Control loops for wakefulness: nutrient-gated orexin signals and their histaminergic transformations.

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The lateral hypothalamus (LH) contains neural circuits that are of paramount importance for maintaining normal patterns of sleep, wakefulness, and feeding. Two types of LH cells will be discussed here, orexin/hypocretin neurons (OHNs) and melanin-concentrating hormone neurons (MCHNs). Electrical activity of OHNs is essential for stable wakefulness (their loss results in narcolepsy), whereas that of MCHNs is critical for generating REM sleep. Glucose inhibits OHNs by opening background K channels, but activates MCHNs by closing Kir6.2 channels. This potentially provides an energy-gated mechanism for sleep and wakefulness control. However, glucose-inhibited OHNs are activated by dietary amino-acids, suggesting that they may not "energy sensors" but rather sensors of dietary balance. For unknown reasons, OHNs co-produce the "anti-narcoleptic" OH peptides and the classical excitatory transmitter glutamate. To explore information communicated by their cotransmission from cell to cell, we investigated how optogenetically-patterned OHN inputs alter the output of wake-promoting histamine neurons (HAN), a key wakefulness-stabilising module downstream of OHNs. This revealed independent and complementary pathways, glutamate → AMPAR and OH → OHR2, through which OHN firing can control HAN firing. Temporal profile of electrical signals generated by OH → OHR2 transmission was strikingly different from that generated by glutamate, suggesting a potential reason for why OH actions are critical for brain state stability. A model for wakefulness stability is discussed where nutrient-gated OHN signals correct wakefulness based on environment, by OHR2-dependent build-up of electrical activity in downstream arousal-promoting neurons.

Key words: glutamate, neuropeptides, synapse, amino acids.