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NEWS AND COMMENTARY

Reconsolidation of Extinction Memories

Targeting the reconsolidation of extinction memories: a novel potential strategy to treat anxiety disorders

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Treatments for anxiety disorders have focused on enhancing fear extinction or blocking fear reconsolidation. New research suggests that enhancing the reconsolidation of fear extinction could be a promising approach.

Extinction-based therapy is a commonly used intervention to attenuate fear responses in patients with anxiety disorders. Fear extinction involves the formation of a new safety memory that suppresses the original fear memory.[1] However, fear memories return in a substantial number of patients treated with extinction-based therapies.[2] Another therapeutical strategy to reduce fear and anxiety is to interfere with the original fear memory by pharmacologically disrupting its reconsolidation mechanisms,[3] but this intervention also has some limitations. For example, clinical treatments usually occur long after the traumatic event, and remote memories are known to be less responsive to reconsolidation blockade.[4, 5] Using a rodent model, a recent study by Radiske *et al.*[6] suggests that pharmacologically enhancing the reconsolidation of fear extinction memories may be a promising target for strengthening extinction-based therapies.

One key molecule that has been implicated in both extinction and reconsolidation of fear memories is the brain-derived neurotrophic factor (BDNF) and its receptor TrkB.[7] BDNF is necessary for fear memory reconsolidation within different brain regions, depending on the environmental conditions and the type of memory. For example, only after a prior history of stress, BDNF in the dorsal hippocampus is necessary for the reconsolidation of contextual-fear memories;[8] whereas in the infralimbic prefrontal cortex, BDNF is critical for the acquisition of fear extinction memories.[9]

To investigate whether BDNF is involved in the reconsolidation of fear extinction memories, Radiske *et al*. used an inhibitory avoidance task in which rats learn that stepping off a platform results in a foot shock. During extinction of inhibitory avoidance, stepping off the platform no longer results in a foot shock and the avoidance response reduces across sessions. Blocking BDNF in the dorsal hippocampus immediately after the reactivation of the extinction memory resulted in the return of the original fear response, suggesting that the reconsolidation of a fear extinction memory is BDNF dependent. Interestingly, blocking BDNF, but not protein synthesis or gene expression, 6 h after extinction reactivation resulted in the return of the original fear memory. This suggests that, during extinction reconsolidation, BDNF release is downstream of protein synthesis and gene expression.

To assess the time frame of BDNF processes, the authors measured the levels of BDNF and its precursor proBDNF at different time points following the reactivation of the extinction memory. proBDNF was increased between 5 and 90 min following extinction reactivation, whereas BDNF was increased between 180 and 360 min following reactivation. Notably, blocking the conversion of proBDNF to BDNF in the dorsal hippocampus caused a return of the original fear response. These results suggest that converting proBDNF to BDNF is required for extinction reconsolidation to occur. Furthermore, infusing BDNF directly into the dorsal hippocampus rescued the impairment in extinction reconsolidation induced by inhibitors of protein synthesis or gene expression. After BDNF production, BDNF is released to activate TrkB receptors. Consistent with this, the authors found that phosphorylation of TrkB receptors was significantly increased during the same time window in which BDNF levels were augmented. These findings suggest that enhancing BDNF-TrkB signaling following retrieval of extinction may strengthen the extinction memory.

Drugs that activate BDNF-TrkB signaling have been proposed as potential therapeutic adjuncts for enhancing extinction-based therapies.[7] Unfortunately, administering recombinant BDNF has not been effective in clinical trials for neurological disorders, likely due to its poor pharmacokinetic properties.[10] A possible alternative to activate BDNF-TrkB signaling could be the use of TrkB agonists, which has been successfully used in rodents.[7] Nevertheless, the safety of TrKB agonists remains to be tested in humans. If safe, administering TrkB agonists after extinction retrieval could be used to strengthen the reconsolidation of fear extinction memories, and thus prevent the re-emergence of fear in patients suffering from anxiety disorders. Alternatively, non-pharmacological strategies that enhance BDNF levels (for example, exercise and caloric restriction)[11] could also be used to increase BDNF-TrKB signaling across fear extinction sessions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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