The orexins: linking circulatory control with behavior

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NORMAL CARDIOVASCULAR CONTROL is accomplished by a close interplay of homeostatic feedback mechanisms, such as the baroreceptor and chemoreceptor reflexes, and adaptive feedforward mechanisms that allow the organism to adapt to environmental changes and behavioral responses, such as exercise, hunting, fighting, or escape from predators. A hallmark of the adaptive mechanisms is an involvement of hypothalamic neural circuits, which integrate somatomotor, hormonal, and autonomic pathways. Such mechanisms include the defense response, “central command,” vasovagal response, and circadian rhythmicity. A common feature of all of these responses is the unidirectional change of heart rate and arterial pressure, which implicates a concomitant modification of the homeostatic mechanisms. For example, during the defense response arterial pressure and heart rate increase, which is associated with a vasodilatation in skeletal muscle and a vasoconstriction in other areas, these reactions are typically evoked by threatening emotional stimuli (9, 15). The perifornical region of the hypothalamus plays a crucial role in the defense response (8) and is part of a vasodilator pathway from the motor cortex through the hypothalamus and brain stem to vasodilator projections to skeletal muscle vasculature (21). Very similar responses can also be elicited by much more subtle stimuli than those leading to a full-grown fight-or-flight reaction (1, 3, 11). Although the concept of cardiovascular control by cortico-hypothalamic mechanisms was introduced nearly 100 years ago, its molecular mediators have remained obscure. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Kayaba and colleagues (11a) provide experimental evidence suggesting that orexins may play such a role.

Orexins (also called hypocretins) were first described in 1998 as the result of a search for unknown regulatory peptides in the hypothalamus (6, 16). The orexin system consists of two closely related neuropeptides, orexin A and orexin B, which are produced from a common precursor, and two receptors, the orexin receptor type-1 (or Hcrtr1) and orexin receptor type-2 (or Hcrtr2) (12). The orexin receptor type-1 has a 10-fold higher affinity for orexin A than orexin B, whereas the orexin receptor type-2 binds the two peptides with equal affinity (16). Both receptors couple to Gq proteins, resulting in elevated intracellular Ca2+ concentrations, protein phosphorylation, and depolarization, ultimately leading to an enhanced neuronal excitability (12, 16). Furthermore, orexins can stimulate the release of the excitatory neurotransmitters glutamate and GABA (22).

The formation of orexins is limited to a very small subset of specific neurons in the lateral prefrontal area of the hypothalamus (6). The input to these neurons includes projections from the hypothalamic orexinergic neurons themselves from the suprachiasmatic nucleus, which is believed to generate the circadian rhythm, as well as those from the arcuate nucleus, a major integration site for metabolic and reproductive hormone regulation (12). Projections of the orexinergic cells and the expression sites of orexin receptors are widespread, including the hypothalamus, thalamus, brain stem, and spinal cord (12). Noteworthy among these sites with respect to cardiovascular regulation are the paraventricular nucleus (PVN) in the hypothalamus, the nucleus of the solitary tract (NTS), and the rostral ventrolateral area (RVLM) in the medulla oblongata, as well as the intermediolateral (IML) column in the spinal cord. The PVN harbors the cells, releasing vasopressin in the hypophysis; the NTS and RVLM provide important relay stations for the baroreceptor and chemoreceptor reflexes and are major determinants of efferent sympathetic tone; and the IML column gives rise to the peripheral preganglionic sympathetic neurons (5). Finally, the perifornical region is also part of the sympathetic cholinergic dilator pathway of the defense response (21). Taken together, the orexinergic neurons are in a perfect strategic position for a central role in hypothalamic cardiovascular control, both with respect to the defense response as well as regarding resting arterial pressure.

Early functional studies using intracerebroventricular infusions of orexins suggested the primary physiological function of the orexin system to be the regulation of food intake by increasing appetite (16). However, changes in the feeding behavior do not constitute the major phenotype of orexin-deficient animals. Although mice carrying a targeted disruption of the orexin-preprohormone eat less than their wild-type littermates, they are not anorexic and show a normal postnatal body growth (4). When orexin-producing neurons are gradually destroyed postnatally by introducing an ataxin-3 transgene under the control of the...
orexin promoter, the animals even become obese although eating less (7). In contrast to these unexpectedly moderate dysfunctions, behavioral studies revealed that orexin-deficient mice show periods of cataleptic attacks and sudden onsets of rapid eye movement (REM) sleep during wakefulness (4, 7). Such symptoms typically occur in patients suffering from a sleep disorder known as narcolepsy. Intriguingly, a genetic linkage analysis demonstrated that dogs with an inherited form of narcolepsy have a dysfunctional orexin receptor type-2 (13). Thus activation of the orexin system appears to favor an increased arousal state and wakefulness.

Further support for a physiological role of orexins as a major determinant of the arousal threshold comes from pharmacological infusion studies. Exogenous intracerebroventricular administrations of orexins suppress REM sleep and lower the arousal threshold, increase locomotor activity and body temperature, and stimulate gastric acid secretion and the release of adrenocorticotropic hormone, corticosterone, insulin, and thyroid-stimulating hormone (12, 19). Along with these responses, intracerebroventricular administration of orexins also increases blood pressure and heart rate (17) associated with parallel augmentation of efferent sympathetic nerve activity after orexin A (17). Overall, these findings are consistent with the idea that orexins may function as major neuromodulators in the corticohypothalamic control of the circulation.

This hypothesis is tested in the comprehensive study by Kayaba and colleagues in this issue. The authors investigate the role of orexins in the defense response in mice lacking both orexin A and orexin B due to a disruption of the prepro-orexin gene. The defense response is assessed both pharmacologically during anesthesia as well as by natural stimuli in conscious animals. In separate experiments, Kayaba and colleagues identify a brain region in the perifornical hypothalamus, from which the strongest parallel increases of arterial pressure and heart rate (17) are associated with parallel augmentation of efferent sympathetic nerve activity after orexin A (17). Overall, these findings are consistent with the idea that orexins may function as major neuromodulators in the corticohypothalamic control of the circulation.

The cardiovascular and behavioral responses to socioemotional stimulation are assessed in conscious animals. In addition, the authors measure basal blood pressure and heart rate and determine the influence of the circadian rhythm in conscious animals by telemetry. Finally, the effects of pharmacological interventions are investigated in conscious animals with chronically implanted catheters. As expected from previous knowledge, the defense response is indeed attenuated in the orexin-deficient mice, but the responses are not completely abolished (see Fig. 2 in their article). This indicates that the orexins exert a permissive role rather than being directly involved in the transmission of the defense response. The locomotor activity recorded in freely moving animals (see Fig. 6 in their article) is dampened to a large extent in orexin-deficient mice over the dark period, during which mice are active, whereas there is no difference between the two strains during the light (resting) period. These results agree very well with the view that orexins are primarily involved in the modulation of the threshold for arousal (18).

Kayaba and colleagues also find a reduced baseline blood pressure in the orexin-deficient mice. Remarkably, blood pressure levels were reduced over the entire 24-h recording period independent of the animals' locomotor activity. This rejects a simple cause-and-effect relationship between orexin levels and arousal-associated changes in blood pressure. The results from the pharmacological studies rather suggest that orexin-secreting neurons may play a central role in setting basal sympathetic tone. Whether a change in sympathetic tone is the sole explanation for the effects of inactivating the orexin system on long-term arterial pressure remains to be shown. Other possible mechanisms may involve a modulation of the vasopressin system (2) or presently unknown functions of the renal and adrenal orexin receptors (10). Finally, the virtually identical heart rate in the presence of the distinctly lower arterial pressure in the orexin-deficient mice (see Fig. 6 in their article) indicates that the baroreceptor reflex is reset in these animals to a lower pressure set point. In light of recent studies presenting evidence against the existence of pressure-induced resetting (14, 20), this may imply a direct role of orexin in this process.

REFERENCES


