Biological Psychiatry: Celebrating 50 Years

Commentary

Augmentation of Exposure Therapy With Cholinergic Blockade: Promising Novel Approach or Too Early to Tell?

Barbara O. Rothbaum and Kerry J. Ressler

Anxiety-related disorders are among the most promising clinical indications for translational neuroscience to identify novel treatments. The neural circuits that mediate the extinction of conditioned fear are well conserved across species and are relatively well understood. Fear extinction is thought to be a robust underlying process mediating exposure therapy (1).

In this issue of *Biological Psychiatry*, Craske *et al.* (2) explore if scopolamine, a predominantly muscarinic-cholinergic receptor antagonist, impairs context renewal (i.e., reduces fear in a novel context) in 60 humans with social anxiety disorder after 7 brief virtual reality (VR) exposure therapy sessions. It did not. But scopolamine augmented the reduction in skin conductance responses (SCRs) across exposure sessions, impaired performance on a cognitive task of hippocampal function, and led to a lower SCR at a long-term extinction retest.

Medication-assisted psychotherapy (3) can enhance psychological interventions via extinction enhancement, altered reconsolidation, and psychotherapy process catalysts, including enhancing cognitive control, increasing behavioral flexibility, and shifting behavior from habitual behavior to goal-oriented behavior, among others. A recent study using dopamine augmentation of extinction learning confirmed that medication-assisted psychotherapy works when exposure therapy has successfully reduced fear (4). Craske *et al.* (2) aimed to enhance the context generalization of extinction, hypothesizing that context specificity of extinction (a hippocampal-mediated process) would be diminished with the systemic administration of scopolamine.

Exposure therapy helps patients confront the feared stimuli in a therapeutic manner so that fear decreases. Exposures need to be long enough and repeated often enough that fear decreases between sessions and must include therapeutic exposure in multiple contexts so that the new learning generalizes. Feared stimuli can be presented in the patient's imagination, in real life, or in VR, which Craske *et al.* (2) used to present the exposure stimuli.

VR has been used in several translational medication-assisted psychotherapy studies as a robust tool offering precise methodological control of the stimuli within and across patients, using D-cyloserine (DCS) in some of the earliest approaches to test augmentation of extinction (5,6). The first was with the fear of heights and incorporated two 40-minute VR sessions combined with DCS or placebo, resulting in significantly less fear in the DCS group at posttreatment and follow-up, including on psychophysiological, clinical, and self-report measures (5). A study in posttraumatic stress disorder compared DCS, placebo, and alprazolam with 5 VR and study medication sessions, reporting mixed results (6). The DCS group showed significantly lower indices of fear and stress on psychophysiological startle response and salivary cortisol, in line with the animal literature, but no differences between groups on clinical measures. This is somewhat similar to the current findings of Craske *et al.* (2), where there was a failure to show a subjective clinical response but an apparent positive result with a physiological measure.

Craske *et al.* (2) aimed to "decontextualize" exposure therapy and decrease the return of fear after therapy for social anxiety. They used exposure to VR audiences for 7 sessions of 1 minute each—which seems too short for normal habituation and extinction. The aim was to make extinction "context independent" so that exposure with scopolamine might allow the context generalization of extinction to occur more rapidly.

This proof-of-concept study potentially targets a previously underappreciated component of exposure—that of context sensitivity. However, there are a number of unanswered questions, and perhaps most importantly the results did not show an effect on clinical measures of social anxiety. There have been several recent examples of failures of translational research; in a reconsolidation paradigm using VR for the fear of flying, there were some minor group differences on psychophysiological measures but not on the clinical measures (7). The fear versus neutral cues were presented 10 minutes before VR exposure sessions within a head-mounted display. The head-mounted display might have served as the salient fear cue for both conditions, which may have occurred in the Craske *et al.* (2) study, such that the head-mounted display may have served as the salient context in both conditions, confounding their efforts to meaningfully manipulate context.

While this is an interesting pilot study, several questions remain. Most critically, why were improvements noted only in physiology but not in clinical measures of decreased fear? Is it possible that anticholinergic blockade via scopolamine leads to enhanced "dryness" and decreased SCR? Decreased sweating and dryness is a common side effect of anticholinergic drugs; the apparent effects on extinction of fear may be direct effects on physiological SCR levels. Craske *et al.* (2) argue that this is not the case, because no group differences were observed on skin conductance in the first exposure session. Nonetheless, it seems possible that there is an additive effect of the decreased sweat gland activation from scopolamine that may not be immediately apparent. An additional examination of scopolamine's effect on the skin conductance level readout is warranted and provides an

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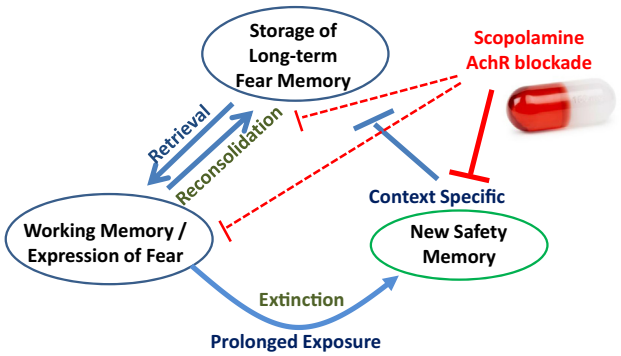

Figure 1. Hypothesized mechanisms of cholinergic antagonism on fear processing. Fear memories, such as social cue–related fears in social anxiety disorder, are thought to be modulated by reactivation when they are retrieved through cue reminders. While in working memory, they are then subject to strengthening via reconsolidation or inhibition via extinction, the process thought to underlie exposure-based psychotherapy. Craske *et al.* (2) hypothesize that cholinergic blockade through scopolamine will block the context specificity of extinction memories, allowing their generalization to new environments. Other data suggest that anticholinergic blockade may also affect reconsolidation and expression of fear memories, as well as decreasing peripheral measures of fear, such as sweating, that may impair detection with electrodermal skin response. AchR, acetylcholine receptor.

additional reason why fear-potentiated acoustic startle would be an important measure in future studies.

Another concern relates to the predicted effect of context generalization. The role of the hippocampus in context modulation of fear extinction is well established, but it is not entirely convincing that this effect is what was manipulated with scopolamine in these studies. The most robust effect was the near immediate drop in skin conductance level during the second exposure while the drug was on board, a rapidity of action during essentially within-session extinction that seems hard to reconcile with a model of generalization of consolidated extinction. In addition, the primary predicted outcome of increased context generalization during extinction context renewal testing showed only a trend-level difference with scopolamine.

Reconsolidation blockade might better explain the findings of decreased renewal and immediate potential effects after initial exposure (Figure 1). The 7 single sessions of 1 minute each—for 7 minutes of overall exposure—is an extremely limited exposure period for extinction learning and may be more consistent with a reconsolidation-based brief reactivation paradigm. While there is limited published literature on the potential effects of cholinergic antagonism on reconsolidation blockade (8), and there remains controversy around reconsolidation blockade in humans, such a mechanism of action would explain the findings equally if not better. Future testing for reinstatement and spontaneous recovery effects as well as whether just a single 1-minute exposure is sufficient for the reduced skin conductance level would further address the possibility that this may be an effect primarily on reconsolidation blockade.

Other possible concerns include the following: 1) How did Craske *et al.* (2) know the correct dose to test, why were 0.5 mg and 0.6 mg doses used, what might the effects have been of higher or lower doses, and why might scopolamine's effect on general hippocampal processing and memory not be expected to interrupt some of the other important effects of the hippocampus on extinction? 2) Did the investigators use the correct paradigm to prove that scopolamine works by impairing context generalization or are things too confounded to not see differences between the contexts and scopolamine versus placebo? The authors hypothesize that medicine side effects may have increased subjective fear measures, but if that were so, there should have been significant improvement on placebo, which there was not. It is curious that Craske *et al.* (2) excluded those who failed to extinguish, as it potentially limits what can be concluded about its effects on extinction. 3) Why would scopolamine only interfere with context generalization given that muscarinic receptors are involved in many hippocampal functions? Cholinergic receptors are also implicated in regulating fear recall and extinction retention in the amygdala (9), the medial prefrontal cortex (10), and presumably in other regions/processes.

In summary, social anxiety disorder is complicated, and this and other fear- and anxiety-related disorders clearly need better treatment options. Overall, using the progress in translational neuroscience to enhance psychotherapy is an exciting and relatively new discipline that has led to novel ideas and potentially powerful strategies—while not yet producing a "home run." Craske *et al.*'s study (2) on the possible effect of scopolamine augmentation of exposure is an exciting next step in this field because it examines an interesting new view of how medications might interact with behavioral interventions. Additional studies are needed to rule out the direct effects of scopolamine on skin conductance as a physiological readout, on the possibility of it blocking reconsolidation more than enhancing extinction, on disambiguating the physiological effects versus the clinical effects, and on the study design overall. Nonetheless, such work is needed and continues the important process of identifying new targets, based on an ever more sophisticated neuroscience of emotion and behavior, toward eventual much-needed improved treatment approaches.

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