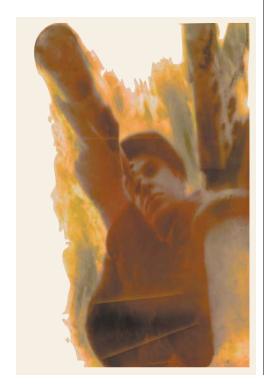
potentials. So, blocking is more efficient when the membrane is depolarized. Early measurements implied that the voltage dependence of the blocking reaction is greater than would be predicted from the charge of the blocker alone, and the elongated shape of the mGIRK1 channel provides an explanation for this observation. The length of the channel allows it to accommodate extra K⁺ ions that are expelled outwards when the blockers bind, and this additional charge displacement accounts for the increased voltage dependence of channel block.

Nishida and MacKinnon have shown that structural analysis can provide fascinating insights into the phenomenon of rectification, and it has also enabled them to identify new targets for mutational studies of the IRK channels.

Heather Wood

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NEUROPHYSIOLOGY

Orchestrating arousal

How does the brain coordinate the activity of neuronal systems involved in sleep–wake regulation to set our level of arousal? A possible answer to this question was unearthed in the late 1990s, when researchers discovered a neuropeptide system in the lateral hypothalamus that is central to the regulation of arousal states and energy metabolism. Since then, much has been learned about the functions of the hypocretins (also known as orexins), but the cellular mechanisms that govern the activity of hypocretin neurons have received little attention. A recent study by Li *et al.* shows how the output of this system might be orchestrated at the cellular level.

The hypocretin system makes reciprocal connections with other homeostatic centres within the hypothalamus. Its densest projections outside the hypothalamus are to structures that regulate wakefulness, including the dorsal raphe nucleus (DRN) and the locus coeruleus (LC); hypocretins increase wakefulness and suppress rapid eye movement (REM) sleep. So, the hypocretin system seems to provide a link between our homeostatic needs and our level of arousal.

Li and colleagues reasoned that there must be some orchestration of output from cells that regulate arousal; this would explain why neurons in other regions of the brain, including the DRN and the LC, show changes in group activity across the sleep-wake cycle. They made electrophysiological recordings from hypocretin neurons of the lateral hypothalamus, identified in transgenic mouse brain slices by their expression of green fluorescent protein. Hypocretin neurons responded to hypocretins 1 and 2 with a depolarization and excitation that depended on an increase in the synaptic release of glutamate; no direct effects of hypocretin on the membrane properties of these cells were detected. So, the hypocretin system seems to employ a positive feedback loop that involves the activation of a glutamatergic interneuron.

Li *et al.* then looked for a factor that might reduce the activity of hypocretin cells. In view of the fact that hypocretins have excitatory effects on serotonergic neurons of the DRN and on noradrenergic neurons of the LC, the authors examined the effects of serotonin and noradrenaline on hypocretin neurons. These transmitters directly hyperpolarized and inhibited hypocretin cells. So, negative feedback from REM-off cells of other arousal systems might suppress the output of hypocretin neurons.

How, then, do the hypocretins exert their effects on other neuronal systems? In a recent experiment, Follwell and Ferguson examined the actions of hypocretin on the membrane properties of neurons of the rat paraventricular nucleus of the hypothalamus (PVN). The PVN receives a dense projection from the hypocretin system, and it is well positioned to mediate the effects of hypocretins on autonomic and endocrine functions. The authors found that most magnocellular neurons were depolarized by hypocretin 1, apparently through the activation of a glutamatergic interneuron. This peptide depolarized parvocellular neurons by the enhancement of a non-selective cation conductance

These studies remind us that, although considerable advances have been made in our understanding of the hypocretin system, further studies are needed to describe the cellular events that underpin its interactions with other systems, its role in regulating arousal states, and its involvement in sleep disorders such as narcolepsy. *Rebecca Craven, Senior Subeditor, Nature*

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