

Research report

Evaluating the protective effect of etazolate on memory impairment, anxiety- and depression-like behaviors induced by post traumatic stress disorder

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ARTICLE INFO

Keywords:

Etazolate
PTSD
Memory
Anxiety
Depression

ABSTRACT

Post-traumatic stress disorder (PTSD) is a neuropsychiatric disorder that develops after an individual experiences severe life-threatening traumatic stress. Etazolate is a selective phosphodiesterase-4 inhibitor that is specific for cAMP. Etazolate showed anxiolytic and antidepressant activity, and could be useful in managing PTSD comorbidities. The current study was done to evaluate the role of etazolate in preventing PTSD induced memory impairment, anxiety and depression-like symptoms. PTSD was induced in rats using single prolonged stress model. Etazolate was administered via oral gavage at a dose of 1 mg/kg/day. The radial arm water maze was used to assess learning and memory. The elevated plus maze, open field, and tail suspension tests were conducted to test anxiety- and depression-like symptoms. The PTSD was associated with short- and long-term memory impairment, which was prevented by etazolate administration. Moreover, PTSD was associated with symptoms of anxiety and depression. Etazolate administration prevented these symptoms. In conclusion, our data suggests that memory impairment, anxiety, and depression symptoms that are induced by PTSD can be prevented using etazolate.

1. Introduction

Post-traumatic stress disorder (PTSD) is a neuropsychiatric disorder that is associated with traumatic events, such as violent personal assault, natural or man-made disasters, torture, diagnosis of life-threatening illness, admission to intensive care unit, or loss of beloved person (Akk et al., 2005; Kelmendi et al., 2016). Exposure to such traumatic events leading to PTSD is particularly high among certain subgroups, such as military veterans, crime victims, and following rape (Javidi and Yadollahie, 2012; Milliken et al., 2007). The characteristic symptoms of PTSD are intrusive recollections of traumatic event, avoidance of event reminders, hyperarousal, negative alterations in cognition and mood, and being out of realism (Kelmendi et al., 2016; Pineles et al., 2017). In addition, many PTSD patients suffer from other co-morbid conditions, such as anxiety, major depression, substance abuse, alcoholism, and sleep disturbances (Leskin and White, 2007; Serova et al., 2014). Therefore, PTSD is a long-standing disorder that highly affects patients' quality of life, and is associated with significant disability and morbidity (American Psychiatric Association, 2000; Hopper et al., 2007; Kessler, 2000).

Several biological abnormalities were cross-linked in PTSD

pathophysiology, including dysfunction in noradrenergic, serotonergic, and glutamatergic systems (Yehuda et al., 2004), and disturbance in neurochemicals such as Gamma-aminobutyric acid (GABA), glutamate, neuropeptide-Y, and neurotrophins (Kloet et al., 2006). Furthermore, dysregulation of hypothalamic pituitary adrenal (HPA) axis characterized by enhanced cortisol negative feedback, inhibition of adrenocorticotropic hormone (ACTH), and low plasma and urinary cortisol, were closely linked with the development of anxiety- and depression-like symptoms in PTSD patients (Ravindran and Stein, 2009; Shea et al., 2005). PTSD is also associated with functional and structural changes in several brain regions, mainly the hippocampus and amygdala (Nutt, 2000), which may lead to cognitive impairment. Furthermore, PTSD represents a form of prolonged stress that potentiates oxidative stress and cellular aging (Miller and Sadeh, 2014).

Different drug classes are available to treat PTSD symptoms, such as antidepressants, anxiolytics, antipsychotics, and anticonvulsants. However, the response to treatment rarely exceeds 60% (Davidson, 2006; Kozlovsky et al., 2009). Studies have shown that PTSD patients continue to suffer from symptoms for an average of 64 months, even after treatment, and more than one third will never completely recover (Kessler, 1995; Shalev, 2009). Therefore, the available pharmacologic

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Serum Corticosterone

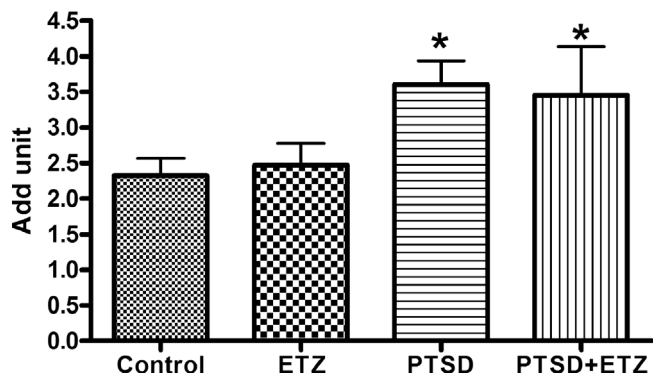


Fig. 1. PTSD increased corticosterone levels. Levels of corticosterone were significantly elevated in PTSD and PTSD + ETZ groups. *Indicates significant difference compared with control ($P < 0.05$). Values are mean \pm SEM. $N = 18\text{--}24/\text{group}$. ETZ stands for etazolate.

options have many shortcomings, such as limited treatment efficacy, delayed onset of action, and significant adverse effect profile that leads to patient noncompliance (Brady and Clary, 2003; Nothdurfter et al., 2012).

Etazolate, a pyrazolopyridine class derivative, is a phosphodiesterase-4 (PDE4) inhibitor and GABA_A receptor modulator (Marcade et al., 2008). PDE-IV is a hydrolytic enzyme that is highly specific for cAMP (Jindal et al., 2012). Enhanced cAMP signal transduction by inhibiting PDE-4 is known to be beneficial in depression disorders (Jindal et al., 2012; Manji and Duman, 2001). Etazolate showed anxiolytic-like effect in rats (Ankur et al., 2013; Beer et al., 1972), and exhibited antidepressant-like activity, which is at least in part related to its modulating effects on the HPA axis and neurotrophins levels (Jindal et al., 2013a,b, 2012). Furthermore, PDE4 inhibitors including etazolate could be beneficial for treating Alzheimer's disease (AD) given their effects in preclinical models of memory impairment and Alzheimer's disease (Heckman et al., 2015; Prickaerts et al., 2017). The good safety and tolerability of etazolate is another encouraging factor (Vellas et al.,

2011). In this study, we hypothesized that etazolate could have a beneficial effects in preventing PTSD-induced memory impairment, and anxiety and depression symptoms.

2. Method

2.1. Animals and treatment

Adult male Wistar rats weighing between 150 and 200 g were provided from the animal facility at Jordan University of Science and Technology (JUST). The rats were housed under hygienic condition in plastic cages, three to four rats per cage. Wood shaving was provided as bedding. Animals were kept on a 12:12-h light-dark cycle (lights on at 7 AM), and room temperature of 25 °C with free access to food and water. The study protocol was approved by the Institutional Animal Care and Use Committee at JUST.

Animals were randomly assigned into four groups (18–24 rats/group): Control group, which received tap water via oral gavage, etazolate group (ETZ), which received etazolate (1 mg/kg, orally), PTSD group that were exposed to Single prolonged stress (SPS) model and vehicle treatment, and PTSD + ETZ group, which was exposed to SPS model and administered etazolate (1 mg/kg, orally).

Etazolate (1-ethyl-4-(*N*'-isopropylidene-hydrazino)-1H-pyrazolo [3,4-*b*]pyridine-5-carboxylic acid ethyl ester hydrochloride) was purchased from ApexBio (Hsinchu, Taiwan) in powder form. Distilled water was used to prepare etazolate solution with a concentration of 1 mg/mL. The prepared solution was stored at 4 °C in dark vials shielded from light. Etazolate preparation, storage, and dosing regimen used in this study was based on previous studies (Drott et al., 2010; Jindal et al., 2013a,b, 2012). Rats in ETZ and PTSD + ETZ groups received oral etazolate at a dose of 1 mg/kg in a volume of 1 mL/kg via oral gavage for 6 days per week for a total of 5 weeks, starting 1 weeks before the induction of PTSD.

2.2. PTSD induction

Single prolonged stress (SPS) model of PTSD was conducted in all animals of the PTSD and PTSD + ETZ groups. Induction of SPS was performed in three stages in a single day as previously described (Patki

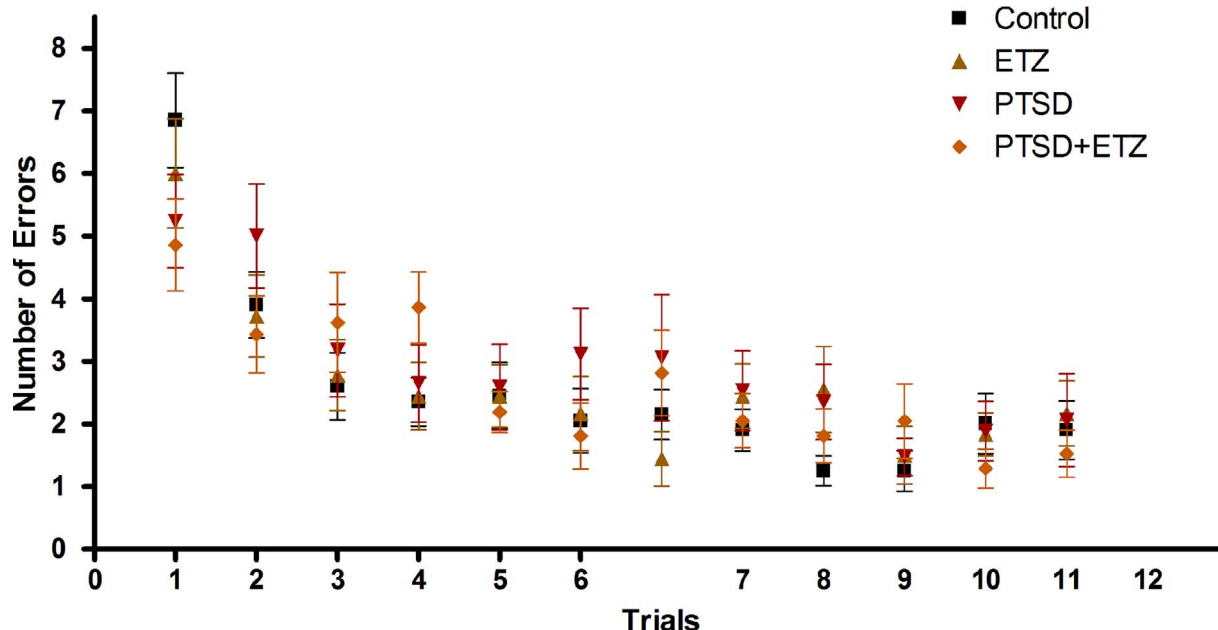


Fig. 2. Animals' learning performance in the radial arm water maze. Comparison of control, etazolate (ETZ), PTSD, and PTSD + ETZ. Each animal was trained for six consecutive trials separated by 5 min rest, then another six consecutive trials (the learning phase). No difference was observed in learning performance among experimental groups. Values are mean \pm SEM. $N = 18\text{--}24/\text{group}$.

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