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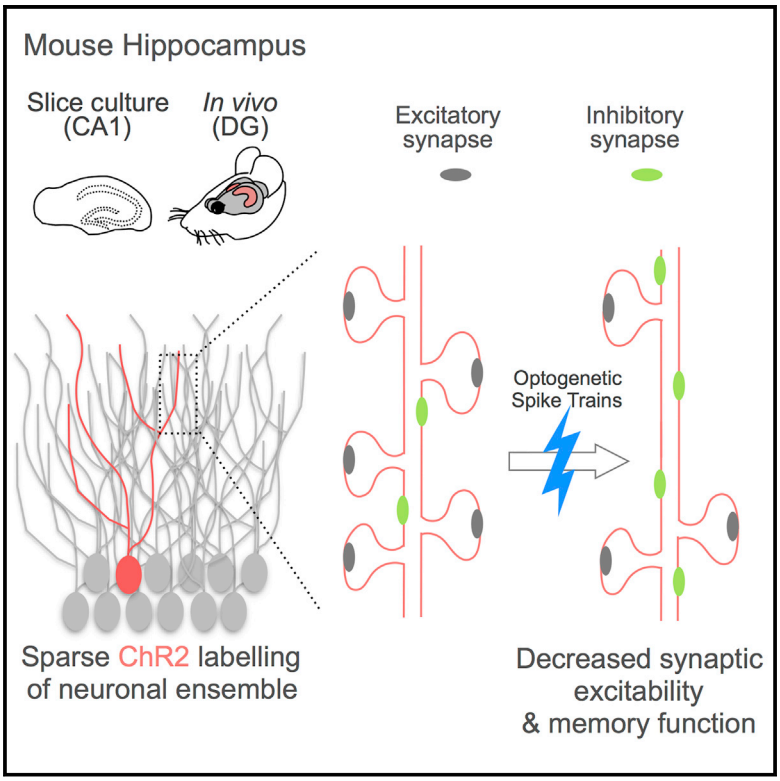
Homeostatic Plasticity in the Hippocampus Facilitates Memory Extinction

Graphical Abstract



Highlights

- Optogenetic spike trains are uncoupled from synaptic input in hippocampal neurons
- Dendritic spine formation is reduced via L-type VDCC activity and protein synthesis
- Reducing synaptic excitability in the cellular engram facilitates memory extinction

Authors

Pablo Mendez, Thomas Stefanelli, Carmen E. Flores, Dominique Muller, Christian Lüscher

Correspondence

pmendez@cajal.csic.es

In Brief

Mendez et al. show that homeostatic synaptic adaptations induced by optogenetic spike trains regulate the function of memory-bearing hippocampal neuronal ensembles.

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Homeostatic Plasticity in the Hippocampus Facilitates Memory Extinction

Pablo Mendez,[1,3,5,*] Thomas Stefanelli,[1] Carmen E. Flores,[1] Dominique Muller,[1,4] and Christian Lüscher[1,2]
[1]Department of Basic Neurosciences, Faculty of Medicine, University of Geneva, Michel-Servet 1, 1211 Geneva, Switzerland
[2]Service of Neurology, Geneva University Hospital, Perret-Gentil 4, 1211 Geneva, Switzerland
[3]Present address: Cajal Institute (CSIC), Av. Dr. Arce 37, 28002 Madrid, Spain
[4]Deceased April 29, 2015
[5]Lead Contact
*Correspondence: pmendez@cajal.csic.es
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SUMMARY

Correlated activity in the hippocampus drives synaptic plasticity that is necessary for the recruitment of neuronal ensembles underlying fear memory. Sustained neural activity, on the other hand, may trigger homeostatic adaptations. However, whether homeostatic plasticity affects memory function remains unknown. Here, we use optogenetics to induce cell autonomous homeostatic plasticity in CA1 pyramidal neurons and granule cells of the hippocampus. High-frequency spike trains applied for 10 min decreased the number of excitatory spine synapses and increased the number of inhibitory shaft synapses. This activity stopped dendritic spine formation via L-type voltage-dependent calcium channel activity and protein synthesis. Applied selectively to the ensemble of granule cells encoding a contextual fear memory, the spike trains impaired memory recall and facilitated extinction. Our results indicate that homeostatic plasticity triggered by optogenetic neuronal firing alters the balance between excitation and inhibition in favor of memory extinction.

INTRODUCTION

Potentiation of excitatory transmission, such as long-term potentiation (LTP), believed to underlie many forms of learning and memory, is eventually reset by non-Hebbian forms of plasticity in the interest of long-term network stability (Abbott and Nelson, 2000). Homeostatic and experience-dependent plasticities are calcium dependent (Vitureira et al., 2012), use receptor distribution as expression mechanism (Turrigiano and Nelson, 2004), and are associated with structural remodeling of excitatory (Zuo et al., 2005) and inhibitory synapses (van Versendaal et al., 2012). In the present study, we investigated the role of homeostatic plasticity in memory function.

Ensembles of neurons recruited during memory formation are a "bona fide" substrate for the memory engram. Hebbian forms of synaptic plasticity support the formation of neuronal ensembles, thus contributing to encoding, consolidation, and expression of memory (Gruart et al., 2006). This has been experimentally demonstrated in the case of contextual fear conditioning (CFC) (Josselyn et al., 2015; Tonegawa et al., 2015), where potentiation of excitatory synapses occurs specifically in neurons of the dentate gyrus that express the immediate early gene cFos marking the memory ensemble (Ryan et al., 2015). LTP and long-term depression (LTD) may bidirectionally modulate fear memory expression by acting on ensembles of neurons coding for the conditioned and unconditioned stimuli (CS-US) association in the amygdala (Nabavi et al., 2014). Whereas much evidence supports a causal role for Hebbian forms of plasticity in recruiting neuronal ensembles for contextual fear memory, it remains elusive whether and how homeostatic synaptic plasticity affects memory processes.

With repetitive CS presentation that is not followed by the US, the association is lost, a process referred to as extinction (Herry et al., 2010). Some models propose that extinction constitutes a form of re-learning that creates a new memory trace to counteract the fear memory, but the cellular mechanisms at play remain poorly understood (Myers and Davis, 2007; Maren, 2011). Here, we provide evidence that homeostatic synaptic plasticity in the neuronal ensemble promotes fear extinction. This may not only be relevant for the neuronal mechanisms of extinction but also provides a strategy to facilitate the attenuation of traumatic memories.

Homeostatic synaptic plasticity can adjust neuronal firing rates (Hengen et al., 2016). For example, chronic low-frequency spiking results in non-Hebbian decrease of synaptic strength via glutamate receptor redistribution (Goold and Nicoll, 2010) and changes in axon initial segment excitability (Grubb and Burrone, 2010). Homeostatic adaptations control the strength and structure of γ-amino butyric acid (GABA) synapses onto hippocampal CA1 principal neurons (Flores et al., 2015). Calcium (through Ca^{2+}/calmodulin-dependent protein kinase II [CamKII]) and protein synthesis orchestrate homeostatic synaptic adaptations (Marsden et al., 2010; Petrini et al., 2014; Flores et al., 2015; Goold and Nicoll, 2010).

Structural synaptic plasticity is a core mechanism of homeostatic plasticity (Holtmaat and Svoboda, 2009). The continuous formation and elimination of excitatory and inhibitory synapses participates in the compensatory adaptations to hippocampal network activity changes (De Roo et al., 2008a; Bloodgood et al., 2013). Interestingly, many examples of structural remodeling described to date represent Hebbian forms of plasticity of excitatory synapses and are critically involved in learning, memory