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Review Article

REVIEW ARTICLE

Hypothalamic MCH Neurons: From Feeding to Cognitive Control

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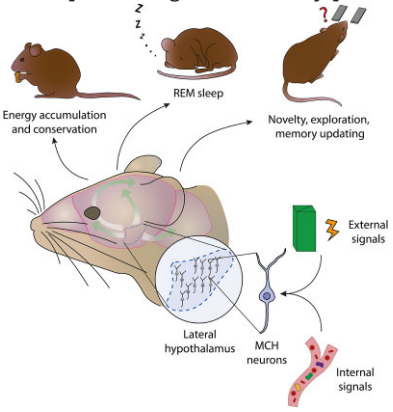
Abstract

Modern neuroscience is progressively elucidating that the classic view positing distinct brain regions responsible for survival, emotion, and cognitive functions is outdated. The hypothalamus demonstrates the interdependence of these roles, as it is traditionally known for fundamental survival functions like energy and electrolyte balance, but is now recognized to also play a crucial role in emotional and cognitive processes. This review focuses on lateral hypothalamic melanin-concentrating hormone (MCH) neurons, producing the neuropeptide MCH—a relatively understudied neuronal population with integrative functions related to homeostatic regulation and motivated behaviors, with widespread inputs and outputs throughout the entire central nervous system. Here, we review early findings and recent literature outlining their role in the regulation of energy balance, sleep, learning, and memory processes.



Cognition, Emotion, and Survival

> *"Those who study the hypothalamus have a somewhat larger commission than dealing with its role in maintaining the physical functions of the body. Man possesses a complexity of characteristics and behavior that is of an order quite different from contraction, secretion, digestion, metabolism, reproduction and adaptation, though related to all of these. That relationship is the mystery."*[1]

The above quote expresses the sense of awe in trying to conceptually reconcile basic physiological functions fundamental for the survival of the organism and its species, and seemingly more complex, "higher-order" cognitive, and social activities in which humans engage, such as math, politics, and the construction of complex technologies and societies.

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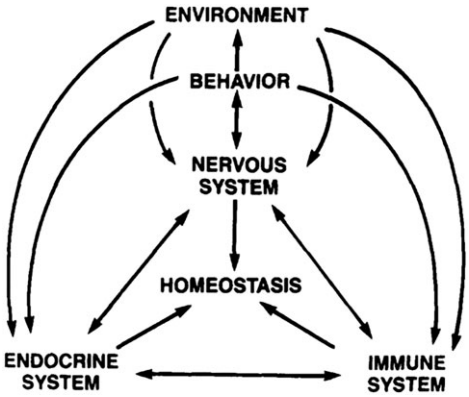

Figure 1. Conceptual representation of the nervous system as the central regulator of internal and external inputs and outputs (reproduced with permission from Brooks[1]). The hypothalamus is a structure uniquely positioned to fulfil this role.

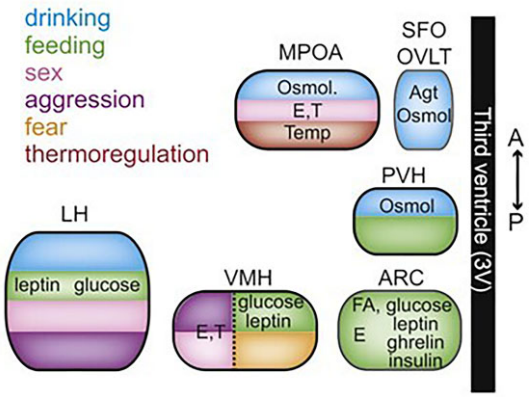

Figure 2. Simplified representation along the antero-posterior and medio-lateral axes of the organization and functions of hypothalamic nuclei, including homeostatic functions and motivated behaviors (reproduced with permission from Sternson[5]).

An influential theory of the past, which has attempted to do so has been the "triune brain" theory, developed by Paul McLean and posing that the brain is composed by three distinct structures, which evolved separately and function independently. The oldest part is the "reptilian brain," which consists of the ventral-most brain structures such as the basal ganglia and the brainstem, and is responsible for the basic, instinctual, and stereotyped behaviors and functions essential for survival. The second structure is the limbic system, involved in emotional responses and representing an evolutionary progress from reptiles to mammals. The third, most recent structure and prominent in humans is the cortex, involved in more sophisticated functions such as cognition, reasoning, planning, and rational decision-making.[2–4]

Today, this theory is outdated,[3] as we now know that the brain did not evolve in stages, but rather that all brain structures are shared among vertebrates with differences in proportion. Additionally, brain structures do not function independently, and neither are survival, emotion, and cognition separable brain functions. Finally, the brain does not function solely by reacting to stimuli, instead, it continuously predicts and adjusts to the ever-changing internal and external factors, optimizing its responses to the environment both inside and outside the body.[3]

One anatomically defined region of the brain, the hypothalamus, exemplifies how survival, emotion, and cognition are interdependent in the brain. It has been known for a long time to underlie fundamental homeostatic functions, essential for the survival of the individual and the species, like energy balance, electrolyte balance, endocrine function, and reproduction. Over time, it has become increasingly clearer that it is essential also for emotional and cognitive functions (Figure 1).

This review focuses on how a genetically defined neuronal population in the hypothalamus, named melanin-concentrating hormone (MCH) neurons, in addition to energy homeostasis and sleep, controls cognitive and emotional processes.

The Hypothalamus

"*This bit of brain, 4 grams in weight, integrates almost all higher physiological functions.*"

Fred Plum and Robert Van Uitert, 1978

The hypothalamus is a heterogeneous region located at the base of the brain, which controls a variety of physiological processes essential for survival, such as feeding and energy homeostasis, thirst and osmotic homeostasis, hormone release, body temperature, sleep, locomotion, and basic social behaviors like sexual and reproductive behavior, escape and aggression.

It is an ancient and conserved structure of the forebrain,[6,7] made up of several nuclei and neuronal populations, which act as internal sensors (interoceptors) of homeostatic states and orchestrate the essential behaviors aimed at counteracting needs,[5] such as foraging and consuming food when in a state of energy deprivation (Figure 2). Neurons in the hypothalamus sense and respond to internal signals (hormones, nutrients, and other molecules) and initiate complex, motivated behaviors when stimulated exogenously, as shown in classical studies.[5] More recently, it has been shown that hypothalamic neurons not only respond to internal stimuli on a slow timescale (minutes, hours), but are also responsive to external stimuli on a faster timescale (seconds).[8] The latter are environmental cues used to predict future homeostatic needs and to orchestrate complex behaviors flexibly and depending on environmental context—as opposed to the generation of stereotyped behaviors.[9,10]

The hypothalamus controls the autonomic nervous system by innervating autonomic preganglionic neurons and various nuclei in the brainstem that control autonomic reflexes.[10] It controls the endocrine system directly through groups of neurons that connect to the anterior and posterior pituitary gland and indirectly through autonomic innervation of endocrine glands.[10]

The Lateral Hypothalamic Area (LH or LHA)

Many structural and functional studies support a role of the LH in the control of feeding behavior,[11] arousal,[12,13] and reinforcement processes—early lesion studies showed that the LH is necessary for feeding behavior, while electrical self-stimulation revealed the LH as one of the brain areas supporting the strongest self-stimulation.[14–16] The LH has extensive connections with the brainstem and hypothalamic areas that process homeostatic signals from the body, and with forebrain cognitive and hedonic systems and areas mediating stress, anxiety, arousal, and sleep.[17]

The LH has two main non-overlapping neuronal populations, unique to the LH and defined by their neuropeptides: orexin/hypocretin (ORX) neurons and MCH neurons. Other, less well-characterized cell types are also present in the LH, such as GAD65 neurons,[18] Trh-expressing, and Sst-expressing neurons.[19] Additionally, other neurotransmitter markers (glutamate and glutamate transporters, gamma-aminobutyric acid (GABA) transporters),[20] neuropeptides [cocaine- and amphetamine-regulated transcript (CART), dynorphin, nesfatin], and receptors (leptin receptor) are expressed and/or co-released by LH neurons to various degrees.[19,21]

ORX and MCH neurons are thought to have opposing roles on arousal and feeding, as they show reciprocal activity profiles[22] and are differently modulated by glucose.[23,24] However, they show similarities in that both neuronal types have brain-wide inputs and outputs, not only to regions regulating feeding and arousal, but also locomotion, cognition, and reward.[22,25,26]

ORX neurons are identified by the expression of the neuropeptide orexin, which has an excitatory action on postsynaptic neurons.[27–29] Additionally, they express and release glutamate.[20] They are known to promote stable wakefulness,[30,31] as their loss results in narcolepsy, a sleep disorder.[32–34] They also mediate feeding,[35] and control behavior under situations of high motivational relevance.[36] More recently, they have also been found to be involved in locomotion[37] and cognition.[38]

GAD65 neurons are inhibited by glucose[18] and are active during sleep.[39] Locally, they synapse onto neighboring MCH neurons[40] and are activated by ORX neurons.[41] They likely participate in GABAergic LH projections to more distant brain regions, such as the ventral tegmental area (VTA).[42]

MCH neurons are the focus of this review and are covered more extensively below.

The MCH System

Early Findings

The MCH peptide was first isolated from the pituitary of teleost fish, where it is secreted in circulation and causes the concentration of melanin granules in the scales, thus determining color change in response to the environment.[43] Subsequently, it was found in the hypothalamus[44] of rodents and humans[45] (and in some peripheral tissues,[46] see the section "Functions—Overview"). The mammalian MCH peptide (Figure 3) consists of 19 amino acids, encoded by the *Pmch* gene, which gives rise to a longer precursor peptide (165 amino acids), prepro-MCH. The *Pmch* gene is highly conserved between teleost fish and mammals and the MCH peptide is identical in all mammals analyzed so far.[47,48] In contrast to fish, MCH in the mammalian brain is found in the LH and zona incerta (or incerto-hypothalamic area).[26] In spite of slight differences in localization, in all vertebrates analyzed, MCH has been found exclusively in the hypothalamus or homologous structures.[47] Alternative processing of the prepro-MCH precursor generates 2 other peptides, NGE and NEI,[49] the function of which is not well known.[26]

Functions—Overview

The MCH system is implicated in a variety of processes within the central nervous system (CNS). This ubiquitous peptide acts as an important neuromodulator for the organism's homeostatic balance, acting over a large spectrum of integrative functions, especially those related to homeostatic regulation and motivated behaviors. Early evidence implicated the MCH peptide in the regulation of feeding behavior, finding its expression increased after fasting[50,51] and intracerebroventricular (ICV) injection of MCH increased food consumption.[51] Later, MCH peptide has also been found to be implicated in sleep[52] and, more recently, learning and plasticity processes, emotion,[53–55] and reproduction.[56,57] The MCH system has also been found to have a role in the periphery: in the gut,[54,58] in pancreatic islet function,[59] in brown adipose tissue (BAT),[60,61] and in the immune system,[62,63] and to exert neuroendocrine actions[64] in addition to non-neuroendocrine roles. MCH neurons project widely throughout the brain[65,66] and receive inputs from several brain regions.[22]

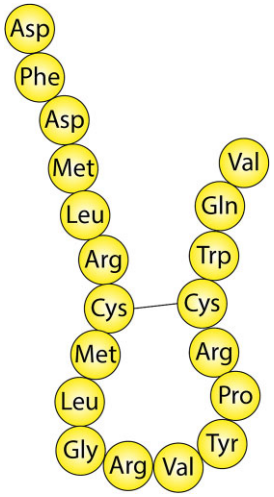

Figure 3. Amino-acid sequence and structure of the mammalian MCH peptide after precursor processing.

Transmitters and Receptors Involved in the MCH System

The MCH peptide has 2 known G-protein coupled receptors: MCHR1,[67–71] found in all vertebrates, and MCHR2, found in primates and carnivores but not in rodents.[72,73] The two receptors are highly homologous[48] and both are found predominantly expressed in the brain compared to other tissues.[73–77] The binding of MCH peptide to MCHR1 can activate $G_{i/o}$ coupled pathways, which decrease intracellular cAMP levels and are associated with neuronal inhibition, but also G_q coupled pathways, which lead to an increase in intracellular Ca^{2+} levels and are associated with neuronal activation. Instead, activation of MCHR2 causes exclusively increase in intracellular Ca^{2+} levels through Gq[73,75] pathways. Most rodent studies on the functions of the MCH system only involve MCHR1, due to the lack of MCHR2. A mouse model engineered to express MCHR2 under the promoter of MCHR1 showed protection against diet-induced obesity by reducing feeding,[78] an effect similar to MCHR1. However, additional studies are needed to fully elucidate the physiological role of MCHR2. MCH peptide itself has been reported to have mainly inhibitory effects on other hypothalamic neuron types.[79]

As many other neuron types,[20] MCH neurons likely co-release other neurotransmitter molecules in addition to MCH peptide. This is suggested by differences in the phenotypes of animal models lacking the MCH gene (MCH-KO mice) compared

to those lacking MCH neurons altogether (MCH-ablated mice), as is the case for glucose tolerance profiles.[80] Evidence for the release of both classic neurotransmitters glutamate and GABA from MCH neurons and the presence of their molecular machinery in MCH neurons[81,82] has been reported. A study[83] found that nearly all MCH neurons express the glutamate transporter VGlut2 and that its knockout leads to a phenotype partially overlapping but different from the knockout of MCH peptide. Another study[84] reported that a small subset (about 5%) of MCH terminals projecting to the locus coeruleus (LC) contains the machinery for GABA release and transmission. Finally, it has also been reported that MCH terminals projecting to the lateral septum (LS)—a site of very dense MCH innervation—release glutamate.[85]

MCH neurons also express the CART peptide and endocannabinoids, but this is not a specific characteristic of MCH neurons, since these molecules are expressed by several neuronal populations in the hypothalamus[86] and in the rest of the brain.[87,88]

Inputs and Outputs of MCH Neurons

MCH neurons send extensive projections to most brain areas, notably the cortex, the olfactory areas, the hippocampal formation, the septal nuclei, the amygdala, the nucleus accumbens, the LC, the raphe and nuclei of the reticular formation, and the spinal cord.[89] Intra-hypothalamic MCH projections target the arcuate nucleus, dorsomedial hypothalamus, lateral and posterior hypothalamus and tuberomammillary nuclei (TMN).[89] MCH axons also contact the median eminence (ME),[90] which is an interface between the CNS and the periphery and a major site of blood-brain barrier permeability. Additionally, MCH neurons have been hypothesized to interact with tanycytes,[149] elongated cells in the ME and third ventricle which control the blood-hypothalamus barrier and, therefore, the entry of peripheral signals into the hypothalamus.[150–152] MCH peptide has been shown to affect the beating frequency of cilia on ependymocytes[91,92,148] and to regulate the permeability of the blood–brain barrier by controlling microvessel fenestration and facilitating leptin action in the arcuate nucleus.[93] Additionally, MCH peptide itself is released in the cerebrospinal fluid (CSF), thus potentially reaching non-synaptically connected brain regions, which has been shown to be one of the routes for its regulation of feeding.[94] MCH may act through non-synaptic communication also in the brain itself, as the expression of MCHR1 has been found associated to a subcellular structure called the primary cilium, which is involved in the detection of neurochemical messengers in the extracellular space.[95] In general, MCHR1 expression in the brain largely mirrors that of MCH-containing axons.[26]

MCH neurons receive and respond to a wide variety of signals (Figure 4). They are depolarized by glutamate and hyperpolarized by GABA.[96,97] They express ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) glutamate receptors, group I metabotropic glutamate receptors[97,98] and GABA-A receptors.[81,97,99,100] MCH neurons express MCHR1 autoreceptors, but no effect of their activation has been found.[96,101]

In the LH, MCH neurons are intermingled with ORX neurons. Orexin neurons possess the MCHR1 and its activation by MCH peptide has an inhibitory effect.[102] MCH neurons, in turn, express orexin receptors whose activation depolarizes them,[97] but orexin neurons also inhibit MCH neurons through excitation of local GAD65 neurons.[103]

MCH neurons receive dense inputs from other hypothalamic nuclei and neuronal populations, such as oxytocin and vasopressin neurons in the paraventricular nucleus, POMC (Pro-opiomelanocortin) neurons in the arcuate nucleus, and the supraoptic nucleus.[22] MCH neurons also receive projections from NPY-producing neurons of the arcuate nucleus[104] and express NPY receptors,[81] but their effect is not clear.[96,97] MCH neurons also express the MC4R for α-MSH produced by POMC neurons in the arcuate nucleus, but this receptor may not be functional.[97]

They also receive inputs from cerebral nuclei (bed nucleus of the stria terminalis, nucleus accumbens, LS, and diagonal band nucleus), from the midbrain (VTA, reticular nucleus, periaqueductal gray, nucleus raphe), and from cortical areas (mostly hippocampus and amygdala nuclei).[22,105] In vitro evidence shows that noradrenaline (norepinephrine) hyperpolarizes MCH neurons through α2 adrenergic receptors, and acetylcholine hyperpolarizes MCH neurons through its muscarinic receptors[96,97,106] and both transmitters modulate synaptic inputs to MCH neurons.[97] Serotonin also hyperpolarizes MCH neurons.[97] Dopamine also depresses MCH neuron activity.[107] These transmitters are involved in arousal, stress, attention, memory, motivation, and reward. MCH neurons also interact with opioids and cannabinoids in the LH[108]—where they have indirect excitatory actions on MCH neurons by inhibiting local GABAergic neurons[109]—and in the nucleus accumbens,[110] and with thyrotropin-releasing hormone (TRH).[111]

MCH neurons also sense signaling molecules from the periphery. They respond to physiological concentrations of glucose by depolarizing[24] and are affected—presumably indirectly—by feeding-related hormones such as leptin and insulin (see below).

MCH Neurons and Energy Balance

Energy homeostasis is the process through which energy stored in the body is held constant over time, and for this the amount of energy consumed and energy expended is made to match, by integrating the body's short-term and long-term energy needs. The hypothalamus is a crucial regulator of this process, in which MCH neurons take part among others.

Several peripheral signals act to regulate food intake and energy expenditure: adiposity-related leptin secreted by the adipose tissue, blood-glucose regulating insulin and glucagon secreted from pancreatic cells, and meal-generated satiety signals secreted from the gut, such as CCK and ghrelin.[113] These are transported into the brain through the blood–brain barrier and exert their action especially in the hypothalamus, in several nuclei and neuronal populations.

MCH neurons are considered "second order" feeding neurons as they are under the control of "first order" arcuate nucleus neurons, which receive direct signals from the periphery.[108,114] Arcuate POMC neurons, expressing alpha-melanocyte stimulating hormone (α-MSH) and CART, signal satiety and inhibit food intake and energy storage. Neighboring neurons containing neuropeptide Y (NPY) and agouti-gene related peptide (AgRP) signal hunger and promote food intake and weight gain.[115] NPY-AgRP are inhibited by leptin and insulin, whereas POMC neurons are stimulated by them. Both populations send projections to MCH neurons, which, in turn, negatively regulate POMC neurons.

It has emerged from various studies that MCH promotes energy conservation and accumulation by increasing food intake and reducing energy expenditure.[116–118] Elevating MCH

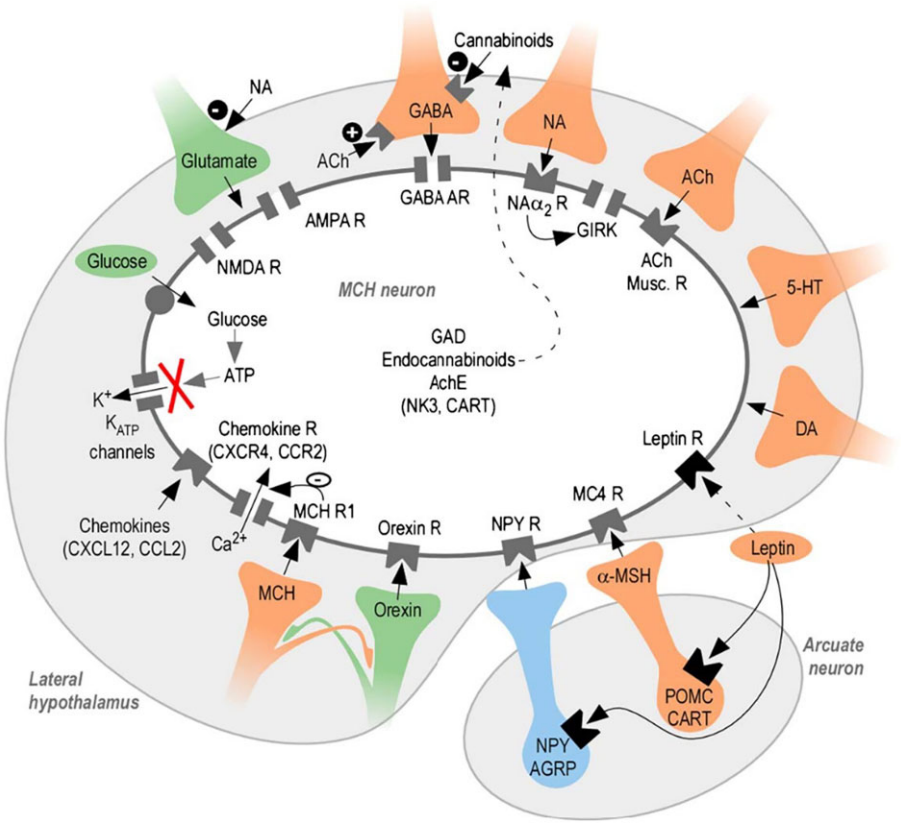

Figure 4. Neurotransmitters and neuropeptides acting on MCH neurons and their receptors (from Guyon et al.[112]). MCH neurons respond to a wide variety of local and long-range signaling molecules.

in the brain increases food intake[51,119–122]: acute effects of ICV MCH injection are washed out after 24 h, while chronic infusion increases food intake and body weight over time.[123] Both acute and chronic ICV infusions of MCH in mice and rats lead to hyperphagia,[51,119–121,124,125] which persists even in obese animals.[121] Indeed, MCH levels are increased in most mouse models of obesity.[126–128] Overexpression of MCH in transgenic mouse models increases body weight and leads to obesity.[116] Conversely, pharmacological[129–132] or genetic inhibition of MCH or blockade of MCHR1[80,117,133–135] leads to weight loss in both lean and obese mice, independently of food palatability.[136] Additionally, MCH neuron ablation reduces age-associated weight gain.[133,134]

MCH neurons respond to and interact with several peripheral feeding-related signals. They are stimulated by glucose[24] and regulate peripheral glucose homeostasis.[137] Central infusion of MCH induces glucose intolerance.[138,139] Glutamate signaling in MCH neurons is necessary for the MCH-neuron-mediated effects on glucose tolerance[83] and mice with glucose-insensitive MCH neurons have altered glucose tolerance.[137] Insulin, which stimulates glucose uptake and metabolism and decreases food intake and body weight when administered centrally, also modulates MCH neurons,[140] as they increase the level of MCH peptide expression after insulin administration, and deletion of the insulin receptor from these neurons improves insulin sensitivity in obese mice.[140] Chronic central administration of MCH promotes insulin resistance via a mechanism that is independent of weight gain.[134,139] The MCH system interacts with leptin, with several studies showing evidence of a negative interaction between the two.[108,141–143] Additionally, estrogen has been reported to regulate the orexigenic effect of MCH neurons, making it sexually dimorphic.[144–147]

MCH neurons interact with other neuronal populations involved in the control of energy balance, both in the hypothalamus and in the rest of the brain. Since LH ORX neurons have an anorexigenic action[153–155] and engage in reciprocal inhibitory circuits with MCH neurons,[103] these two nutrient-sensing populations are likely to generate an intra-LH circuit for antagonistic regulation of feeding and energy balance. Outside the hypothalamus, MCH neurons project, among others, to reward areas such as the VTA and nucleus accumbens (Nac).[65,66,89] MCH injection and antagonism in the Nac respectively increase and decrease food intake.[156,157] MCH activation is able to increase preference for palatable foods[158] and rats fed a high-fat diet continue to show increased levels of MCH even after switching to a standard diet.[159] Moreover, activation of MCH neurons alone is rewarding and reinforces ongoing feeding.[160] These results have led to the hypothesis that MCH neurons are involved in the motivational components of feeding and food-seeking behaviors. This function likely depends on an interaction with dopamine in the Nac, as MCH-KO mice show increased dopamine release and dopamine transporters expression[157,161] and GABAergic medium spiny neurons (MSNs)—the primary projection neurons of the Nac—express the MCH-R1.[162]

MCH neurons are involved in the regulation of energy expenditure beyond feeding alone, regulating locomotion and thermogenesis. ICV injection of MCH in mice reduces energy expenditure[163] and genetic deletion of components of the MCH system results in a lean phenotype with an increased metabolic rate and increased oxygen consumption, independently of their

diet.[117,135,147,164] Additionally, deletion of the *Pmch* gene in obese leptin-deficient mice results in a reduction of body weight due to increased energy expenditure and locomotor activity.[165] MCH neurons are polysynaptically connected to the BAT.[60,166] In mice, ICV injection of MCH reduces thermogenesis of the BAT, reducing core body temperature[125] and mice with MCH-R1 knockout have a higher core body temperature.[167] MCH neurons thus promote energy saving by reducing locomotion and BAT thermogenesis. Additionally, activation of MCH signaling in the arcuate nucleus favors fat storage in the white adipose tissue and increases body weight independent of feeding.[124] MCH also induces adiposity by reducing sympathetic neural activity and regulating liver metabolism.[124,138]

Together, these studies show that MCH neurons are involved in the control of energy homeostasis on multiple levels, by promoting feeding and, possibly, the rewarding properties of food, by promoting energy storage in the adipose tissue and by reducing energy expenditure. The latter function may be related to their role in sleep and sleep transitions.

MCH Neurons and Sleep

In addition to the regulation of energy balance, MCH neurons are involved in another homeostatic process: sleep. For some time, they have been thought to only be active during sleep,[168] although now it is clear that they are also active during wakefulness.[22,40,61]

Sleep is a highly conserved physiological state across animals, and it serves to provide rest, memory processing, and recovery of all bodily systems. It is characterized by a decreased muscle tone and an increased threshold for responsiveness to stimuli. It has 2 main phases, non-rapid eye movements (NREM) and rapid eye movements (REM). In NREM sleep, brain activity as measured by electroencephalogram (EEG) is highly synchronized, with high amplitude and low frequency. In REM sleep, EEG activity appears similar to activity during wakefulness, with low amplitude, high frequency, and general de-synchronization. Several systems and neuronal types in the brain have been found to regulate wake and sleep. The wake-promoting system includes several areas in the ascending reticular activating system in the pons and midbrain—among which noradrenergic neurons in the LC and dopaminergic neurons of the VTA and substantia nigra pars compacta (SNc)—and another group of neurons in the forebrain—among which histaminergic neurons in the TMN ORX neurons in the LH. The sleep-promoting system includes GABAergic neurons in the thalamic reticular nucleus, in the hypothalamic preoptic area (POA) and in the cortex. Sleep onset is thought to be due to the accumulation of various metabolites produced during wakefulness, which inactivate wake-promoting neuronal populations and activate sleep-promoting neuronal populations.[169]

MCH neurons appear to be sleep-promoting, as ICV injections of MCH peptide induce hypersomnia, with an increase in REM and slow-wave sleep (a stage of NREM sleep).[170,171] Mouse models with deletions of components of the MCH system show increased locomotor activity and wakefulness, especially during the dark (active) phase.[80,83,117,133,135,140,162,164,172,173] Additionally, MCH neurons show activation during REM sleep[174,175] and after sleep rebound following sleep deprivation.[170,176,177] Accordingly, in rodents MCH levels increase in the CSF during the light (sleep) phase and decrease during the dark (active) phase.[178] MCH axons and the MCH-R1 are present in brain regions implicated in the control of sleep.[65,71,89] For example, MCH neurons receive direct afferents from the hypothalamic suprachiasmatic nucleus (SCN), the master circadian pacemaker,[178,179] and SCN neurons express MCH-R1.[178,180] Activation of the MCH system in several target sites also increases the number and duration of REM sleep episodes.[181–183] Optogenetic activation of MCH neurons during NREM sleep facilitates the onset of REM sleep, while activation during REM sleep extends the duration of REM sleep episodes.[181,184] Interestingly, a recent study has found that MCH neurons regulate REM sleep in response to ambient temperature.[185] The sleep-related functions of MCH neurons are fine-tuned by local astrocytes,[186] which modulate presynaptic glutamatergic transmission onto MCH neurons in response to sleep deprivation.[187]

Together, these findings demonstrate an interaction between MCH neurons and sleep systems, with a role for MCH neurons especially in REM sleep. This sleep phase is important for memory consolidation,[188,189] therefore it might be one of the ways through which MCH modulates learning and memory processes.

MCH Neurons and Learning

Living in a changing and partially unknown environment requires behavioral adaptation. Upon specific events, new behaviors must be learned, consolidated, stored, and then recalled in response to specific stimuli. Therefore, learning and memory processes are crucial for the survival of organisms. Learning is the process of acquiring new knowledge about the world, and memory is the process of retaining and reshaping that knowledge over time.[190]

Behavioral adaptation requires the integration of internal and external signals, therefore learning in the brain needs to be adapted to changing external variables, such as rewards,[191] punishments, context, and internal variables such as nutritional state,[192] attention, and motivation. Likewise, memory storage is not a linear and fixed sequence of events but is the dynamic outcome of several interacting processes—from initial acquisition, to consolidation, retrieval, and integration with other memories—and it is modulated by those variables. The biological basis for learning and memory storage in the brain is synaptic plasticity, the ability of neurons to change the strength of their synapses with use.[190] Thus, memory storage does not need to rely on specialized "storage neurons," but rather the capacity for storing memory is built into the architecture of neuronal circuits and is made possible by a plethora of cellular mechanisms that allow synapses to strengthen and weaken in the short and long term.[190]

Accumulating evidence points to a role of MCH neurons in the modulation of learning and memory (Figure 5), alongside other hypothalamic populations, such as orexin and AgRP neurons.[38,193–195] While the evolutionary reasons for the involvement of a brain region devoted to homeostasis and survival, as the hypothalamus, in learning and memory processes may not appear obvious at first, recent evidence linking metabolism and memory may help. In the *Drosophila* fruit fly, it has been found that under conditions of starvation, the formation of long-term memory is suppressed and the activity of neurons normally underlying it is absent.[192] Exogenously stimulating these neurons restores long-term memory but reduces survival, providing evidence that the brain coordinates memory processes, which have a high energy cost, with metabolic needs to favor survival.[192] Additionally, fruit flies are able to form "metabolic memories," which help balance food choice with caloric intake and

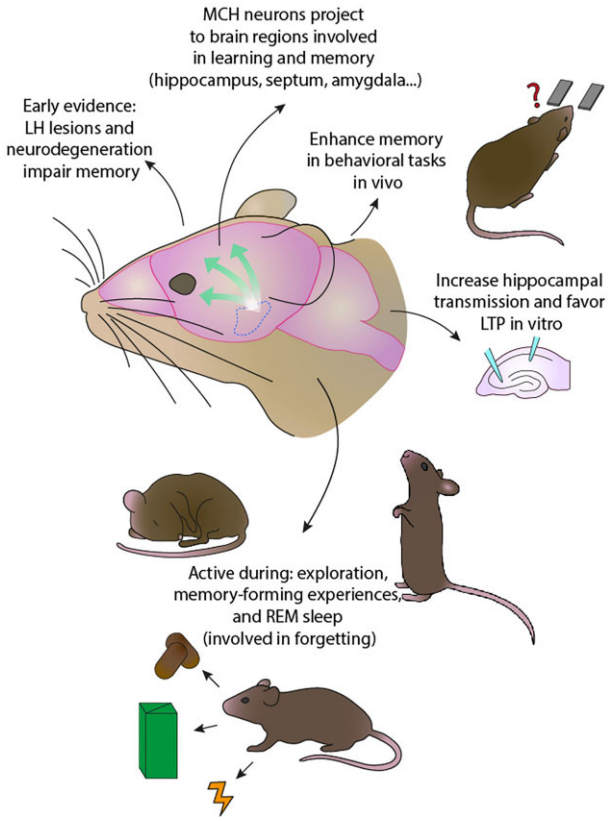

Figure 5. Summary of evidence supporting a role of MCH neurons in cognitive function, as suggested by early and recent studies.

the hypothalamus-like pars intercerebralis of the Drosophila brain is necessary for this kind of learning.[196] High-fat diet, which impairs this process in the fruit fly, also alters the expression of memory-related genes in the hypothalamus of mice, suggesting that this structure may be involved in metabolism-related learning also in mammals and that this learning may be disrupted in obesity.[196]

Early evidence for the involvement of the hypothalamus in learning and memory dates back to the 60s and 70s. Rats with lesions to the LH were unable to form a new associative memory, but retained an association formed before the lesion.[197] Electrical stimulation of the LH after a learning task was found to facilitate long-term memory,[198] while LH lesion impaired the formation of flavor-to-nutrient (appetitive) and flavor-to-toxin (aversive) post-ingestive associations.[199] On the clinical side, "Alzheimer's neurofibrillary changes" were found in the hypothalamus and brainstem of "senile dementia," ie, Alzheimer's disease (AD), patients, in addition to the hippocampus.[200] Other, non-neurodegenerative, lesions in the hypothalamus are also associated with memory impairment[201] (for more information on MCH neurons and neurodegenerative disorders, see below).

MCH neurons project to brain regions involved in learning and memory, such as the hippocampal formation, subiculum, cerebral cortex, basolateral amygdala, and shell of the nucleus accumbens (Nac).[65,66,89,202] They were shown to be required for learning to select nutrient-containing foods[158] and responding to food cues[203] but also for non-food-related memory formation, such as object recognition,[40] and activation of MCH neurons seems to enhance learning and memory processes.[204–208] MCH peptide was found to improve memory performance when infused in the hippocampus and amygdala in rats[209] and to revert the amnesic effects of a nitric-oxide-synthase inhibitor, a known disruptor of hippocampal plasticity.[206] In vitro, MCH peptide applied to brain slices induces a dose-dependent and long-lasting increase in hippocampal synaptic transmission.[207] In hippocampal slices from rats injected with MCH and trained in a memory task, the frequency threshold for the induction of long-term potentiation (LTP) was found to be reduced and expression of NMDA-receptor subunits important for plasticity was increased.[208,210] Additionally, MCH peptide was found to decrease hippocampal LTP thresholds by increasing synaptic transmission.[208,211] On the other hand, mice with a knock-out of the MCHR1 show impairments in various behavioral learning tasks,[204,212] reduced expression of both AMPA[213] and NMDA[204] glutamate receptors in the hippocampus and impaired LTP and long-term depression.[212,213]

MCH neurons project to the hippocampus, specifically to GABAergic basket cells, and they also innervate cholinergic neurons of the medial septal nucleus, which, in turn, project to the hippocampus.[214] Thus, MCH neurons communicate with the hippocampus both directly and indirectly, and these circuits have been hypothesized to participate in the organization of exploratory behavior during foraging, as the hippocampus is well known to be crucial for spatial exploration and memory. Additionally, they have been found to increase the signal-to-noise ratio of the dorsolateral septum (dLS),[215] an output structure of the hippocampus. This would allow hippocampal cognitive maps to be transformed into behavioral actions, and, indeed, enhancing MCH signaling in the dLS facilitates hippocampal-dependent memory formation.[215]

MCH neurons themselves may also play a direct role in exploratory behavior, as they have been found to be active especially when animals explore novel objects.[22,175] MCH activity during encounters with objects is higher if the object is novel and decreases over time as the object becomes familiar.[40] Optogenetic silencing of object associated MCH activity during initial exploration prevents the recognition of the object on subsequent exposure, showing the necessity of MCH activity for the acquisition of memory about the object.[40] MCH activity is under inhibitory control of local hypothalamic GAD65 neurons, whose silencing instead improves future object recognition.[40] These results suggest a role of MCH signaling as a "novelty signal" favoring memory acquisition.

MCH neurons have also been found to be endogenously active during learning-driving aversive experience and this activation is necessary for a correct extinction of fear as, in its absence, mice display overactive, relapsing fear behavior.[216] A hallmark of pathological fear in human PTSD is the presence of fear responses in safe situations erroneously perceived as dangerous, due to inflexible coupling of cues which are no longer predictive of danger to fearful behavioral responses.[217–219] Exposure therapy is often not enough to provide a full recovery from these fear responses[220–222] and these results closely mirror this phenomenon with silencing of MCH neurons during the initial aversive experience. Therefore, this can be used as an animal model for dysfunctional safety learning without disruption of the initial and useful fear learning. In this study,[216] as in the study investigating MCH function during novel object exploration,[40] the activity of MCH neurons during the early stages of a sensory experience determines whether the memory of that experience is correctly expressed behaviorally later on. Together, they point to an important role of MCH neurons in memory updating.

More recently, MCH activity has been found to co-occur with and to specifically drive events of self-paced exploratory rearing in mice,[223] an innate behavior during which animals stand on their hind legs to sample the environment.[224] This finding opens the possibility that MCH neurons participate in the active seeking of novel information, in addition to processing it for storage in memory and future retrieval. Furthermore, LC noradrenergic (LC-NA) neurons—classically involved in stress responses[225–227]—have been found to inhibit MCH neurons and thus impair exploratory rearing,[223] thus providing a mechanistic substrate for the reduction of exploration under stressful conditions.[228]

Whether wake-active and REM-sleep-active MCH neurons constitute two functionally separate subpopulations is still not fully elucidated, as one study reported a 70% overlap,[175] while another reported that only a minority of recorded MCH neurons were active during both wakefulness and REM sleep[229] (these differences could be due, for example, to recording MCH neurons in slightly different anatomical locations). Although most studies on MCH neuron function in learning and memory processes suggest that they facilitate memory formation (including hippocampus-dependent forms of memory), a recent study has reported that inhibition of MCH neurons active during REM-sleep facilitates the retention of hippocampus-dependent memory,[229] therefore proposing that REM-active MCH neurons favor hippocampal forgetting (or disrupt hippocampal consolidation[188]) during sleep.[229] An explanation for these apparently conflicting results could be that MCH neurons are indeed functionally separated into wake-active and sleep-active, and the former facilitate memory formation while the latter facilitate instead memory erasure. Alternatively, it is possible that MCH neurons themselves do not drive plasticity processes towards a specific direction, but rather function as generic "eligibility trace" for plasticity, facilitating either potentiation or depotentiation depending on other incoming inputs, promoting memory updating in general.[230] In this case, the exact timing and context of MCH manipulations (activation/inactivation) during behavioral experiments would be crucial in determining the outcome on learning and memory processes.

MCH System and Cognitive Decline: Alzheimer's and Parkinson's Diseases

AD patients show neurofibrillary degeneration in the LH[231] and MCH neurons show aggregates in AD, which, together with loss of ORX neurons, may underlie the sleep disturbances associated with this pathology.[232] In scopolamine-induced memory impaired mice and in AD mouse models, nasal cavity administration of MCH peptide improved memory impairments and reduced amyloid beta in AD mice.[233]

Some Current Questions

Although causal evidence is accumulating that MCH neurons control cognition, many key questions remain, some of which we highlight here.

First, which actions of MCH neurons are mediated by the MCH neuropeptide vs GABA/glutamate that they also co-release? In some cases, this has been probed by antagonists, and the data suggest that key actions of MCH neurons indeed rely on MCH peptide. This could be probed further by targeted, and preferably conditional/inducible, knockout of MCH receptors in specific neurons.

Second, are "sleep" and "wake" MCH neurons the same or different subsets of neurons? This is a point of current debate: Some studies indicated that a major subset of MCH cells active during sleep are also active during exploration,[175] but others find that sleep and wake MCH cells are separate.[229]

Third, is cognitive modulation by MCH neurons related to (or even explained by) their role in arousal/sleep? In other words, is sleep-promotion the primary role of MCH cells, and do their other impacts arise secondarily to that? If this is the case, then awake activity dynamics of MCH cells should be inversely correlated with arousal dynamics. This remains to be directly tested.

Finally, are the "classic" functions of MCH in feeding and energy balance separate from their "new" functions in cognitive control? This is not necessarily so, since much of cognitive control presumably evolved to facilitate survival, and energy optimization (eating, metabolism) is a critical element of survival. Therefore, it is possible that the energy and cognition roles of MCH neurons are tied together to facilitate integrated control of cognition and energy balance. There are some recent indications about how some elements of this might work,[94,160,203,234,235] but an integrated model accounting for all findings remains to be produced.

Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability

All relevant data are already included in this review article.

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