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MCH Neurons: The End of the Beginning

Commentary on: Blouin et al. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. Nat Commun 2013;4:1547; Konadhode et al. Optogenetic stimulation of MCH neurons increases sleep. J Neurosci 2013;33:10257-63; and Jego et al. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nat Neurosci 2013 Sep 22. doi: 10.1038/nn.3522. [Epub ahead of print].

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A role for melanin-concentrating hormone (MCH)-expressing neurons in sleep regulation, especially for REM sleep regulation, has been strongly supported, based on the sleep-wake activity profile of these neurons as well as the pharmacological effects of this peptide on sleep.[1,2] The three excellent recent papers that stimulated this discussion about the functions of hypothalamic MCH neurons reached somewhat different conclusions regarding their role in sleep regulation. Does MCH only extend REM sleep,[3] or does it facilitate both NREM and REM sleep,[4] or facilitate both sleep onset and eating?[5]

In the tuberal hypothalamus, MCH neurons are intermingled with hypocretin neurons, with which they are interconnected, and they receive inhibitory inputs from noradrenergic, serotoninergic, and cholinergic arousal systems, and from neuronal groups associated with feeding regulation.[6] MCH neurons have widespread projections within the hypothalamus and to limbic and brainstem areas. This is a perfect storm of complexity. In the rat, there are about twice as many MCH neurons as hypocretin neurons, and they have a more widespread distribution within the hypothalamus. Bittencourt[6] has emphasized that in the rat and mouse hypothalamus, MCH cells are localized in several distinct, although overlapping groups, including a dorsomedial group spreading horizontally from the top of the 3rd ventricle. This group appeared to be the primary target of the channelrhodopsin-inserting vector in the study by Konadhode et al.[4] In addition, there is a diffuse group adjacent to the 3rd ventricle, including a ventricular "cap," a large cluster in the far lateral hypothalamus just medial to the internal capsule, a perifornical group, and a more posterior medial group above the tuberomammillary nucleus. Bittencourt notes that a similar distribution is found in the human. The primarily REM-active MCH neurons described in the landmark paper of Hassani et al.[7] were localized in a restricted part of the MCH field dorsolateral to the fornix.

The two new optogenetic stimulation studies[3,4] seem to be in agreement on a REM sleep induction/extension effect. One of the studies[4] also showed facilitation of NREM sleep during the dark phase, and the facilitation of NREM delta power during the light phase, effects not seen in the other study. However, the optogenetic stimulation paradigm used by Jego et al.[3] did not appear to be designed to increase total sleep and used transient stimulation only after the onset of NREM and REM sleep and not during waking; whereas Konadhode et al. used chronic stimulation, which is comparable to pharmacological studies. The MCH population studied by Konadhode et al. was delineated by the spread of the viral vector used to insert channelrhodopsin, a limitation not associated with the transgenic method of Jego et al. In both studies, the neurons stimulated were limited by the distribution of light from the fiberoptic probes. Studies of c-Fos expression associated with REM sleep rebound following 72 h REM sleep deprivation indicate that only a subset (< 60%) of MCH neurons may be REM-active.[8] Although the optogenetic method is selective for MCH neurons, it does not provide information about what MCH neurons are stimulated, or how many are stimulated.

Both optogenetic studies found sleep-facilitating effects with stimulus frequencies of 10-30 Hz, and not at 1 or 5 Hz, although 1 Hz was the approximate average REM-related discharge rate of MCH neurons, a rate that included the contribution of occasional discharge bursts.[7] These are normally very slowly discharging neurons. We do not know why such supranormal stimulation is needed in the optogenetic studies, or if the normal function of these cells is revealed by high-frequency stimulation studies.

Most MCH neurons co-localize glutamic acid decarboxylase (GAD), the enzyme identifying GABAergic neurons, as well as cocaine and amphetamine-regulated transcript, and nesfatin-1, each of which could also play a role in sleep regulation. One of the fascinating findings in the study by Jego et al. was that extension of REM duration by optogenetic stimulation of MCH neurons was effective in mice lacking the MCHR1 receptor, the sole receptor in the mouse brain. They also showed that the inhibition of histaminergic neurons was mediated by GABA *in vitro*. Del Cid-Pellitero and Jones[9] previously suggested that such a mechanism mediates the inhibition of locus coeruleus neurons by MCH neurons. Indeed, some evidence suggests that many of the actions of peptidergic neurons are mediated by traditional neurotransmitters.[10] For example, the initial excitation of histaminergic neurons by hypocretinergic neurons may be mediated by glutamate.[10] The sleep-related inhibition of hypocretinergic neurons seems to be primarily generated by GABA, not a neuropeptide.[11] Neuropeptides are usually packaged in large dense vesicles that are localized further from

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the synaptic membrane than vesicles containing glutamate or GABA. The release of neuropeptides is thought to require higher-frequency discharge or discharge bursts. It has been suggested that traditional neurotransmitters and peptides play complimentary roles, the first generating a rapid action, the second producing a sustained action. Thus, activation of MCH neurons could produce both rapid GABA-mediated inhibition contributing to wake-NREM or NREM-REM transitions and more sustained MCH peptide-mediated inhibition to sustain REM sleep. One can envisage many versions of such a mechanism, including the possibility of opposing actions.

Optogenetic stimulation is selective for a particular neuronal phenotype, but it can generate heat, and some hypothalamic neurons, including lateral hypothalamic neurons are temperature-sensitive. Hypothalamic warming induces sleep. Future studies should examine this factor. Optogenetic stimulation must induce synchronous discharge in all target neurons that are exposed to light pulses, an unlikely pattern in dispersed cells like MCH cells. The possible effects of such synchrony are unknown.

In the unique study of release of hypocretin and MCH in the human amygdala, Blouin et al.[5] found increased MCH release at sleep onset, during sleep, and during eating. Hypocretin levels were elevated particularly during emotional activation. They also showed that, in rats, hypothalamic release and amygdala release were significantly correlated, supporting the likely relevance of amygdala release to general functions of MCH. There is substantial evidence that MCH facilitates feeding in rats (reviewed[12]). For example, microinjection of MCH in hypothalamic sites increases food intake. Fos-expression in MCH neurons is increased by food deprivation, and following consumption of palatable food. Such studies cannot be explained by changes in sleep-wake. MCH knockout mice have both feeding and sleep abnormalities. We do not know if the orexigenic and hypnogenic actions of MCH are mediated by distinct sets of neurons, or if the actions of neurons can be switched, depending on other inputs. For example, the circuitry could induce feeding during usual feeding periods and sleep during usual sleep periods, both behaviors serving to compensate for negative energy balance.[1] Clearly, although much is known, we are only at the beginning of our understanding of these cells.

CITATION

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