



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



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ABSTRACT

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 impacts seizure susceptibility in postnatal male mice due to a role of hippocampal nitric oxide (NO). To do this, we used the pentylenetetrazole (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. 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. 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. In summary, we showed that SIS enhanced seizure susceptibility in the PTZ model of clonic seizures through the activation of the nitrenergic system in the hippocampus. Also, we proved that nNOS, but not iNOS, accounts for these changes following SIS.

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1. Introduction

People with epilepsy (PWE) experience greater psychosocial challenges compared with the general population, thereby contributing to poor quality of life [1]. Among psychosocial problems, stress and social isolation have been reported as the most determinant factors which affect the severity of epilepsy and social functioning of PWE, respectively [2,3]. Previous studies have reported that social isolation stress (SIS) in the adolescent period induces considerable psychobiological abnormalities, neurobehavioral disturbances, and hypothalamic–pituitary–adrenocortical (HPA) axis malfunction [4,5]. In addition, the social isolation paradigm has been suggested as a reliable animal model for the investigation of neurobehavioral changes in psychiatric disorders similarly seen in humans [6]. Under chronic stress

circumstances, the neurotoxic action of excitatory neurotransmitters such as glutamate causes an overproduction of nitric oxide (NO) via the excessive activity of nitric oxide synthase (NOS) [7,8].

Nitric oxide contributes to a variety of physiological and pathophysiological processes in the hippocampus (HIPP), such as learning, memory, depression, and seizure susceptibility [9–13]. Among NOS isoforms, both iNOS (inducible NOS) and nNOS (neuronal NOS) have been reported to increase the NO levels in the HIPP in response to stressful paradigms [14,15]. In addition, early stressful life events have negative enduring effects on the HIPP which are relevant to increased susceptibility to seizures in adulthood [16]. Recently, it has been demonstrated that endogenous NO is a key factor for initiation of seizure-like events [17]. In another study, Watanabe et al. showed that elevated NO levels in the murine brain are associated with increased seizure susceptibility in the pentylenetetrazole (PTZ) model of convulsive seizures. They also showed that PTZ-induced convulsive seizure is sensitive to small changes of NO levels in the brain; therefore, it is a valid animal model for the evaluation of epileptic activity [13,18]. Surprisingly, there are few studies about the effects of social isolation,

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