Commentary

Biological Psychiatry

Propranolol Inhibits Reactivation of Fear Memory

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Most of the U.S. population will experience a life-threatening and incredibly stressful experience at some point in their lives. Of these individuals, many will go on to develop the persistent and debilitating symptoms of posttraumatic stress disorder (PTSD), such as anxiety, sleep disturbances, and intrusive thoughts (1). Individuals who suffer from PTSD often exhibit heightened fear responses and/or resistance to extinction learning. Cognitive behavioral therapy alone has proven ineffective for many patients, and there has been a surge of interest in whether pharmacological interventions can be used alongside cognitive behavioral therapy to support the treatment of PTSD.

Among the potential pharmacotherapies for PTSD, there is evidence that propranolol, a nonselective beta-adrenergic antagonist, may help diminish fear responses and enhance extinction learning. Propranolol has been used in the clinic for its short-term effect in performance anxiety, such as test taking and oral presentations, but its long-term use in anxiety disorders has produced mixed results (2). More recently, there has been growing interest in whether propranolol can be used to support treatment of PTSD and phobias alongside exposure therapy, by modulating fear memory retrieval and reconsolidation (3). Propranolol has been hypothesized to decrease fear responses by disrupting plasticity mechanisms required for reconsolidation of a fear memory, thus weakening the fear memory. Alternatively (or in addition to this mechanism), propranolol has been hypothesized to decrease the psychological stress associated with recalling a fearful memory, promoting a dissociation of the negative affective state and stimuli associated with the memory, and in this way promote extinction. However, the results from both clinical and preclinical studies have been mixed (3,4). To better understand the potential therapeutic implications for propranolol we need to better understand the cognitive/behavioral and biological processes it targets.

In the current issue of *Biological Psychiatry*, Leal Santos *et al.* (5) characterized how a single dose of propranolol affected retrieval of a fearful memory and its neural representation. They found that a single dose of propranolol given before a retrieval trial was able to attenuate retrieval of the fear memory while the drug was on board (for both contextual and cued fear memories). The authors then asked if the decreased fear response was due to general anxiolytic effects of the drug or to a specific alteration in the fear memory representation in the brain. Their results suggest that the decreased fear response was specific to accessing the fear memory, as propranolol neither altered anxiety-like behaviors after fear conditioning (elevated plus maze and open field) nor decreased memory retrieval for a nonfearful memory (social recognition memory).

To ask how propranolol administered before a retrieval trial affected the fear memory representation in the brain, the authors used an activity-dependent, brainwide tagging approach to take a "snapshot" of neurons that were active during both the acquisition and retrieval of the fear memory, with or without propranolol on board during retrieval. Previous research has shown that memories are encoded and stored in sparse neural ensembles distributed across the brain, termed the memory engram; memory retrieval requires reactivation of those neurons active during initial encoding (6). If propranolol impaired the ability to access the memory, we would expect decreased reactivation of the memory engram. Indeed, the authors observed decreased reactivation of the memory engram in the dorsal dentate gyrus, which has been previously shown to be critical in storing and retrieving contextual fear memories.

While these results suggest that a single dose of propranolol has a robust dampening effect on the retrieval of a fear memory, the authors' findings also suggest that it may not be enough to support long-term amelioration of the fear memory. In subsequent retrieval trials, when the animals were off the drug, the fear memory re-emerged, and in the case of a tone fear memory, fear was even stronger in propranolol-treated animals. This suggests that a single dose of propranolol is not sufficient to support long-term extinction. Interestingly, during the memory retrieval with propranolol, Leal Santos *et al.* (5) found decreased activity of the infralimbic area of the prefrontal cortex. Other studies have shown that the infralimbic area is important to support extinction learning. It is possible that despite propranolol inhibiting access to the fear memory engram in the hippocampus during memory retrieval, the decreased activity in the infralimbic area weakened extinction learning.

Leal Santos *et al.* (5) found that while propranolol administered before the retrieval trial decreased fear memory retrieval, it had either no effect or a negative effect on extinction (i.e., subsequent fear was heightened). These results add to the mixed findings of propranolol on extinction in the literature. Previous studies have shown that the timing of propranolol can have a bidirectional effect on fear extinction. A single dose of propranolol after memory recall may support extinction, potentially by interfering with reconsolidation (7). However, receiving propranolol just before memory retrieval (if the retrieval was at least a day after learning) can lead to an increased fear response in a subsequent retrieval test while off the drug (8). Lastly, further studies need to characterize how repeated administration of propranolol might affect fear memory retrieval and extinction. It might be the case in the study by Leal Santos *et al.* (5) that while propranolol was able to suppress fear memory retrieval by inhibiting reactivation of the memory engram, a single trial may not have been enough

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to permanently weaken the fear memory. Could additional retrieval trials with propranolol lead to a more permanent weakening of the fear memory and enhance extinction? Some studies with humans suggest that chronic propranolol treatment may be more effective in reducing PTSD symptoms (9,10). Leal Santos *et al.* (5) highlight the complexity of propranolol's effects on fear memory processing and the need for future studies to further characterize how we can combine behavioral and pharmacological methods to more effectively dampen pathological fear while retrieving a fearful memory and enhance extinction learning.

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