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Role of MCH Neurons in Paradoxical (REM) Sleep Control

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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Two recent publications take advantage of optogenetics to determine the effect on the sleep-waking cycle of stimulation or inhibition of MCH neurons. This method allows, for the first time, the specific manipulation of MCH neurons in contrast to previous systemic and local pharmacology experiments.[1,2] This is crucial since the lateral and perifornical hypothalamus also contain hypocretin neurons with presumed opposite role than MCH neurons.[3] A third publication measures the level of MCH during the sleep-waking cycle. These publications address three unknowns which we will discuss successively: the role of MCH neurons in sleep, the importance of release of MCH versus GABA from MCH neurons, and the identification of critical downstream targets of MCH neuronal projections.

Role in Sleep of the MCH neurons

In the first study, Konadhode et al.[4] transfected channelrhodopsin in 53% of the MCH neurons dorsal to the fornix, especially in the zona incerta, and only 20% in the ventral and lateral hypothalamus. They then stimulated the transfected neurons at 5, 10, and 30 Hz using application of blue light (1 min on 4 min off) for 24 h, starting at lights-off. They obtained a 60% increase in NREM sleep and a 95% increase in REM sleep in the six first hours of 10-Hz stimulation.

Jego et al.[5] used a different strategy to manipulate the activity of MCH neurons. They developed pMCH-Cre mice, and by this means succeeded in transfecting ChETA, SSFO, or halorhodopsin in most (88%) of the MCH neurons. They found that 1- or 20-Hz stimulation at the onset of NREM sleep episodes did not affect NREM sleep duration but increased the probability of NREM-REM sleep transitions, while 20-Hz stimulations at the onset of REM sleep episodes significantly extended their duration. These results convincingly demonstrate a specific role of MCH neurons in the induction and maintenance of REM sleep. They fit well with the demonstration that MCH neurons express Fos specifically after REM sleep hypersomnia[6,7] and fire exclusively during REM sleep.[3] The increase of NREM sleep obtained by Konadhode[4] might be due to the fact that, in contrast to Jego, they stimulated MCH neurons during waking. Indeed, if the role of MCH is to specifically induce REM sleep, a period of NREM sleep is nevertheless required before reaching this state. Activation of MCH neurons during waking might thus induce an increase in NREM sleep quantities.

To fully demonstrate the functional role of MCH neurons, Jego[5] inhibited them using halorhodopsin. Unexpectedly, they found that the inhibition of MCH neurons at the onset of REM sleep did not reduce bout duration, inducing only a shift in the peak theta frequency. One interpretation would be that not all MCH neurons were inhibited, but it is also possible that inhibiting MCH neurons after REM sleep is initiated is not sufficient to impact the state. It could be necessary to inhibit MCH neurons before REM sleep onset to obtain an effect. The slowing of theta rhythms reported strongly suggests that ascending MCH neurons play a role in cortical/hippocampal activation during REM. It needs to be determined whether MCH action on theta is mediated by the projection of MCH neurons to the hippocampus or to the medial septum or other forebrain structures. This is an important question since REM sleep plays a role in memory and hippocampal LTP is abolished in MCH-R1 KO mice.[8]

Neurotransmitter(s) Involved in the Effect of MCH Neurons on Sleep

The promotion of NREM and REM sleep in the Konadhode[4] study was obtained only at light offset. We have previously shown that ICV administration of MCH at light offset induces a similar effect (up to 300% increase in REM sleep and 150% increase in NREM sleep quantities).[6]

Jego[5] found that the extension of REM sleep episodes in response to MCH neuron stimulation during the light phase persists in MCH-R1 KO mice. These results fit with studies showing that mice with genetically inactivated MCH signaling exhibit only minor modifications for REM parameters and homeostasis.[9,10] Jego demonstrated that in vitro optical stimulation of MCH terminals in the tuberomammillary nucleus (TMN) releases GABA, confirming our finding that MCH neurons co-express glutamate decarboxylase 67 and are GABAergic.[11] More importantly, they indicate that the promoting effect on REM sleep of optically stimulating MCH neurons is mainly due to GABA release. One wonders whether optogenetic stimulation also effectively induces the release of neuropeptides like MCH. Indeed, the optogenetic stimulation data are at variance with the effect of subcutaneous injection of an MCH antagonist, which decreases NREM and REM quantities.[12]

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In that context, what is missing in both optogenetic papers is the demonstration that MCH is released after optical stimulation. Measures of extracellular MCH are difficult but, Blouin et al.[14] made the "tour de force" of measuring MCH levels in the human amygdala of presurgical epileptic patients across the sleep-waking cycle. They demonstrated that MCH level greatly increases at sleep onset and to a minor extent after eating while it is minimal during waking and social interactions. This is of great interest since MCH has been linked with food intake and MCH neurons have been shown in vitro to be excited by increase of glucose concentration.[15] It is tempting to speculate that MCH neurons might be responsible for the induction of postprandial sleep. The fact that MCH release increases at sleep onset and then decreases during sleep is puzzling when compared to the two optogenetic studies and previous ones indicating that MCH neurons are specifically active during the whole duration of the REM sleep episodes.

In summary, these recent studies suggest that the main neurotransmitter of MCH neurons involved in REM sleep promotion is GABA. However, MCH is clearly released by these neurons, and pharmacological studies have shown that MCH administration can promote NREM and REM sleep. The finding that MCH facilitates GABAergic neurotransmission[16] may be an explanation for differences in experimental results.

What Are the Neuronal Targets Responsible for the Effect on Sleep of the MCH Neurons?

It has been previously shown that microinjection of MCH in the lateral preoptic area increases NREM sleep.[17] In contrast, injections in the horizontal limb of the diagonal band of Broca, the dorsal pontine reticular formation and the dorsal raphe specifically increase REM sleep quantities.[18-20]

Jego[5] tested the hypothesis that MCH neurons might inhibit the wake-inducing neurons located in the TMN, medial septum, and dorsal raphe. They found that optogenetic stimulation of MCH fibers in the TMN and medial septum increased the duration of REM sleep as effectively as stimulation of MCH cell bodies.

Knowing the multiple targets of MCH neurons, it is surprising that optogenetic stimulation of only one target is sufficient to induce an effect comparable to global stimulation of MCH neurons. It suggests that the inhibition of only one of the REM sleep inhibitory systems is sufficient to delay the awakening from REM sleep. This could indicate that the inhibition of the REM sleep generating system at the end of REM episodes is regulated by multiple weak inhibitory systems. This is conceptually interesting.

To test this hypothesis, the effect of the optic stimulation and inhibition of the MCH projections to other structures known to strongly regulate REM sleep should be studied. It seems particularly important to manipulate the MCH descending pathway to the REM-off GABAergic neurons localized at the border of the ventrolateral periaqueductal gray. Indeed, we have recently shown that these neurons gate the activation of the REM-on glutamatergic neurons generating REM sleep localized in the sublaterodorsal tegmental nucleus.[2,21]

CITATION

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