Medical Hypotheses xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Proconvulsant effect of post-weaning social isolation stress may be associated with dysregulation of opioid system in the male mice

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ARTICLE INFO

Article history:
Received 8 October 2014
Accepted 27 January 2015
Available online xxxx

ABSTRACT

Opioid system has been reported to be involved in the consequences of post-weaning social isolation stress (SIS) such as hypoalgesia and social behaviors. Also, previous studies have shown that SIS increases mu opioid receptor expression in the regions of the brain associated with epileptogenesis such as basolateral amygdala and cortex. Interestingly, experiencing SIS increases seizure risk in the adulthood. Regarding the SIS-induced alterations in the opioid system, we hypothesize that increase in opioidergic system activity (mostly by mu receptor) may be associated with increase in vulnerability to seizures. In non-stressed mice, morphine at low doses (1 mg/kg) has an anticonvulsant effect on seizure threshold while higher doses (60 mg/kg) are proconvulsant. To support the hypothesis, we showed that administration of anticonvulsant dose of morphine (1 mg/kg) to socially isolated male mice not only was not able to reverse the negative effect of SIS on seizure susceptibility to pentylenetetrazole but also enhanced it. These results support our hypothesis that proconvulsant effect of post-weaning social isolation stress may be associated with dysregulation of opioid system in the adult male mice.

Introduction

Post-weaning social isolation stress and seizure risk

Loneliness or perceived social isolation (SI), a painful social condition, contributes to fatigue, depression and predisposes individuals to various diseases [1,2]. The adolescence period of life is most sensitive state to the adverse effects of loneliness [3]. Many animal studies have been focused in the adolescence stage to find out the underlying pathophysiological mechanisms of SI. In the animal studies, maladaptive neurobehavioral changes as well as development of psychopathological abnormalities has pervasive outcomes of experiencing the SI in the adolescence [4,5]. There are evidences reported that SI increases the seizure risk in both humans and rodents. Studies on people with epilepsy showed that SI not only decrease the quality of their lives but also exacerbates the seizures [6]. Moreover, Matsumoto et al. reported that applying 7 weeks of SI to adolescent mice alters GABAergic system which leads to a decrease in seizure threshold in adult subjects [7]. In this context, it is believed that SI is able to antagonize the effects of $GABA_A$ receptor agonist [8] and enhance the proconvulsant effect of picrotoxin [7].

Opioid system and seizure modulation

Opioid agonists and their receptors are diversely expressed with varying degree in different parts of central and peripheral nervous systems as well as in endocrine tissues and their target sites. In this regard, opioid system plays a role in modulation of a variety of functions like social behaviors, pain, addiction, neurotransmission, and seizure susceptibility [9,10]. It is well documented that opioids like morphine, have both anticonvulsant and proconvulsant effects in different experimental models of seizure [11,12]. The dual effect of morphine is linked to its dose. Various studies have reported that acute administration of morphine (0.5, 1, and 3 mg/kg) exert anticonvulsant effect in various paradigms of seizure models [11,13]. Also in our lab we showed that low dose of agmatine has synergistic anticonvulsant effect with morphine

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http://dx.doi.org/10.1016/j.mehy.2015.01.041
0306-9877/