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PSYCHIATRIC DISORDERS

Why two is better than one

Many depression and anxiety disorders are most effectively treated with a combination of psychotherapy and antidepressant drugs. The biological basis for this observation is not well understood, but Castrén and colleagues now show that the antidepressant fluoxetine increases synaptic plasticity in the amygdala and thereby facilitates long-lasting fear extinction.

The authors used a Pavlovian fear conditioning–extinction paradigm, in which mice are exposed to a painful stimulus together with a neutral conditioned stimulus (a tone). When mice are subsequently exposed to the tone alone they show a fear response, but repeated exposure to the tone in a different context can extinguish this response — reminiscent of exposure therapy in humans with anxiety disorders. Importantly, extinction is not permanent: the fear response can recover spontaneously and can also be re-induced by exposing the mice to the tone in the original, conditioning context.

Adult mice on a treatment regimen of the selective serotonin-reuptake inhibitor fluoxetine starting 3 weeks before fear conditioning showed faster extinction and greatly reduced spontaneous recovery and renewal of fear. Fluoxetine treatment after fear conditioning — a more clinically relevant scenario — also accelerated extinction and prevented both spontaneous recovery and renewal.

Juvenile mice show no fear recovery after extinction training, but this phenomenon disappears with the development of perineuronal nets (PNNs) in the amygdala. The authors therefore investigated whether fluoxetine treatment might promote extinction by disrupting PNNs. They found that fluoxetine reduced the number of parvalbumin-expressing PNN-positive neurons in the basolateral nucleus of the amygdala (BLA) and the hippocampal CA1. Furthermore, it increased and decreased, respectively, the expression of molecular markers of immature and mature neurons in the BLA. Thus, fluoxetine treatment seems to induce an 'immature' state in fear-relevant brain areas and, as subsequent electrophysiology experiments showed, this results in increased synaptic plasticity.

Fluoxetine also increased levels of brain-derived neurotrophic factor (BNDF) mRNA and BDNF transcript 1 in the BLA and hippocampus. Moreover, it had no effect on fear extinction in mice with reduced BDNF levels, and mice overexpressing BDNF in the amygdala did not show fear renewal after extinction.

Together, these findings suggest that fluoxetine treatment induces a plastic, immature state in the amygdala, possibly by increasing BDNF expression, and this facilitates the erasure of fear by extinction training. They further indicate that combining exposure therapy and antidepressant treatment may be the best approach for treating anxiety disorders such as post-traumatic stress disorder.

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ORIGINAL RESEARCH PAPER Karpova, N. N. *et al.* Fear erasure in mice requires synergy between antidepressant drugs and extinction training. *Science* **334**, 1731–1734 (2011)

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