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PHYSIOLOGICAL REVIEW

Melanin-concentrating hormone control of sleep–wake behavior

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SUMMARY

The melanin-concentrating hormone (MCH) is a 19 aminoacid peptide found in mammals predominantly in neurons located in the lateral hypothalamus and incerto-hypothalamic area. The biological function of MCH is mediated by two G-protein-coupled receptors known as MCHR1 and MCHR2, although the latter is expressed only in carnivores, primates and man. The MCHR1 couples to G_i, G_q and G_o proteins, with G_i leading to the inhibition of both excitatory and inhibitory synaptic events. Within the central nervous system (CNS) MCH participates in a number of functions including sleep–wake behavior. In this respect, MCHergic neurons project widely throughout the CNS to brain regions involved in the regulation of behavioral states. MCHergic neurons are silent during wakefulness (W), increase their firing during slow wave sleep (SWS) and still more during REM sleep (REMS). Studies in knockout mice for MCH ($MCH^{-/-}$) have shown a reduction in SWS and an increase of W during the light and the dark phase of the light-dark cycle. Moreover, in response to food deprivation a marked reduction in REMS time was observed in these animals. Conflicting effects on sleep variables have been reported in $MCHR1^{-/-}$ mice by different authors. The i.c.v. administration of MCH increases REMS and SWS in the rat. In addition, an enhancement of REMS has been described following the microinjection of the neuropeptide into the nucleus pontis oralis of the cat, while its infusion into the dorsal raphe nucleus (DR) and the basal forebrain (horizontal limb of the diagonal band of Broca) is followed by an increase of REMS and a reduction of W in the rat. Immunoneutralization of MCH in the DR augmented W and suppressed REMS in the rat, as did the s.c. injection of selective MCHR1 antagonists. The robust REMS-inducing effect of MCH is likely related to the deactivation of monoaminergic, orexinergic, glutamatergic, cholinergic (W-on) and GABAergic (REM-off) neurons involved in the generation of W and the inhibition of REMS. On the basis of preclinical studies, it can be proposed that selective MCHR1 receptor agonists could constitute potential therapeutic modalities in the arsenal of insomnia pharmacotherapy. Due to the lack of adequate animal models, the role of the MCHR2 on sleep is still unknown.

Introduction

Neural structures and neurotransmitters that participate in the regulation of wakefulness, slow wave sleep and REM sleep

The neural structures involved in the generation and maintenance of wakefulness (W) are found in the brain stem, hypothalamus, and basal forebrain (BF). The structures located in the brain stem include the dorsal and median raphe nuclei (DR/MRN), locus coeruleus (LC), ventral tegmental area (VTA), substantia nigra pars compacta (SNC), ventral periaqueductal gray (VPAG), laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) and medial pontine reticular formation (mPRF) that comprise predominantly serotonergic (5-HT), noradrenergic (NA), dopaminergic (DA), cholinergic (ACh) and glutamatergic (GLU) neurons, respectively. The hypothalamic component of the arousal system includes histamine (HA)- and orexin (OX)-containing cells that are located in the tuberomammillary nucleus and the posterior lateral hypothalamus around the fornix, respectively. The cholinergic and glutamatergic neurons of the BF involved in the regulation of the behavioral state are found mainly in the medial septum, diagonal band of Broca and substantia innominata.[1–3]

Neurons of the preoptic area, lateral hypothalamus, and adjacent BF constitute the sleep-inducing system.[4,5] Sleep active neurons of the preoptic area are predominantly located in the ventrolateral preoptic area (VLPO). A majority of these neurons contain γ-aminobutyric acid (GABA) and galanin, and project to the brain stem, hypothalamus and BF W-promoting areas described above. Recently, the melanin-concentrating hormone (MCH) has been added to the neurotransmitters involved in the regulation of

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Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
ACh	acetylcholine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainate
BF	basal forebrain
BZD	benzodiazepine
ChAT	choline acetyltransferase
CNS	central nervous system
DA	dopamine
DR	dorsal raphe nucleus
GABA	γ-aminobutyric acid
GLU	glutamate
HA	histamine
HDB	horizontal limb of the diagonal band of Broca
LC	locus coeruleus
LDT/PPT	laterodorsal and pedunculopontine tegmental nuclei
MCH	melanin-concentrating hormone
MCH-ir	MCH-immunoreactive
mPRF	medial pontine reticular formation
MRN	median raphe nucleus
mRNA	messenger ribonucleic acid
NA	noradrenaline
NEI	neuropeptide EI
NGE	neuropeptide GE
NMDA	N-methyl-D-aspartate
OX	orexin
REM	rapid eye movement
REMS	REM sleep
SNC	substantia nigra pars compacta
SWS	slow wave sleep
VLPO	ventrolateral preoptic area
VPAG	ventrolateral periaqueductal gray
VTA	ventral tegmental area
W	wakefulness

sleep. MCH-containing neurons would facilitate SWS and REMS occurrence by inhibiting neurotransmitter systems involved in the induction of W.[6]

On grounds of studies performed in the cat, it has been proposed that different subregions of the mPRF are involved in the generation of REMS.[7–9]

The reciprocal-interaction hypothesis of REMS generation originally proposed by McCarley and Hobson[10] identifies interconnected populations of REMS "on" and REMS "off" neurons compatible with reciprocal interaction as a physiological basis of sleep cycle oscillation. In the updated version of the reciprocal-interaction model[11] cholinergic neurons of the LDT/PPT are identified as promoting REMS, and interact with serotonergic and noradrenergic neurons of the DR and the LC that inhibit REMS. In addition, McCarley[11] includes GABAergic mechanisms that deactivate neurotransmitter systems responsible for the inhibition of LDT/PPT cholinergic (REM-on) neurons. This would lead to the activation of pontine reticular formation glutamatergic neurons and the occurrence of REMS.

Structure and mechanism of action of MCH

In mammals MCH is a cyclic neuropeptide with 19 amino acids which has the following structure: Asp–Phe–Asp–Met–Leu–Arg–Cys–Met–Leu–Gly–Arg–Val–Tyr–Arg–Pro–Cys–Trp–Gln–Val.[12] It is generated by the cleavage of a precursor of 165 amino acids, the prepro-MCH (ppMCH). ppMCH contains two additional peptides designated as neuropeptide EI (NEI) and neuropeptide GE (NGE).[13] MCH has been shown to prevent some of the behavioral effects produced by NEI in the rat.[14] MCH itself is involved in a number of functions including sleep, wakefulness, energy homeostasis and mood.

MCH is confined to a group of neurons in the lateral hypothalamus and incerto-hypothalamic area, and acts through its G-protein-coupled receptors named MCHR1 and MCHR2. Rodents present only the MCHR1.[15] The MCHR1 is intronless and is located at the chromosomal locus 22q13.3 while the MCHR2 has several exons and is mapped to locus 6q21.[16]

The binding of MCH to MCHR1 activates diverse intracellular signaling pathways by coupling to G_i, G_q, and G_o proteins, while MCHR2 is known to couple to the G_q protein.[17,18] Blockade of the G_i/G_o protein with pertussis toxin abolishes the actions of MCH at the synaptic level.[19]

Location, structure and projections of MCH-containing neurons

Sekiya et al.[20] determined the distribution of MCH-like immunoreactivity by radioimmunoassay in the central nervous system (CNS) of the rat, guinea-pig, pig and man. The highest concentrations of MCH were found in the hypothalamus of all these species.

A little later, Bittencourt et al.[21] characterized the organization of the system using antisera raised against rat MCH in immunohistochemical studies at the light and electron microscopic levels, together with hybridization histochemical localization of prepro-MCH.

It was shown that medium-sized and multipolar to fusiform MCH-containing cells were localized predominantly in the lateral hypothalamic area and zona incerta of the rat. In addition, monosynaptic fibers stained for MCH were broadly distributed throughout the CNS. In this respect, MCH-immunoreactive (MCH-ir) axons innervate several neuroanatomical structures located in the telencephalon, diencephalon, mesencephalon and rhombencephalon that are involved in the regulation of the sleep–wake cycle (Fig. 1 and Table 1).

In addition, Bittencourt and Elias[22] established that the origin of MCH-ir projections in the medial septal nucleus, vertical and horizontal limbs of the diagonal band of Broca and spinal cord resides mainly in the lateral hypothalamus. Moreover, dense MCH innervation was reported in the cerebral motor cortex and LDT/PPT of the rat; the latter originating mainly from the dorsal half of the lateral hypothalamus.[23,24]

Distribution of MCHR1

Hervieu et al.[25] determined the distribution of MCHR1 messenger ribonucleic acid (mRNA) and its protein product in the rat CNS. The distribution of MCHR1 receptor agreed with the distribution of the MCHergic fibers. Of note, MCHR1 receptor labelling was particularly high in CNS structures involved in the control of W, SWS and REMS including: 1) cerebral cortex; 2) hippocampal formation; 3) amygdala; 4) basal forebrain (medial septal nucleus, bed nucleus of the stria terminalis, horizontal and vertical limbs of the diagonal band of Broca; substantia innominata; magnocellular preoptic nucleus); 5) thalamus; 6) hypothalamus (medial preoptic area, anterior and lateral hypothalamus, tuberomammillary nucleus); 7) periaqueductal gray; 8) substantia nigra pars compacta; 9) ventral tegmental area; 10) dorsal and median raphe nuclei; 11) locus coeruleus; 12) pontine reticular formation.