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Prazosin administered prior to inescapable stressor blocks subsequent exaggeration of acoustic startle response in rats

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Abstract

Exposure to traumatic stress can result in a number of pathophysiological conditions, including post-traumatic stress disorder (PTSD). PTSD is characterized by a number of persistently heightened physiological and behavioral indicators, including increased sensory arousal and increased startle response. Similar effects can be seen in an animal model of PTSD in which stress results from restraint and inescapable tailshocks to rats. The present study used this animal model to investigate the effects of prazosin, an α_1 adrenoceptor antagonist, on stress-induced elevation of acoustic startle response (ASR). To investigate this, male Sprague–Dawley rats were injected with 0.5 mg/kg of prazosin 30 min before restraint and inescapable tail shock on three consecutive days. ASR testing was performed 1, 4, 7 and 10 days post-stress and compared to baseline and control values. Results show a significant reduction of ASR hyperarousal in the group treated with prazosin prior to stress compared to vehicle treated stressed animals and controls. Pre-stress treatment with lower levels of prazosin (0.25, 0.1 and 0.05 mg/kg) showed similar results. These findings further implicate an α_1 adrenoceptor role in the pathophysiological response to traumatic stress and suggest a potential preventative role for prazosin.

Keywords: Prazosin; α_1 adrenoceptor antagonist; Traumatic stress; Inescapable tail shock; Acoustic startle response; Sprague–Dawley rats; Body weight; Behavior

1. Introduction

Stress triggers biological and behavioral responses that enable the organism to cope with the stressor. Extreme or chronic stress can cause a variety of detrimental effects that may lead to lasting pathophysiology associated with the systems involved in the stress response (Vermetten and Bremner, 2002; McEwen, 2002). In humans, this can result in anxiety disorders including acute stress disorder (ASD) and post-traumatic stress disorder (PTSD) (Osuch et al., 2004). Research has shown that many different neurotransmitter systems play significant roles in the stress response, including the central α-adrenergic system (Southwick et al., 1997; Stone et al., in press). This system may therefore be a potential target for prevention or treatment of stress-induced pathophysiologies.

Within the noradrenergic system, norepinephrine (NE), also known as noradrenaline, is a catecholaminergic neurotransmitter that plays an important role in the stress response, both peripherally and centrally. The noradrenergic system in the brain is centered in the locus coeruleus (LC) which has efferents connecting it to a number of other brain areas involved in the stress response. The α_1 subtypes of the alpha adrenoceptor family are found widely distributed throughout the CNS, including such areas as cortex, hypothalamus, thalamus, amygdala and midbrain (Miyahara et al., 1999).

An inescapable tail shock model of traumatic stress in rats has been shown to cause physiological and behavioral changes similar to those seen in humans with PTSD (Servatius et al.,

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1995). Specifically, after exposure to a three day restraint and tailshock protocol, rats show persistent hyperarousal (Servatius et al., 2000) and exaggerated ASR (Beck et al., 2002). ASR is the unconditioned response to brief, loud acoustic stimuli that can be seen across various mammalian species. It is frequently used to characterize the CNS response to various pharmaceuticals. The cross-species validity of these measurements allows them to be used to evaluate animal models of various pathophysiologies and to explore the efficacy of pharmaceuticals in humans (Faraday and Grunberg, 2000). Increased startle response is a common symptom of PTSD and is thought to be related to the increased NE release associated with the stress (Southwick et al., 1997).

Widely used for the treatment of hypertension for more than 30 years, prazosin is the prototypic quinazoline-bearing α_1 selective adrenoceptor antagonist (Antonello et al., 2005). It has also been shown to act in the CNS upon peripheral delivery (Menkes et al., 1981; Rogawski and Aghajanian, 1982) based on its ability to readily cross the blood–brain barrier. In rats, prazosin has been shown to block short and long term habituation effects of ASR (Leaton and Cassella, 1984), as well as to block apomorphine enhancement of startle (Davis et al., 1985). In humans, it has been shown to reduce trauma-related nightmares and sleep disturbances associated with PTSD (Raskind et al., 2000, 2003) at dosages comparable to those used to treat hypertension. The effectiveness of prazosin, combined with its established safety and minimal side effects, makes it an ideal candidate for further study to determine its ability to intervene in the pathophysiologies that can result from exposure to traumatic stress.

This study was undertaken to test the hypothesis of whether administration of prazosin before stress would affect stress-induced exaggerations of ASR in rats. Results showed for the first time that prazosin was effective at blocking these stress-induced exaggerations of ASR when administered before stress. These results give further insight into the mechanisms underlying lasting changes in response to stress, and may indicate that prazosin could serve as a potential prophylactic agent to block the development of ASD and PTSD in situations where extreme or traumatic stress can be foreseen, such as combat or disaster relief.

2. Materials and methods

2.1. Subjects and experimental design

Subjects were 120 male Sprague–Dawley rats weighing 125–175 g at the beginning of the experiments (Taconic Farms, Germantown, NY, USA). Animals were pair-housed in standard polypropylene cages on hardwood chip bedding in a climate controlled environment (23 °C, 70% humidity) with a reverse light/dark cycle (lights on at 1730 h) and had *ad libitum* access to food and water. Three different experiments were conducted. In Experiment 1, 42 rats were divided into two groups, stressed ($n=15$) and control ($n=27$). In Experiment 2, 48 rats were divided into four groups, stressed/saline ($n=12$), stressed/prazosin 0.5 mg/kg ($n=12$), control/saline ($n=12$) and control/prazosin 0.5 mg/kg ($n=12$). In Experiment 3, 30 rats were divided into five groups, control/saline ($n=6$), stressed/saline ($n=6$), stressed/prazosin 0.25 mg/kg ($n=6$), stressed/prazosin 0.10 mg/kg ($n=6$) and stressed/prazosin 0.05 mg/kg ($n=6$). All animal experiments were performed in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International) directives after obtaining the approval of the USUHS Institutional Animal Care and Use Committee.

2.2. Acclimation

In order to avoid undue stress to the animals and better focus on the effects of intentional stress on specific groups, all animals were handled for approximately 5 min/day for two days prior to acclimation. Animals were weighed throughout the experiment, both as a physiological measure and as a metric for balancing the groups. Animals had to be a minimum of 150 g at the time of baseline procedure in order to be included. Animals were acclimated to the acoustic startle equipment (details below) for three consecutive days, one day without sound followed by two days with sound. This acclimation was finished three days prior to baseline recordings in order to avoid desensitization effects.

2.3. Baseline

A baseline recording of acoustic startle response (details below) was taken for each of the animals on the day prior to beginning the stress procedure.

2.4. Stress

Stress exposure consisted of a 2-h per day session of immobilization and tail-shocks for three consecutive days. Stressing was done during the dark or active phase of the light–dark cycle. Animals were restrained by being wrapped in a cloth jacket and having their head and torso immobilized in a ventilated plexiglass tube. Forty electric shocks (2–3 mA, 3 s duration; Animal Test Cage Grid Floor Shocker, Coulbourn Instruments, USA) were delivered to their tails at semi-random intervals of 150 to 210 s (Graphic State Notation software, Habitest Universal Link, Coulbourn Instruments, USA). This stress protocol was adapted from the learned helplessness paradigm in which animals undergo an aversive experience under conditions in which they cannot perform any adaptive response (Seligman and Maier, 1967; Seligman and Beagley, 1975). The duration of stress was based on previous demonstrations that repeated stress sessions for 3 days are more effective than a single stress session in producing lasting physiological and behavioral abnormalities, such as elevations in basal plasma corticosterone levels, exaggerated acoustic startle responses and reduced body weight (Servatius et al., 1995; Ottenweller et al., 1989). Previous studies have shown that additional stress sessions, beyond the 3 days, do not appear to produce greater

physiological and/or behavioral changes (Servatius et al., 1995; Ottenweller et al., 1989).

2.5. Drugs

Prazosin hydrochloride (Sigma Chemical Co., St. Louis, MO), an α_1 specific adrenergic antagonist, in a 0.9% sodium chloride solution vehicle (Abbott Laboratories, North Chicago, IL) or vehicle alone was delivered by intraperitoneal injection (1 mL latex free syringe with 27G 1/2-inch needle, B–D, Franklin Lakes, NJ). Prazosin was delivered to the drug group animals, both stress and control, at a dosage of 0.5 mg/kg, 30 min prior to the stress procedure on each of the three stress days in the initial prazosin study. Saline vehicle was delivered to the appropriate groups at the same time. In the dosage experiment, dosages of 0.05, 0.1 or 0.25 mg/kg were delivered to associated groups 30 min prior to each stress session, with vehicle being delivered to appropriate groups at the same time.

2.6. Acoustic startle

ASR testing was conducted with a Startle Response Acoustic Test System (Coulbourn Instruments, PA). This system consists of four weight-sensitive platforms in a sound-attenuated chamber, though only one platform was used at a time. This was done to reduce interactive effects between animals. The animals' movements in response to stimuli were measured as a voltage change by a strain gauge inside each platform and were converted to grams of body weight change following analog to digital conversion. These changes were recorded by an interfaced computer as the maximum response occurring within 200 ms of the onset of the startle-eliciting stimulus. All acoustic stimuli were administered by an amplified speaker mounted 24 cm above the test cage. During testing, animals were individually placed in holding cages (14.5×7×6.5 cm) that were small enough to restrict extensive locomotion but large enough to allow the subject to turn around and make other small movements. These were then placed on the weight sensitive platform.

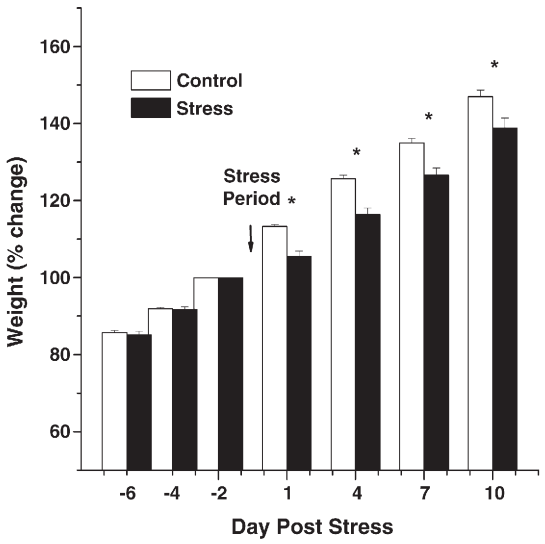

Fig. 1. Percentage of body weight immediately prior to stress procedure (group means±SEM) for control and stressed rats on 6, 4 and 2 days preceding and 1, 4, 7 and 10 days following the three day stress procedure. Asterisks (*) indicate significant differences between the two groups (n=27 control, 15 stress; $p<0.05$).

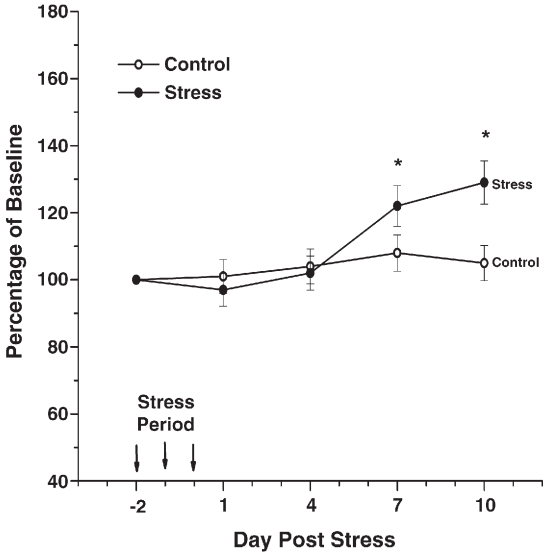

Fig. 2. Percentage of pre-stress baseline of acoustic startle (group means±SEM) for groups of stressed and control animals. Asterisks (*) indicate significant differences in ASR between stressed animals and control (non-stressed) animals (n=26 control, 15 stress; $p<0.05$).

Following placement of the animal into the chamber, the chamber lid was closed, leaving the subject in darkness. A 3 min adaptation period occurred in which no startle stimuli were presented. Startle stimuli consisted of 110 dB sound pressure level (unweighted scale; re: 0.0002 dynes/cm^2) noise bursts of 20 ms duration, sometimes preceded by 100 ms with 68 dB, 1 kHz pure tones (pre-pulses). Decibel levels were verified by a Radio Shack Sound Meter (El Paso, TX). Each stimulus had a 2 ms rise and decay time such that onset and offset were abrupt, a primary criterion for startle. There were four types of stimulus trials: 110 dB alone, with pre-pulse, pre-pulse alone and no stimulus. Each trial type was presented eight times. Trial types were presented in random order to avoid order effects and habituation. Inter-trial intervals range randomly from 15 to 25 s. All animals were tested 1, 4, 7 and 10 days following the final day of the stress procedure.

2.7. Data analysis

Each animal's responses were averaged within trial type. Trials during which no stimuli were presented were used to control for normal subject movements on the platform. Amplitudes for each trial type were derived by subtracting grams of platform displacement on the no-stimulus trials (i.e., the body weight of each subject) from platform displacement in response to specific stimuli. The remainder from this calculation represented the amount of platform displacement related to the stimulus (e.g., 110 dB, 110 dB with pre-pulse). Analysis of variance (ANOVA) for repeated measures with factors of stress status and drug dosage and test day as the repeated measure was

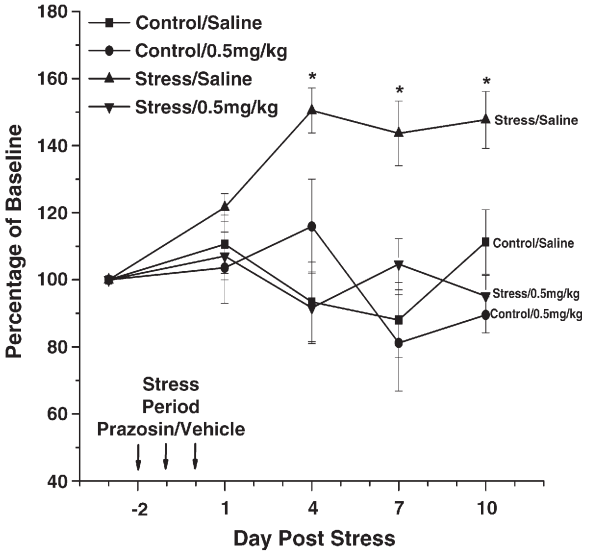

Fig. 3. Percentage of pre-stress baseline of acoustic startle (group means ± SEM) for groups treated with Prazosin (0.5 mg/kg) or vehicle (saline) 30 min prior to the stress experience. Asterisks (*) indicate significant differences in mean ASR between stressed, vehicle-treated rats and all other groups (n=12–15 for each group; p<0.05).

performed for each experiment. These global tests were used to reveal interactive effects among the variables. These results were followed with ANOVAs on individual test days to determine the effect of stress and drug treatments. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Stress and weight

As seen in Fig. 1, the 3 day stress protocol of restraint and inescapable tail-shock showed an effect of stress status on body weight. As was consistent with previous experiments, Student's t-tests showed that change in percentage of baseline body weight was significantly higher in the control animals (n=27) as compared to the stressed animals (n=15) on day 1 [$t(40)=6.32$; $p<0.001$], day 4 [$t(40)=5.34$; $p<0.001$], day 7 [$t(40)=4.05$; $p<0.001$] and day 10 [$t(40)=2.71$; $p=0.010$] following stress. Similar weight differences existed for all stress versus control groups, with no significant effect of drug on weight (data not shown).

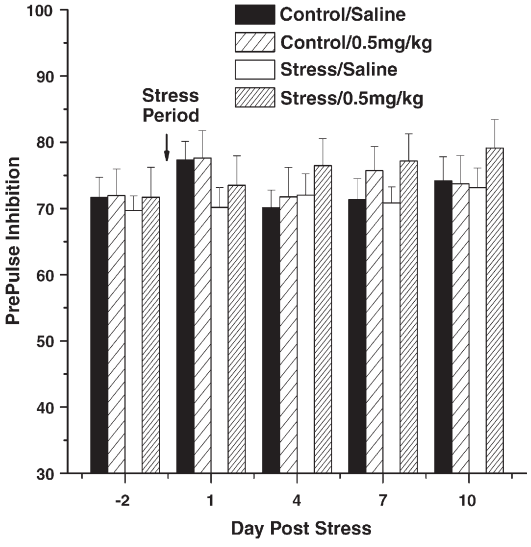

Fig. 4. Percentage of prepulse inhibition (group means ± SEM) for groups treated with Prazosin or vehicle 30 min prior to stress. There were no significant differences between the groups (n=12 for each group, p>0.05).

3.2. Stress and ASR

Acoustic startle testing was used to measure hyperarousal following stress (Fig. 2). Repeated measures ANOVAs showed that there was a significant effect of [Day: $F(4,156)=5.70$, $p<0.001$] and a significant interaction of [Day × Stress: $F(4,156)=2.86$, $p=0.025$]. Student's t-test for specific days showed that ASR was significantly higher in the stressed animals (n=15) as compared to the control animals (n=26) at day seven [$t(39)=2.11$; $p=0.041$] and day ten [$t(39)=2.21$; $p=0.033$] following stress.

3.3. Pre-stress prazosin

In animals treated with 0.5 mg/kg of prazosin 30 min prior to stress (Fig. 3), ANOVAs for repeated measures with factors of stress status, drug dosage and test day as the repeated measure showed an effect of [Day: $F(3.4,196)=2.3$, $p=0.07$], and significant interactions between [Day × Stress: $F(3.4,196)=4.8$, $p=0.001$], [Day × Drug: $F(3.4,196)=4.0$, $p=0.004$] and [Day × Stress × Drug: $F(3.4,196)=5.24$, $p<0.001$]. Tukey's post hoc on each day indicated that the stress/saline group differed from all other groups on days 4, 7 and 10 following stress (n=12–15 for each group, p<0.05).

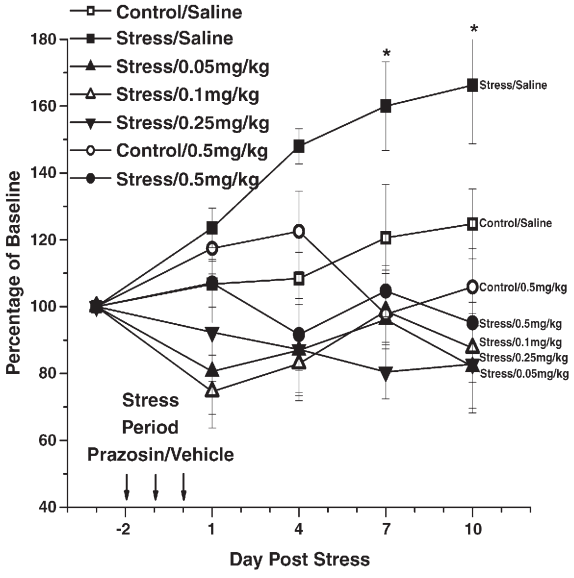

Fig. 5. Percentage of pre-stress baseline of acoustic startle (group means ± SEM) for groups treated with prazosin or saline 30 min prior to stress on each of the three day stress procedures. Asterisks (*) indicate significant differences between the stressed animals that received saline compared to all other groups (n=6 for each group; p<0.05).

3.4. Pre-pulse inhibition

With respect to levels of pre-pulse inhibition (PPI) of ASR, ANOVAs for repeated measures with factors of stress status, drug dosage and test day as the repeated measure showed no effect of stress or drug on any test day following stress (Fig. 4). There was no significant difference between stress or control animals treated with vehicle or 0.5 mg/kg of prazosin 30 min before each stress session ($n=12$ for each group, $p>0.05$).

3.5. Prazosin dosage

Fig. 5 summarizes ASR in animals given various doses (0.05, 0.1, 0.25 and 0.5 mg/kg) of prazosin or vehicle. ANOVAs for repeated measures with factors of stress status, drug dosage and test day as the repeated measure showed an effect of [Day × Stress × Drug: $F(16,100)=2.41$, $p=0.016$]. Tukey's post hoc on each day indicated that the stress/saline group differed significantly from every other group on days 7 and 10 following stress and from all prazosin treated groups on day 4 following stress ($n=6$ for each group, $p<0.05$).

4. Discussion

The primary finding of this study was that prazosin treatment prior to stress reduces the elevated ASR induced by stress, at doses ranging from 0.05 to 0.5 mg/kg. It was also found that levels of PPI were not significantly affected by administration of prazosin before or after stress. Previous studies have shown a short-term effect of restraint stress on PPI in certain sex and strains of rats, but it was not seen in male Sprague–Dawley rats (Faraday, 2002). Consistent with these findings, no significant effect of restraint and tailshock stress on PPI was observed in the present study.

Exposure to inescapable tail shock stress has been shown to result in reduced food consumption and reduced body weight in adult and young rats (Dess et al., 1989; Servatius et al., 1994, 2001; Job and Barnes, 1995; Braga et al., 2004). In the current study, the growth rate was significantly reduced in the stressed group. This reduction in body weight was not affected by three bolus administrations of prazosin in this study or by chronic administration of prazosin in a cold stress model in a previous study (Fregly et al., 1994). This reduction in growth rate was observed in our study to persist for more than 10 days after cessation of the 3 day repetitive stress regimen to which these young adult rats were exposed, thus indicating the long lasting impact of stress on appetitively motivated behaviors in these rats. The stress-induced inhibition of food intake has been reported to be mediated by corticotrophin-releasing factor (CRF) (Dunn and Berridge, 1990; Hotta et al., 1999; Sekino et al., 2004) and to be associated with alterations of noradrenaline levels in the hypothalamus (Avraham et al., 2002). Inescapable tail shock stress has also been shown to induce locomotor inhibition as shown by open field measurements (Plaznik et al., 1992; Servatius et al., 1994).

In this study, a heightened acoustic startle response was not immediately observed until 4 to 7 days poststressor depending on manipulations (with or without saline injection), suggesting that development of increased startle may take up to 7 days to reach evident levels after removal of the precipitating stressors in young adult male rats. While the underlying mechanisms of such delayed enhancement of acoustic startle response are not well addressed in the current literature, the overwhelming effects of stress-induced locomotor inhibition or physical fatigue following the stressor exposure appear to contribute to the delayed acoustic startle sensitization (Plaznik et al., 1992; Servatius et al., 1994).

The model of traumatic stress used in this study has previously been shown to result in a number of dysfunctions similar to some symptoms of PTSD in humans, including noradrenergic hyper-responsiveness, memory deficits and increased startle response (Seligman and Maier, 1967; Servatius et al., 1995; Ottenweller et al. 1989). While the age of the animals used in this study was younger than those used in previous studies, the same 3 day protocol of restraint and tail shock resulted in similar effects on body weight and stress-induced ASR elevation (Figs. 1 and 2). Many studies using milder forms of stress (e.g. restraint only) have shown short term effects of stress but fewer long-term, persistent effects; whereas this model of repeated restraint combined with tailshock has been shown to result in persistent physiological and behavioral abnormalities (Servatius et al., 1995; Braga et al., 2004). This paradigm, therefore, is ideal for evaluating pharmacological treatments for traumatic stress.

Given its ability to cross the blood–brain barrier and long history of safe use, prazosin seemed the ideal candidate to use as the antagonist to experimentally test for reduction in α_1 adrenoceptor mediated stress effects. There is growing evidence to indicate that prazosin may have potential therapeutic value for treatment of PTSD in human populations (Vieweg et al., 2006). It has been shown to improve sleep and reduce nightmares (Taylor and Raskind, 2002; Raskind et al., 2003; Griffith, 2005) as well as to reduce distress resulting from trauma specific cues (Taylor et al., 2006). These studies used dosages of prazosin between 1 and 5 mg/day for adult males. While the pharmacokinetic responses to prazosin in humans and rodents may be different, it is notable that the effective dosages in the human studies were commensurate with the lower levels evaluated in this study (0.05, 0.1 mg/kg). The results of this study give a specific indication that prazosin may also be useful in reducing or preventing pathophysiologies related to traumatic stress when it can be given prior to stressful events.

Pharmacological prevention of stress-related psychiatric disorders such as PTSD is a topic of current medical interest that has received limited attention by clinical and neurobiological investigations (Pitman et al., 2002). Most of the research performed thus far has focused on the effectiveness of a few classes of compounds in alleviating the symptoms of stress-related disorders (for review see Albucher and Liberzon, 2002; Marmar et al., 2002). These include tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake

inhibitors. Although clinical research has shown that these agents can alleviate symptoms and facilitate recovery, their overall efficacy is limited and very often hindered by their serious side effects. The development of more specific pharmacological agents, with potentially less significant side effects, as a therapeutic strategy aimed at preventing the establishment of stress-related disorders is an important step in the treatment of these illnesses. While instances of trauma often cannot be foreseen, pretreatment with prazosin may be beneficial in the limited situations when it can be foreseen and pretreatment is logistically feasible, such as disaster response, international aid missions and combat.

In summary, this study found that prazosin can reduce persistently elevated ASR due to traumatic stress, when administered to rats prior to exposure to the stressor. This further implicates the role of α_1 adrenoceptors in regulating the response to traumatic stress and its subsequent pathophysiologies. It also offers the potential for preventive, rather than just therapeutic treatment of stress-related anxiety disorders such as PTSD.

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