Neuron Preview

O-LM interneurons: gatekeepers of pyramidal neuron activity in the hippocampus

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ABSTRACT

A balanced and fine-tuned ratio of neuronal excitation and inhibition is a crucial prerequisite for information processing. In this issue of *NEURON*, He et *al.* reveal a causal link between reduced input to local somatostatin-expressing, MeCP2-negative O-LM interneurons in CA1 and long-term memory impairment in a mouse model of Rett syndrome.

KEYWORDS

Rett syndrome, MeCP2, E/I imbalance, O-LM interneurons, somatostatin-expressing interneurons, CA1, long-term memory impairment

MAIN

Alterations in the excitation-inhibition (E/I) balance within neuronal circuits have been hypothesized to be an fundamental characteristic of Rett syndrome (Li, 2022), a postnatal neurodevelopmental disorder caused by mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene. The network hypersynchrony resulting from an aberrant E/I ratio is reflected by the frequent comorbidity of epileptiform activity and seizures in neurodegenerative and neuropsychiatric disorders like Rett syndrome (Landi et al., 2018). Precisely timed and controlled inhibition is crucial to guarantee proper information flow between and within brain regions supporting consolidation of memories (Roux and Buzsáki, 2015). Therefore, a disrupted E/I ratio has been proposed as a commonly underlying mechanism behind the cognitive impairments that occur not only in Rett

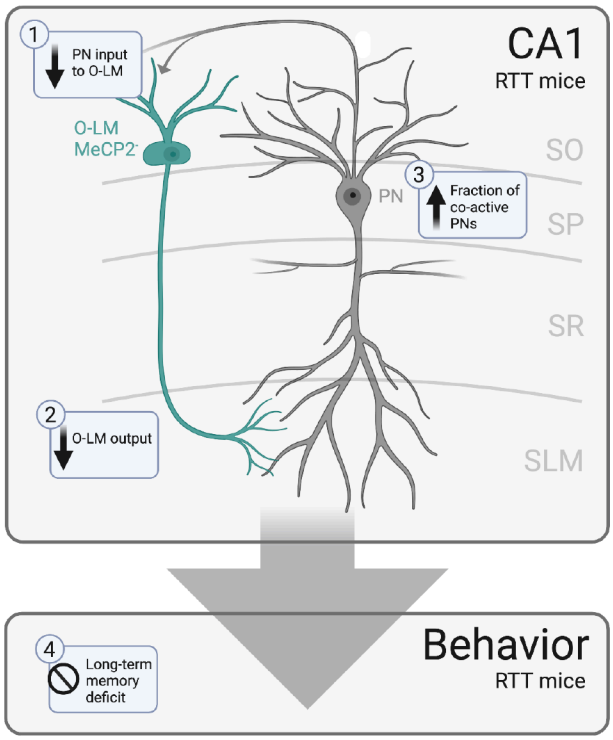

Figure 1. Decreased input to O-LM interneurons from pyramidal neurons (PNs) as a mechanism for memory impairment in a mouse model of Rett syndrome.

syndrome, but also in Alzheimers's disease (Palop and Mucke, 2016) and autism (Nelson and Valakh, 2015).

In the hippocampus, a brain region important for spatial representation, learning, and memory, somatostatin (SST)-expressing inhibitory interneurons reside in *stratum oriens* (SO) and presynaptically target distal dendrites of pyramidal neurons (PNs) in *stratum lacunosum moleculare* (SLM), hence their name O-LM interneurons (**Figure 1**). Upon presentation of an aversive stimulus, during associative aversive learning, O-LM interneurons are recruited by cholinergic input from the medial septum (MS). In this scenario, O-LM interneurons serve as gatekeepers of PNs, as they limit and counteract the strong dendritic depolarization induced by the sensory component of the unconditioned stimulus, encoded by excitatory entorhinal afferents to the SLM (Lovett-Barron et al., 2014). Therefore, dendritic inhibition provided by O-LM interneurons supports contextual encoding and discrimination, one of the most relevant functions of the hippocampus. Lack of inhibitory control in disease conditions can thus be an important underlying cause of disease-related memory deficits. He et *al.* discovered a novel mechanism based on a reduced recruitment of O-LM interneurons leading to impaired long-term memory in a mouse model of Rett syndrome (RTT mice) (He et al., 2022). The authors recorded neuronal Ca^{2+}-events in the hippocampus of freely behaving mice with miniaturized microscopes and the genetically encoded Ca^{2+}-sensor GCaMP6f. This technique enabled them to record repetitively from the same hundreds of CA1 neurons throughout a hippocampus-dependent memory test. This allowed the authors to observe the average population activity of PNs, by measuring their Ca^{2+}-event rate. In favor of a sparse representation of mnemonic information, the authors found the Ca^{2+}-event rate reduced in a familiar (and learned) vs. a novel environment in healthy mice. RTT mice lacked this reduction of Ca^{2+}-event rate associated with memory recall. In addition, the recall network of RTT mice contained an elevated fraction of co-activated hippocampal neurons in comparison to wildtype mice (**Figure 1**). Strikingly, O-LM interneurons were shown to not only mediate contextual fear encoding (Lovett-Barron et al., 2014), but also to control the size of neuronal ensembles relevant for memory encoding, thus appointing to the dysfunction of O-LM interneurons a

potential mechanism behind the excessive size of the recall network in RTT mice. Patch-Clamp recordings of pyramidal neurons in hippocampal slices did not reveal any difference in spontaneous inhibitory post-synaptic currents between wildtype and RTT neurons. In contrast, RTT O-LM interneurons received reduced excitatory input as shown by decreased spontaneous excitatory post-synaptic currents and pyramidal cell to O-LM connectivity. The authors suggest that this lack of input leads to impaired timing of feedback inhibition in CA1 and thus, an altered activation of pyramidal neurons. Ultimately, He et *al.* performed a convincing set of contextual fear conditioning experiments with artificial silencing and activating O-LM interneurons to establish causality between O-LM activity and memory recall. Namely, silencing O-LMs with DREADDs during recall mimicked the RTT phenotype, whereas activation of O-LM interneurons in RTT mice restored memory.

The discovered overactivation of CA1 neuronal ensembles in RTT mice, as indicated by a higher fraction of co-activated PNs, is hypothesized to dilute or hide the mnemonic information, similar to a noisy radio channel and thus, impair long-term memory recall (**Figure 1**). A comparable mechanism of long-term memory impairment due to a CA1 PN ensemble interfering with recall was found in a mouse model of Alzheimer's disease (Poll et al., 2020). Similar to the current study, successful recall was associated with a sparse CA1 activity, whereas the recall network of mice with memory impairment was characterized by excessive recruitment of CA1 PN cells. Accordingly, mimicking an overly activated CA1 region interfered with memory recall, whereas a reduction of this extra activity restored memory. This supports the hypothesis that sparse ensemble activity in CA1 is associated with mnemonic content and is therefore crucial for correct information processing. Given that CA1 is thought to act as a comparator of past and current experience, it is tempting to speculate that this function is impaired due to the decreased recruitment of O-LM interneurons in RTT mice, leading to a false evaluation of an actual known and fearful conditioned context to be neutral.

In the light of recent advances in engram research, a critical question remains: what is the identity and fate of the recorded CA1 neurons and their Ca^{2+}-event rates throughout the contextual fear conditioning task in RTT mice? Is the memory trace disrupted in RTT mice or

rather not accessible (Ryan and Frankland, 2022)? Moreover, how can the identification of this disrupted mechanism lead to the development of future therapies for Rett syndrome or other brain diseases? As intervening with O-LM activity had a profound influence on cognitive processes, the authors suggest a promising improvement of existing therapeutic strategies that utilize deep brain stimulation, by directly targeting the MS to drive cholinergic input to CA1 PNs. This would on the one hand compensate for the lack of excitatory drive to local O-LM interneurons and on the other hand allow to arrest seizures that often occur in late stages of the disease. Another pending question refers to whether the *MECP2* gene loss might also affect other cells types than OL-M interneurons and thus contribute to other aspects of memory impairment. Answering these questions might help to identify novel targets for developing treatment strategies to interfere with disease progression. Regardless of these yet unanswered questions, increasing evidence supports the role of inhibitory neurons in controlling mnemonic processing and engram recruitment (Yap et al., 2021), and further research will be needed to promote the development and translation of therapeutic approaches targeting the inhibitory compartment.

In summary, He et *al.* provide a convincing set of experiments to reveal a novel circuit dysfunction in a mouse model of Rett syndrome. By utilizing state-of-the-art Ca^{2+}-imaging in freely behaving mice, complemented with brain slice electrophysiological recordings and *in vivo* circuit manipulations, they identify reduced recruitment of hippocampal gatekeepers, the O-LM interneurons, by PNs, which leads to long-term memory impairment.

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