RESEARCH HIGHLIGHT

Unraveling the Mechanisms of Memory Extinction

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Memory is a crucial biological function conserved across almost all organisms. Once established and consolidated, a memory is considered stable and long-lasting unless it is disrupted or manipulated by behavioral, physical, or chemical interventions. Behaviorally, the original memory can be extinguished by a re-learning process termed memory extinction [1]. Both memory acquisition and extinction are necessary for adaptation and survival of organisms in a changing environment. Like the original memory acquisition process, extinction learning also depends on the plastic cellular and molecular changes occurring in specific brain regions and neuronal circuits responsible for the corresponding behavior. The process of memory extinction is regulated *via* manipulation of these changes at the synaptic level (referred to as synaptic plasticity), which may even result in a “memory erasure” state, in which the original memory can no longer be retrieved. Such manipulation may actually be beneficial for the treatment of many psychiatric disorders with aberrant persistent memory. Here, we summarize three examples of recent work on memory extinction or even erasure and the associated synaptic plasticity that have provided novel insights into mechanisms of learning and memory.

Eating disorders involve multiple forms of aberrant memory related to food cues, such as taste. Conditioned taste aversion (CTA), an aversively-motivated memory model based on the association of a novel food taste with subsequent abdominal malaise, occurs commonly in

children when learning to eat. In a recent study published in *Nature Communications* [2], the authors investigated whether targeting synaptic plasticity can affect memory extinction learning, namely, CTA extinction (Fig. 1, upper left). Previously, it was suggested that long-term potentiation (LTP) in the excitatory synapses of insular cortex that receive projections from the basolateral amygdala (BLA) is actively involved in CTA memory acquisition [3]. Conversely, the new evidence suggests that a significant reduction of excitatory transmission in the insular synapses is associated with the extinction of CTA memory. Moreover, extinction training precluded further induction of long-term depression (LTD), another well-known form of synaptic plasticity, suggesting that LTD is a synaptic mechanism to actively drive the extinction of CTA memory. To further probe the molecular mechanisms, the researchers unraveled a profound dependence of insular LTD induction on a type of ion channel termed acid-sensing ion channel 1a (ASIC1a). ASIC1a is highly expressed in brain neurons, including those in the insular cortex, hippocampus, and amygdala, but the channel had only previously been suggested to be involved in LTP induction in the amygdala and hippocampus. The authors found that ASIC1a acts through glycogen synthase kinase-3 β signaling in the insular cortex, which eventually leads to endocytosis of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtype of glutamatergic receptors and subsequently, synaptic depression. Collectively, the data establish the involvement of an ASIC1a-mediated insular synaptic depression mechanism in extinction learning. It is hoped that targeting this mechanism may be helpful for managing adaptive eating behaviors. Coincidentally, another study also yielded results showing that low-frequency electrical stimulation-induced LTD in the BLA to insular cortex projection prior to CTA training

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Fig. 1 Schematic of different approaches to the manipulation of synaptic plasticity in corresponding brain regions for the treatment of different types of memory disorders. (Upper left) The ASIC1a channel in insular cortex contributes to the induction of insular long-term depression (LTD) and is required for extinction learning of conditioned taste aversion [2]. (Upper right) Optical inactivation of the GluA1-homomeric AMPA receptor (AMPA) after fear

conditioning erases the fear memory in a contextual fear memory paradigm termed the inhibitory avoidance task [5]. (Lower) Transplantation of embryonic day 13.5 (E13.5) MGE interneurons into the amygdala of young adult mice attenuates fear memory renewal and spontaneous recovery after extinction learning, a process that is likely dependent on remodeling of the host synaptic network in the amygdala [6]. See text for details.

substantially facilitated the extinction training, while LTP had the opposite effect [4]. These studies not only underscore the importance of insular neuroplasticity in the extinction of aversive taste memory, but also hint at potential new cellular and molecular targets for treating psychiatric disorders like anorexia nervosa.

Glutamate receptors are the major executors of excitatory synaptic plasticity, and constitute the molecular substrates underlying many memory processes. There are several different subtypes of glutamate receptors in the brain. It has been postulated that selective inactivation of particular subtypes of glutamate receptors within certain brain regions and specific phases of memory corresponding

to memory acquisition may cause extinction of the existing memory. In a recent study published in *Nature Biotechnology* [5], the authors developed a new technique termed chromophore-assisted light inactivation (CALI) to achieve selective inactivation of synaptic AMPA receptors that contain homomeric GluA1 subunits *in vivo*, which successfully erased an acquired fear memory (Fig. 1, upper right). Typically, AMPA receptors are heteromeric channels formed by GluA1 and GluA2 subunits in the resting state. Synaptic plasticity in the hippocampus associated with fear learning results in a proportional increase of homomeric GluA1 AMPA receptors in a manner that depends on membrane trafficking of the receptors. Unlike the GluA2-containing channels, the homomeric GluA1 AMPA receptors exhibit prominent inward rectification and more importantly are Ca^{2+} -permeable. They are critically engaged in several learning processes including fear conditioning and drug addiction. To specifically target this subtype of glutamate receptors, the researchers screened monoclonal antibodies against AMPA receptors that contain only the GluA1 subunit. Then they labeled the antibody they identified with eosin as a photosensitizer, which enabled inactivation of the antibody-bound receptors by light delivery through the production of reactive oxygen species around the antibody-receptor complexes. By using this CALI approach in the hippocampus of fear-conditioned mice *in vivo*, the researchers attenuated AMPA receptor-mediated synaptic responses and successfully erased the contextual fear memory. By further investigating the time-course of fear memory erasure using this optical approach, the researchers revealed that CALI should be applied within a short period (up to ~ 2 h) after fear conditioning in order to effectively erase the acquired fear memory. More interestingly, the application of CALI before learning had no such impact, implying that CALI selectively incapacitates homomeric GluA1 AMPA receptors that are newly delivered to the synapses, rather than the pre-existing heteromeric GluA1-GluA2 channels, during fear training. Overall, this study is of great significance as it sheds new light on the practical manipulation of synaptic proteins, which can be substantially beneficial to delineating their cognitive functions *in vivo*, and demonstrates again the feasibility of memory modulation by targeting molecular substrates for synaptic plasticity.

The idea of completely changing a person's thoughts or memories by brain transplantation has always stimulated the imagination but remains only a subject of science fiction. Moral issues and government regulations would also make it unlikely to realize such a practice. However, transplanting neurons in animal models has been shown to allow remodeling of neural network connections and reverse some persistent behaviors. In a recent article published in *Neuron* [6], the authors demonstrate that fear

erasure can be facilitated by transplantation of certain juvenile interneurons (Fig. 1, lower). In this study, the researchers transplanted embryonic interneurons from the medial ganglionic eminence (MGE) into the amygdala of young adult mice and investigated the impact on fear behavior. They found that the transplanted progenitor MGE cells were able to differentiate, develop, and form reciprocally functional synaptic connections with host neurons. Moreover, both excitatory and inhibitory synaptic transmission of the host neurons were modulated toward a juvenile stage in a temporally dependent manner, and strikingly, both the likelihood of inducing long-term synaptic plasticity and its amplitude in the amygdala host neurons were enhanced. Overall, the transplanted MGE cells rejuvenated the mature circuits of the host neurons by offering an expanded capacity of plasticity. As a result, in conjunction with extinction training, fear memory erasure was more complete under paradigms when spontaneous recovery and renewal of fear response normally occurred in control animals. This study shows that transplantation of immature interneurons and the resultant rejuvenation of the amygdala can expand synaptic plasticity and hence facilitate fear extinction. This may be useful as a potential cell-based therapeutic approach for treating extinction-resistant pathological fear, such as post-traumatic stress disorder.

In summary, various strategies targeting synaptic plasticity to modulate the extinguishing process of aberrant memory are highlighted here, namely the optical/electrical stimulation of certain neuronal circuits, manipulation of key molecular mediators or synaptic substrates, and immature interneuron transplantation. Although many questions remain unsolved, it is undeniable that these studies are of great significance and very helpful for further mechanistic exploration and translation studies related to memory regulation.

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