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A role for Melanin-Concentrating Hormone in learning and memory

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ABSTRACT

The neurobiological substrate of learning process and persistent memory storage involves multiple brain areas. The neocortex and hippocampal formation are known as processing and storage sites for explicit memory, whereas the striatum, amygdala, neocortex and cerebellum support implicit memory. Synaptic plasticity, long-term changes in synaptic transmission efficacy and transient recruitment of intracellular signaling pathways in these brain areas have been proposed as possible mechanisms underlying short- and long-term memory retention. In addition to the classical neurotransmitters (glutamate, GABA), experimental evidence supports a role for neuropeptides in modulating memory processes. This review focuses on the role of the Melanin-Concentrating Hormone (MCH) and receptors on memory formation in animal studies. Possible mechanisms may involve direct MCH modulation of neural circuit activity that support memory storage and cognitive functions, as well as indirect effect on arousal.

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1. Introduction

Living in a constantly changing environment requires behavioral adaptation. Upon specific events or sequence of events, new behaviors are learned, consolidated, stored and eventually, recalled upon specific stimuli. Thus, learning and memory processes are mandatory for survival of an organism.

Multiple neurotransmitters and cell-specific neuropeptides have been identified as critical components of neuronal circuits and brain regions involved in learning and memory. Those include glutamate, gamma-aminobutyric acid (GABA), acetylcholine and the monoaminergic systems of the brain (dopamine, serotonin, norepinephrine, histamine). In addition to these neurotransmitters, neuronal populations that produce and secrete neuropeptides have been recently shown to modulate a wide variety of brain functions including memory storage, stress, locomotor activity, anxiety and depressive symptoms.

This review will focus on the role of the Melanin-Concentrating Hormone (MCH) peptides and its receptors – identified further as the MCH system – in learning and memory processes and their possible modulation of brain circuit plasticity in goal-oriented mammalian behaviors. Possible links between arousal setting and cognitive function are discussed.

2. The Melanin-Concentrating Hormone: a modulator of memory storage

Behavioral adaptation to a naturally occurring event (energy homeostasis, predation, reproduction), or during an experimental task in a laboratory, results from the integration of external and internal signals. These signals are processed by different regions or combination of regions of the brain that support cognitive (limbic system, cortex), homeostatic (hypothalamus) and sensory (thalamus) functions. Explicit memory (facts, events) is preferentially encoded by the medial temporal lobe (hippocampal formation and the adjacent perirhinal, entorhinal, and parahippocampal cortices) while implicit memory is represented in multiple regions that includes the neocortex (priming), the striatum (skills and habits), the amygdala (emotional responses in associative learning), the cerebellum (motor response) and reflex pathways (non-associative learning). Thus, integration of these signals into behavior requires timely physiological and cortical arousal of the organism.

Interestingly, neurotransmitters involved in cognitive functions are also responsible for tuning of arousal [24,43]. Activation of neurons producing acetylcholine and monoamines neurotransmitters have long been associated with an increased in arousal and vigilance, as well as increased responsiveness of cortical and thalamic cells to sensory stimuli [29].

The MCH system is the target of these ascending and descending arousal and cognitive-promoting neuronal populations from the brainstem and forebrain structures [60]. In turn, MCH neurons project reciprocally to these nuclei and to other brain areas [9]. Thus, the MCH system – MCH peptide, MCH

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receptors and MCH-related peptides and transcripts – modulates multiple brain functions, including learning and memory processes, energy homeostasis, stress, anxiety and depression (this issue, reviewed in [40]).

2.1. Neuroanatomy of the MCH system

The *Pmch* gene encodes for a large precursor named preproMCH (ppMCH) which generates MCH and the Neuropeptides EI and GE [38]. Alternative splicing of the *Pmch* gene generates a peptide with unknown function, coined MCH-gene-overprinted-polypeptide [57] and two additional chimeric MCH genes, *PMCHL1* and *PMCHL2* have been identified in the human lineage [18], suggesting a complex evolution of the original *MCH* gene. The MCH system is highly conserved in the animal kingdom [7,39], suggesting an important role in multiple brain functions.

MCH-producing neurons are located in the lateral hypothalamus (LH) and the Zona Incerta (ZI) and send extensive projections to the cortex, the hippocampal formation, the medial, lateral and basolateral nuclei of the amygdala, the nucleus accumbens (NAcc), the locus coeruleus, the raphe and nuclei of the reticular formation [9] (Fig. 1). Intra-hypothalamic MCH projections target the arcuate nucleus, dorsomedial hypothalamus, lateral and posterior hypothalamus and tuberomammillary nucleus [9]. Two MCH receptors, MCH-R_1 and MCH-R_2, have been identified in mammals, however the MCH receptor 2 is not functional (i.e. capable to bind MCH peptide) in several non-human species (rat, mouse, hamster, guinea pig, and rabbit) [55]. MCH-containing fibers match the distribution of MCH receptors [10,26,47]. MCH neurons generally co-localize with GABAergic markers [19], suggesting an inhibitory function in energy homeostasis [48], locomotor activity [35,51,52,58,59], sexual behavior [22], autonomic functions [5], and arousal [25,36,64].

2.2. MCH modulation of learning and memory processes

The hippocampus plays a crucial role in episodic, declarative, contextual and spatial learning and memory, but also integrates emotional components, such as stress, in cognitive processing. The amygdala and prefrontal cortex integrate emotional memories, whereas the striatum has been involved in goal-directed learning and the acquisition of habits [6,67].

Consistent with its modulation of learning and memory processes, high levels of MCH-R_1 mRNA expression have been found in the CA_1 field of the hippocampal formation, subiculum, cerebral cortex, basolateral amygdala, shell of the nucleus accumbens [10,26,47]. Dense MCH terminals have also been localized in these structures [9] (Fig. 1). In contrast to other GABAergic cell types and neuroinhibitory transmitters, activation of MCH-producing neurons appears to increase learning and memory processes [1,37,61–63]. Intra-hippocampal infusions of the MCH peptide increase the response latency in a one-trial step down inhibitory avoidance test in rats [37,61]. In this experimental paradigm, animals are placed on a platform and latency to step down from this platform is considered as a measurement of learning and memory processes. On the training session, immediately after stepping down from the platform, the animal receives a footshock. Then, short- and long-term memory retention is carried out by re-testing the same animal 24 h and several days after training. Memory storage of this paradigm involves the hippocampus, entorhinal cortex and amygdala [14], which contain high densities of MCH-containing fiber terminals and MCH-R1 transcripts. After the training session, rats showed an increase in memory retention when MCH is administered to the CA_1 region of the hippocampus immediately and 4 h after the training session. A similar effect was found after infusion of MCH in the amygdala of rat immediately, but not 4 h, after training. These data suggest that

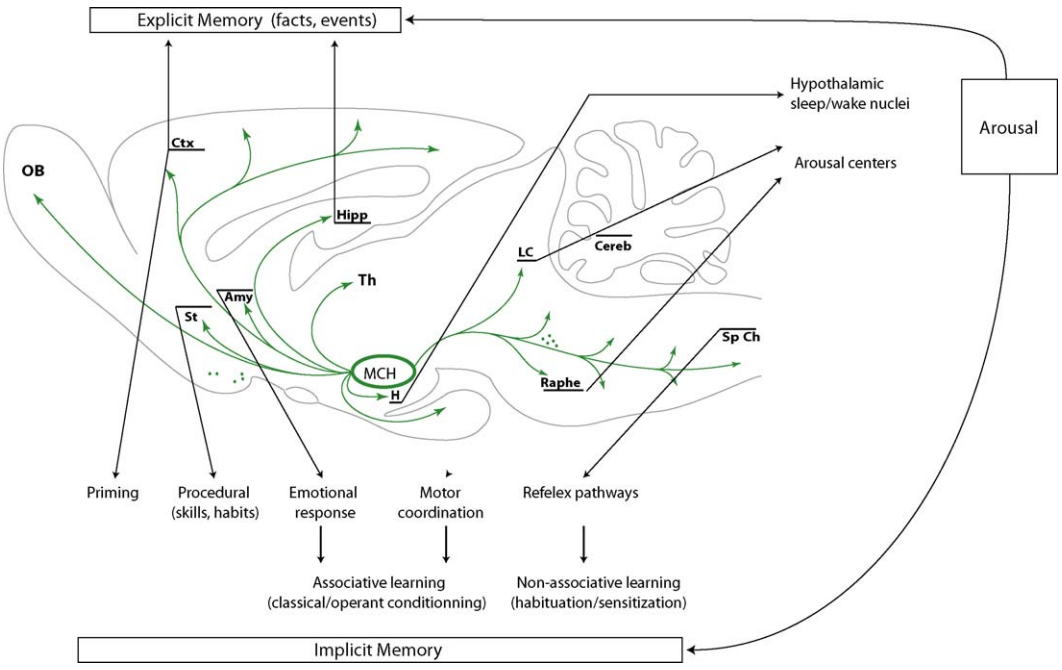

Fig. 1. The Melanin-Concentrating Hormone system targets memory circuits of the brain. Schematic drawing of a saggital section through the rat brain showing the neuroanatomical organization of the MCH system. MCH-expressing cell bodies are restricted to the lateral hypothalamus and zona incerta. Arrows point out some of the more prominent terminal fields. Targets of the MCH neurons include brain region involve in explicit memory (medial temporal lobe) and implicit memory, in particular the neuronal circuits that participates in procedural and associative (classical/operant conditionning) and non-associative (habituation/sensitization) learning including the putamen, caudate nucleus, nucleus accumbens, amygdala, cortex with the exception of the cerebellum. Note that MCH neurons project to the main arousal center of the brain including LC (noradrenergic cells), histaminergic neurons of the posterior hypothalamus, cholinergic cells of the basal forebrain and brainstem and serotonine-producing neurons of the raphe. This suggests that MCH may modulate learning and/or memory processes by modulating arousal. Abbreviations used: *Amy*, amygdala; *Ctx*, cortex; *H*, Hypothalamus; *Hipp*, hippocampus; *LC*, locus coeruleus; *OB*, olfactory bulb; *Sp Ch*, spinal chord; *Th*, thalamus.

MCH peptide modulates the activity of both the hippocampus and the amygdala to directly affect cognitive and emotional functions during the cognitive task. Interestingly, these cognitive changes correlate with increased potentiation (as measured by the amplitude of excitatory post-synaptic potential), nitric oxide (NO) and cGMP levels in the hippocampus of rats showing memory impairment [61]. These results suggest that NO-mediated signaling in the hippocampus may be responsible for the effect of MCH on memory retention. Whether the increase of NO or the increase of intracellular calcium concentration, and subsequent intracellular signaling cascades, induced by MCH [16,46] is responsible for the observed effect remains to be determined.

Furthermore, *in vitro* studies have demonstrated that MCH decreases long-term potentiation (LTP) thresholds by increasing hippocampal synaptic transmission through a NMDA receptor (NMDAR)-dependent pathway [63]. Animals injected with MCH show an increase in the steady-state concentration of NMDA receptor subunit 1 (NR_1) – whose expression is necessary for NMDA receptor function and memory formation in an inhibitory avoidance task [15] – as well as NR_{2A} and NR_{2B} subunit transcripts in the dentate gyrus, suggesting a NMDA-mediated effect.

Analysis of MCH-receptor 1 (MCH-R_1) knockout (KO) mice has confirmed the pro-mnesic effect of MCH brain infusion. Since the MCH-R_1 is the solely MCH receptor in mice [55]), this strain is a valuable tool to selectively assess the contribution of the MCH peptide to brain functions. Thus, MCH neurotransmission is selectively blocked in MCH-R_1 KO animals [1,17,35] compared to ppMCH KO mice [30,49] that lack other peptides encoded by the gene [4,11,38]. MCH-R_1 KO animals show impaired memory retention when tested in a modified inhibitory avoidance paradigm [1]. In these experiments, the latency to re-enter a compartment where animals received an electric shock is reduced in MCH-R_1 KO animals compared to controls when the tests are conducted one and six days after the training. Intracellular recordings of CA_1 pyramidal neurons in hippocampal slices from the MCH-R_1 KO mice show significantly decreased NMDA responses. Finally, NR_1 transcripts are reduced in CA_1 field of the hippocampus in MCH-R_1 KO animals compared to controls. Pharmacological screening has identified several potent MCH receptor 1 antagonists [33], which have not yet been tested on learning and memory paradigms.

Given the wide distribution of MCH-containing projection and MCH receptors expression, it is possible that MCH-mediated modulation of cognition results from indirect modulation of neuronal circuits in the amygdala and nucleus accumbens (Fig. 1). Infusion of MCH in the amygdala increases memory retention in emotion-dependent tasks [37,61]. Although MCH has no effect no effect on dopamine and non-dopamine neurons of the VTA [31,71], administration of the peptide to the NAcc shell increases food intake in rats, possibly by blocking dopamine-induced phosphorylation of the AMPA glutamate receptor subunit GluR1 at Ser^{845} [21,71]. In opposite, infusion of a MCH-R_1 antagonist in the same region blocks feeding and has an antidepressant-like effect [21]. These data suggest a direct effect of MCH on the amygdala and striatal circuits to modulate emotional and motivation components of learning and memory consolidation.

Interestingly, although the relative concentrations of dopamine, norepinephrine and serotonin remain unaltered in MCH-R_1 KO mice, D_1-like and D_2-like receptor binding properties are significantly higher within the olfactory tubercle, ventral tegmental area, and NAcc core and shell of these animals compared to controls [51]. Norepinephrine transporter (NET) binding properties are also significantly elevated within the NAc shell and globus pallidus of MCH-R_1 KO mice, whereas serotonin transporter binding is decreased in the NAcc shell [51]. Finally, MCH-R1 antagonist have recently been found to improve social recognition and elevate extracellular ACh levels in frontal cortex of rats [71]. Collectively, these studies identify extra-hypothalamic targets for MCH-mediated molecular modulation of cognitive processes that involve olfaction, emotion and motivation.

3. Memory, arousal and goal-oriented behaviors

MCH-producing neurons of the LH and ZI receive inputs from intra- and extra-hypothalamic neuronal cell types, and reciprocally project to multiple brain areas [9] (this issue). Thus, MCH neurons may interact with numerous other circuits of the brain, including the arousal centers of the brain. Functional synaptic inputs to MCH neurons include Glutamate (along with AMPA and NMDA), ATP and Hypocretin-1 and 2 (Hcrt) which all increased activity of MCH neurons [60]. In opposite, neurotransmitters from extra-hypothalamic arousal systems, including norepinephrine, serotonin, acethylcholine agonists (muscarin, carbachol), inhibit MCH neuron activity *in vitro* [8,60]. Interestingly, the appetite-promoting peptide Neuropeptide Y (NPY) inhibit MCH neurons by pre-and post-synaptic mechanisms [60], while the appetite-suppressing melanocortins are without any effect on MCH neurons activity [20,60]. According to these direct synaptic inputs onto MCH cells, subpopulations of MCH neurons express glutamate and GABA receptors [20,60], adrenoreceptor (alpha2) [36], muscarinic and serotoninergic receptors and $HcrtR_1$ and/or $HcrtR_2$ [20,60]. It is noteworthy that MCH cells express the leptin receptor (Ob-R, undefined subtype) [23] and that physiologically relevant concentrations of glucose dose-dependently enhance the electrical excitability of MCH neurons [13]. However, the action of leptin, ghrelin and other hormonal signals on MCH neurons remains unknown.

Thus, MCH neuron activity is under the influence of cognitive, metabolic and arousal neurotransmitters/neuropeptides. In addition, they may act as sensors of metabolism in the elaboration, consolidation or recall of food-seeking behaviors. Whether MCH and related peptides affect, in turn, the activity of arousal centers of the brain, including the noradrenergic cells of the locus coeruleus, the serotonin neurons for the raphe and the cholinergic cells form the brainstem and basal forebrain remains to be investigated.

In addition, recent studies suggested a modulatory role for the MCH system in arousal. MCH projections target the arousal centers of the brain stem and sleep- and wake-promoting nuclei of the hypothalamus, where the MCH-R_1 is strongly expressed [9,10,26,47] (Fig. 1). MCH cells have been found to be positive for c-Fos during a sleep rebound induced by REM sleep or total sleep (both REM and non-REM sleep) deprivation procedure [36,64]. PpMCH KO mice are hyperactive, exhibited accelerated weight loss and a marked decrease of REM sleep in response to fasting [65] and juxtacellular recordings of MCH neurons in rats have shown that these cells are silent during wakefulness and increase their firing rate during non-REM sleep, with maximal discharge during REM sleep [25]. Compared with Hcrt neurons, MCH cells exhibit a complementary pattern of activity, and unlike Hcrt neurons, MCH activity seems to be important during, rather than at the onset REM sleep. Based on previous reports underscoring the role of REM sleep in memory consolidation, it is reasonable to speculate that MCH neurons may have an indirect effect on memory through stabilization of vigilance states.

Maintaining body homeostasis (i.e. stable internal parameters in a fluctuating environment) requires optimal behavioral strategies and adaptation. A major goal of current research is to understand how the hypothalamic circuits compute internal and environmental inputs and how those are translated into a coherent goal-oriented behavior. Yamanaka et al. showed that mice with genetic ablation of Hcrt cells do not show the typical fasting-induced increased of arousal [66], suggesting that the Hcrt system

integrates both energy- and arousal-related signals in the elaboration of adaptive behavior to recover from negative energy balance. There is accumulating evidence suggesting that, like Hcrt cells, MCH neurons are exquisite sensors of the metabolic status of the organism. Thus, MCH neurons show an increase of cAMP response element (CRE) activity after fasting in mice [21] and *ppMCH* and *MCH-R1* gene transcripts are increased upon fasting [41]. Also, glucose enhances electrical excitability of MCH neurons by inducing depolarization and increasing membrane resistance *in vitro* [13]. Thus, in contrast to the Hcrt system that promotes arousal [3,54], activation of the MCH system may decrease arousal, energy expenditure and physical activity in normal conditions or during negative or a positive energy balance [48,65].

Stringent environmental conditions, including prolonged wakefulness or energy imbalanced, alter synaptic plasticity of neuronal circuits in the hippocampus, cortex, amygdala, striatum and the hypothalamus. Such plastic changes of neighbouring Hcrt neurons have been reported in response to food and sleep deprivation [28,42]. Sleep deprivation (4 h) as well as pharmacologically induced wakefulness produces long-term potentiation (LTP) of glutamatergic synapses onto Hcrt neurons [42]. Therefore, it is possible that similar plastic changes may occur at excitatory or inhibitory synapses onto MCH neurons, which could result in a facilitation of memory retention and energy conservation. Although the functions of sleep in memory consolidation remain a matter of debate and may depend on the cognitive task considered [27,34,50,53,56], plastic changes of inputs to the MCH neurons or their outputs, may also promote sleep or rest period, and eventually memory consolidation and adaptive behaviors. Finally, whether the MCH system modulates memory by preferentially inhibiting locomotor activity [17,35], promoting sleep [36,64] or increasing emotional arousal [10,44,45] remains to be determined.

4. Conclusions and perspectives

Since the identification of the MCH system in mammals, a vast amount of anatomical and functional data on its physiological role in energy homeostasis, arousal and locomotor activity has accumulated. Experimental evidences support a facilitatory role for the MCH system in memory storage and sleep. Although the consolidation of explicit and implicit memories during NREM sleep or REM sleep has resisted simple interpretations [27,34,50,56], the MCH system may facilitate memory storage indirectly, by fine-tuning arousal depending on environmental or physiological pressure.

Progress in elucidating shared functions by the MCH system have been hampered by the complex anatomy of the hypothalamus, the cellular heterogeneity of the considered neuronal populations, the difficulty to record neuronal activity in the hypothalamus of in freely moving animals and the low temporal resolution and possible compensatory mechanisms associated with genetically engineered mouse models (gene KO or over-expressing in transgenic animals). For instance, c-fos colocalization in MCH neurons and single unit recording of MCH neurons in restrained animals suggested a sleep-promoting role for the MCH system whereas studies using MCH-R1 KO animals suggested opposite effect (see [2,25,64]). Thus, identifying the role of MCH in memory from other confounding effect in arousal [36,64], anxiety and depression [10,44,45] or reward will requires adapted experimental strategy. Next-generation tools may help to resolve some of these limitations. Those include genetically defined multicolor tagging of neuronal groups [32], which could help define subpopulations of MCH neurons that may have separate physiological outputs. A second method involve the use of light-sensitive proteins, such as channelrhodopsin-2 and halorhodopsin [12,68–70], to enable optical activation and inhibition of MCH neuron activity with high temporal and spatial resolutions. Combination of such optical tools with cellular and molecular techniques will open new ways of interrogating the role of the MCH system in the physiological functions of the hypothalamus in normal and patho-physiological conditions, including addiction and mood disorders.

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