Involvement of the nitrergic system in the proconvulsant effect of social isolation stress in male mice

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Background: Social isolation stress (SIS) in adolescence is accompanied by neurobehavioral disturbances and pathophysiological changes in certain regions of the CNS such as the hippocampus. In this study, we tested whether SIS affects seizure susceptibility in postnatal male mice due to a role of hippocampal nitric oxide (NO).

Methods: To do this, we used the pentylentetrazole (PTZ) model of clonic seizures, open-field test, hole-board test, forced swimming test, and plasma corticosterone assay. We aimed to evaluate if 4 weeks of SIS is capable of decreasing seizure threshold along with altering affective and neuroendocrine responses in isolated conditioned (IC) animals in comparison with socially conditioned (SC) animals. In addition, we applied subeffective doses of NO precursor L-arginine (25, 50, and 100 mg/kg) and NOS inhibitors 7-NI (15 and 40 mg/kg), aminoguanidine (50 and 100 mg/kg), and L-NAME (10 and 15 mg/kg) to both IC and SC groups prior to the determination of seizure threshold. Comparison between the groups was analyzed using t-test and one-way ANOVA followed by Tukey's post-hoc test. P<0.05 was considered statistically significant.

Results: Injection of a single dose of all mentioned drugs did not induce changes in seizure threshold of SC mice. On the other hand, L-NAME and 7-NI, but not aminoguanidine, modulated the proconvulsant effect of SIS, while L-arginine augmented the latter effect (P<0.05). We also measured the hippocampal nitrite levels after the administration of the aforementioned drugs. Social isolation stress increased the nitrite levels in comparison with those in SC mice, whereas 7-NI and L-NAME, unlike aminoguanidine, mitigated the effect of SIS. Additionally, L-arginine boosted the effects of SIS on nitrite production (P<0.05).

Conclusions: In summary, we showed that SIS enhanced seizure susceptibility in the PTZ model of clonic seizures through the activation of the nitrergic system in the hippocampus. Also, we proved that nNOS, but not iNOS, accounts for these changes following SIS.