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Research paper

Antimanic activity of minocycline in a GBR12909-induced model of mania in mice: Possible role of antioxidant and neurotrophic mechanisms

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ABSTRACT

Background: Mania/hypomania is the cardinal feature of bipolar disorder. Recently, single administration of the dopamine transporter (DAT) inhibitor, GBR12909, was related to mania-like alterations. In the present study we aimed at testing behavioral and brain oxidant/neurotrophic alterations induced by the repeated administration of GBR12909 and its prevention/reversal by the mood stabilizing drugs, lithium (Li) and valproate (VAL) as well as by the neuroprotective drug, minocycline (Mino).
Methods: Adult Swiss mice were submitted to 14 days protocols namely prevention and reversal. In the reversal protocol mice were given GBR12909 or saline and between days 8 and 14 received Li, VAL, Mino (25 or 50 mg/kg) or saline. In the prevention treatment, mice were pretreated with Li, VAL, Mino or saline prior to GBR12909.
Results: GBR12909 repeated administration induced hyperlocomotion and increased risk taking behavior that were prevented and reversed by the mood stabilizers and both doses of Mino. Li, VAL or Mino were more effective in the reversal of striatal GSH alterations induced by GBR12909. Regarding lipid peroxidation Mino was more effective in the prevention and reversal of lipid peroxidation in the hippocampus whereas Li and VAL prevented this alteration in the striatum and PFC. Li, VAL and Mino25 reversed the decrease in BDNF levels induced by GBR12909.
Conclusion: GBR12909 repeated administration resembles manic phenotype. Similarly to classical mood-stabilizing agents, Mino prevented and reversed GBR12909 manic-like behavior in mice. Thus, our data provide preclinical support to the design of trials investigating Mino's possible antimanic effects.

1. Introduction

Bipolar disorder (BD) is a severe and recurrent neuropsychiatric disorder, affecting approximately 1–5% of the population including BD type 1 and 2 (Merikangas et al., 2011). Mania/hypomania is the cardinal feature of BD. In acute episodes, mania can include a variety of multifaceted symptoms, such as hyperactivity, euphoric or irritable mood, hyperverbosity, decreased need for sleep and impulsivity (Zhang et al., 2017). Despite the etiology and pathophysiology of mania remain unclear, increased dopaminergic drive is a core neurobiological aspect underlying this mood state (Berk et al., 2007).

Compelling evidence has supported the involvement of abnormal expression of the dopamine transporter (DAT) in the neurobiology of BD. Of note, single nucleotide polymorphisms (SNPs) in DAT gene are

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significantly prevalent in BD patients (Pinsonneault et al., 2011). Also, genetic linkage studies have consistently associate variants in human DAT1 gene and increased convey susceptibility to BD (Greenwood et al., 2006). Some of these variants, such as rs27072 C > T, have important functional consequences on DA homeostasis, as demonstrated by the reduction of cell surface DAT expression in transfected cultured cells (Horschitz et al., 2005; Pinsonneault et al., 2011). Conversely, mice with genetic deletion of DAT (DAT-KO) (Barr et al., 2004) or with reduced DAT expression (DAT-KD) (Young et al., 2011) present hyperdopaminergic tone and marked behavioral alterations resembling mania in rodent-human cross-translational behavioral tests.

Based on the aforementioned evidences of DAT involvement in BD susceptibility, the administration of GBR12909 [1-{2-[bis-(4- fluorophenyl)methoxy]-ethyl}-4-(3-phenylpropyl)piperazine], a high affinity, long-acting DAT transporter inhibitor, has been proposed as a useful pharmacological model of BD mania. GBR12909 administration in rodents induced several features of mania-like behavior, such as hyperactivity and increased exploration (Young et al., 2010), as well as motor impulsivity and risk preference (Van Enkhuizen et al., 2013a, 2013b). Also, the predictive validity of this model was determined by the use of the mood stabilizing drugs valproate (VAL) (Van Enkhuizen et al., 2013a, 2013b) and lithium in the reversal of GBR12909 effects (Queiroz et al., 2015). Recently, our research group demonstrated a time course (within 24 h) of behavioral alterations induced by GBR12909 in locomotor activity and exploration in the open field test in mice (Queiroz et al., 2015), corroborating the previous findings of mania-like behavior induced by this drug (Young et al., 2010). Altogether, the use of the selective DAT inhibitor GBR12909 has emerged as an animal model with adequate translational validity for BD mania presenting a great potential for the screening of new effective drugs for BD treatment.

The neurobiology of BD comprises: i) oxidative imbalance observed in clinical (Benes et al., 2006; Kuloglu et al., 2002; Kunz et al., 2008; Selek et al., 2015; Tsai and Huang, 2015) and preclinical research (de Souza Gomes et al., 2015; Kanazawa et al., 2016; Macêdo et al., 2012; Valvassori et al., 2016), ii) neurotrophic alterations, such as deficits in brain-derived neurotrophic factor (BDNF) (Monteleone et al., 2008; Tunca et al., 2014). Treatment with mood stabilizing drugs attenuate/suppress these alterations (De-Paula et al., 2016; Frey et al., 2006; Macedo et al., 2013; Newton et al., 2017).

In the last decades, pharmacotherapy for BD has raised important concerns. In this regard lithium is associated with serious side effects that make patient compliance difficult and burdensome (Cipriani et al., 2011; Yildiz et al., 2015). In addition, no drug has proven efficacy in all phases of BD (Smith et al., 2007). Therefore, the use of animal models with appropriate translational validity should ultimately aid in the development of novel, safe and potentially effective treatments for this complex disorder (Logan and McClung, 2016).

Several studies have highlighted the potential role of the second generation tetracycline minocycline as a neuroprotective agent against multiple neurodegenerative and neuroinflammatory conditions, such as Parkinson's (Quintero et al., 2006), Huntington's (Kumar et al., 2013) and Alzheimer's disease (El-Shimy et al., 2015). These beneficial effects of minocycline have been attributed to its important anti-inflammatory, neurotrophic, antioxidant and direct radical-scavenging properties (Kim and Suh, 2009). In recent years, the benefits of minocycline for the treatment of psychiatric disorders have been explored. Regarding mood disorders, some studies highlighted the potential of minocycline as an adjunctive treatment for bipolar depression (Husain et al., 2017; Savitz et al., 2012) and psychotic unipolar depression (Miyaoka et al., 2012a). Nevertheless, there is a lack of preclinical and clinical studies about the possible effects of minocycline in BD mania as well as exploring the possible mechanisms related to this action.

Based on the extensive evidence about the involvement of oxidative/nitrosative stress and neurotrophins, especially BDNF, in BD pathophysiology (Anderson and Maes, 2015; Newberg et al., 2008), the present study sought to investigate the effects of minocycline in the prevention and/or reversal of behavioral changes (hyperlocomotion and risk-taking behavior) and neurochemical [glutathione (GSH), thiobarbituric acid- reactive substance (TBARS), and BDNF levels] induced by GBR12909 administration in mice. We hypothesize that minocycline can present important protective effects against behavioral/neurochemical effects of GBR12909 being a promising therapeutic approach for improving BD treatment.

2. Methods

2.1. Drugs

GBR12909 dihydrochloride (Sigma, St. Louis, USA), minocycline (Mino, Sigma, St. Louis, USA), sodium valproate (VAL; Life Pharmaceutical Company) and lithium carbonate (Li; Sigma, St Louis, USA) were used. Mino was dissolved in 2% dimethyl sulfoxide (DMSO). The other drugs were directly dissolved in saline solution (NaCl 0.9%, w/v). The animals received freshly made up solutions, prepared within 1–2 h of dosing, administered in a volume of 0.1 ml/10 g body weight. All other chemicals used were of analytical grade.

2.2. Animals

The experiments were performed in a total of 213 adult male Swiss mice (weighting: 20–25 g) obtained from the Animal House of Universidade Federal do Ceará. The animals were housed at the maximum of 8 per cage in standard polycarbonate cages (42 × 20.5 × 20 cm) and standard environmental conditions (22 ± 1 °C; humidity 60 ± 5%; 12-h light/dark cycle with lights on at 7:00 a.m.) with access to food (Laboratory RodentDiet - LabDiet®) and water ad libitum. All behavioral procedures were conducted between 8:00 and 14:00 h by raters blinded to the experimental groups. The methods were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals (NIH 1996) and with approval of the local ethical committee of Universidade Federal do Ceará. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.3. Study design

Two treatment protocols (prevention and reversal) were used in accordance to Frey et al. (2006). For the prevention and reversal protocols 114 and 99 animals were used, respectively. Each group consisted of 6–8 randomly allocated animals. In the reversal model, we aimed to simulate the treatment of an acute maniac state. For this, mice received for 14 days one daily intraperitoneal injection (i.p.) of GBR12909 [10 mg/kg intraperitoneally (i.p.)] or 2% DMSO (vehicle). Between the 8th and 14th days of treatment, GBR12909 and vehicle-treated animals additionally received Mino (25 and 50 mg/kg i.p.), Li (47.5 mg/kg, i.p.), VAL (200 mg/kg, i.p.) or vehicle once daily. In the prevention model, we aimed to simulate the maintenance phase of BD treatment (Frey et al., 2006). For this, animals were treated daily with Li (47.5 mg/kg, i.p.), VAL (200 mg/kg, i.p.), Mino (25 and 50 mg/kg, i.p.) or vehicle (i.p.) once a day for 14 days. On the 8th treatment day, animals were additionally treated with either GBR12909 (10 mg/kg, i.p.) or vehicle once a day until the 14th day of the protocol. The time interval between drugs administration in all situations was 30 min. The doses of Mino used here were based on previous studies of our laboratory (Monte et al., 2013). In the case of Li and VAL, the dosage regimens were based on previous preclinical reports of anti-maniac-like effect of these drugs (de Souza Gomes et al., 2015; Macêdo et al., 2012; Queiroz et al., 2015). Control animals received saline (Sal) and vehicle.

The behavioral determinations of locomotor and exploratory activity (open field test) and risk assessment behavior (predator odor paradigm) were conducted at the14t^{h} day of treatment, 2 h after the last drug administration. Distinct animals were used for each behavioral