Psychophysiologic effect of post-retrieval Propanolol on traumatic memories in post-traumatic stress disorder

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According to a translational model of the pathogenesis of post-traumatic stress disorder (PTSD) based upon hormonal modulation of Pavlovian conditioning (1), a terrifying event (unconditioned stimulus, UCS) overstimulates endogenous stress hormones as part of an unconditioned fear response (UCR). These hormones overly strengthen the consolidation of conditioned fear, which is later manifest in durable fear responses (conditioned responses, CRs) to reminders of the event (conditioned stimuli, CSs). Animal and human data indicate that the effects of stress hormones on conditioning are mediated by central noradrenergic activity and can be opposed by the ?-adrenergic blocker propranolol (reviewed in (2). In a previous study, we found that administration of propranolol in the emergency department within six hours of a psychologically traumatic event reduced subsequent physiologic responses (CRs) during mental imagery (CS) of the event (3).

In rodents, the period of time during which stress hormones can modulate the consolidation of conditioned learning is typically no more than a few hours after the learning has occurred. After this, ?-blockers are no longer able to attenuate fear conditioning (4). PTSD cannot be diagnosed in humans until a full month after the traumatic event (three months for chronic PTSD), which presumably is long after this window of opportunity has closed. In previously conditioned animals, however, administration of propranolol following presentation of the CS has been found to

reduce subsequent conditioned inhibitory avoidance (5) and cue-elicited freezing (6). We wondered whether reactivating PTSD subjects' memories of their traumatic events might similarly re-open the window of opportunity for propranolol to weaken subsequent physiologic responding.

We employed the same validated psychophysiologic script-driven imagery technique (7) used in the acute, post-trauma psychophysiologic PTSD study cited above (3). Physiologic responses during traumatic imagery using this technique have consistently been shown to be larger in PTSD compared to non-PTSD trauma victims (8).

In the present study, 19 patients with chronic PTSD resulting from various psychologically traumatic events described the event that caused their PTSD. This served to reactivate of their traumatic memories. Immediately thereafter the subject received either randomized, double-blind oral 40 mg short-acting propranolol followed two hours later by oral 60 mg long-acting propranolol (n=9), or look-alike placebo capsules (n=10). A trained research assistant composed scripts portraying the event in the subject's own words and recorded them for playback. A week later, in the psychophysiology laboratory, the subject listened to the audio recording of their personal traumatic scripts and imagined the event as if it were happening to them again, while physiologic responses were measured. We hypothesized that subjects who had received propranolol a week earlier would show smaller physiologic responses during script-driven traumatic imagery than those who had received placebo.

Methods

Nineteen individuals with chronic PTSD according to the Structured Interview for DSM-IV (9) were randomized to propranolol (n=9, 5M/4F) or placebo (n=10, 4M/6F) groups. Respective group means (SDs) included: age 34.8 (10.1) vs. 35.1 (10.5), $t(17)=0.1$, $p=0.95$; years elapsed since traumatic event 10.9 (12.5) vs. 10.1 (10.8), $t(17)=0.2$ $p=0.88$; Impact of Event Scale-Revised 56.3 (10.8) vs. 55.0 (10.7), $t(17)=0.3$, $p=0.79$. Etiologic traumatic events

included: *propranolol* group: childhood sexual abuse (3), motor vehicle accident (3), rape, being taken hostage, and witnessing a physical assault; *placebo* group: rape (2), physical assault (2), childhood sexual abuse (2), being taken hostage, severe death threats, house fire, and witnessing a physical assault. Subjects gave written informed consent after the procedures had been fully explained.

Exclusion criteria included a.) systolic blood pressure (SBP) <100 mm Hg; b.) bronchial asthma, congestive heart failure, heart block, certain cardiac arrhythmias, or insulin-requiring diabetes; c.) previous adverse reaction to a ?-blocker; d.) use of another ?-blocker; e.) use of medication that could involve potentially dangerous interactions with propranolol; f.) pregnant or breast feeding; g.) "recovered" memory of traumatic event; or h.) Dissociative Experiences Scale (10) score > 20.

Comorbid mental disorders included: *propranolol* group: major depressive disorder (MDD, 1), panic disorder (PD) with (1) and without agoraphobia (2), social phobia (1), bulimia (1); *placebo* group: MDD (1), PD without agoraphobia (2), bulimia (1), generalized anxiety disorder (1).

An approximate 20-minute script preparation procedure (7) entailed the preparation of two personal traumatic scripts for each subject, each addressing an aspect of the traumatic experience that caused the PTSD. The subject described the experience in writing on a standard script preparation form. The investigator reviewed the descriptions and requested additional details. Later, the investigator composed an approximate 30-second "script" portraying each experience, which was recorded for playback. There were also two standard neutral "filler" scripts. Each subject then received 40 mg short-acting propranolol or placebo. Two hours later, if the participant's systolic blood pressure had not fallen by 30% or more, or to below 100 mmHg, and the short-acting dose was otherwise well tolerated, the subject received 60 mg of long-acting propranolol or placebo. All participants received both the short- and long-acting doses of study medication.

The psychophysiologic script-driven imagery procedure (7) took place one week later. After a 30-second baseline period, the subject listened during the playing of each script and then imagined the event portrayed, as if it were happening again, for 30 seconds. Heart rate (HR), skin conductance (SC), and left corrugator (facial frowning muscle) electromyogram (EMG) were recorded. Responses (change scores) were calculated by subtracting the preceding baseline period mean for each physiologic measure from the mean for the imagery period that followed it. Responses to the subject's two traumatic scripts were averaged, and the averaged responses were square-root transformed to reduce heteroskedacicity.

Physiologic responses were subjected to MANOVA with HR1⁄2, SC1⁄2, and EMG1⁄2 responses as simultaneous dependent variables, as well as univariate t-tests. The criterion for statistical significance was p<0.05. Additionally, data from 152 individuals with (n=79) or without (n=72) PTSD previously studied using the same technique employed here (8) were entered into univariate discriminant function analyses in order to determine optimal PTSD cut-offs for HR1⁄2, SC1⁄2, and EMG1⁄2 responses separately. These cut-offs are shown as dashed lines in Fig. 1.

Additional methodological details appear under Supplemental Material.

Results

Overall physiologic responding during mental imagery of the traumatic event was significantly smaller in the PTSD subjects who had received propranolol a week earlier compared to those who had received placebo (multivariate p=0.007, Fig. 1). Drug condition accounted for 49% of the variance in overall physiologic responding. The univariate analyses indicated that HR and SC, but not EMG, responses were significantly smaller in the propranolol compared to the placebo subjects (Fig. 1). The mean HR and SC responses of the placebo subjects were above the normative cut-offs for PTSD (dashed lines), whereas the mean HR and SC responses of the propranolol subjects were below the

normative PTSD cut-offs. The mean EMG responses of both groups fell below the normative PTSD cut-off. The observed effect sizes (Cohen's d, shown in Figure 1) were all in the predicted direction. By conventional standards (11), these effect sizes were very large for SC, large for HR, but small for EMG.

Discussion

A comparison of the results of the present study with those of a previously reported study in which propranolol was administered in the emergency room setting (3) reveals that propranolol given after the occurrence of a traumatic event and propranolol given after retrieval of the memory of a past traumatic event similarly reduce physiologic responding during subsequent mental imagery of the event, compared to placebo. In the present study, the subjects who received post-retrieval placebo showed physiologic responses typical of trauma victims with PTSD, whereas the subjects who received post-retrieval propranolol showed physiologic responses typical of trauma victims without PTSD.

A candidate explanation for the reduced physiologic responses in the propranolol group is pharmacologic blockade of reconsolidation (5,12). Such an explanation would assume that a.) physiologic responding during script-driven imagery is an index of the strength of the memory of the traumatic event; b.) retrieval returned the traumatic memory to a labile state that needed to be restabilized (reconsolidated) to persist (13); and c.) propranolol blocked this restabilization (5,6). However, in the absence of additional controls such an explanation is premature. The present study did not include a group that received propranolol in the absence of traumatic memory reactivation (retrieval). To infer blockade of reconsolidation, it should be shown that the physiologic responses of a non-reactivated propranolol group are lower than those of a reactivated propranolol group, in order to rule out nonspecific effects of propranolol (14). Blockade of reconsolidation is putatively a permanent

effect, in that the memory is presumed to have been lost (15). Additional research is needed to test the duration of the traumatic memory weakening induced by post-

retrieval propranolol.
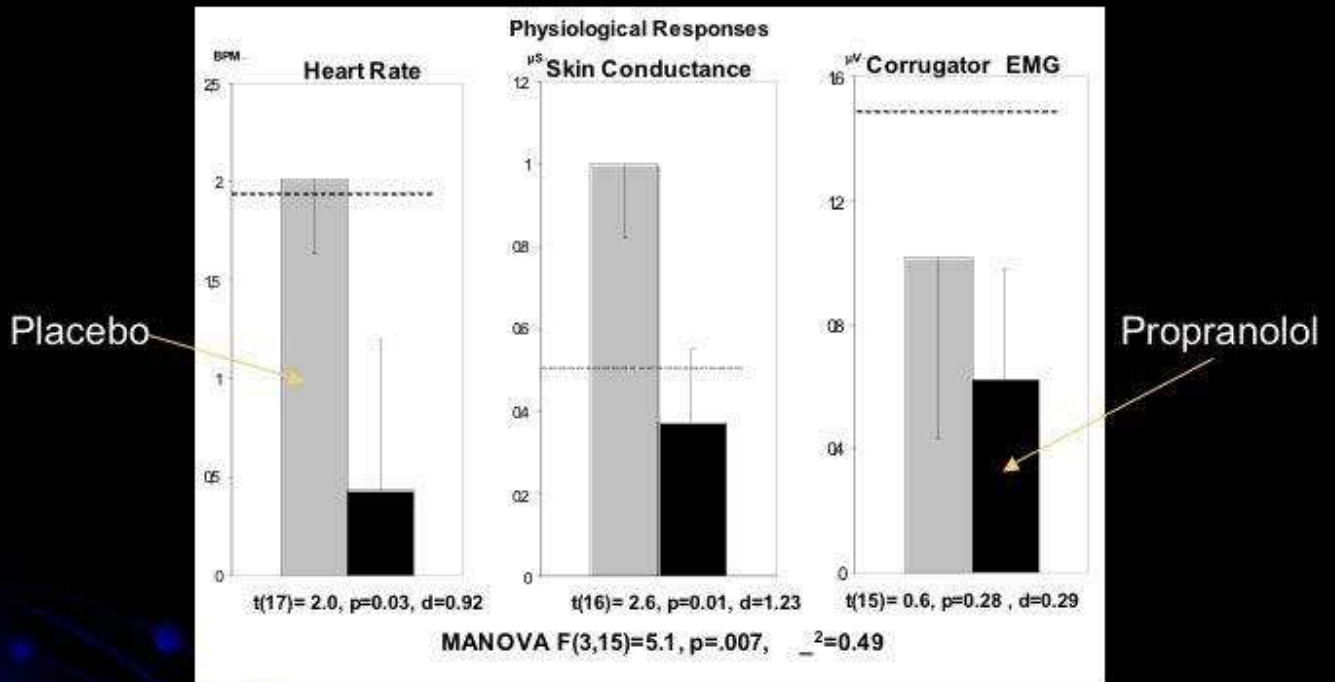
Physiological responses of Ss with PTSD during mental imagery of personal traumatic events, measured 1 week after memory reactivation that was followed by propranolol or placebo. Error bars represent SEM. Dashed lines represent empirical cut-offs for PTSD based upon prior research. Abbreviations: EMG-electromyogram, BPM-beats per minute, µS-µSiemens, µV-µVolts.   SOBP 2006

Figure Legend

Figure 1. Physiologic responses of participants with post-traumatic stress disorder (PTSD) during mental imagery of personal traumatic events, measured one week after memory retrieval that was followed by propranolol or placebo. Gray bars (left)-placebo; black bars (right)-propranolol. Error bars represent SEM. Dashed lines represent empirical cut-offs for PTSD based upon prior research. Abbreviations: EMG-electromyogram, BPM-beats per minute, ?S-?Siemens, ?V-?Volts.

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