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Research report

# Attenuation of oxidative and nitrosative stress in cortical area associates with antidepressant-like effects of tropisetron in male mice following social isolation stress

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ABSTRACT

Tropisetron, a 5-HT3 receptor antagonist widely used as an antiemetic, has been reported to have positive effects on mood disorders. Adolescence is a critical period during the development of brain, where exposure to chronic stress during this time is highly associated with the development of depression. In this study, we showed that 4 weeks of juvenile social isolation stress (SIS) provoked depressive-like behaviors in male mice, which was associated with disruption of mitochondrial function and nitric oxide overproduction in the cortical areas. In this study, tropisetron (5 mg/kg) reversed the negative behavioral effects of SIS in male mice. We found that the effects of tropisetron were mediated through mitigating the negative activity of inducible nitric oxide synthase (iNOS) on mitochondrial activity. Administration of aminoguanidine (specific iNOS inhibitor, 20 mg/kg) augmented the protective effects of tropisetron (1 mg/kg) on SIS. Furthermore, L-arginine (nitric oxide precursor, 100 mg/kg) abolished the positive effects of tropisetron. These results have increased our knowledge on the pivotal role of mitochondrial function in the pathophysiology of depression, and highlighted the role of 5-$HT_3$ receptors in psychosocial stress response during adolescence. Finally, we observed that tropisetron alleviated the mitochondrial dysfunction through decreased nitrergic system activity in the cerebral cortex.



## 1. Introduction

Chronic psychological stress, mainly during the developmental timing of the brain, is considered to be a potent risk factor in the development of psychiatric disorders, including depression (Lupien et al., 2009). Major depressive disorder (MDD) is a debilitating mental disorder with high prevalence, morbidity, and costly socioeconomic burden (Mrazek et al., 2014). Emerging lines of research indicate that experiencing social adversity during adolescence is linked to the onset of mood-related psychopathologies (Andersen and Teicher, 2008). Evidence from animal studies has demonstrated that post-weaning social isolation stress (SIS) induces a wide variety of behavioral abnormalities including depressive-like behaviors (Berry et al., 2012; Fone and Porkess, 2008). Adolescence is a critical time during brain development with specific importance in the development of cortical areas (Andersen and Teicher, 2008).

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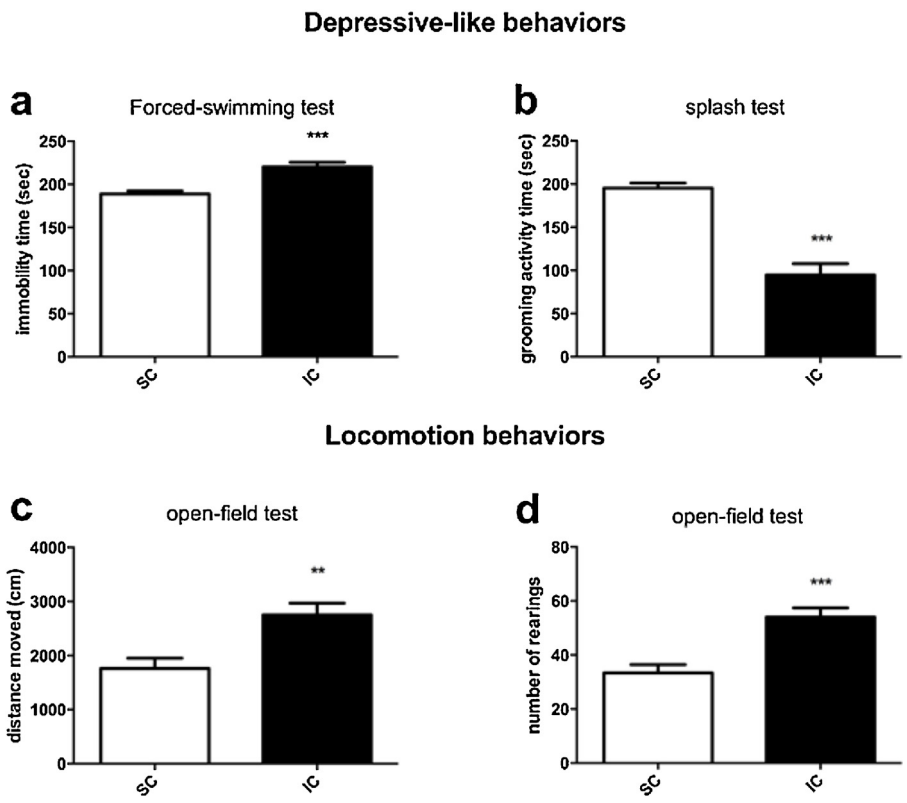


**Fig. 1.** Effect of housing condition on behaviors related to depression. Effect of different housing conditions, social condition (SC) and isolated condition (IC), on the immobility time in the FST (a), grooming activity time in the splash test (b), total distance moved in the OFT (c), and number of rearings in the OFT (d). Values are expressed as the mean ± S.E.M. of 8 animals and were analyzed using *t*-test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the SC control group.

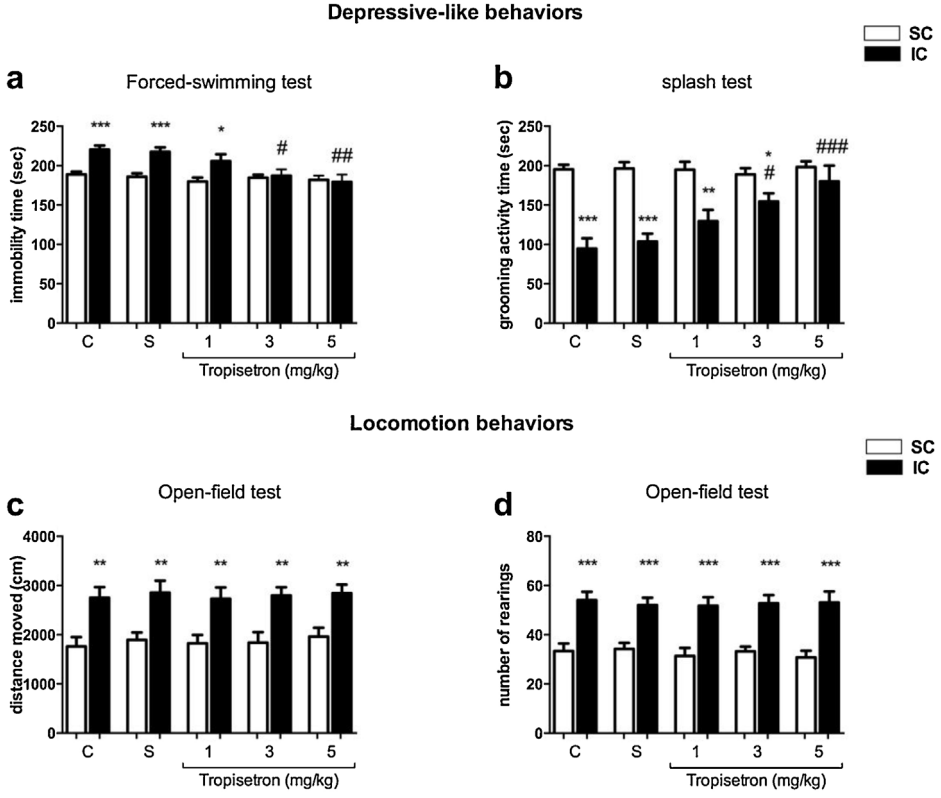


**Fig. 2.** Effect of tropisetron treatment on behaviors related to depression in different housing conditions. Effects of tropisetron (1, 3, and 5 mg/kg) on the immobility time in the FST (a), grooming activity time in the splash test (b), total distance moved in the OFT (c), and number of rearings in the OFT (d) in different housing conditions, social condition (SC) and isolated condition (IC). Values are expressed as the mean ± S.E.M. of 8 animals and were analyzed using one-way ANOVA followed by Tukey's post hoc test. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with the SC control group. $\#P < 0.05$, $\#\#P < 0.01$, and $\#\#\#P < 0.001$ compared with the IC saline-treated group (S group). C: control group; S: saline group.