COMMENTS

We welcome comments by our readers reflecting agreement or disagreement with the material published in this section and, at the discretion of the Editor-in-Chief, will publish such comments.

Comments to the Editor Concerning the Paper Entitled "Orexin-A Regulates Body Temperature in Coordination with Arousal Status" by Yoshimichi et al.

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Maintenance of normal body temperature (thermoregulation) involves an integrated network of neural connections involving the hypothalamus, limbic system, lower brainstem, the reticular formation, spinal cord, and the sympathetic ganglia (1). The recent work by Yoshimichi et al. in the May issue of *Experimental Biology and Medicine* suggests that orexins play a role in the central control of thermogenesis (2). The results indicate that orexin-A injected into the third cerebroventricle provokes a rise in ambulatory activity followed by a sustained increase in core body temperature. It is not clear, however, if the elevated temperature results from a direct effect of orexin-A upon hypothalamic neurons bearing orexin receptors or results from a secondary, pyrogenic effect of the injected neuropeptide.

The preoptic area of the anterior hypothalamus (POAH) is believed to be the critical thermoregulatory site within the central nervous system for coordinating a febrile response following appropriate pyrogenic stimuli (3). Prostaglandin E_2 (PGE_2) produced within the POAH is responsible for provoking thermoregulatory neurons to induce fever (reviewed in [4]). PGE_2 production is stimulated by endogenous pyrogenic cytokines such as interleukin-1 and interleukin-6 (reviewed in (5)) and exogenous pyrogenic substances such as lipopolysaccharide (6). In addition, inhibitors of the prostaglandin-generating enzyme cyclooxygenase can suppress fever following exposure to pyrogens (7).

It is difficult to tell from the study by Yoshimichi et al. whether intracerebroventricular injection of orexin-A may be inducing fever through the stimulation of PGE_2 within the POAH. A reasonable control experiment might sort this out. For instance, administration of a cyclooxygenase inhibitor (such as indomethacin) to the rats prior to treatment with orexin-A would be expected to prevent or suppress the subsequent elevation in body temperature if PGE_2 were involved. Also helpful would be measurement of cerebrospinal fluid PGE_2 following orexin-A (and phosphate-buffered saline) in the presence or absence of the cyclooxygenase inhibitor. Cerebrospinal fluid levels of PGE_2 generally mimic changes in core body temperature in animals experiencing pyrogen-induced fever (6). Demonstrating that the rise in temperature seen after orexin-A injection is independent of PGE_2-mediated pyrogenesis would further support the important data presented by Yoshimichi et al. implicating orexins as possible mediators of circadian thermoregulation.

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