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A role for MCH neuron firing in modulating hippocampal plasticity threshold

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ABSTRACT

It has been revealed that hypothalamic neurons containing the peptide, melanin-concentrating hormone (MCH) can influence learning [1] and memory formation [2], but the cellular mechanisms by which they perform this function are not well understood. Here, we examine the role of MCH neural input to the hippocampus, and show in vitro that optogenetically increasing MCH axon activity facilitates hippocampal plasticity by lowering the threshold for synaptic potentiation. These results align with increasing evidence that MCH neurons play a regulatory role in learning, and reveal that this could be achieved by modulating plasticity thresholds in the hippocampus.

1. Introduction

Synaptic plasticity in the hippocampus is a major cellular substrate for learning, but the plastic changes that occur there do not happen in isolation. The hippocampus receives a variety of input projections from different brain regions, which could theoretically modulate synaptic plasticity during learning, according to their unique environmental responses. One such candidate are hypothalamic neurons containing the neuropeptide transmitter, melanin-concentrating hormone (MCH). MCH neurons project widely from the lateral hypothalamus (LH) throughout the brain [3–6], with particularly dense innervation of the hippocampus [3]. Infusion of the MCH peptide itself directly into the hippocampus improves memory retention [4,5], and silencing MCH neurons during an object recognition task disrupts memory formation [2]. In vitro work has shown that when MCH neurons [6] or MCH receptors [7] are genetically deleted, hippocampal plasticity is impaired such that a larger stimulus is required to induce long term potentiation (LTP).

These lines of evidence suggest that MCH input to the hippocampus may be capable of modulating synaptic plasticity, and would predict that *increased* MCH input should *facilitate* synaptic plasticity. Here, we tested this hypothesis directly, by optogenetically activating MCH axons in hippocampal slices. We found that increased MCH neuron activity in the hippocampus lowered the threshold for lasting synaptic potentiation. These results provide evidence that MCH neuron activity in the hippocampus can facilitate local synaptic plasticity, and support the idea that MCH neurons may regulate hippocampus-dependent learning, through modulatory effects on the threshold of hippocampal synaptic plasticity.

2. Results

We stereotaxically injected cre-inducible channelrhodopsin (ChR2 (H134R)-EYFP) bilaterally into the mouse lateral hypothalamus of MCH-Cre mice (Fig. 1A and B). Whole-cell patch-clamping confirmed that all EYFP-expressing cells tested (11/11) responded to blue light stimulation (Fig. 1C).

We examined the effects of optogenetic activation of MCH axons in the hippocampus on the plasticity of pyramidal cell excitatory field potentials (fEPSPs, Fig. 2A). We implemented three classical plasticity protocols: a weak potentiating stimulus (1 tetanus; typically inducing brief post-tetanic potentiation, PTP), a strong potentiating stimulus

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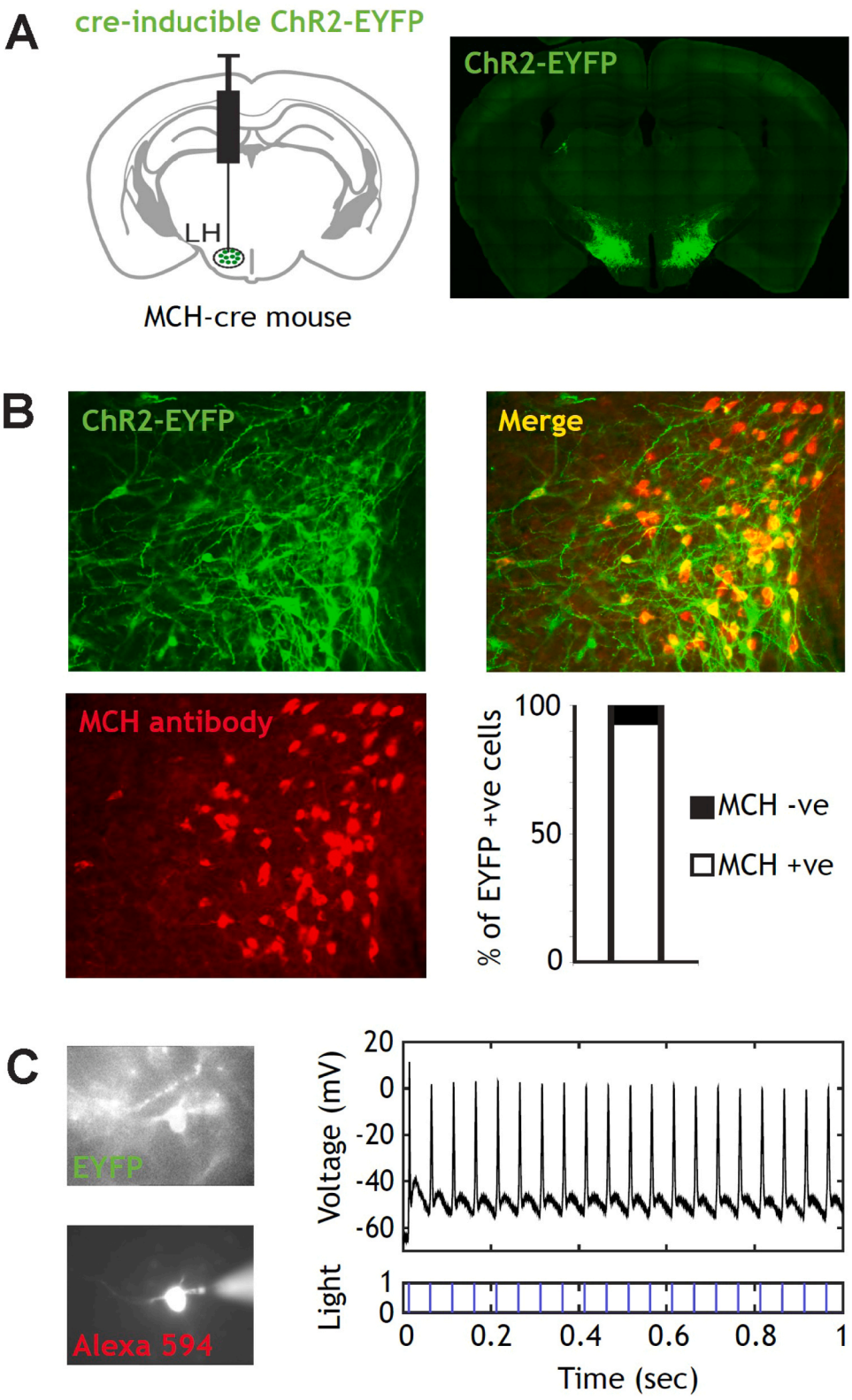

Fig. 1. Channelrhodopsin expression in hypothalamic MCH neurons. (A) Bilatereral stereotaxic injection of cre-inducible ChR2(H134R)-EYFP into the lateral hypothalamus (LH) of MCH-cre mice. (B) ChR2-EYFP is expressed in cell bodies and axons of neurons in the LH. 93% (311/336 cells; slices=6; mouse=1) of cell bodies expressing ChR2-EYFP also stain for MCH antibody. (C) Whole cell patch clamping in the LH. 100% (11/11) of EYFP-expressing cells fire action potentials in response to blue light. 0% (0/9) of non-fluorescent cells respond to blue light (slices = 20; mice = 6).

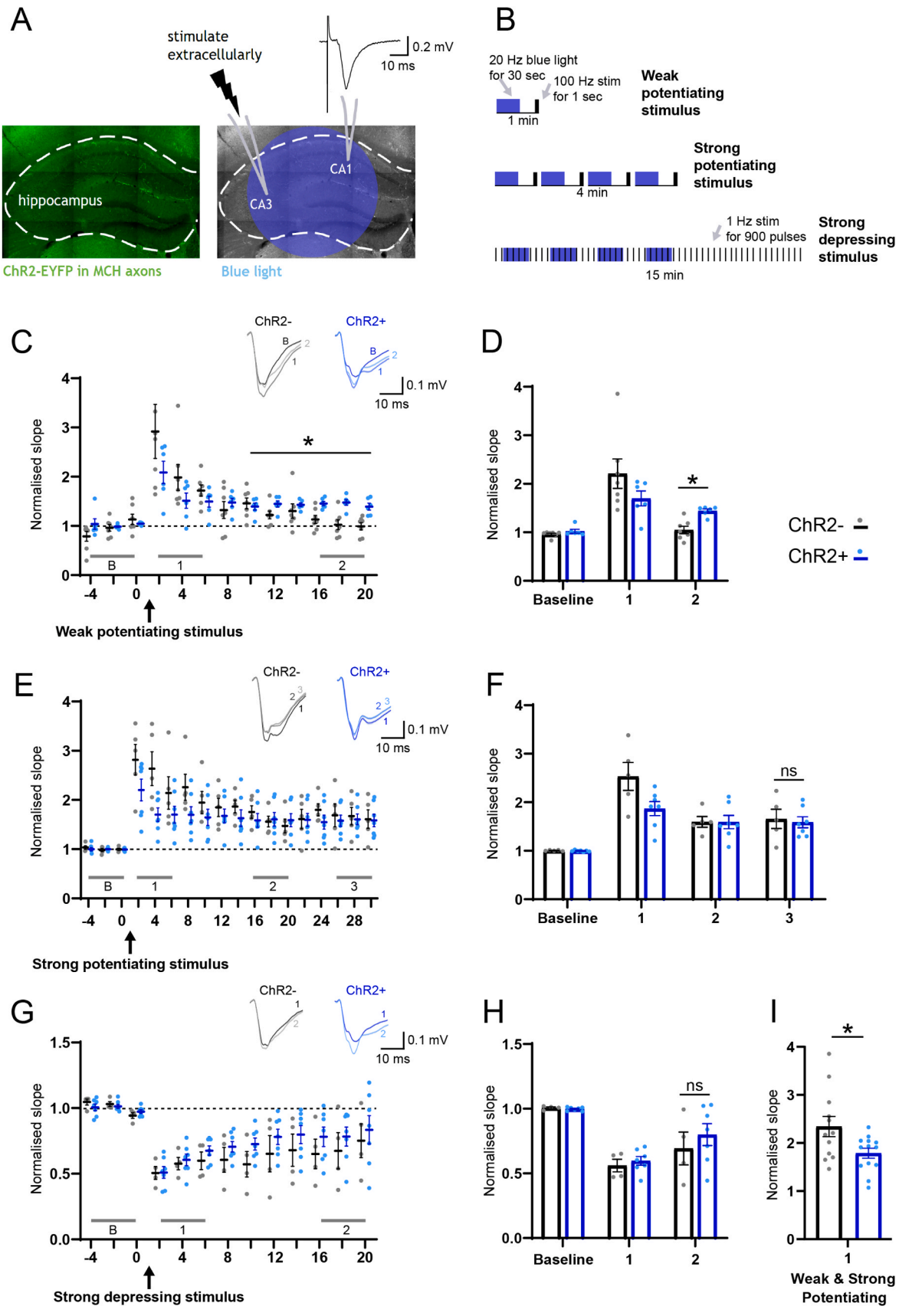

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Fig. 2. MCH axon activation lowers threshold for synaptic potentiation. (A) ChR2-EYFP-expressing MCH axons were visible in the hippocampus (left). Excitatory postsynaptic field potentials (fEPSPs) were generated by extracellular stimulation in CA3 and recorded in CA1 (right). Blue light illuminated the hippocampus, interleaved with electrical stimuli, as in B. (B) Electrical stimulation patterns designed to trigger three different types of classical synaptic plasticity were combined with blue light illumination (20 Hz for 30 s) of the hippocampus to active MCH axons. (C) Optogenetic activation of MCH axons in the hippocampus altered the lasting plasticity response to a weak potentiating stimulus. The fEPSPs in MCH-ChR2- control slices (n = 7) and MCH-ChR2+ slices (n = 6) behaved differently over time (RM ANOVA interaction effect: $F(5, 55) = 3.121$, $p = 0.0150$). (D) In MCH-ChR2- control slices, fEPSPs decayed back to baseline, while in MCH-ChR2+ slices, fEPSPs remained greater than baseline (paired *t*-test, $p < 0.001$) and control slices (independent *t*-test, $p = 0.001$) at 16–20 min. (E) Optogenetic activation of hippocampal MCH axons did not alter the lasting response to a strong potentiating stimulus (RM ANOVA, no significant interaction: $F(10, 100) = 1.79$, $p = 0.072$) (MCH-ChR2- slices=5; MCH-ChR2+ slices=7). (F) In both MCH-ChR2+ and MCH-ChR2- slices, fEPSPs did not decay to their baseline levels by 16–20 min (paired t-tests, ChR2- $p = 0.004$; ChR2+ $p = 0.005$), and by 26–30 min the two conditions were still statistically similar (independent *t*-test, $p = 0.61$). (G) Optogenetic activation of hippocampal MCH axons did not alter the response to a strong depressing electrical stimulus (RM ANOVA, no significant interaction: $F(5, 45) = 0.24$, $p = 0.94$) (MCH-ChR2- slices=4; MCH-ChR2+ slices=7). (H) fEPSPs in MCH-ChR2- slice and MCH-ChR2+ slices were not different at 16–20 min (independent *t*-test, $p = 0.48$). (I) For the weak and strong potentiating conditions pooled together, the initial post-tetanic potentiation was smaller in the MCH-ChR2+ slices (n = 13) than the MCH-ChR2- slices (n = 12) (independent *t*-test, $p = 0.024$). Insets in C,E and G are the averaged fEPSP traces across each indicated time period for two example slices. (Total mice: MCH-ChR2- mice=6; MCH-ChR2+ mice=6).

(four tetani; typically inducing long-term potentiation, LTP), and a depressing stimulus (900 single pulses delivered at 1 Hz, typically inducing long-term depression, LTD), each interleaved with blue light stimulation of MCH axons (Fig. 2B). We stimulated MCH axons at 20 Hz for 30 sec, which was designed to encourage peptide release [8], although it is important to note that either glutamate and or GABA release could also be triggered by this stimulation [9].

Optogenetic activation of MCH axons in the hippocampus significantly altered the lasting plasticity response to the weak potentiating stimulus. After the immediate and short-term PTP seen in both conditions (period 1, Fig. 2C), the fEPSPs in MCH-ChR2- control slices and MCH-ChR2+ slices behaved differently (repeated measures ANOVA interaction effect: $F(5, 55) = 3.121$, $p = 0.0150$). In MCH-ChR2- control slices, fEPSPs decayed back to baseline levels by ~15 mins (black points). In MCH-ChR2+ slices, the same electrical and optogenetic stimulation led to potentiation that did not decay after 10 min, and remained significantly elevated comparted to both baseline (paired *t*-test, $p < 0.001$) and control slices (independent *t*-test, $p = 0.001$) at 16–20 min (Fig. 2D; see Supplementary Table 1 for exact means and p values).

On the other hand, optogenetic activation of MCH axons in the hippocampus did not alter the response to the strong potentiating stimulus (Fig. 2E; repeated measures ANOVA, no significant interaction: $F(10, 100) = 1.79$, $p = 0.072$). In both MCH-ChR2+ and MCH-ChR2- slices, fEPSPs did not decay to their baseline levels by 16–20 min (paired *t*-tests, ChR2- $p = 0.004$; ChR2+ $p = 0.005$), and by 26–30 min the two conditions were still statistically similar (independent *t*-test, $p = 0.61$) (Fig. 2F; see Supplementary Table 1 for all exact mean values and p values).

Similarly, optogenetic activation of MCH axons in the hippocampus did not alter the response to a strong depressing electrical stimulation (Fig. 2G; repeated measures ANOVA, no significant interaction: $F(5, 45) = 0.24$, $p = 0.94$) (MCH-ChR2- slices=4; MCH-ChR2+ slices=7). fEPSPs in MCH-ChR2- slice and MCH-ChR2+ slices were not significantly different at 16–20 min (independent *t*-test, $p = 0.48$) (Fig. 2H; see Supplementary Table 1 for all exact mean values and p values).

Thus, while the activation of MCH axons in the hippocampus has no impact on the lasting potentiation or depression triggered by a strong electrical induction stimulus, it can convert the effects of a weak induction stimulus from a transient potentiation to a lasting potentiation. Interestingly, MCH activation does not augment the initial transient potentiation itself: in fact, the size of the fEPSP increase during post-tetanic potentiation is smaller in MCH-ChR2+ slices compared to MCH-ChR2- slices (independent *t*-test, $p = 0.024$; pooled across weak and strong conditions; Fig. 2I; Supplementary Table 1).

The mechanism by which MCH axon activity is influencing hippocampal plasticity is currently unclear. To examine whether there is a direct connection between MCH and axons and hippocampal pyramidal neurons, we whole-cell patch-clamped hippocampal pyramidal neurons while light-triggering MCH axons. This experiment did not reveal any direct synaptic input from MCH axons (0/18 pyramidal neurons showed time-locked responses to blue illumination of MCH-ChR2 axons in the hippocampus, Supplementary Fig. 1A). To examine the possibility of an indirect effect of MCH axon activity on pyramidal neurons, we recorded spontaneous excitatory postsynaptic currents (sEPSCs) and spontaneous inhibitory postsynaptic currents (sIPSCs; Supplementary Fig. 1B), before and after the same blue light stimulation that was used in the plasticity protocol (20 Hz for 30 s). This did not affect the frequency of sEPSCs or sIPSCs recorded in pyramidal cells, nor the amplitude of sIPSCs (Supplementary Fig. 1C), but mean sEPSC amplitude was slightly reduced in the three minutes following blue light, in MCH-ChR2+ compared to MCH-ChR2- brain slices (Supplementary Fig. 1C; time-courses shown in Supplementary Fig. 1D).

3. Discussion

We have found that optogenetically activating MCH axons in the hippocampus facilitates synaptic plasticity in vitro, by lowering the threshold for lasting potentiation induced by electrical stimulation. These results point towards a mechanistic explanation of how MCH neurons could provide an online learning signal, lowering the initial threshold for hippocampal synapse strengthening in order to facilitate learning in response to salient cues.

Previous studies have shown that abolishing MCH neuron activity in the brain impairs hippocampal plasticity and learning: in mice congenitally lacking MCH receptors, the threshold for hippocampal plasticity is increased [7], and in mice with selective deletion of MCH neurons in adulthood, hippocampal post-tetanic potentiation is diminished and short-term memory is disrupted [6]. These works suggest that MCH neural input to the hippocampus may be necessary for normal hippocampal plasticity, but as with all genetic knockout approaches, it is hard to rule out the possibility that compensatory mechanisms are responsible for the effects. Here, we show in intact circuits that *increasing* MCH axon activation in the hippocampus *reduces* the threshold for plasticity induction and *increases* the longevity of post-tetanic potentiation (Fig. 2C,D). Interestingly, this long-lasting potentiation follows a reduction in the size of the initial post-tetanic potentiation (Fig. 2I), similar to what is seen when MCH neurons are genetically deleted [6], although in that case the potentiation never recovers, while here it exceeded control conditions when the induction stimulus was weak. These results together suggest that there may be an optimal range of MCH input for short-term potentiation, and that the effects of MCH neuron activity on short-term and long-term plasticity may be independent. Overall, the emerging picture is that MCH input to the hippocampus could play an influential role in modulating the threshold, strength and timescale of hippocampal plasticity.

It is important to point out that the present experiments cannot link the effects of MCH neuron activation on hippocampal plasticity to the release of MCH peptide itself. As MCH neurons are thought to release multiple transmitters (MCH, GABA and glutamate), potentially

dependent on context [9], it is possible that the effects we have observed on both plasticity and sEPSC amplitude are mediated by one or a combination of these, and a key next step will be to take a combined approach using both pharmacological antagonists and cell-type specific receptor deletions (e.g. [7]) to dissect out the pathway that is responsible for reducing the plasticity threshold. Neither can we claim that the observed effects on sEPSC amplitude are related to the effects on plasticity. However, our speculative hypothesis is that, while MCH neurons do not directly contact hippocampal interneurons (Supplementary Fig. 1A), they may act on hippocampal interneurons, thus modulating the level of local inhibition (as they do in the septo-hippocampal formation; [1, 10]). Reduced tonic inhibition is known to increase the amplitude of sEPSCs and sEPSPs [11,12], and so the decreased amplitude of sEPSCs that we observed (Supplementary Fig. 1C) would suggest an increase in tonic inhibition. This could effectively increase the signal-to-noise ratio for evoked postsynaptic currents in hippocampal pyramidal neurons, facilitating synaptic potentiation, a mechanism that has previously been proposed to explain the enhanced inhibition of dentate gyrus granule cell dendrites during spatial learning [13]. In this way, MCH neurons could provide a learning signal to the hippocampus, which operates through an inhibition-mediated increase in signal-to-noise ratio, enabling a reduced threshold for synaptic plasticity.

Whether this is likely to be operating in vivo depends on whether MCH neurons are actually active during learning. Previous work from the lab showed that MCH neurons are active during object learning, and that this activity is crucial for the formation of new object memories [2]. Infusion of the MCH peptide directly into the hippocampus has also been shown to increase learning in a step-down avoidance task [4,5] and recently, MCH projections to the dorsolateral septum have been revealed to increase the efficacy of its hippocampal inputs, ultimately facilitating spatial learning [1].

These in vivo studies, together with the present in vitro work, all point towards the possibility of MCH neurons performing a regulatory role during learning, through their direct responses to the environment and their projections to many brain regions, where they have the capacity to directly alter synaptic transmission and plasticity. The importance of MCH neurons in cognition is underlined by the memory-preserving effect of MCH peptide found in mouse models of Alzheimer's disease [14].

One interesting feature of MCH neurons is that they are highly active during REM sleep [15,16] and it therefore seems plausible that this activity contributes to the proposed memory role of REM sleep (reviewed in [17]). It was therefore surprising when [3] recently revealed apparently the opposite: that MCH activity during REM sleep aids *forgetting*. Importantly, Izawa and colleagues also found evidence that wake-active and REM-active MCH neurons are distinct subsets within the hypothalamus. These subsets could modulate hippocampal plasticity in different ways. For instance, the REM-active MCH neurons were found to increase IPSC occurrence in the hippocampus, while we did not see this effect. It is possible that wake-active and REM-active MCH neurons target different populations of interneurons, for example, which could either increase tonic or evoked inhibition respectively, thus increasing the signal-to-noise ratio for learning during the day and promoting depression-mediated forgetting during sleep. Alternatively, it is possible that MCH neurons do not drive remembering or forgetting per se, but instead play a permissive role by acting as "eligibility traces" for plasticity, whereupon other inputs can potentiate or depotentiate synaptic connections [18].

To understand the full picture of how MCH neurons contribute to remembering and forgetting, it will be essential to examine how their activity modulates the cellular mechanisms of plasticity in combination with learning behaviour across different vigilance states and in a subpopulation-specific manner. By lowering the threshold for lasting potentiation, the results presented in this paper contribute a potential mechanism by which some of these neurons could aid memory formation during learning.

4. Methods

4.1. Animals

Animal research has been approved by the United Kingdom Home Office and the Animal Welfare and Ethical Review Panel of the Francis Crick Institute, and Zurich Cantonal Veterinary Office. All procedures were performed in accordance with the Animals (Scientific Procedure) Act of 1986 (UK) and the Animal Welfare Ordinance (TSchV 455.1) of the Swiss Federal Food Safety and Veterinary Office (Switzerland). Mice were kept on a standard chow and water ad libitum and on a 12-h/12-h light/dark cycle. Behaviour experiments were performed during the dark phase, using males and females at least 8 weeks of age. Injections for slice physiology experiments were performed on males and females at least 4 weeks of age, and slices were obtained 14–28 days later.

4.2. Genetic targeting

To target the light-gated ion channel, ChR2 to MCH neurons, we injected Cre-dependent AAV1. EF1a.DIO.hChR2(H134R)-eYFP.WPRE.hGH (>1.4 × 1013 gc/ml; Penn Vector Core, as in [27] bilaterally into the lateral hypothalamus of the previously characterised and validated MCH-Cre mice [19]. Confirmation of functional ChR2 expression was performed using whole-cell patch clamping combined with photostimulation in acute brain slices (Fig. 1).

For stereotaxic brain injections, mice were anaesthetised with isoflurane and injected with meloxicam (Metacam, 2 mg/kg of body weight, s.c.) for analgesia. In a stereotaxic frame (Kopf Instruments), a craniotomy was performed, and a 33-gauge needle mounted on a Hamilton syringe was used to inject AAV vectors into the hypothalamus. Three injections (each 50 nL, at a rate of 50 nL/min) were administered per hemisphere at the following coordinates: bregma, −1.35 mm; midline, ±0.90 mm; depth, 5.70 mm, 5.40 mm, and 5.10 mm [2,20,28]. Before the behaviour experiments, the mice were allowed to recover from surgery for at least 10 days. Before the slice experiments, ChR2 expression was allowed to develop for 14–28 days.

4.3. Immunohistochemistry

50 μm cryosections were stained for MCH using the primary antibody, rabbit polyclonal MCH (1:2000; Phoenix Pharmaceuticals, H-070–47) and the secondary antibody, Alexa Fluor 555 anti-rabbit IgG (1:500; Invitrogen, A-21244). Slices were DAPI-stained and mounted on slides, and images were captured using a Nikon NIS microscope or a Zeiss Axioscan slide scanner.

4.4. Slice physiology

After cervical dislocation, the brain was rapidly removed and immersed in ice-cold, slicing solution containing (in mM) 87 NaCl, 25 NaHCO3, 7 MgCl2, 2.5 KCl, 1.25 NaH2PO4, 0.5 CaCl2, 25 glucose and 75 sucrose, saturated with 95% O2/5% CO2 (modified from [21,22]). The brain was sectioned into 350 μm coronal slices while submerged in ice-cold continuously oxygenated slicing solution. Slices were placed in a storage chamber containing continuously oxygenated artificial cerebrospinal fluid (aCSF) containing (in mM) 124 NaCl, 26 NaHCO3, 1 glucoise, 2.5 KCl, 2.5 CaCl2, 1 NaH2PO4, and 1 MgCl2, which was pre-heated to 30 °C, and allowed to come to room temperature naturally. After 60–90 min of recovery, slices were transferred to a recording chamber (volume = 2.5 ml) in the optical path of a fixed-stage microscope (Olympus BX51WI). During the experiment, slices were continuously perfused (4 ml/min) with 35 °C aCSF, which was constantly bubbled with 95% O2/5% CO2.

MCH neurons in the lateral hypothalamus were selected for whole-

cell recording by their expression of ChR2-EYFP, visualised using a customised filter set (excitation 510/10 nm, dichroic 520 nm, emission 542/27 nm, Laser 2000; Fig. 1). Pyramidal cells in the hippocampus were selected according to the shape and size of the soma, using differential interference contrast optics (Olympus; Supplementary Fig. 1). Whole-cell recordings from MCH neurons in the LH and pyramidal neurons in the hippocampus were obtained using 2- to 3-MΩ borosilicate glass electrodes filled with internal solution containing (in mM) 130 K-gluconate, 10 EGTA, 10 HEPES, 4 NaCl, 4 MgATP, 1 CaCl2, 0.5 Na2GTP, and Alexa Fluor 594 dye. Although recorded spontaneous currents were small (on the order of "mini" currents observed in hippocampal pyramidal neurons [23] as a result of quantal release), these recordings were not done in the presence of TTX and so we have not labelled them as minis.

Recordings were made with a HEKA EPC10 USB Patch Clamp Amplifier, filtered at 5 kHz, and sampled at 20 kHz, and data were acquired using the PatchMaster software system (HEKA Electronik). Spontaneous intracellular currents (Supplementary Fig. 1) were analysed using Mini Analysis (Synaptosoft Software).

4.5. Plasticity protocols and photostimulation

For plasticity experiments, slices containing intact CA3 and CA1 regions of the hippocampus were selected, and the presence of EYFP-expressing MCH fibres in the hippocampus was confirmed (Fig. 2A). Excitatory postsynaptic field potentials (fEPSPs) were evoked in the stratum radiatum of CA3 using 200 μs current pulses delivered via a concentric bipolar stimulating electrode. An extracellular recording electrode (patch pipette filled with aCSF, as above) was placed at least 500 μm from the stimulating electrode, and paired pulse stimuli were used to confirm facilitation (average paired pulse ratio was 1.41 ± 0.08 for ChR2- slices and 1.61 ± 0.16 for ChR2+ slices). The stimulating current was adjusted until the maximal fEPSP was recorded extracellularly (required to be at least 0.5 mV), and then reduced by half so that the evoked slope was approximately 50% of its maximal. This strength was then kept constant for the rest of the experiment. A single current pulse was then delivered every 10 s to record a 5 min baseline before the first plasticity induction protocol was delivered. The average baseline fEPSP was 0.28 ± 0.08 mV in amplitude with 0.064 ± 0.02 slope for ChR2- slices, and 0.24 ± 0.05 in amplitude with 0.04 ± 0.01 slope for ChR2+ slices.

Then the first plasticity protocol was delivered: the weak potentiating stimulus, which consisted of one electrical tetanus (i.e. one second of stimulation at 100 Hz). This typically leads to post-tetanic potentiation (PTP) where the fEPSP is briefly facilitated, decaying back to baseline between 30 s to several minutes [24]. We therefore tracked the fEPSP for 20 min after this protocol. The strong potentiating stimulus was then delivered, which consisted of four electrical tetani (one per second for four seconds). This typically leads to long-term potentiation (LTP), where the fEPSP remains facilitated well beyond 10 min [25]. We therefore tracked the fEPSP for 30 min after this protocol. Finally, the strong depressing stimulus was delivered, which consisted of 900 single electrical pulses at 1 Hz. This typically leads to long-term depression (LTD) which plateaus around 10–15 min [26], and we therefore tracked the fEPSP for a final 20 min after this protocol. The rising slope of the field potential was continuously monitored (0.1 Hz), and changes in its gradient were taken as an indication of synaptic potentiation (increased slope) or depression (decreased slope; [25] Fig. 2).

Each of these plasticity induction protocols were interleaved with blue light stimulation (Fig. 2 and Supplementary Fig. 1) in both ChR2-positive and -negative (control) slices. Specifically, 5 ms pulses of 470 nm light (10 mW) were delivered at 20 Hz for 30 seconds (designed to promote peptide release, [8], using a Lambda DG-4 fast beam switcher (Sutter Instruments) with a xenon lamp and ET470/40 nm band pass filter, delivered through the 5 × 0.1 NA microscope objective. Blue light was also delivered in this manner to examine the effects of MCH axon activation on spontaneous excitatory and inhibitory currents in hippocampal pyramidal cells (Supplementary Fig. 1).

4.6. Data analysis

Statistical tests and descriptive statistics were performed as specified in Results and the figure legends. Data are presented as mean ± SEM, and a P-value < 0.05 was considered to indicate significance. Analysis was performed using Synaptosoft, GraphPad Prism 8 and MATLAB R2019b (MathWorks).

CRediT authorship contribution statement

Julia Jade Harris: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Denis Burdakov:** Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.peptides.2023.171128.

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