NEUROPEPTIDES

Orexin neurons on acid

DOI:
10.1038/nrn2198

Orexin, also known as hypocretin, regulates the adaptive processes that maintain physiological homeostasis. It was previously unknown how orexin-producing neurons, located in the lateral hypothalamus, sense basic environmental signals, but Burdakov and colleagues now show that they act as chemosensors of extracellular H^+ and CO_2 levels and might thereby play a part in the homeostatic regulation of breathing.

Breathing and arousal are stimulated by respiratory acidosis arising from increased extracellular levels of H^+ and CO_2 — chemicals that are monitored by chemosensory neurons in the brain stem. Orexin neurons project to this area, and breathing responses to changing CO_2 levels were recently found to be reduced in orexin-knockout mice. The authors therefore examined whether orexin neurons might also be sensitive to extracellular acidity.

The authors measured the electrical activity of orexin neurons in acute mouse brain slice preparations. Increasing the pH of this solution reversibly suppressed the neurons' spontaneous firing rate, induced membrane hyperpolarization and increased membrane conductance. Orexin neurons were especially sensitive to small changes in extracellular pH within the physiological range. Moreover, the relationship between extracellular pH and the neurons' spontaneous firing rate resembled that of chemosensory neurons in the brain stem. Changes in extracellular pH also modulated the neurons' evoked firing rate: lowering the pH increased the neurons' intrinsic excitability, whereas a more alkaline pH suppressed it.

Chemosensory responses in the brain stem are thought to be mediated by ion channels, including several kinds of K^+ channel. To establish whether K^+ channels also modulate the effects of pH on orexin neuron activity, the authors used whole-cell voltage-clamp recordings of membrane currents. The currents generated in orexin neurons in response to changes in extracellular pH had the properties of acid-sensitive 'leak' K^+ channels, indicating that these channels are involved in the mechanism by which orexin neurons sense extracellular pH levels.

The study showed that orexin neurons are as sensitive to changes in extracellular H^+ and CO_2 levels as brain stem chemosensory neurons, which were previously thought to be the only neurons that could sense extracellular acidity. How orexin and brain stem neurons interact to regulate respiration remains to be elucidated.

Leonie Welberg

ORIGINAL RESEARCH PAPER Williams, R. H., Jensen, L. T., Verkhratsy, A., Fugger, L. & Burdakov, D. Control of hypothalamic orexin neurons by acid and CO2. *Proc. Natl Acad. Sci.* **104**, 10685–10690 (2007)
FURTHER READING Sakurai, T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nature Rev. Neurosci.* **8**, 171–181 (2007)