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Melanin-concentrating hormone and sleep

Jozelia Gomes Pacheco Ferreira[1,3], Jackson Cioni Bittencourt[1,2] and Antoine Adamantidis[3,4]

The melanin-concentrating hormone (MCH) is an essential neuromodulator involved with homeostatic regulation and motivated behaviors. The majority of MCH neurons are localized within the zona incerta, lateral hypothalamic and incerto-hypothalamic areas but others regions, as the olfactory turbecle, the laterodorsal tegmental nucleus, the paramediam pontine reticular formation and the medial preoptic area, can also express the peptide depending on the gender and metabolic state of the animal. If the MCH on these novel sites of expression are also related with the control of wake–sleep cycle will be discuss in this review.

Addresses
[1] Department of Anatomy, Institute of Biomedical Sciences, University of Sao Paulo, Sao Paulo, Brazil
[2] Neuroscience and Behavior Center, Institute of Psychology, University of Sao Paulo, Sao Paulo, Brazil
[3] Department of Neurology, Inselspital University Hospital, University of Bern, Bern, Switzerland
[4] Department of Clinical Research, Inselspital University Hospital, University of Bern, Bern, Switzerland

Corresponding author: Adamantidis, Antoine (antoine.adamantidis@dkf.unibe.ch)

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Introduction

The melanin-concentrating hormone (MCH) was first discovered in fish [1,2] before its identification in the mammalian brain [3,4]. The MCH neurons are mainly located in the lateral hypothalamic (LHA) and incerto-hypothalamic (IHy) areas of both male and female rats [5,6] (Figure 1), non-human primates [5] and human [7,5,8,9]. MCH-expressing LHA and IHy neurons also co-express the neuropeptide EI (NEI) and neuropeptide GE (NGE), two peptides clived from the same MCH pre-propeptide precursor (ppMCH) [5], however, the role of NGE remains unknown [5]. Interestingly, a small number of MCH neurons have also been identified in the olfactory tubercle and the paramedian pontine reticular formation (PPRF) [5] (Figure 1b).

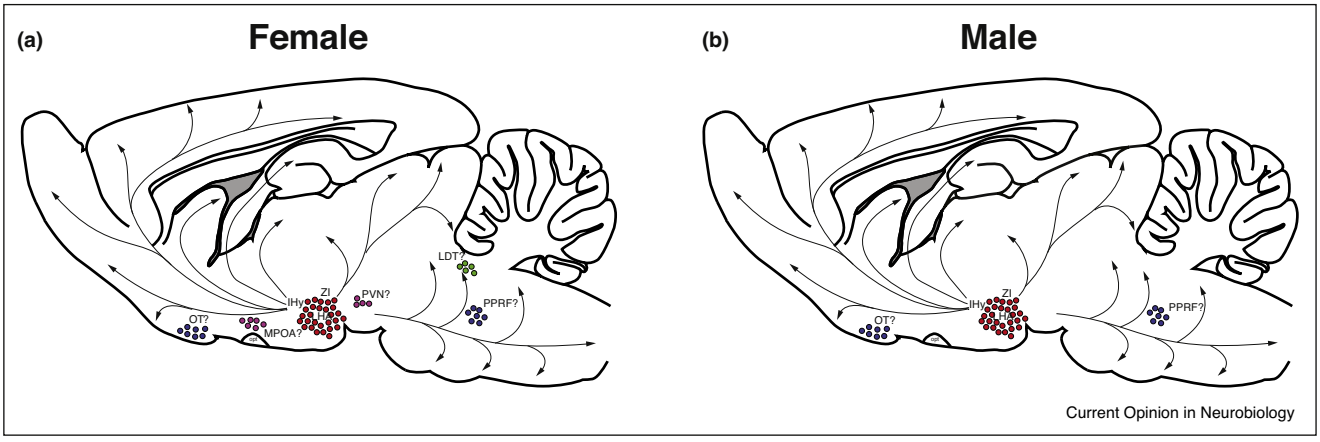
This ubiquitous peptide acts as an important neuromodulator for the organism homeostatic balance, acting over a large spectrum of integrative functions, especially those related to homeostatic regulation and motivated behaviors [10,11]. One of its best described function is the ability of MCH peptide to dampens energy expenditure, and to a lesser extend its orexigenic properties [12••,13,14]. There is, however, an increase in the number of physiological functions associated with it, including learning and memory [15,16], attention modulation [17], stress and anxiety [18,19], reproductive system modulation [20,21]. Amassing experimental evidence support a role for the MCH system in the sleep–wake state control [22••,23,24,25•,26]. In this review, we will provide a brief overview of prior work linking MCH to sleep, followed by a discussion of recent results and future perspectives.

Mechanism of action of MCH

To perform its multiple roles, MCH peptide binds to a G-protein-coupled receptors (GPCRs), termed MCHR1 and MCHR2. MCHR1 was simultaneously described by four groups in 1999 [27–30], acting selectively through of $G\alpha_{i/o}$ and $G\alpha_{q}$ proteins, promoting the inhibition of adenylate cyclase, increased Ca^{2+} influx and activation of MAP kinase [31], which confer to MCHR1 activation a predominant inhibitory mode of action. On the other hand, MCHR2 mechanisms are still largely unknown, as MCHR2 is a pseudogene in rabbits and guinea-pigs that is truncated and nun-functional in rats, mice and hamsters [32]. In humans, the distribution of MCHR2 mRNA is very similar to that of MCHR1, including in the hypothalamus, hippocampus and amygdala [33]. MCHR2 is coupled to Gq proteins [33], which trigger intracellular signaling pathways associated with the stimulation of neuronal activity. The function of MCHR2 remains unknown due to the lack of available animal models.

The MCHR1 protein and its coding mRNA are widely expressed in the mammalian central nervous system. Indeed, it is intensely expressed in the hippocampal formation, subiculum, basolateral amygdala, shell of the nucleus accumbens, ventromedial nucleus of the hypothalamus, arcuate nucleus and zona incerta. In most of those regions there is a good anatomical correlation between the distribution of MCHR1 and MCH immunoreactive fibers. Thus, MCH may act in several brain levels

Figure 1



MCH expressing neurons in the rat brain. Schematic sagittal representation of the female **(a)** and male **(b)** rat central nervous system illustrating the main areas where MCH neurons are found in both male and female: the zona incerta, lateral hypothalamic and the incerto hypothalamic areas (ZI, LHA, IHy; red) and their projections pattern. Extra-hypothalamic sites in both male and female: the olfactory tubercle and the paramedian pontine reticular formation (OT, PPRF; blue). The projections of these extra-hypothalamic sites are unknown. Novel sites of MCH expression only in female: the laterodorsal tegmental nucleus (LDT; green). During lactation, the MCH-expressing neurons can be found in the medial preoptic area and the paraventricular hypothalamic nucleus (MPOA, PVN; purple). The projections of these regions are still unknown.

for integrating various aspects of motivated behaviors, including feeding and reproductive behavior [34,35].

MCH and sleep

The lateral hypothalamic area integrates internal and environmental signals to orchestrate many behaviors including sleep and metabolism. The two major neuronal populations expressed into the lateral hypothalamic area are the hypocretins/orexin neurons [36,37] and the MCH neurons [5]. Although orexin and MCH neurons are known for their orexigenic effects and support of goal-oriented behaviors [38,39], they have opposite effects on wake–sleep state control. Furthermore, it was shown by Pelluru *et al.* [40] that CSF levels of MCH in rats is higher during the day, while the orexin levels is higher during the night, when the rats were awake. The orexin neurons are characterized by their wake-promoting system [41]. Indeed, these neurons are practically quiet during NREM and REM sleep and completely activated during attention and active walking [42]. The wake promoting action of hypocretins neurons is mediated, at least, by histaminergic [43] and noradrenergic cells in the *locus coeruleus* [44,45]. Lack-of-functions approaches in animals recapitulate the main symptoms of narcolepsy, indicating the essential nature of hypocretins neurons in the maintenance of proper sleep–wake boundaries during both sleep and wakefulness [46–49]. In agreement with these findings, optogenetic activation of hypocretin neurons increase the probability of sleep–wake transitions [50–52,45].

In contrast, MCH system has been identified as a sleep-promoting system. Pharmacological approaches using MCH injections can also help us to understand how the MCH system influences the sleep–wake states. Intracerebroventricular (icv) injections of MCH induced hypersomnia, characterized by a significant and dose-dependent increase of REM and slow waves sleep [22••]. In particular, MCH neurons appear to mediate homeostatic recoveries after sleep deprivation, as there is an increased number of neurons containing-Fos in MCH neurons after sleep rebound, relative to controls and sleep deprived animals [22••,53,54]. According with this, MCH administration into the dorsal raphe could produce a dose-dependent increase of the time spent in REM as well as a modest increase of slow wave sleep (SWS) in the rat [55]. In a similar way, it has been shown that the MCHR1 antagonist administration was able to decrease REM and SWS in rats [56]. Finally, it was demonstrated by Adamantidis *et al.* [23] that in MCHR1 knockout mice there is an increase in the number of paradoxical sleep episodes compared with control animals. These contradictory effects could be related to the development of compensatory mechanisms [23]. Together, these results indicate that MCH can have an inhibitory effect since it has been demonstrated the presence of MCHergic fibers in regions related to the control of sleep and wakefulness, as well as its receptor [5,30,34]. Finally, others regions as the ventrolateral periaqueductal gray (vlPAG), the locus coeruleus (LC) and the medial septum areas medial septal nucleus (MS) are keys in the control of the sleep–wake cycle and contain dense MCH terminals and strongly express MCHR1 receptor gene [5,34], suggesting that it could mediate MCH effect on REM sleep [57,25•]. Indeed, the bilateral inhibition or lesions of the vlPAG generates an important increase in REM