important factor contributing to the occurrence of heat stroke. Metabolic acidosis is a well-known predictor of heat exhaustion and heat stroke, and it has been attributed to the failure of multiple organ systems (1, 10). The present study (11), however, supports the exciting hypothesis that metabolic acidosis in and of itself can induce central hyperthermia by inhibition of heat loss mechanisms that are controlled by the POAH, resulting in heat stroke (5).

Future studies, therefore, will want to address several questions that have been raised by the work of Wright and Boulant (11). Do metabolic disturbances in acid-base balance alter various behavioral and physiological mechanisms of thermoregulation? For example, are there differences in the effects of hypercapnic acidosis or metabolic acidosis on evaporative heat loss versus increased skin blood flow? At the cellular level, does acidosis alter the warm sensitivity of individual hypothalamic neurons? If so, what are the effects of pH on ionic currents and synaptic mechanisms that underlie neuronal thermosensitivity? Moreover, are temperature-induced changes in pH an important aspect of the thermosensing mechanism? If the above hypothesis is true, then one would predict that warm sensitivity of hypothalamic neurons and thus heat loss responses will be reduced during acidosis.

REFERENCES


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