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Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: Three negative psychophysiological studies

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ABSTRACT

Posttraumatic stress disorder (PTSD) may involve over-consolidated emotional memories of the traumatic event. Reactivation (RP) can return a memory to an unstable state, from which it must be restabilized (reconsolidated) if it is to persist. Pharmacological agents administered while the memory is unstable have been shown to impair reconsolidation. The N-methyl-D-aspartate (NMDA) partial agonist D-cycloserine (DCS) may promote memory destabilization. In the three studies reported here, we investigated whether the β-adrenergic blocker propranolol or the glucocorticoid (GR) antagonist mifepristone, given at the time of traumatic memory reactivation, could reduce PTSD symptoms and physiological responding during subsequent traumatic imagery. Individuals with PTSD were randomized as follows: Study One: propranolol with memory reactivation ($n=10$) or without reactivation ($n=8$); Study Two: reactivation mifepristone ($n=13$), non-reactivation (NRP) mifepristone ($n=15$), or double placebo (PL) ($n=15$); Study Three: reactivation mifepristone plus D-cycloserine ($n=16$), or two placebos ($n=15$). Subjects underwent memory retrieval by describing their traumatic event. A week later they engaged in script-driven traumatic mental imagery, while heart rate (HR), skin conductance (SC), and facial electromyogram (EMG) responses were measured. There were no significant group differences in physiological responsivity or change in PTSD symptoms in any of the studies. These results do not support successful blockade of reconsolidation of traumatic memories in PTSD.

1. General introduction

Animal research suggests that under favorable conditions, the retrieval (reactivation (RP)) of a consolidated memory may return it to a labile state from which it must be restabilized in order to persist (Nader et al., 2000). This restabilization process is termed reconsolidation. It involves neurobiological mechanisms that are similar but not identical to those involved in memory consolidation (Lee et al., 2004). Reconsolidation is largely demonstrated by its blockade. It derives its support from experiments in many species including humans, and a variety of experimental paradigms using a broad range of interventions, including localized or systemic drug administration (Nader and Einarsson, 2010; Debiec and Ledoux, 2004). Pharmacological reconsolidation blockade is a two-stage process. First, the memory must be destabilized by reactivating (retrieving) it. Only destabilized memories are able to undergo modification or blockade. Second, reconsolidation of the memory must be antagonized by a pharmacological agent. Reactivated fear memories have been shown to be sensitive to β-adrenergic blockers such as propranolol in animals (Przybyslawski et al., 1999; Debiec and Ledoux, 2004) and in humans (Kindt et al., 2009; Soeter and Kindt, 2010), and to glucocorticoid (GR) antagonists such as mifepristone (RU-486) in animals (Jin et al., 2007; Taubenfeld et al., 2009; Pitman et al., 2011). Many articles about reconsolidation blockade conclude with the suggestion that it could offer a novel treatment for posttraumatic stress disorder (PTSD), which is characterized by durable, distressing emotional memories. Administering a suitable

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drug during retrieval-induced destabilization might reduce the strength of a traumatic memory by blocking its reconsolidation.

In a preliminary, placebo (PL)-controlled, clinical investigation of pharmacological reconsolidation blockade, Brunet et al. (2008) employed a validated psychophysiological script-driven imagery technique in 19 subjects with PTSD resulting from various traumatic events. In previous studies, physiological responses during traumatic imagery had been shown to reliably discriminate trauma-exposed individuals with PTSD from trauma-exposed individuals without PTSD (Orr et al., 2002). Subjects in the Brunet et al. study underwent a script preparation procedure that entailed their describing their traumatic event, which hypothetically served to reactivate the traumatic memory. Immediately afterwards they received propranolol or placebo. A week later, they engaged in script-driven mental imagery of their traumatic event, while heart rate (HR), skin conductance (SC), and left corrugator electromyogram (EMG) were measured. In comparison to subjects who had received placebo, overall physiological responding during mental imagery of the traumatic event was significantly smaller in the subjects who had received post-reactivation propranolol a week earlier, suggesting that the traumatic memory had been weakened. The objectives of the three studies reported here were to expand upon this previous study and to investigate new pharmacological agents as potential reconsolidation blockers in PTSD.

2. Study One

2.1. Introduction

One limitation of the Brunet et al. (2008) study was that it did not include a non-reactivation (NRP) propranolol group; consequently, the possibility that non-specific actions of propranolol were responsible for the effect could not be ruled out. Study One therefore had two aims: first, further to investigate whether propranolol administered with memory reactivation weakens traumatic memories associated with PTSD; and second, to rule out the possibility that such an effect, if found, is due to non-specific actions of this drug. We hypothesized that individuals with PTSD who underwent memory reactivation via script preparation accompanied by propranolol (reactivation, RP) would show smaller physiological responses during script-driven imagery testing a week later compared to those who received propranolol in the absence of the script preparation procedure (non-reactivation, NRP).

2.2. Methods

2.2.1. Subjects

2.2.1.1. Recruitment and inclusion criteria. Subject candidates were male veterans ages 24–64 who had received a clinical diagnosis of combat-related PTSD (American Psychiatric Association, 2000). They were drawn from referrals from the VA Medical Centers in Bedford, MA and Manchester, NH, as well as from advertisements in the media.

2.2.1.2. Exclusion criteria. Prior to enrollment, subject candidates were clinically screened and excluded if they had a history of a psychotic or bipolar I disorder; a current substance use disorder; a medical condition that contraindicated the administration of propranolol, e.g., congestive heart failure, diabetes, chronic bronchitis, or emphysema; a history of an asthmatic attack within the past 10 years, a history of an asthmatic attack precipitated by a β-adrenergic blocker at any time in the past, or currently being treated for asthma regardless of when the last attack occurred; previous adverse reaction to, or non-compliance with, a β-adrenergic blocker; initiation of, or change in, psychotropic medication within 1 month prior to recruitment; current use of a medication that may have dangerous interactions with propranolol, e.g., other β-adrenergic blockers, antiarrhythmics, and calcium channel blockers; resting heart rate < 60 beats per minute or resting systolic blood pressure < 100 mm Hg.

2.2.1.3. Ethical approval and informed consent. After a complete explanation of the study procedures, which had been approved by the Partners Human Research Committee, the Manchester/Bedford VA Medical Centers Human Studies Subcommittee, and the U.S. Army Medical Research and Materiel Command Human Research Protection Office, subjects gave written informed consent for participation.

2.2.2. Study medication

A double-blind 1:1 randomization schedule was utilized. Propranolol hydrochloride is a lipophilic, non-selective synthetic β_1- and β_2-adrenoreceptor antagonist that crosses the blood brain barrier. On Day 0 and Day 2, we administered either a first dose of 0.67 mg/kg short-acting (SA) oral propranolol (rounded to the nearest 10 mg) or matching placebo. If the SA dose was well-tolerated (which it was in all subjects), and if systolic blood pressure had not decreased by more than 10 mm Hg to below a level of 100 mm Hg (which did not happen in any subject), 90 min later (and immediately prior to script preparation), either 1 mg/kg of long-acting (LA) oral propranolol (rounded to the nearest 20 mg) or placebo was also administered. Subjects were given the SA propranolol 90 min prior to memory retrieval in order to allow the drug to have reached an adequate plasma concentration at the time of traumatic memory reactivation. The study medication was well tolerated by all subjects.

2.2.3. Equipment and physiological measures

A Coulbourn Lablinc V Human Measurement System (Coulbourn Instruments, Allentown, Pennsylvania) was used to record physiological analog signals, including heart rate (HR), skin conductance (SC), and electromyogram (EMG) of the left corrugator and left lateral frontalis facial muscles. Interbeat interval was recorded via standard limb electrocardiogram leads connected to a High Gain Bioamplifier (V75-04) and converted to HR. SC was measured by a Coulbourn Isolated Skin Conductance coupler (V71-23) using a constant 0.5 V through 8 mm (sensor diameter) Invivo Metric Ag/AgCl electrodes placed on the hypothenar surface of the subject's non-dominant hand in accordance with published guidelines (Fowles et al., 1981). The SC electrodes were separated by 14 mm, as determined by the width of the adhesive collar. For EMG recordings, the skin was lightly abraded, and 4 mm (sensor diameter) Invivo Metric Ag/AgCl electrodes filled with electrolyte paste were placed over the corrugator and frontalis muscle sites according to published specifications (Fridlund and Cacioppo, 1986). The EMG was amplified by a Coulbourn High Gain Bioamplifier (V75-04), filtered so as to retain the 90–1000 Hz frequency range, and integrated by a Coulbourn Contour Following Integrator (V76-23A) with a 200 ms time constant. Physiological analog signals were digitized by a Coulbourn analog to digital converter (V19-16). A Cobalt notebook computer (IBM-compatible) with custom-designed software was used to sample and store the digitized physiological signals.

2.2.4. Procedures

On Day 0 (non-reactivation), subjects randomized to the NRP group received SA and LA propranolol, whereas subjects randomized to the RP group received matching placebo capsules. All subjects then viewed a 90 min emotionally neutral movie. By