Differential effect of c-Fos activation associated with JNJ16259685 after an agonistic encounter as compared with grouped mice

Abstract:

Glutamate is the major excitatory neurotransmitter in the brain, with widespread projections and localization of its various receptors. In a recent study, Navarro et al. [1] demonstrated that JNJ16259685 (a selective antagonist of mGlu1 receptors) produced a robust reduction in offensive behaviours of mice, suggesting a role for these receptors in aggression modulation. This antiaggresive effect was associated with changes in the c-Fos expression patterns in limbic structrures [2]. In the present study we extend the previous work to confirm the specific c-fos expression pattern of aggressive behaviour and its effect after JNJ16259685 administration. For this aim, male mice were treated acutely and subchronically with JNJ16259685 (0.25, 0.5, 1 mg/kg, i.p). Animals were divided into two groups: one group was assessed for changes on agonistic behaviour (using the isolation-induced aggression model) and for the c-Fos expression, while the second one were housed in group of five and assessed for the c-Fos activation (grouped mice). The following brain structures were studied: Prefrontal cortex (prelimbic, infralimbic and cingular cortex), lateral septum (dorsal and ventral), hypothalamus (paraventricular, anterior and ventromedial nucleus), amygdala (basolateral and medial), periacueductal gray (anterior, lateral and dorsolateral) and ventral tegmental area. Individually housed mice were exposed to anosmic 'standard opponents' 30 min after drug administration. Ten min of diadic interactions were staged between a singly housed and an anosmic mouse in a neutral area. The encounters were videotaped and the accumulated time allocated by subjects to ten broad behavioural categories was estimated using an ethologically based analysis [1]. After the encounters, the animal was removed from the test cage and was left undisturbed until sacrifice perfusion. A 2-h interval between drug injection and perfusion was used. Inmunohistochemical techniques were applied [3]. Non-parametric statistical analysis were used. Results showed that JNJ16259685 (0.5 and 1 mg/kg) produced a significant reduction of aggressive behaviour (threat and attack) in mice acutely and subchronically treated with the drug, without affecting motility, as compared with the vehicle group ($p<0.001$-$p<0.05$), accompanied by a decrease of c-Fos expression (variable in function of the doses and the pattern of treatment used) in infralimbic and cingular cortex, dorsal septum, hypothalamus anterior nucleus, basolateral and medial amygdala, lateral and dorsolateral periacueductal gray and ventral tegmental area, as compared with the vehicle group ($p<0.001$-$p<0.05$). In the other hand, grouped animals remaining showed an increase of c-Fos expression in prelimbic cortex (0.5 mg/kg, subchronic treatment) and paraventricular hypothalamic nucleus (0.25 mg/kg, acute treatment; 0.25, 0.5 and 1 mg/kg, subchronic treatment). Furthermore, an increase of c- fos activation ($p<0.001$-$p<0.05$) was observed for the animals that had the agonistic experience compared with the grouped one in the following areas: Infralimbic and cingular cortex, dorsal and ventral septum lateral, paraventricular and anterior hipothalamic nuclei, medial amygdala and lateral periacueductal gray. It is concluded that the blockade of mGlu1 glutamate receptors produces remarkable antiaggressive effects, which are associated with specific changes in the c-Fos. Moreover, the experience of agonistic encounter elicited a particular pattern of cfos brain activation in mice.

Reference(s):

[1] Navarro, J.F., De Castro, V., Martín-López, M., 2008. JNJ16259685, a selective mGlu1 receptor antagonist, suppresses isolation-induced aggression in male mice. Eur J Pharmacol 586, 217-220.

[2] De Castro, V., Suarez, D., Rivera A., Martin-Lopez, M., Navarro, J.F., 2012. c-Fos expression pattern associated to the antiaggressive effects of JNJ16259685, a selective antagonist of mGlu1 receptors, in mice. Eur Neuropsychopharmacol. 22, S184.

[3] Navarro, J.F., Rivera, A., Maldonado, E., Cavas, M., De la Calle, A., 2004. Anxiogenic-like activity of MDMA ('ecstasy') in the 'social interaction test' is accompanied by an increase of c-fos expression in mice amygdala. Prog NeuroPsychopharmacol Biol Psychiatry 28, 249-254.

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