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Early post-stressor intervention with propranolol is ineffective in preventing posttraumatic stress responses in an animal model for PTSD

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Abstract

The therapeutic value of β-adrenoceptor blockage, using propranolol, in the aftermath of traumatic experience is uncertain. A prospective, controlled animal model of posttraumatic stress disorder (PTSD) was employed to assess the effects of propranolol on long-term behavioral responses to stress. Animals exposed to predator scent stress received a single bolus of propranolol (10 or 15 mg/kg) or vehicle 1 h post-exposure. Outcomes were assessed using the elevated plus-maze (EPM) and acoustic startle response (ASR) at 30 days and freezing response to a trauma reminder (unsoiled litter) on Day 31. Individual animals were classified as having "extreme", "partial" and "minimal" behavioral responses, according to pre-set cut-off criteria for EPM and ASR response patterns. The physiological efficacy of the doses of propranolol was verified by collecting cardiovascular data telemetrically (from exposed or unexposed individuals given propranolol or vehicle). The effect of propranolol on long-term memory was verified using a non-spatial memory task. Both doses of propranolol effectively reduced mean heart rate and impaired the object–recognition task, as expected. No significant effect on prevalence rates of PTSD-like behavioral responses or on trauma reminder response was observed for either dose of propranolol as compared to vehicle. Despite adequate efficacy in terms of heart rate and disruption of memory, single-dose, post-stress β-blockage with propranolol was ineffective in reducing onset of PTSD-like behavioral disruption and trauma cue responses in the long term. Traumatic stress-related processes appear to be affected differently than the others.
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1. Introduction

Traumatic memories are a fundamental feature of posttraumatic stress disorder (PTSD) and underlie many aspects of its clinical manifestations (American Psychiatric Association, 1994). Together with sensory and emotional factors present at the time of the event, these memories influence the character of symptoms such as intrusive thoughts, physiological hyperarousal caused by triggers, and avoidance of traumata reminders.

Preclinical and clinical research studies have clearly shown that emotionally neutral events are not remembered as well as emotionally arousing events (e.g. fear-related events) (McGaugh, 2002; Roozendaal et al., 2008; Roozendaal et al., 2004). Enhanced memory associated with emotional experiences involves activation of the β-adrenergic system, and β-adrenergic blocking agents have been shown to diminish the impact of emotional valence on the formation and retention of memories (Cahill et al., 1994, 1995; McGaugh, 2002). Post-training administration of adrenaline to humans enhances memory consolidation for emotionally arousing material (Cahill and Alkire, 2003), while blockage of (nor)adrenergic function selectively impairs this (Cahill et al., 1994; Hurlemann et al., 2005; van Stegeren et al., 1998). Recent studies indicate that the combined action of noradrenaline and corticosteroid hormones potently affects memory function (Hurlemann et al., 2007; McGaugh and Roozendaal, 2002; Putnam et al., 2005; Roozendaal et al., 2002, 2006; van Stegeren et al., 2010).

The ability of propranolol to reduce anxiety and fear has been quite firmly established by studies in human subject and animals, although this is not true for every experimental paradigm involving anxiety and fear. In humans, propranolol has proven effective in eliminating the physical responses that impede performance caused by stage fright (Brantigan et al., 1982), in improving performance in students prone to cognitive dysfunction due to test anxiety (Faigel, 1991) and in reducing emotional arousal upon returning to the conditioning context (Grillon et al., 2004), although in a double-blind study using propranolol and atenolol, no effects were found on subjective anxiety in phobic subjects (Fagerstrom et al., 1985).

This controlled prospective study set out to examine the effect of two different doses of propranolol (10.0 and 15.0 mg/kg) administered once immediately after stress exposure in an animal model of psychogenic PTSD.

The basic model involves brief (10 min) inescapable exposure of rats to the scent of male cat urine (an intangible "psychological" threat) and subsequent behavioral response-testing in the elevated-plus maze (EPM) and acoustic startle response (ASR). The key factor is a two-step method of data analysis which models clinical diagnostic criteria, allowing the study to focus on individual differences in the degree of response to the stressor. Data are analyzed initially for entire study-groups and subsequently re-analyzed according to a classification system based on the severity of individual behavioral response patterns. At either extreme of the range of responses, the method defines classification-criteria ("Cut-off Behavioral Criteria", CBC) for distinct response-groups — extreme behavioral response (EBR) and minimal behavioral response (MBR) respectively at either end of the spectrum, and a middle group of "partial responders" (PBR) (Cohen et al., 2003, 2004; Cohen and Zohar, 2004; Matar et al., 2006). The proportion of the entire exposed population in the CBC model, fulfilling criteria for extreme responses (EBR) is repeatedly found to be approximately 22.0% from the total exposed population, as compared to 1.3% in unexposed control populations (Cohen et al., 2003; 2005; 2004). In human studies, the lifetime prevalence of PTSD in the general population stands at about 7% (Fairbank et al, 2000). This suggests that about 20–30% of individuals exposed to any given severe stressor will develop PTSD (Breslau et al., 1991). This compatibility further supports the concept of criterion-based classification in terms of face validity of this animal model.

Regarding the conceptual validity of the model itself, "predator exposure trauma" is a potentially life-threatening situation (criteria A) and it may represent a more "natural" setting than other types of stressors. The demonstrated reduction in the time spent by rats in the open arms of the plus maze may parallel the avoidance behavior seen in human PTSD (criteria C). The total amount of exploratory behavior of the EBR animals is unchanged, but is limited to the closed arms only. The open areas appear to be actively avoided. Thus, this behavior may reflect not only the hyperarousal symptoms cluster, but also an avoidant behavior.

The physiological efficacy of the doses of propranolol was verified by collecting cardiovascular data telemetrically. Animals in this study were monitored telemetrically from baseline throughout 3 days following stress exposure, allowing 24 h/day sampling of heart rate (HR) without the presence of a human.

It has been reported that stress-related activation of the noradrenergic system strengthens the formation of aversive memories and β-adrenergic receptors seem to be involved in this emotional memory processing (McGaugh and Roozendaal, 2002). With the aim to assess the effects of β-adrenergic blocking agents on non-traumatic memory, the effect of post-training administration of propranolol (a lipophilic β-blocker that readily crosses the blood brain barrier (BBB)), nadolol (a hydrophilic β-blocker that does not cross the BBB) or vehicle on rats' 24-h object recognition memory was assessed. This task is based on the spontaneous tendency of rats to explore a novel object more than a familiar one.

2. Materials and methods

All procedures were carried out under strict compliance with ethical principles and guidelines of the NIH Guide for the Care and Use of Laboratory Animals. All treatment and testing procedures were approved by the Animal Care Committee of Ben-Gurion University of the Negev, Israel.

2.1. Animals

Adult male Sprague–Dawley rats weighing 150–200 g were employed (N = 159). The animals were housed four per cage in a vivarium with stable temperature and a reversed 12-hour light/dark cycle (lights off: 08:00 a.m.) with unlimited access to food and water. All experiments were performed during the activity phase of the animals between 09:30 and 17:00 h.

2.2. Experimental design

The study comprised three different experiments: immediate post-stress propranolol treatment (N = 89), HR measurement (N = 20) and a

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