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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.

Keywords

fear; extinction; reconsolidation; propranolol; PTSD; consolidation; norepinephrine

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Conflicts of Interest

None declared.

Author Contributions

TFG, PJF and SM wrote and edited the manuscript.

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, Dahlgren, 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, 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, & 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 Figures 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, & LeDoux, 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 that freezing always provides a reliable readout of the subjective state of fear in animals.

When a consolidated fear memory is retrieved or reactivated it is believed to enter a labile state and may be reconsolidated in a protein synthesis dependent manner (Nader et al., 2000). This idea has far reaching implications for the treatment of trauma-related disorders such as PTSD, insofar as PTSD is characterized by recurring thoughts or images of the traumatic event. It follows then, that one may be able to disrupt the reconsolidation of a fearful memory when it is retrieved and this would partially abolish that fear memory (Maren, 2011). It is unlikely that even very effective disruption of reconsolidation could *fully* erase a fear memory, as some degree of declarative knowledge of the memory would probably remain intact, both in human subjects and in rodents. Nonetheless, there is high interest in gaining a greater understanding of the neurobiology of reconsolidation and pharmacological means of its disruption as a treatment for PTSD.

2.1 Rodents

In a potentially major breakthrough, Debiec and LeDoux (2004) found that systemic administration of propranolol successfully blocked reconsolidation in rodents. In this study, rats were fear conditioned and the following day received one CS “reactivation” trial followed by propranolol. This single injection was sufficient to reduce conditioned responding to the CS when tested at several time points beyond drug (see Figure 1 for schematic data) (Debiec & LeDoux, 2004). In a follow up study, it was shown that β-adrenoceptor stimulation enhanced fear memory reconsolidation (making that memory resistant to extinction) and that this can indeed be blocked by propranolol (Dębiec et al., 2011). This effect has been replicated in the rodent literature, further demonstrating that

propranolol reduces fear when delivered after a brief memory reactivation (Abrari, Rashidy-Pour, Semnanian, & Fathollahi, 2008; Muravieva & Alberini, 2010). In addition to cued fear memories, propranolol effectively blocks reconsolidation of context fear in rats (Schneider et al., 2014). Collectively, these data indicate that propranolol administration immediately after brief memory retrieval dampens fear responding long term and may do so by interfering with reconsolidation.

The mechanism by which propranolol attenuates reconsolidation is unknown; however, many studies have proposed that it indirectly disrupts protein synthesis, thought to be a necessary component of reconsolidation (Nader et al., 2000). Given that PTSD is a chronic disorder and trauma reminders occur frequently, it is possible that remote fear memories are less sensitive to disruption due to overconsolidation processes (Pitman & Delahanty, 2005). Interestingly, it has been shown that recent, but not remote, fear memories are susceptible to disruption via protein synthesis inhibitors (Milekic & Alberini, 2002; Suzuki et al., 2004; Taherian et al., 2014). Moreover, others have shown that post-reactivation propranolol has no effect on reconsolidation in rats (Pitman et al., 2011). The reasons for these discrepancies are unclear, but it is possible that the weak conditioning parameters (1 CS-US pairing) used in the majority of these reconsolidation studies results in weak fear memories, making them more susceptible to erasure and interference. There is some evidence, however, to suggest that strong fear memories are also susceptible to manipulation (Duvarci, Nader, & LeDoux, 2008; Taherian et al., 2014). Additionally, the initial reactivation tests are typically given 24 hrs post-conditioning in these studies, making them fairly recent memories as opposed to more remote ones that would be associated with chronic PTSD. Overall, propranolol may be mildly effective at disrupting reconsolidation, but this is likely limited by the age and strength of the memory.

2.2 Humans

Due to the debilitating nature of stress and trauma-related disorders such as PTSD, there is high interest in both behavioral and pharmacotherapies aimed at alleviating symptoms or preventing these disorders from developing at all. Considerable effort has been placed on erasing the original fear memory by disrupting reconsolidation after memory retrieval in humans. Indeed, many studies have shown that propranolol appears to disrupt reconsolidation processes, thereby dampening fear responding in healthy volunteers as well as individuals with PTSD (Brunet et al., 2008, 2011, 2014; Kindt, Soeter, & Vervliet, 2009; Lonergan et al., 2013; Poundja, Sanche, Tremblay, & Brunet, 2012; Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012; Soeter & Kindt, 2011, 2012). Typically, the experimental designs in these studies consisted of one or more memory reactivation trials with or without propranolol. Fear memories were then tested at a later time point, in a drug free state. Propranolol treatment attenuated physiological fear measures (Brunet et al., 2008, 2011, 2014; Kindt et al., 2009; Soeter & Kindt, 2011, 2012), and both men and women with chronic PTSD reported a better quality of life (Poundja et al., 2012). Collectively, these data appear to strongly suggest that propranolol effectively blocks the reconsolidation of fear memories in both healthy volunteers and individuals with PTSD.

It is, however, somewhat surprising that a single, acute dose of propranolol (or any drug for that matter) would permanently erase, or even strongly weaken, a longstanding fear memory. Many studies have argued that targeting reconsolidation may be unlikely to work given that only weak and recently formed memories are most susceptible to erasure (Milekic & Alberini, 2002; Parsons & Ressler, 2013; Suzuki et al., 2004) and that memories do not necessarily undergo reconsolidation upon reactivation, unless there is new information to be encoded (Sevenster, Beckers, & Kindt, 2012). This suggests that there may be certain "boundary conditions" influencing reconsolidation. For example, Nader and colleagues have suggested that reconsolidation may only occur when certain conditions are met, including that strong, recent memories resist reconsolidation but that extinction learning is not sufficient to block reconsolidation (Duvarci, Mamou, & Nader, 2006; Wang, de Oliveira Alvares, & Nader, 2009). Moreover, individuals with PTSD may also exhibit enhanced conditioning, possibly making these fear memories even more difficult to target (Pitman, 1988). These strongly encoded fear memories also undergo frequent reactivation which may result in overconsolidation, further limiting the idea that acute propranolol could abolish them (Pitman & Delahanty, 2005).

Additionally, given the nature of the reconsolidation procedures used in many of the human studies, it is unclear whether propranolol is blocking reconsolidation, enhancing extinction learning, or some combination of the two. For example, Poundja and colleagues (2012) examined subjects with chronic PTSD. Individuals were asked to actively recall a traumatic event while under the influence of propranolol. This process was repeated once a week for six weeks. While the authors claim that the observed decrement in fear responding reflected disruption of reconsolidation and a weakened fear memory, an alternative interpretation is that these recall sessions trigger extinction-like processes which may be enhanced by repeated propranolol administration (Pitman et al., 2002). A similar confound arises in the studies by Brunet and colleagues (2008, 2011, 2014). Because patients received multiple drug-reactivation sessions, it is difficult to parse the outcomes, although this does not preclude the observation that propranolol appears to be an effective fear-reducing agent in some situations. Additional issues arise in the interpretation of these results because the effects are not always replicable, even when carried out by the same laboratory in some cases (Spring et al., 2015; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009a, 2009b; Wood et al., 2015), bringing into question whether propranolol modulates reconsolidation. In summary, compelling evidence to support the notion that acute or even subchronic propranolol treatment effectively blocks reconsolidation in human subjects is lacking and many of the experimental designs make it difficult to dissociate effects on extinction versus reconsolidation processes.

3. Does propranolol enhance extinction learning and augment exposure therapy?

Conditional fear can be extinguished with repeated presentation of the CS in the absence of the US, ultimately resulting in a reduction of CRs. Extinction, however, is highly susceptible to various forms of relapse as indexed by increased conditioning responding with the passage of time (spontaneous recovery), the presentation of an unsignaled US

(reinstatement), upon encountering the CS in a non-extinguished context (renewal), (Bouton, 2000; Goode & Maren, 2014; Hermans, Craske, Mineka, & Lovibond, 2006; Maren et al., 2013; Vervliet, Craske, & Hermans, 2013), and relapse can be promoted by psychological stress (Maren & Holmes, 2015). Extinction learning is also sensitive to the timing relative to trauma, and it is typically less effective when given soon after the traumatic experience (Chang, Berke, & Maren, 2010; Fitzgerald, Giustino, Seemann, & Maren, 2015; Kim, Jo, Kim, Kim, & Choi, 2010; Maren, 2014; Maren & Chang, 2006). The notion that stress and the timing of extinction learning relative to trauma can disrupt its long-term efficacy calls into question the benefit of early therapeutic interventions such as psychological debriefing, which is often used to reduce the impact, or even prevent the development, of PTSD. A number of studies have shown that these early intervention strategies are ineffective when used alone (Bryant, 2002; Mayou et al., 2000; Rose et al., 1999), but may be improved by pharmacological adjuncts (de Kleine, Rothbaum, & van Minnen, 2013).

3.1 Rodents

Despite a vast literature on extinction and its relevance to PTSD treatment, no existing drugs stand out for their ability to broadly reduce conditional fear. Propranolol has been studied extensively, but with mixed results, leading many to believe it is an ineffective therapeutic option (Raskind et al., 2003; Strawn & Geracioti, 2008; Tawa & Murphy, 2013). In addition, many studies in rodents have shown that systemic propranolol prior to delayed extinction *impairs* long-term retention (Cain et al., 2004; Do-Monte et al., 2010; Fitzgerald et al., 2015). One possibility is that, similar to extinction learning itself, the efficacy of propranolol as a fear-reducing agent is sensitive to the timing of administration. This may reflect differences in basal levels of NE at the onset of extinction (high in “immediate” extinction (i.e., when extinction is carried out minutes to several hours after fear conditioning, and relatively low in delayed extinction). In line with this hypothesis, it is well established that elevated NE signaling impairs prefrontal function (Arnsten, 2009) and that the prelimbic (PL) and infralimbic (IL) subdivisions of the medial prefrontal cortex (mPFC) crucially regulate fear and its extinction (Giustino & Maren, 2015; Milad & Quirk, 2012; Quirk & Beer, 2006; Riga et al., 2014; Sotres-Bayon & Quirk, 2010).

We have recently shown that footshock stress rapidly and persistently alters mPFC single-unit activity for up to an hour after conditioning (a time frame that corresponds with the immediate extinction deficit) (Fitzgerald et al., 2015). Systemic propranolol administered prior to conditioning acted to normalize mPFC firing in the aftermath of trauma, blunting both increases and decreases in firing rate in separate populations of neurons. Thus, propranolol delivered immediately after conditioning may stabilize mPFC function and promote successful extinction. Indeed, propranolol effectively enhances extinction learning under conditions where it normally fails; that is, when extinction trials are delivered soon after conditioning, when psychological stress is high (Figure 2a). Systemic propranolol administered immediately after conditioning (and 30 min prior to immediate extinction training) produced marked effects on extinction learning. Propranolol treatment attenuated the normally high levels of baseline fear (prior to CS presentation) associated with immediate extinction while reducing fear throughout extinction training (Figure 2a). When animals were tested for extinction retrieval 48 hrs later, prior propranolol treatment reduced

the spontaneous recovery of fear (Figure 2a). It is possible that propranolol treatment immediately post conditioning resulted in a weaker fear memory, by interfering with consolidation processes. However, animals that received post-conditioning propranolol and underwent a “no-extinction” protocol (i.e., no CS presentations) showed similar levels of spontaneous recovery to vehicle controls on test (Figure 2b). Interestingly, propranolol still effectively reduced baseline freezing levels in this no-extinction procedure, but had no long-term effect on fear memory, suggesting that propranolol treatment indeed facilitated extinction learning as opposed to dampening the strength of the CS-US association (Figure 2b) (Fitzgerald et al., 2015).

As noted above, propranolol given prior to *delayed* extinction may have detrimental effects on learning (Cain et al., 2004; Do-Monte et al., 2010; Fitzgerald et al., 2015). To explore this bi-directional effect of timing, in the same study described above (Fitzgerald et al., 2015), a separate group of animals received propranolol 30 min prior to delayed extinction (24 hrs post conditioning) (Figure 2c). Whereas this treatment had no within session effect (while on drug), it actually impaired retrieval when tested the following day (Figure 2c). These data suggest that the timing of propranolol administration relative to trauma is a key factor in its therapeutic efficacy. Importantly, propranolol administration alone would not be expected to dampen long-term fear responding as propranolol had no long-term effect in the no-extinction animals. In summary, propranolol appears to effectively enhance immediate extinction while impairing delayed extinction.

Rodent microdialysis studies have linked footshock stress, which is typically the stressor used in animal fear conditioning, with amygdalar (Galvez, Mesches, & McGaugh, 1996), hippocampal (Hajós-Korcsok et al., 2003), and medial prefrontal cortical (Ishizuka et al., 2000) release of NE, bolstering the hypothesis put forth by Fitzgerald et al. (2015) that recent footshock exposure during immediate extinction is characterized by elevated NE signaling. Less appears to be known about endogenous NE signaling during fear extinction or reconsolidation, where many studies of these two phenomena have focused on manipulating such signaling with exogenous noradrenergic drugs. Two older studies found that forebrain depletion of NE (with little effect on dopamine) using the drug 6-hydroxydopamine produced resistance to extinction learning (Mason & Fibiger, 1979; Mason, Roberts, & Fibiger, 1979). More recently, Berlau and McGaugh (2006) showed that infusion of NE into right hemisphere amygdala enhanced extinction, and others have shown that β-adrenoceptor activation in infralimbic cortex is necessary for extinction (Mueller, Porter, & Quirk, 2008). These four studies, which are probably more relevant to delayed than immediate extinction, collectively suggest that enhancing endogenous NE signaling promotes delayed extinction whereas depleting NE impairs such extinction, consistent with the Fitzgerald et al. (2015) propranolol data.

3.2 Humans

In humans, psychological debriefing can be given soon after trauma in an attempt to reduce or prevent PTSD development. The timing of this behavioral therapy mirrors that of immediate extinction procedures in rodents, where the latter approach often yields unsuccessful long-term fear reduction, as described above. It is possible that propranolol

may effectively enhance the long-term efficacy of debriefing in humans. Interestingly, several studies have reported that propranolol treatment soon after trauma produced no difference from untreated controls (McGhee et al., 2009; Nugent et al., 2010; Stein, Kerridge, Dimsdale, & Hoyt, 2007). Importantly, these studies suggest that propranolol alone may be ineffective, but did not address the efficacy of propranolol as an adjunct to behavioral therapies aimed at reducing fear.

Similar to its use in rodents, it is possible that propranolol is most effective when coupled with behavioral therapies soon after trauma in humans, and is less effective or even worsens the outcome at delayed time points. In support of this idea, Bos and colleagues (2012) showed that propranolol delivered prior to extinction training had no effect on physiological response properties (startle reflex and skin conductance), but impaired extinction learning based on levels of US expectancy in healthy humans (Bos, Beckers, & Kindt, 2012). In addition, it has been shown that propranolol delivered either right before or right after extinction training failed to line with our data and other studies demonstrating that propranolol administration impairs delayed extinction in rodents (Cain et al., 2004; Do-Monte et al., 2010; Fitzgerald et al., 2015). It remains possible that propranolol would be most effective soon after trauma when coupled with behavioral therapies, acting to reduce psychological stress and enhance learning. In a pilot study, Pitman and colleagues (2002) have shown that propranolol administered four times daily for 10 consecutive days (with the first dose coming within 6 hrs of trauma exposure), coupled with behavioral counseling, significantly reduced long-term fear; this suggests that propranolol can be used to prevent PTSD development. Moreover, propranolol given three times daily for 1 week immediately following trauma reduced the development of PTSD symptomatology (Vaiva et al., 2003). These data also lend support to the idea that chronic propranolol treatment, starting soon after trauma, might effectively reduce PTSD symptomatology long-term, although there is little empirical evidence on this topic (Ostrowski & Delahanty, 2014).

4. Conclusions

There remains an unmet need regarding effective treatment for PTSD, although various behavioral interventions, pharmacotherapies, or their combination have shown some promise (Bukalo, Pinard, & Holmes, 2014; Fitzgerald, Seemann, & Maren, 2014; Ostrowski & Delahanty, 2014). An ambiguous view on propranolol has emerged in the literature, given discrepant findings in both rodents and humans and a debate on the memory processes propranolol is most effective at modulating (reconsolidation versus extinction). Here we propose that propranolol may be most effective as a long-term fear-reducing agent when administered soon after trauma and coupled with extinction training. We suggest that propranolol effectively dampens elevated NE signaling under high psychological stress, thereby promoting successful extinction learning. This can also explain why propranolol may be ineffective at modulating or even hinder delayed extinction in rodents and humans. The fact that propranolol facilitated immediate extinction and impaired delayed extinction indicates that it may be most useful under conditions in which stress is high (e.g., at the onset of immediate extinction) and NE levels are likely elevated beyond what is optimal for learning (Fitzgerald et al., 2015). In contrast, stress is relatively low at the onset of delayed extinction and the fear-inducing stimulus might elicit an “optimal” amount of NE release to

facilitate learning; this signaling via β-adrenoceptors may be reduced to a suboptimal level by acute propranolol. This line of reasoning may also suggest that if too high a dose of propranolol is administered before immediate extinction, it could also impair learning by reducing NE signaling below an optimal level. In addition, long-term administration of propranolol may effectively reduce tonically elevated NE signaling for individuals with chronic PTSD (i.e., those who would no longer benefit from acute propranolol paired with exposure therapy).

We also suggest here that propranolol is less likely to disrupt reconsolidation, especially in individuals with chronic PTSD in which fear memories are neither recent nor weak, which was not the case in many of the animal studies that showed propranolol blocks reconsolidation. The human literature on propranolol and reconsolidation may actually strengthen the argument that propranolol facilitates extinction learning under stress given the multiple reactivation experimental designs described above, rather than this drug solely dampening or eliminating the fear memory. Overall, the mixed findings on propranolol and reconsolidation make it difficult to support the notion that propranolol might permanently abolish fear memories, although it may dampen them when certain boundary conditions for reconsolidation are met (Wang et al. 2009, Duvarci et al. 2006).

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Highlights

- Propranolol coupled with extinction soon after trauma reduces long-term fear
- Chronic propranolol may block tonically elevated levels of NE associated with PTSD
- It is unlikely that acute propranolol erases strong fear memories in PTSD

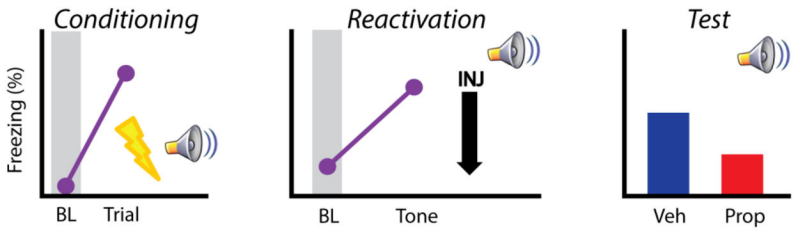

Figure 1.

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).

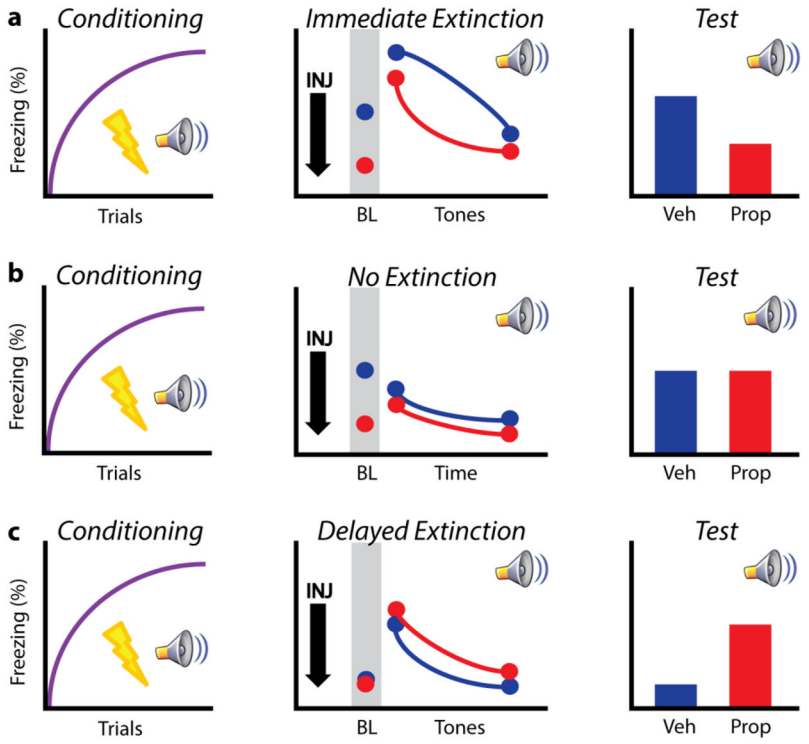

Figure 2.

Schematic data showing the bi-directional effect of propranolol treatment on extinction learning at different time points. a) Animals are typically conditioned with several CS-US pairings (left). In an immediate extinction procedure, animals received either vehicle or propranolol 30 min prior to extinction training (and immediately after conditioning). Propranolol treatment reduced elevated baseline levels of freezing and attenuated fear throughout the session (middle). When tested for extinction recall later (in a drug free state), prior propranolol treatment significantly reduced the spontaneous recovery of fear, ameliorating the immediate extinction deficit (right). b) Similar to animals undergoing immediate extinction procedures, “no-extinction” controls received vehicle or propranolol immediately following conditioning, but were exposed to the extinction context in the absence of CS presentation. Propranolol reduced elevated levels of baseline freezing, although no difference was observed between groups throughout the session (middle). Upon test, animals froze at similarly high levels (right). c) In delayed extinction, animals were conditioned using the same protocol as in a and b. However, animals were returned to their home cage following conditioning and not injected. The following day, rats received vehicle or propranolol administration 30 min prior to an extinction session. No differences were observed at baseline or during tone presentation (middle). When tested for extinction recall (in a drug free state), prior propranolol treatment impaired retrieval relative to vehicle controls (right). Abbreviations as in Figure 1 legend. Data are adapted from Fitzgerald et al. (2015).