The hypothalamus as a primary coordinator of memory updating

Physiology & Behavior 223 (2020) 112988

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

Invited review, "Physiology and Behaviour"

The hypothalamus as a primary coordinator of memory updating

Denis Burdakov*, Daria Peleg-Raibstein*

Laboratory of Neurobehavioural Dynamics, Institute for Neuroscience, Department of Health Sciences and Technology, ETH Zürich, Schorenstrasse 16, Schwerzenbach 8603, Switzerland

ARTICLE INFO

Keywords:
Hypothalamus
Learning
Memory
Melanin-concentrating hormone
Orexin
Hypocretin
Arousal
Anxiety
Fear
Food
Reward
Punishment
Reinforcement
Associative learning
Non-associative learning: Energy balance
Neuropeptides
Nutrients

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).

* Corresponding authors:
E-mail addresses: denis.burdakov@hest.ethz.ch (D. Burdakov), daria-peleg@ethz.ch (D. Peleg-Raibstein).

https://doi.org/10.1016/j.physbeh.2020.112988
Received 3 February 2020; Received in revised form 5 May 2020; Accepted 26 May 2020
Available online 30 May 2020

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 threatful 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

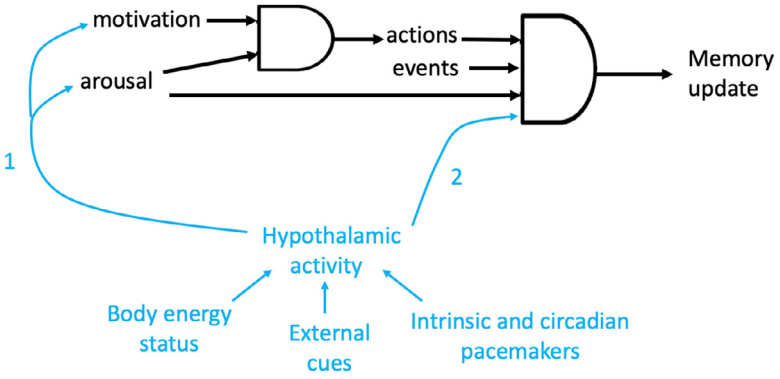

Figure. 1. Schematic of a possible logic for hypothalamic influence on memory updating. Hypothalamic activity may influence memory updating via secondary effects of behavioural states such as arousal/attention/motivation (1), and/or in a behaviour-independent manner by direct actions of hypothalamic 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 import 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 of 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.

References

[1] G.D. Petrovich, Lateral Hypothalamus as a Motivation-Cognition Interface in the Control of Feeding Behavior, Front Syst Neurosci 12 (2018) 14.
[2] C. Kosse, D Burdakov, Natural hypothalamic circuit dynamics underlying object memorization, Nature communications 10 (2019) 2505.
[3] S. Izawa, S. Chowdhury, T. Miyazaki, Y. Mukai, D. Ono, R. Inoue, et al., REM sleep-active MCH neurons are involved in forgetting hippocampus-dependent memories, Science 365 (2019) 1308–1313.
[4] T. Aitta-Aho, E. Pappa, D. Burdakov, J. Apergis-Schoute, Cellular activation of hypothalamic hypocretin/orexin neurons facilitates short-term spatial memory in mice, Neurobiol Learn Mem 136 (2016) 183–188.
[5] M.R. Zimmer, A.E. Schmitz, M.O. Dietrich, Activation of Agrp neurons modulates memory-related cognitive processes in mice, Pharmacol Res (2019).
[6] G. Huguet, L. Aldavert-Vera, E. Kadar, S. Pena de Ortiz, I. Morgado-Bernal, P. Segura-Torres, Intracranial self-stimulation to the lateral hypothalamus, a memory improving treatment, results in hippocampal changes in gene expression, Neuroscience 162 (2009) 359–374.
[7] B. Beck, G Pourie, Ghrelin, neuropeptide Y, and other feeding-regulatory peptides active in the hippocampus: role in learning and memory, Nutr Rev 71 (2013) 541–561.
[8] S.V. Mahler, D.E. Moorman, R.J. Smith, M.H. James, G Aston-Jones, Motivational activation: a unifying hypothesis of orexin/hypocretin function, Nat Neurosci 17 (2014) 1298–1303.
[9] S.M. Sternson, A.K. Eiselt, Three Pillars for the Neural Control of Appetite, Annu Rev Physiol 79 (2017) 401–423.
[10] G.D. Stuber, R.A. Wise, Lateral hypothalamic circuits for feeding and reward, Nat Neurosci 19 (2016) 198–205.
[11] M. Schwartz, P. Teitelbaum, Dissociation between learning and remembering in rats with lesions in the lateral hypothalamus, J Comp Physiol Psychol 87 (1974) 384–398.
[12] T. Ishii, Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia, Acta Neuropathol 6 (1966) 181–187.
[13] C.B. Saper, D.C. German, Hypothalamic pathology in Alzheimer's disease, Neuroscience letters 74 (1987) 364–370.
[14] B. Pachoud, A. Adamantidis, P. Ravassard, P.H. Luppi, T. Grisar, B. Lakaye, et al., Major impairments of glutamatergic transmission and long-term synaptic plasticity in the hippocampus of mice lacking the melanin-concentrating hormone receptor-1, J Neurophysiol 104 (2010) 1417–1425.
[15] A. Adamantidis, L. de Lecea, A role for Melanin-Concentrating Hormone in learning and memory, Peptides 30 (2009) 2066–2070.
[16] K. Touzani, A. Sclafani, Lateral hypothalamic lesions impair flavour-nutrient and flavour-toxin trace learning in rats, Eur J Neurosci 16 (2002) 2425–2433.
[17] A.M. Rosenwasser, R.J. Pelchat, N.T. Adler, Memory for feeding time: possible dependence on coupled circadian oscillators, Physiol Behav 32 (1984) 25–30.
[18] R. Ptak, B. Birtoli, H. Imboden, C. Hauser, J. Weis, A. Schnider, Hypothalamic amnesia with spontaneous confabulations: a clinicopathologic study, Neurology 56 (2001) 1597–1600.
[19] A.G. Reeves, F Plum, Hyperphagia, rage, and dementia accompanying a ventromedial hypothalamic neoplasm, Arch Neurol 20 (1969) 616–624.
[20] K. Devarakonda, P.J.Energy Balance Kenny, Lateral Hypothalamus Hoards Food Memories, Current biology : CB 27 (2017) R803–R8R5.
[21] C. Destrade, R Jaffard, Post-trial hippocampal and lateral hypothalamic electrical stimulation. Facilitation on long-term memory of appetitive and avoidance learning tasks, Behav Biol 22 (1978) 354–374.
[22] D. Coulombe, N. White, The effect of post-training lateral hypothalamic self-stimulation on aversive and appetitive classical conditioning, Physiol Behav 25 (1980) 267–272.
[23] M.J. Krashes, S. DasGupta, A. Vreede, B. White, J.D. Armstrong, S. Waddell, A neural circuit mechanism integrating motivational state with memory expression in Drosophila, Cell 139 (2009) 416–427.
[24] S.M. Sternson, Hypothalamic survival circuits: blueprints for purposive behaviors, Neuron 77 (2013) 810–824.
[25] P.M. Itskov, C. Ribeiro, The dilemmas of the gourmet fly: the molecular and neuronal mechanisms of feeding and nutrient decision making in Drosophila, Front Neurosci 7 (2013) 12.
[26] C. Ribeiro, B.J. Dickson, Sex peptide receptor and neuronal TOR/S6K signaling modulate nutrient balancing in Drosophila, Curr Biol 20 (2010) 1000–1005.
[27] D. Raubenheimer, S.J. Simpson, A.H Tait, Match and mismatch: conservation physiology, nutritional ecology and the timescales of biological adaptation, Philos Trans R Soc Lond B Biol Sci 367 (2012) 1628–1646.
[28] V.M. Corrales-Carvajal, A.A. Faisal, C. Ribeiro, Internal states drive nutrient homeostasis by modulating exploration-exploitation trade-off, Elife 5 (2016).
[29] M. Fujita, T. Tanimura, Drosophila evaluates and learns the nutritional value of sugars, Curr Biol 21 (2011) 751–755.
[30] C.J. Burke, S. Waddell, Remembering nutrient quality of sugar in Drosophila, Curr Biol 21 (2011) 746–750.
[31] Y. Zhang, G. Liu, J. Yan, Y. Zhang, B. Li, D. Cai, Metabolic learning and memory formation by the brain influence systemic metabolic homeostasis, Nature communications 6 (2015) 6704.
[32] V. Hartenstein, The neuroendocrine system of invertebrates: a developmental and evolutionary perspective, J Endocrinol 190 (2006) 555–570.
[33] A.I. Domingos, A. Sordillo, M.O. Dietrich, Z.W. Liu, L.A. Tellez, J. Vaynshteyn, et al., Hypothalamic melanin concentrating hormone neurons communicate the nutrient value of sugar, Elife 2 (2013) e01462.
[34] V. Mavanji, T.A. Butterick, C.M. Duffy, J.P. Nixon, C.J. Billington, C.M. Kotz, Orexin/hypocretin treatment restores hippocampal-dependent memory in orexin-deficient mice, Neurobiol Learn Mem 146 (2017) 21–30.
[35] P.Y. Placais, T Preat, To favor survival under food shortage, the brain disables costly memory, Science 339 (2013) 440–442.
[36] Y. Niv, Reinforcement learning in the brain, Journal of Mathematical Psychology (2009) 139–154.
[37] P. Dayan, Y Niv, Reinforcement learning: the good, the bad and the ugly, Current opinion in neurobiology 18 (2008) 185–196.
[38] P. Iordanidou, D Burdakov, Brain glucose feedback predicts food choice (Commentary on Wakabayashi et al.), Eur J Neurosci 43 (2016) 1420–1421.
[39] J.W. de Jong, S.A. Afjei, I. Pollak Dorocic, J.R. Peck, C. Liu, C.K. Kim, et al., A Neural Circuit Mechanism for Encoding Aversive Stimuli in the Mesolimbic Dopamine System, Neuron 101 (2019) 133-51 e7.
[40] M.J. Sharpe, N.J. Marchant, L.R. Whitaker, C.T. Richie, Y.J. Zhang, E.J. Campbell, et al., Lateral Hypothalamic GABAergic Neurons Encode Reward Predictions that Are Relayed to the Ventral Tegmental Area to Regulate Learning, Current biology : CB 27 (2017) 2089-100 e5.
[41] M.M. Karnani, J. Apergis-Schoute, A. Adamantidis, L.T. Jensen, L. de Lecea, L. Fugger, et al., Activation of central orexin/hypocretin neurons by dietary amino acids, Neuron 72 (2011) 616–629.
[42] J.A. Gonzalez, P. Iordanidou, M. Strom, A. Adamantidis, D. Burdakov, Awake dynamics and brain-wide direct inputs of hypothalamic MCH and orexin networks, Nature communications 7 (2016) 11395.
[43] D. Burdakov, J.A. Gonzalez, Physiological functions of glucose-inhibited neurones, Acta Physiol (Oxf) 195 (2009) 71–78.
[44] C. Kosse, C. Schone, E. Bracey, D. Burdakov, Orexin-driven GAD65 network of the lateral hypothalamus sets physical activity in mice, Proceedings of the National Academy of Sciences of the United States of America 114 (2017) 4525–4530.
[45] R.H. Williams, H. Alexopoulos, L.T. Jensen, L. Fugger, D. Burdakov, Adaptive sugar sensors in hypothalamic feeding circuits, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 11975–11980.
[46] C. Schöne, J. Apergis-Schoute, T. Sakurai, A. Adamantidis, D. Burdakov, Coreleased orexin and glutamate evoke nonredundant spike outputs and computations in histamine neurons, Cell reports 7 (2014) 697–704.
[47] C. Blomeley, C. Garau, D Burdakov, Accumbal D2 cells orchestrate innate risk-avoidance according to orexin signals, Nature neuroscience 21 (2018) 29–32.
[48] M.J. Burton, E.T. Rolls, F. Mora, Effects of hunger on the responses of neurons in the lateral hypothalamus to the sight and taste of food, Exp Neurol 51 (1976) 668–677.
[49] F. Mora, E.T. Rolls, M.J. Burton, Modulation during learning of the responses of neurons in the lateral hypothalamus to the sight of food, Exp Neurol 53 (1976) 508–519.
[50] E.T. Rolls, M.J. Burton, F. Mora, Hypothalamic neuronal responses associated with the sight of food, Brain Res 111 (1976) 53–66.
[51] W.J. Giardino, A. Eban-Rothschild, D.J. Christoffel, S.B. Li, R.C. Malenka, L. de Lecea, Parallel circuits from the bed nuclei of stria terminalis to the lateral hypothalamus drive opposing emotional states, Nature neuroscience 21 (2018) 1084–1095.
[52] W.J. Giardino, de Lecea, L. Hypocretin, (orexin) neuromodulation of stress and reward pathways, Current opinion in neurobiology 29 (2014) 103–108.
[53] A. Yamanaka, C.T. Beuckmann, J.T. Willie, J. Hara, N. Tsujino, M. Mieda, et al., Hypothalamic orexin neurons regulate arousal according to energy balance in mice, Neuron 38 (2003) 701–713.
[54] G. Provensi, M.B. Passani, A. Costa, I. Izquierdo, P. Blandina, Neuronal histamine and the memory of emotionally salient events, Br J Pharmacol (2018).
[55] D. Burdakov, O. Gerasimenko, A. Verkhratsky, Physiological changes in glucose differentially modulate the excitability of hypothalamic melanin-concentrating hormone and orexin neurons in situ, J Neurosci 25 (2005) 2429–2433.
[56] M. Karnani, D Burdakov, Multiple hypothalamic circuits sense and regulate glucose levels, Am J Physiol Regul Integr Comp Physiol 300 (2011) R47–R55.
[57] A. Venner, M.M. Karnani, J.A. Gonzalez, L.T. Jensen, L. Fugger, D. Burdakov, Orexin neurons as conditional glucosensors: paradoxical regulation of sugar sensing by intracellular fuels, J Physiol 589 (2011) 5701–5708.
[58] Y. Oomura, T. Ono, H. Ooyama, M.J. Wayner, Glucose and osmosensitive neurones

of the rat hypothalamus, Nature 222 (1969) 282–284.
[59] H. Nishino, Y. Oomura, Z. Karadi, L. Lenard, Y. Kai, A. Fukuda, et al., Internal and external information processing by lateral hypothalamic glucose-sensitive and insensitive neurons during bar press feeding in the monkey, Brain Res Bull 20 (1988) 839–845.
[60] D Burdakov, Reactive and predictive homeostasis: Roles of orexin/hypocretin neurons, Neuropharmacology 154 (2019) 61–67.
[61] L. de Lecea, T.S. Kilduff, C. Peyron, X. Gao, P.E. Foye, P.E. Danielson, et al., The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity, Proceedings of the National Academy of Sciences of the United States of America, 95 1998, pp. 322–327.
[62] T. Sakurai, A. Amemiya, M. Ishii, I. Matsuzaki, R.M. Chemelli, H. Tanaka, et al., Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior, Cell 92 (1998) 573–585.
[63] C. Schöne, Z.F. Cao, J. Apergis-Schoute, A. Adamantidis, T. Sakurai, D. Burdakov, Optogenetic probing of fast glutamatergic transmission from hypocretin/orexin to histamine neurons in situ, J Neurosci 32 (2012) 12437–12443.
[64] C. Schöne, D. Burdakov, Glutamate and GABA as rapid effectors of hypothalamic "peptidergic" neurons, Front Behav Neurosci 6 (2012) 81.
[65] O.K. Hassani, M.R. Krause, L. Mainville, C.A. Cordova, B.E. Jones, Orexin Neurons Respond Differentially to Auditory Cues Associated with Appetitive versus Aversive Outcomes, J Neurosci 36 (2016) 1747–1757.
[66] T. Sakurai, The role of orexin in motivated behaviours, Nat Rev Neurosci 15 (2014) 719–731.
[67] A. Inutsuka, A. Yamashita, S. Chowdhury, J. Nakai, M. Ohkura, T. Taguchi, et al., The integrative role of orexin/hypocretin neurons in nociceptive perception and analgesic regulation, Sci Rep 6 (2016) 29480.
[68] E.H. Nieh, C.M. Vander Weele, G.A. Matthews, K.N. Presbrey, R. Wichmann, C.A. Leppla, et al., Inhibitory Input from the Lateral Hypothalamus to the Ventral Tegmental Area Disinhibits Dopamine Neurons and Promotes Behavioral Activation, Neuron 90 (2016) 1286–1298.
[69] D. Burdakov, D. Peleg-Raibstein, Hypothalamic Heuristics for Survival, Trends Endocrinol Metab 30 (2019) 689–691.
[70] O. Selbach, N. Doreulee, C. Bohla, K.S. Eriksson, O.A. Sergeeva, W. Poelchen, et al., Orexins/hypocretins cause sharp wave- and theta-related synaptic plasticity in the hippocampus via glutamatergic, gabaergic, noradrenergic, and cholinergic signaling, Neuroscience 127 (2004) 519–528.
[71] O. Selbach, C. Bohla, a. Barbara, N. Doreulee, K.S. Eriksson, O.a. Sergeeva, et al., Orexins/hypocretins control bistability of hippocampal long-term synaptic plasticity through co-activation of multiple kinases, Acta physiologica (Oxford 198 (2010) 277–285 England).
[72] A. Adamantidis, E. Thomas, A. Foidart, A. Tyhon, B. Coumans, A. Minet, et al., Disrupting the melanin-concentrating hormone receptor 1 in mice leads to cognitive deficits and alterations of NMDA receptor function, Eur J Neurosci 21 (2005) 2837–2844.
[73] D. Burdakov, M.M. Karnani, Ultra-sparse connectivity within the lateral hypothalamus, bioRxiv. (2020).
[74] B Roozendaal, Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval, Neurobiol Learn Mem 78 (2002) 578–595.
[75] D.M. Bannerman, R. Sprengel, D.J. Sanderson, S.B. McHugh, J.N. Rawlins, H. Monyer, et al., Hippocampal synaptic plasticity, spatial memory and anxiety, Nature reviews. Neuroscience 15 (2014) 181–192.
[76] P.L. Johnson, W. Truitt, S.D. Fitz, P.E. Minick, A. Dietrich, S. Sanghani, et al., A key role for orexin in panic anxiety, Nat Med 16 (2010) 111–115.
[77] P. Bonnavion, A.C. Jackson, M.E. Carter, L. de Lecea, Antagonistic interplay between hypocretin and leptin in the lateral hypothalamus regulates stress responses, Nat Commun 6 (2015) 6266.
[78] W. Heydendael, A. Sengupta, S. Beck, S. Bhatnagar, Optogenetic examination identifies a context-specific role for orexins/hypocretins in anxiety-related behavior, Physiol Behav 130 (2014) 182–190.
[79] A. Flores, R. Saravia, R. Maldonado, F Berrendero, Orexins and fear: implications for the treatment of anxiety disorders, Trends Neurosci 38 (2015) 550–559.
[80] P.L. Johnson, A. Molosh, S.D. Fitz, W.A. Truitt, A Shekhar, Orexin, stress, and anxiety/panic states, Prog Brain Res 198 (2012) 133–161.
[81] T Kuwaki, Orexin links emotional stress to autonomic functions, Auton Neurosci 161 (2011) 20–27.
[82] R. Winsky-Sommerer, A. Yamanaka, S. Diano, E. Borok, A.J. Roberts, T. Sakurai, et al., Interaction between the corticotropin-releasing factor system and hypocretins (orexins): a novel circuit mediating stress response, J Neurosci 24 (2004) 11439–11448.
[83] M. Suzuki, C.T. Beuckmann, K. Shikata, H. Ogura, T Sawai, Orexin-A (hypocretin-1) is possibly involved in generation of anxiety-like behavior, Brain Res 1044 (2005) 116–121.
[84] E.A. Lungwitz, A. Molosh, P.L. Johnson, B.P. Harvey, R.C. Dirks, A. Dietrich, et al., Orexin-A induces anxiety-like behavior through interactions with glutamatergic receptors in the bed nucleus of the stria terminalis of rats, Physiology & behavior 107 (2012) 726–732.
[85] L.A. Grafe, D. Eacret, J. Dobkin, S Bhatnagar, Reduced Orexin System Function Contributes to Resilience to Repeated Social Stress, eNeuro 5 (2018).
[86] D. Eacret, L.A. Grafe, J. Dobkin, A.L. Gotter, J.J. Renger, C.J. Winrow, et al., Orexin signaling during social defeat stress influences subsequent social interaction behaviour and recognition memory, Behav Brain Res. 356 (2019) 444–452.
[87] D Burdakov, How orexin signals bias action: Hypothalamic and accumbal circuits, Brain Res (2018).
[88] J.C. Bittencourt, Anatomical organization of the melanin-concentrating hormone peptide family in the mammalian brain, Gen Comp Endocrinol 172 (2011) 185–197.
[89] C. Blanco-Centurion, S. Luo, D.J. Spergel, A. Vidal-Ortiz, S.A. Oprisan, A.N. Van den Pol, et al., Dynamic Network Activation of Hypothalamic MCH Neurons in REM Sleep and Exploratory Behavior, J Neurosci 39 (2019) 4986–4998.
[90] M.M. Karnani, C. Schone, E.F. Bracey, J.A. Gonzalez, P. Viskaitis, H.T. Li, et al., Role of spontaneous and sensory orexin network dynamics in rapid locomotion initiation, Prog Neurobiol (2020) 101771.
[91] B.Y. Mileykovskiy, L.I. Kiyashchenko, J.M. Siegel, Behavioral correlates of activity in identified hypocretin/orexin neurons, Neuron 46 (2005) 787–798.
[92] D. Kong, L. Vong, L.E. Parton, C. Ye, Q. Tong, X. Hu, et al., Glucose stimulation of hypothalamic MCH neurons involves K(ATP) channels, is modulated by UCP2, and regulates peripheral glucose homeostasis, Cell Metab 12 (2010) 545–552.
[93] M.M. Karnani, G. Szabo, F. Erdelyi, D. Burdakov, Lateral hypothalamic GAD65 neurons are spontaneously firing and distinct from orexin- and melanin-concentrating hormone neurons, J Physiol 591 (2013) 933–953.
[94] M. Crawford, F.A Masterson, Species-specific defense reactions and avoidance learning. An evaluative review, Pavlov J Biol Sci 17 (1982) 204–214.
[95] S.C. Motta, M. Goto, F.V. Gouveia, M.V. Baldo, N.S. Canteras, L.W. Swanson, Dissecting the brain's fear system reveals the hypothalamus is critical for responding in subordinate conspecific intruders, Proc Natl Acad Sci U S A 106 (2009) 4870–4875.
[96] J.E. LeDoux, Emotional memory systems in the brain, Behav Brain Res 58 (1993) 69–79.
[97] D.C. Blanchard, G. Griebel, R.J Blanchard, Mouse defensive behaviors: pharmacological and behavioral assays for anxiety and panic, Neurosci Biobehav Rev 25 (2001) 205–218.
[98] N.S. Canteras, S. Chiavegatto, L.E. Ribeiro do Valle, L.W. Swanson, Severe reduction of rat defensive behavior to a predator by discrete hypothalamic chemical lesions, Brain Res Bull 44 (1997) 297–305.
[99] R.C. Martinez, E.F. Carvalho-Netto, V.C. Amaral, R.L. Nunes-de-Souza, N.S. Canteras, Investigation of the hypothalamic defensive system in the mouse, Behav Brain Res 192 (2008) 185–190.
[100] A.F. Cezario, E.R. Ribeiro-Barbosa, M.V. Baldo, N.S. Canteras, Hypothalamic sites responding to predator threats–the role of the dorsal premammillary nucleus in unconditioned and conditioned antipredatory defensive behavior, Eur J Neurosci 28 (2008) 1003–1015.
[101] A. Ponz, R. Khatami, R. Poryazova, E. Werth, P. Boesiger, S. Schwartz, et al., Reduced amygdala activity during aversive conditioning in human narcolepsy, Ann Neurol 67 (2010) 394–398.
[102] C. Schiappa, S. Scarpelli, A. D'Atri, M. Gorgoni, L De Gennaro, Narcolepsy and emotional experience: a review of the literature, Behav Brain Funct 14 (2018) 19.
[103] C. Peyron, J. Faraco, W. Rogers, B. Ripley, S. Overeem, Y. Charnay, et al., A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains, Nat Med 6 (2000) 991–997.
[104] V. Tucci, G.Cataplexy Plazzi, an affair of pleasure or an unpleasant affair? Neurosci Lett 450 (2009) 90–91.
[105] R.M. Sears, A.E. Fink, M.B. Wigestrand, C.R. Farb, L. de Lecea, J.E. Ledoux, Orexin/hypocretin system modulates amygdala-dependent threat learning through the locus coeruleus, Proceedings of the National Academy of Sciences of the United States of America, 110 2013, pp. 20260–20265.
[106] S. Soya, H. Shoji, E. Hasegawa, M. Hondo, T. Miyakawa, M. Yanagisawa, et al., Orexin receptor-1 in the locus coeruleus plays an important role in cue-dependent fear memory consolidation, J Neurosci 33 (2013) 14549–14557.
[107] M.A. Steiner, H. Lecourt, F. Jenck, The brain orexin system and almorexant in fear-conditioned startle reactions in the rat, Psychopharmacology (Berl) 223 (2012) 465–475.
[108] X. Chen, H. Wang, Z. Lin, S. Li, Y. Li, H.T. Bergen, et al., Orexins (hypocretins) contribute to fear and avoidance in rats exposed to a single episode of footshocks, Brain Struct Funct 219 (2014) 2103–2118.
[109] J. Apergis-Schoute, P. Iordanidou, C. Faure, S. Jego, C. Schone, T. Aitta-Aho, et al., Optogenetic evidence for inhibitory signaling from orexin to MCH neurons via local microcircuits, J Neurosci 35 (2015) 5435–5441.
[110] A.N. van den Pol, C. Acuna-Goycolea, K.R. Clark, P.K. Ghosh, Physiological Properties of Hypothalamic MCH Neurons Identified with Selective Expression of Reporter Gene after Recombinant Virus Infection, Neuron 42 (2004) 635–652.
[111] S. Jego, S.D. Glasgow, C.G. Herrera, M. Ekstrand, S.J. Reed, R. Boyce, et al., Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus, Nature neuroscience 16 (2013) 1637–1643.
[112] L. Verret, R. Goutagny, P. Fort, L. Cagnon, D. Salvert, L. Leger, et al., A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep, BMC Neurosci 4 (2003) 19.
[113] A.R. Adamantidis, M.H. Schmidt, M.E. Carter, D. Burdakov, C. Peyron, T.E. Scammell, A circuit perspective on narcolepsy, Sleep (2020).
[114] C.L.A. Bassetti, A. Adamantidis, D. Burdakov, F. Han, S. Gay, U. Kallweit, et al., Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment, Nat Rev Neurol. 15 (2019) 519–539.
[115] T. Sakurai, The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness, Nature reviews. Neuroscience. 8 (2007) 171–181.
[116] B. Borowsky, M.M. Durkin, K. Ogozalek, M.R. Marzabadi, J. DeLeon, B. Lagu, et al., Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist, Nature medicine 8 (2002) 825–830.
[117] C. Kosse, D. Burdakov, A unifying computational framework for stability and flexibility of arousal, Front Syst Neurosci 8 (2014) 192.
[118] C. Schone, D. Burdakov, Orexin/Hypocretin and Organizing Principles for a Diversity of Wake-Promoting Neurons in the Brain, Curr Top Behav Neurosci 33 (2017) 51–74.

[119] C.G. Herrera, A. Ponomarenko, T. Korotkova, D. Burdakov, Adamantidis, A. Sleep & metabolism: The multitasking ability of lateral hypothalamic inhibitory circuitries, Front Neuroendocrinol 44 (2017) 27–34.
[120] M. Varas, M. Perez, O. Ramirez, S.R. de Barioglio, Melanin concentrating hormone increase hippocampal synaptic transmission in the rat, Peptides 23 (2002) 151–155.
[121] M.M. Varas, M.F. Perez, O.A. Ramirez, S.R. de Barioglio, Increased susceptibility to LTP generation and changes in NMDA-NR1 and -NR2B subunits mRNA expression in rat hippocampus after MCH administration, Peptides 24 (2003) 1403–1411.
[122] R.L. Redondo, R.G. Morris, Making memories last: the synaptic tagging and capture hypothesis, Nature reviews. Neuroscience. 12 (2011) 17–30.
[123] M. Carus-Cadavieco, M. Gorbati, L. Ye, F. Bender, S. van der Veldt, C. Kosse, et al., Gamma oscillations organize top-down signalling to hypothalamus and enable food seeking, Nature 542 (2017) 232–236.
[124] C. Kosse, D. Burdakov, Fast and Slow Oscillations Recruit Molecularly-Distinct Subnetworks of Lateral Hypothalamic Neurons In Situ, eNeuro. 5 (2018).
[125] R.H. Williams, L.T. Jensen, A. Verkhratsky, L. Fugger, D. Burdakov, Control of hypothalamic orexin neurons by acid and CO2, Proceedings of the National Academy of Sciences of the United States of America, 104 2007, pp. 10685–10690.
[126] D. Burdakov, H. Alexopoulos, A. Vincent, F.M. Ashcroft, Low-voltage-activated A-current controls the firing dynamics of mouse hypothalamic orexin neurons, Eur J Neurosci 20 (2004) 3281–3285.
[127] E. Eggermann, L. Bayer, M. Serafin, B. Saint-Mleux, L. Bernheim, D. Machard, et al., The wake-promoting hypocretin-orexin neurons are in an intrinsic state of membrane depolarization, J Neurosci 23 (2003) 1557–1562.
[128] Y. Li, X.B. Gao, T. Sakurai, A.N. van den Pol, Hypocretin/Orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system, Neuron 36 (2002) 1169–1181.
[129] M.D. Belle, A.T. Hughes, D.A. Bechtold, P. Cunningham, M. Pierucci, D. Burdakov, et al., Acute suppressive and long-term phase modulation actions of orexin on the mammalian circadian clock, J Neurosci 34 (2014) 3607–3621.
[130] O.J. Marston, R.H. Williams, M.M. Canal, R.E. Samuels, N. Upton, H.D. Piggins, Circadian and dark-pulse activation of orexin/hypocretin neurons, Mol Brain 1 (2008) 19.
[131] D. Burdakov, M.M. Karnani, A. Gonzalez, Lateral hypothalamus as a sensor-regulator in respiratory and metabolic control, Physiol Behav 121 (2013) 117–124.
[132] D. Burdakov, H Alexopoulos, Metabolic state signalling through central hypocretin/orexin neurons, J Cell Mol Med 9 (2005) 795–803.