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Research Highlight

Erasing fear memories — key receptor and essential timeframe discovered

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It is clinically important to suppress or inhibit traumatic memories, which are formed after fearful experiences. In animal models, fear memory is formed by repetitive presentation of a tone paired with an electrical foot-shock[1]. It is well known that an extinction protocol, in which the tone is repeatedly presented without the foot-shock, gradually decreases the pre-acquired fear response to the tone. However, this fear extinction protocol is not sufficient to erase the fear memory; fear responses may recover spontaneously or relapse under some conditions. If the fear memory is retrieved or reactivated by a single presentation of the tone without the shock 1 h before the extinction session, the fear responses are permanently removed by this retrieval–extinction protocol[2]. This suggests that a critical brain state is caused by the retrieval procedure, in which the fear memory becomes labile and can be destroyed by the subsequent extinction procedure. Clem and Huganir[3] have found a critical receptor for the permanent erasure of fear memories by this retrieval–extinction protocol. They focused on the Ca^{2+}-permeable type of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (Ca^{2+}-permeable-AMPAR) located in the lateral amygdala, an essential region of the brain for learning. They suggested that removal of Ca^{2+}-permeable-AMPARs, the content of which in the synapses is elevated for a few days after fear conditioning, is responsible for the permanent erasure of the fear memory by that protocol.

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First, they demonstrated an enhancement of Ca^{2+}-permeable-AMPAR mediated excitatory postsynaptic currents in fear-conditioned animals, suggesting an incorporation of Ca^{2+}-permeable-AMPARs or a change of subunit composition of AMPAR to the Ca^{2+}-permeable type. This increase of Ca^{2+}-permeable-AMPARs peaked at 24 h after conditioning and disappeared by d 7, whereas the total amount of AMPARs remained increased even after 7 d. These results suggest the presence of an important time window, during which AMPARs transiently change their subunit composition to the Ca^{2+}-permeable type. Increased Ca^{2+}-permeable-AMPARs at 24 h after fear conditioning was also supported by an enhancement of long-term depression (LTD), which is caused by selective removal of Ca^{2+}-permeable-AMPARs that become abundant at that time.

Next, they examined the effects of memory retrieval on Ca^{2+}-permeable-AMPARs measured after extinction. They found that reactivation of the fear memory before the extinction session significantly decreased AMPA-mediated current, indicating that memory reactivation followed by extinction attenuates the potentiated transmission caused by fear conditioning. Electrophysiological and pharmacological examinations suggested that this reversal change of synaptic transmission is due to the selective removal of Ca^{2+}-permeable-AMPARs, which are enriched 24 h after conditioning. Consistent with this, LTD induction was greatly reduced in the animals receiving the retrieval–extinction protocol, compared with those receiving extinction alone. This is because memory retrieval prior to the extinction removes the Ca^{2+}-permeable-AMPARs from the synapses, and so further reduction in synaptic transmission would not be observed. In addition, memory reactivation is not effective when carried out 7 d after the conditioning, when the Ca^{2+}-permeable-AMPARs return to the basal level, supporting the idea that successful erasure of the fear memory requires an abundance of Ca^{2+}-permeable-AMPARs at the time of the retrieval-extinction treatment.

Finally, they investigated the molecular mechanisms underlying the elevation of Ca^{2+}-permeable-AMPAR content after fear conditioning, which is a prerequisite for removal of Ca^{2+}-permeable-AMPARs by the retrieval–extinction protocol. It was reported that phosphorylation of the serine 845 (S845) residue of glutamate receptor 1 (GluR1) by protein kinase A (PKA) is required for stable expression

of Ca^{2+}-permeable-AMPARs[4]. Using mutant mice with an alanine substitution mutation of S845 (S845A), they showed that phosphorylation of Ca^{2+}-permeable-AMPARs by PKA is critical for the increase of Ca^{2+}-permeable-AMPAR current and the enhancement of LTD 24 h after fear conditioning. These results suggest the importance of phosphorylation of S845 for the synaptic incorporation of Ca^{2+}-permeable-AMPARs. In parallel with the deficits in the post-conditioning dynamics of Ca^{2+}-permeable-AMPARs, memory erasure by the retrieval-extinction protocol was impaired in these mutant mice. Because phosphorylation of Ca^{2+}-permeable-AMPARs by PKA is blocked throughout the brain in these mutant mice, there is a possibility that the lack of the erasure effect might be due to impairments in other regions outside the lateral amygdala. Combined with other data, however, it is suggested that the transient up-and-down change in the amount of Ca^{2+}-permeable-AMPARs in the lateral amygdala synapses has a crucial role in permanent erasure of the fear memory and that phosphorylation of Ca^{2+}-permeable-AMPARs by PKA is involved in their up-regulation. Interestingly, S845A mutant mice showed a significant post-conditioning synaptic potentiation in the lateral amygdala and learned as successfully as the wildtype mice. These results indicate that phosphorylation of S845 and its resulting Ca^{2+}-permeable-AMPAR dynamics are specifically related to the memory erasure processes triggered by the retrieval–extinction protocol.

In addition to molecular strategies for treatment of traumatic memories, these data also provide important information on the right timing of the treatment: there is a critical or effective period for the memory erasure. Because Ca^{2+}-permeable-AMPARs reach a maximum level 24 h after fear conditioning and then gradually decline within a few days, the treatment will only be effective within this time window. Further attempts to artificially induce Ca^{2+}-permeable-AMPAR accumulation might remove the time limit and make the treatment successful beyond this narrow timeframe.

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