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The hypothalamus as a primary coordinator of memory updating

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ABSTRACT

In the brain, long-term memories correspond to changes in synaptic weights after certain patterns of neural activity. Behaviourally, this corresponds to a change in action evoked by a repeating experience. Forming and updating memories (learning, remembering, forgetting) is fundamental for most aspects of cognitive and motor performance. The roles of the cortex, hippocampus, and amygdala have been studied extensively in this context. However, the lateral hypothalamus – a brain-wide projecting region traditionally known as a nutrient-sensor and controller of arousal and motivation – is also critical for updating many types of associative and non-associative memories. Does the hypothalamus play a primary role in learning, or are hypothalamic effects on learning secondary to changes in brain state such as attention/motivation? We argue that such primary and secondary effects are distinguishable under experimental conditions where attention/motivation states are constant or absent, e.g. during sleep or in reduced *in vitro* preparations. The documented control by hypothalamus-unique transmitters, such as orexin and MCH, of synaptic strength in isolated brain slice preparations implies a primary role for the hypothalamus in synaptic weight updating, rather than a secondary role due to changes in arousal/attention/motivation states (which are absent in brain slices). Such hypothalamic control of memory-related synaptic machinery may enable gating/thresholding/permissive/tagging operations within yet poorly defined logic gates for memory updating. Hypothalamic signals may thus facilitate cost-benefit analysis of learning and memory in real-world settings. Whether the hypothalamus controls only specific types of learning, or broadcasts a global signal for memory updating, remains to be elucidated.

1. Introduction

The hypothalamus is a heterogeneous region located at the base of the brain that controls many physiological processes such as appetite, sexual behaviour, hormone release, body temperature, and movement initiation. It is historically considered to be part of the limbic system with reciprocal interconnections to hippocampus, amygdala, prefrontal cortex. More recent work suggested that the hypothalamus might act as an interface for various types of cognitive functions, such as learning and memory [1] [2] [3] [4] [5] [6] [7]. However, the precise mechanisms and circuitry of how the hypothalamus may be involved in memory and learning processes are largely unknown. Recent methodological developments utilizing chemogenetic and optogenetic approaches have enabled specificity in studying distinct neurons and their pathways in behaving animals. These studies unravelled new insights regarding the structure and function of the hypothalamus as related to learning and memory processes, especially the lateral hypothalamus. The lateral hypothalamus contains genetically-heterogeneous neurons many of which act as nutrient-sensors, project brain-wide, and also

integrate direct neural inputs from much of the brain. It is thus well positioned to link motivated behaviours and cognitive processes [8–10]. In this short review, we highlight a selection of papers relating to how hypothalamic neurons may serve as an interface for converting diverse neural and metabolic information into memory updating. We focus on brain-wide-projecting lateral hypothalamic neurons, rather than on hypothalamic-pituitary axis, and on studies in model organisms rather than humans. For the purposes of this review, our terms are defined as follows: memory – a behavioural or cellular/molecular state (e.g. stimulus-response coupling or synaptic weights) created by an experience, memory updating – experience-dependent memory modification (e.g. memorisation, forgetting, changes in synaptic weights, changes in stimulus-response behavioural coupling), associative learning – memorizing cues/contexts temporally associated with punishments or rewards (e.g. fear conditioning), non-associative learning – learning without explicit punishments or rewards (e.g. habituation, sensitization, spatial learning, object recognition learning).

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2. Hypothalamus as a region critical for learning and memory

The involvement of the hypothalamus in learning and memory is implied by numerous studies in both humans and animal models (e.g. [12] [13] [11,15] [2] [16,17] [18,19]). Anatomical lesions of the lateral hypothalamus, or more selective ablation or silencing of specific lateral hypothalamic neurons, can compromise key behavioural and cellular correlates of learning and memory, while lateral hypothalamic electrical stimulation can improve memory [11,15] [2,3] [1] [20–22]. Numerous classic lesion and electric stimulation experiments could establish the necessity of the hypothalamus as a crucial brain region for the expression of different behaviours. However, limitations such as poor spatial control of lesion site, damage to fibers of passage and post-lesioning compensation, made the control and identification of the neurons responsible for the observed behavioural changes difficult to interpret. Therefore, newer more advanced tools (optogenetic, pharmacogenetic) for measuring and manipulating neural circuitry in freely moving animals, have opened new avenues for research study at the level of genetically-defined cell type. Learning and memory are essential for various biological processes which are crucial for the survival of an organism. For example, the decision to eat involves an evaluation of the internal metabolic information and the external environmental conditions over a certain period of time. This is evident when a subject is deciding which type of food to eat. Depending on which type of nutrients the organism (animals as well as humans) needs, it will decide which food to consume. However, how the internal nutritional state of an organism dictates the selection of a specific food in this decision-making is still unknown [23–28]. The central control of metabolic homeostasis may involve a form of learning and memory, as was shown in flies that were able to dissociate the nutritional value from the taste of food [29, 30]. A further series of studies in *Drosophila* have demonstrated that the animals develop a so-called metabolic learning and memory in order to be able to balance [31] their food choice and match it with caloric intake [31]. Metabolic learning and memory was postulated as a form of learning and memorizing post-ingestive metabolic information independent of the sensory properties of food [31]. The authors showed that *Drosophila* developed a memory independent of taste, which guided them to develop a preference for normal caloric environment and not a high-caloric environment. However, when learning and memory-regulating gene *rutabaga* (*rut*) was inhibited in the brain region equivalent to the mammalian hypothalamus (*pars intercerebralis*, [32]), it resulted in increased caloric intake and to the development of excess of lipids and a diabetes-like phenotype [31]. In line with these results, mice are able to dissociate between normal and high-caloric foods, and the differences in this learning process between different mouse strains is linked to a differential expression of learning and memory genes [31]. In cell-type-specific studies of the rodent hypothalamus, hypothalamic melanin-concentrating hormone expressing neurons (MCH neurons) were shown to be required for the learning to select nutrient-containing foods [33], as well as non-food-related object recognition memory formation [2], while hypothalamic orexin neurons were found to be involved in associative learning and memory, including spatial memory [34] [4]. Overall, these results suggest that hypothalamus or hypothalamus-like regions play critical roles in regulating diverse types of learning and memory, both related and unrelated to food.

3. Hypothalamic representation of variables that govern learning

Important forms of learning depend on rapidly-changing variables such as rewards (e.g. taste), punishments (e.g. electric shock), “neutral” context (e.g. novelty), and slowly-changing variables such as internal body state (e.g. nutrient levels, which can also be considered as a form of reward feedback) [35] [36, 37] [33, 38]. Considerable evidence indicates that changes in neuronal activity of hypothalamic neurons forms a neural representation of some or all of these variables, and

communicates them to downstream neurons implicated in modulating learning and memory [39, 40] [41] [42] [43–45] [24, 46–50] [51, 52] [53] [54] [46] [55] [56] [57] [58] [59] [2] [60]. For example, lateral hypothalamic orexin/hypocretin neurons [61, 62], which co-release glutamate and orexin transmitters both locally and at long-range projections, respond slowly (minutes) to ambient nutrient levels, but can also change their activity rapidly (milliseconds) in response to rewards or punishments (or cues associated with the latter) [63] [46] [47] [64] [42, 52, 65, 66] [67] [59] [45]. Orexin neurons, and likely other hypothalamic cell types [40] [68] [44] [2] [69], are thus capable of representing key variables relevant for learning. Through brain-wide projections of hypothalamic neurons, these representations may be relayed to other brain regions to affect synaptic plasticity underlying learning [70] [71] [14] [72] [15] [73], and/or change global brain states implicated in controlling memory formation. For example, stress and anxiety are global neural, endocrine, and behavioural states that help an organism to sense, evaluate and cope with cues that signal threats in its internal or external environment, and can have a powerful influence on learning and memory [74, 75]. This study also demonstrated that stimulation of orexin neurons in the absence of stress had no effect on anxiety behaviours and object recognition memory [76–79] [52] [67] [47] [80] [51] [81] [82] [83] [84]. Interestingly, chemogenetic inhibition of orexin neurons prior to a social defeat paradigm contributes to resilience to social defeat and may be an important target for treatment of stress-related disorders [85, 86]. This study also demonstrated that stimulation of orexin in the absence of stress had no effect on anxiety behaviours and object recognition memory. These findings imply that orexin neurons may only modulate certain memories under increased levels of stress [86], suggesting the existence of (yet-undefined) logic gates that determine how orexin signals influence downstream circuits [60] [87]. Interestingly, phasic activation of other brain-wide-projecting neurons unique to the lateral hypothalamus, such as those expressing the neurotransmitter MCH [88], appears to represent an at least partly distinct set of learning-related variables, such as novelty during self-paced exploration [2, 42, 89]. Thus, hypothalamic neurons appear to transmit both slow (e.g. nutrients modulating hypothalamus on minute/second timescale) and fast (e.g. sensory cues encoded in hypothalamus on subsecond timescale) signals that may be relevant for memory updating, and both slow and fast signals may be encoded within same hypothalamic subpopulation [90,91] [2] [92,93] [44,56].

4. Causal roles of specific hypothalamic neurons in updating associative and non-associative memories

Associative learning involves a change in behavioural and neural responses to a neutral stimulus (e.g. a tone), after repeated temporal pairing of such stimulus/cue with a punishment or a reward. The simplest form of associative learning is Pavlovian conditioning, which has been typically studied in animal models in the context of fear conditioning, where fear behavioural responses to punishments or threats (i.e. odour, electric foot shock, social defeat, predator) are quantified in response to associated cues. The subject are taught (“conditioned”) that a certain cue signals threat. This perceived environmental threat (natural predators in the wild or electric foot shock in a laboratory setting) will elicit a defence behaviour such as freezing and flight [94]. The formation of fear memory following a threatening situation is an adaptive phenomenon that helps to avoid similar situations in the future as well as to develop better coping strategies. This behavioural response might suggest that an animal's defensive response processes cues about predators and an artificial threat in similar ways [95]. The amygdala was studied extensively in relation to fear learning and is believed to be a central processing region where the level of salience is imparted to a given cue [96]. In turn, the amygdala sends projections to the hypothalamus for further integration and coordination resulting in fight or flight reactions [97]. Canteras and colleagues

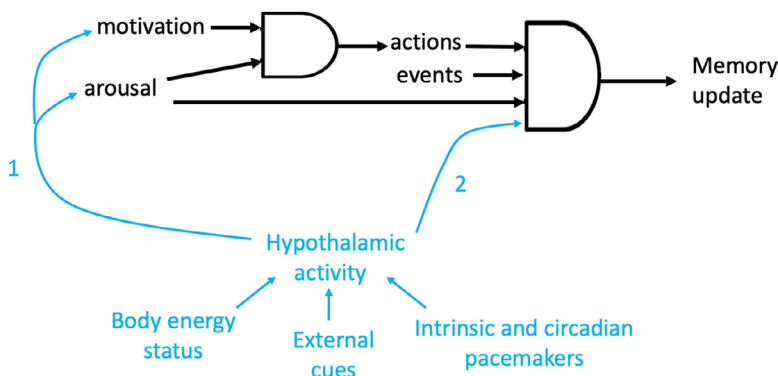


Figure 1. Schematic of a possible logic for hypothalamic influence on memory updating. Hypothalamic activity may influence memory updating via secondary effects of behavioural states such as arousal/attention/motivation (1), and/or in a behaviour-independent manner by direct actions of hypothalamic transmitters on receptors regulating synaptic weights (2) as implied by studies in brain slices mice [71,120,121]. The hypothalamic activity itself depends on interaction between intrinsic electrical pacemakers in lateral hypothalamic neurons [93,126,127,128] with slow influences such as circadian rhythms and body levels of nutrient and gases [125,129,45,130,53,131,132,38], and with fast (subsecond) inputs that inform the hypothalamus of diverse external events [90,91,2,92,93] [44,56].

have shown that the hypothalamus is important for the expression of defensive behaviour, although the exact neural circuits mediating such behaviour is still unclear [98, 99]. In conditioned fear response which is context dependent, cues are relayed from the hippocampus to the hypothalamus. In the case of both conditioned and innate fear response circuits the hypothalamus was shown to act as an “amplifier” by initiating pituitary and adrenal hormone release [98, 100]. Recent studies indicated that the orexin system underlies the regulation of such emotional learning [101, 102]. This is supported by the bidirectional projections between orexin neurons and brain areas mediating motivation and emotion. For example, subjects with narcolepsy, a condition associated with a loss of orexin neurons [103], show alterations in activity in the amygdala when exposed to an aversive stimulus [101]. Further, these patients fail to exhibit startle potentiation during unpleasant stimuli [104]. In animal models, it was shown that orexin plays an important role in the neural mechanisms underlying fear memory formation. Orexin acts upstream of the amygdala via the locus coeruleus to enable fear learning [105]. Once fear memory was formed, it has been proposed that orexin neurons also promote the expression of fear, opposing a decline in conditioned fear responses during fear extinction [106–108]. Orexin neurons have also been implicated in improving hippocampal-dependent associative learning and spatial memory [4] [34]. Lateral hypothalamic MCH neurons have also been linked to several types of memory formation [15] [3] [72] [14] [2]. Studies of mice lacking the MCH receptor reveal deficits in associative learning without changes in anxiety levels [72]. In non-associative learning tasks, such as habituation to novel arenas or forming object recognition memory, MCH neurons display transient bursts of activity when mice encounter novel objects or arenas [2, 42]. Optogenetic interference with these MCH cell activity burst selectively during these moments of memory encoding disrupts subsequent recognition of previously-encountered objects, suggesting that MCH cell activity during memory encoding is essential for formation and expression of certain non-associative memories [2]. While latter studies of MCH neurons suggest that they promote formation of multiple types of memory, especially during wakefulness, recent work also indicates that during sleep MCH neuron activity may promote forgetting [3]. One interpretation of these seemingly opposite roles of MCH neurons in memory (memorizing vs forgetting) could be that MCH cell activity promotes memory updating in general (i.e. either remembering or forgetting), but the mechanistic details and contexts of this emerging function of MCH cells remains to be determined. Optogenetic-assisted circuit mapping and combinatorial neural interference experiments suggest that lateral hypothalamic MCH and orexin cells locally interact with each other, either directly or via local inhibitory GAD65 neurons [2, 44, 109] [110]. Optogenetic interference with the lateral hypothalamic GAD65 neurons during novel object encounters enhances subsequent object recognition in an MCH receptor-dependent manner [2], suggesting that local computations in the lateral hypothalamus may influence memory formation.

5. Through which mechanisms does the lateral hypothalamus modulate learning and memory?

Arousal and motivation are important prerequisites for updating many types of memories. Experience-dependent memory updating often requires motivation to perform certain actions (e.g. to explore a novel object). It also requires sensory awareness, since without wakefulness and arousal, the experiences that shape memory may not be translated into changes in brain activity patterns. The lateral hypothalamic cell types described above, the orexin and MCH neurons, have both been implicated in setting the animals’ level of arousal, motivation, as well as stress/anxiety [111–114] [115] [47, 80, 116] [117–119]. Can the effects of these neurons on memory updating be dissociated from their effects on arousal and motivation (Figure 1)? In many behavioural studies, appropriate control experiments suggested that the impact of hypothalamic neurons on memory updating can be dissociated from their impact on arousal, anxiety, and motivation. For example, associative memory impairment observed in MCH receptor deficient mice does not involve altered anxiety levels [72], and object recognition memory impairment after MCH cell optosilencing during memory encoding can occur without changes in object exploration duration [2]. Perhaps the best evidence to-date that hypothalamic signals can control memory updating independent of stress, arousal and motivation comes from isolated brain slice preparations where synaptic correlates of learning and memory are studied *ex vivo* and thus in total isolation from behaviour. In hippocampal slices, MCH application potentiates synaptic transmission [120] [121] and MCH receptor knockout decreases synaptic weight adaptability (i.e. impairs both LTP and LTD) [14, 72]; while orexin application can induce either long-term synaptic potentiation (LTP) or depression (LTD), depending on the age of the mice [71]. Such studies suggest that hypothalamic transmitters can directly act on synaptic machinery underlying multiple forms of synaptic plasticity that are thought to be responsible for memory updating.

6. Conclusions

The studies reviewed above indicate that hypothalamic signals can directly control multiple forms of memory, through mechanisms that are not explained by traditional hypothalamic roles such as energy homeostasis, motivation, and arousal. When and why should the hypothalamus be involved in memory formation? The answer to this question is not yet clear. One possibility is that the hypothalamic signals representing energy states, arousal, or motivation act as critical inputs to sites of synaptic plasticity, which permit (either acutely or chronically via “synaptic tagging” [122]) or directly create changes in synaptic weights and thus memory formation according to the energy and brain state of the animal (Figure 1). Another key question is whether the hypothalamic neurons act as general controllers for all kinds of experience-dependent synaptic plasticity, or whether they are

selective controllers of specific kinds of memory. It is tempting to speculate that the former is the case, given that hypothalamic projections and activity-dependent long-term synaptic plasticity are found in most brain areas. This can readily be tested by combining new optogenetic ways of targeting specific hypothalamic signals with high temporally specificity with classic assays of long-term synaptic plasticity and behavioural memory expression. The possibility of cell-type-specific control of the lateral hypothalamus through chemical or electrical means [123] [124] [125] [55] [41] could make this region an attractive potential target for the treatment of memory disorders.

Declaration Of Competing Interest

All authors have seen and approved of the final version of this manuscript. None have any conflict of interest to disclose.

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