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Invited Review

Revisiting propranolol and PTSD: Memory erasure or extinction enhancement?

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ABSTRACT

Posttraumatic stress disorder (PTSD) has been described as the only neuropsychiatric disorder with a known cause, yet effective behavioral and pharmacotherapies remain elusive for many afflicted individuals. PTSD is characterized by heightened noradrenergic signaling, as well as a resistance to extinction learning. Research aimed at promoting more effective treatment of PTSD has focused on memory erasure (disrupting reconsolidation) and/or enhancing extinction retention through pharmacological manipulations. Propranolol, a β-adrenoceptor antagonist, has received considerable attention for its therapeutic potential in PTSD, although its impact on patients is not always effective. In this review, we briefly examine the consequences of β-noradrenergic manipulations on both reconsolidation and extinction learning in rodents and in humans. We suggest that propranolol is effective as a fear-reducing agent when paired with behavioral therapy soon after trauma when psychological stress is high, possibly preventing or dampening the later development of PTSD. In individuals who have already suffered from PTSD for a significant period of time, propranolol may be less effective at disrupting reconsolidation of strong fear memories. Also, when PTSD has already developed, chronic treatment with propranolol may be more effective than acute intervention, given that individuals with PTSD tend to experience long-term, elevated noradrenergic hyperarousal.

1. Introduction

Posttraumatic stress disorder (PTSD) affects approximately 8% of the United States general population in their lifetime (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Kessler et al., 2005), and is characterized by heightened arousal and a resistance to extinction learning (Liberzon & Sripada, 2008; Pitman et al., 2012; Rauch, Shin, & Phelps, 2006; Shin & Handwerger, 2009; VanElzakker, Kathryn Dahlgren, Caroline Davis, Dubois, & Shin, 2014). While the pathophysiology of PTSD is poorly understood, dysregulated signaling of the stress-related neurotransmitter norepinephrine (NE) has been identified as a key biomarker underlying PTSD symptomatology (Geracioti et al., 2001; Kosten, Mason, Giller, Ostroff, & Harkness, 1987; Southwick et al., 1997; Southwick et al., 1999; Yehuda, Southwick, Giller, Ma, & Mason, 1992). However, the only FDA approved treatments for PTSD are the selective serotonin reuptake inhibitors, sertraline (Zoloft) and paroxetine (Paxil), which have limited efficacy (Tawa & Murphy, 2013). Nonetheless, pharmacotherapies that either dampen NE transmission, such as the α1-adrenoceptor antagonist prazosin, the α2 agonist clonidine, and the non-selective β antagonist propranolol, or enhance NE transmission such as the α2 antagonist yohimbine, have shown some success in diminishing the exaggerated fear responding associated with PTSD (Belkin & Schwartz, 2015; Morris & Bouton, 2007; Powers, Smits, Otto, Sanders, & Emmelkamp, 2009; Raskind et al., 2003; Strawn & Geracioti, 2008; Tawa & Murphy, 2013; Taylor, Freeman, & Cates, 2008; Wangelin, Powers, Smits, & Tuerk, 2013). Yohimbine, as well as the non-selective β agonist isoproterenol, can enhance extinction learning (Cain, Blouin, & Barad, 2004; Do-Monte et al., 2010; Morris & Bouton, 2007; Powers et al., 2009), as well as memory consolidation or reconsolidation (Dębiec, Bush, & LeDoux, 2011; Gazarini, Stern, Carobrez, & Bertoglio, 2013). For these reasons, there has been a resurgence of interest in using noradrenergic drugs as adjuncts to cognitive-behavioral therapies for PTSD.

In this regard, animal studies of inhibitory avoidance, and Pavlovian fear conditioning studies in both animals and humans have provided insight into the neurobiological underpinnings of aversive learning and memory that contribute to the development and expression of PTSD (Bowers & Ressler, 2015; Fanselow & Poulos, 2005; LeDoux, 2000; Maren, 2001; Maren, Phan, &

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Liberzon, 2013; Myers & Davis, 2007; Roozendaal, McEwen, & Chattarji, 2009). Here we primarily focus on reviewing Pavlovian fear conditioning studies because the interpretation of drug studies using an inhibitory avoidance design may be less clear, since the accuracy and specificity of learning are difficult to parse. In particular, post-training drug manipulations resulting in "better memory" (i.e., a longer latency to enter the aversive chamber) may reflect a more accurate recall of the initial training experience. However, it is possible that this apparent memory enhancement actually reflects reduced accuracy of memory for the training context (Atucha & Roozendaal, 2015). This problem can be bypassed through the use of multiple contexts, which are frequently used in studies of Pavlovian fear extinction, where this literature may better model PTSD relevant processes.

Initially, many studies of Pavlovian fear conditioning focused on NE and memory consolidation, the process through which a temporary short-term memory is stabilized into a persistent long-term memory, a procedure that in part involves protein synthesis (Johansen, Cain, Ostroff, & LeDoux, 2011). NE plays a crucial role in memory consolidation and propranolol can impair consolidation in both animal models and human subjects (Berlau & McGaugh, 2006; Cahill, Pham, & Setlow, 2000; Introini-Collison & Baratti, 1986; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013; McGaugh, 2000; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; Wilson, Pham, & Sullivan, 1994). The molecular mechanisms by which propranolol (and NE itself) affects aversive learning and memory processes are only beginning to be elucidated, but they may include the MAPK and JAK/STAT3 pathways, among others. Johansen, LeDoux and colleagues have suggested that postsynaptic β-adrenergic signaling in the lateral nucleus of the amygdala interacts with the MAPK pathway to modulate acquisition and consolidation of fear memories (Johansen et al., 2011). Another group found that infusion of the inflammatory cytokine IL-6 into the basolateral amygdala modulates fear extinction learning through the JAK/STAT3 pathway (Hao et al., 2014), and other studies have linked NE (and propranolol) with IL-6 signaling (Norris & Benveniste, 1993).

There is growing interest in the role of NE in memory reconsolidation as well as extinction learning. As described below in Figs. 1 and 2, studies of reconsolidation and extinction both typically begin with fear acquisition (i.e., conditioning), comprising the pairing of a neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US), such as a mild footshock. Many reconsolidation studies use a single CS–US pairing, and the following day animals are presented with one CS-alone trial to "reactivate" the fear memory. In contrast, for studies of extinction learning, conditioning typically consists of multiple (3–5) CS–US pairings, perhaps yielding a stronger association. As such, fear extinction requires many CS-alone presentations to acquire a new CS-no US memory. While fear-related measures, such as freezing in rodents and autonomic skin conductance in humans, are similarly used to quantify both reconsolidation and extinction, differences between these two paradigms in the acquisition phase in particular need to be considered when comparing the effects of drug manipulations.

Psychotherapies, some of which are thought to mimic aspects of extinction learning, are frequently used to counteract PTSD, although behavioral therapy alone is not always effective (Bryant, 2002; Mayou, Ehlers, & Hobbs, 2000; Rose, Brewin, Andrews, & Kirk, 1999). Because individuals with PTSD display exaggerated fear responses, clinicians and scientists have attempted to inhibit pathological fear with pharmaceuticals via two distinct mechanisms: (1) blocking memory reconsolidation after reactivating traumatic memories or (2) enhancing long-term extinction learning associated with exposure therapy. When a consolidated memory is retrieved it is thought to enter a labile state which may be subject to manipulation and possibly erasure (Alberini & LeDoux, 2013). It has been shown that inhibiting protein synthesis immediately after a brief memory reactivation is sufficient to attenuate conditional fear in rodents (Nader, Schafe, & Le Doux, 2000; Rudy, Biedenkapp, Moineau, & Bolding, 2006). Propranolol, a commonly prescribed 'beta-blocker' that can cross the blood–brain barrier, has received considerable attention for its noted effects on reconsolidation blockade (Brunet et al., 2008; Debiec & LeDoux, 2004; Soeter & Kindt, 2012). One possibility is that propranolol acts indirectly to inhibit protein synthesis, thereby disrupting reconsolidation and erasing the fear memory. An alternative but not mutually exclusive possibility is that propranolol, which has known anxiolytic effects (Brantigan, Brantigan, & Joseph, 1982), may help reduce the psychological stress associated with encountering a feared stimulus upon extinction training, helping to restore an optimal level of NE signaling to promote extinction learning. Here we review the existing literature comparing the efficacy of propranolol in reconsolidation versus its effects on extinction learning, both in rodents and in humans.

2. Does propranolol prevent reconsolidation and partially erase fear memories?

Individuals who suffer from PTSD often exhibit heightened fear responses. This may reflect hyperconditioning, a resistance to extinction learning, or a combination of the two (Milad et al., 2009; Pitman, 1988; Pitman et al., 2012). In the laboratory setting, Pavlovian fear conditioning is widely used in both rodents and humans to investigate emotional learning and memory. Animals are typically trained by pairing a neutral CS with an aversive US, such as a mild footshock. With one or more pairings, animals learn to exhibit conditioned fear responses (CR) such as freezing (i.e., immobility) or potentiated acoustic startle, which are accompanied by autonomic changes such as increased respiration and heart rate (Davis, 1992; LeDoux, 2000; Maren, 2001). Rodent fear conditioning studies typically use freezing as their principal behavioral measure of fear, although it cannot be assumed with certainty

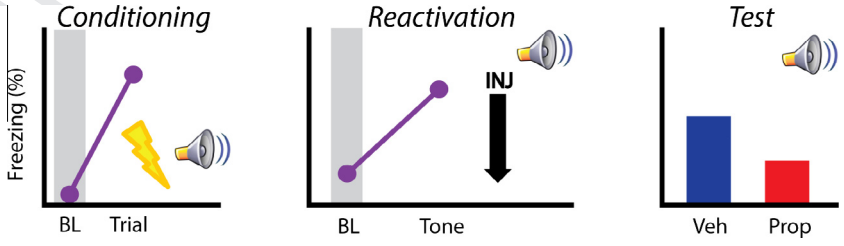

Fig. 1. Schematic representation showing the effect of post-reactivation propranolol on reconsolidation. In rodents, conditioning typically consists of a single CS–US pairing (left). The next day animals receive 1 CS reactivation trial, immediately followed by propranolol or vehicle administration (middle). When tested at later time points in the absence of drug, propranolol treated animals show reduced fear responding (right). Abbreviations: baseline period (BL), injection (INJ), vehicle (Veh), propranolol (Prop).

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