Isolation and Social Instigation in animal models of aggression: Effects of an mGlu1 receptor antagonist administration.

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Isolate-induced aggression in male mice is a model widely used in psychoparmacology of aggression. Animals are usually isolated for 30 days and subsequently treated and confronted with an anosmic opponent in a neutral area. For 10 min, the complete agonistic repertoire exhibited by the experimental animals is examined, allowing a detailed analysis of aggressive behaviors and other exploratory and motor behaviors. We have recently investigated the role of glutamate metabotropic receptors (mGluR) in this experimental model. Glutamate is the major excitatory neurotransmitter in the brain and it acts both at ionotropic (NMDA, AMPA and kainate receptors) and mGluRs, which are members of the G-protein-coupled receptor family. Eight mGluRs have been characterized and grouped into three classes: group I (mGlu1 and 5), group II (mGlu2 and 3) and group III (mGlu4, 6, 7 and 8). We have tested selective ligands available for the subtypes of mGluRs. Group I antagonists were the most effective ones reducing aggression, being especially remarkable the antiaggressive action observed after the administration of JNJ16259685 (an mGlu1 selective antagonist; 0.125-8 mg/kg i.p.), that produced a strong reduction of offensive behaviors (threat and attack), without affecting immobility with all doses. In this context, we wonder whether this drug could also reduce forms of intensified-heightened aggression. In recent years there is an increasing interest in studying excessive-abnormal forms of aggression in rodents, with the aim of providing a higher translational value to the observed violence in humans, in which aggression becomes intense, disproportionate and dysfunctional. We select a social instigation model, where mice are exposed to a brief territory intrusion of an adult male mice physically inaccessible. After this social provocation mice are exposed to a second opponent which now is unprotected. Social instigation dramatically increases aggressive behaviors, which renders this model appropriate for investigating the neurobiological mechanisms of excessive aggressive behavior. Therefore, we implemented a social instigation procedure in the isolation-induced aggression model with a double objective: first, to examine whether “instigation” could increase the aggression obtained by social isolation; and second, to evaluate the antiaggressive effect of an mGlu1 antagonist in heightened aggression. For this purpose, an acute dose of JNJ16259685 (0.5 mg/kg) was administrated to socially instigated animals after isolation, as well as to animals only isolated. Our results revealed that social instigation reduced latency of attack and increased the frequency and duration of attacks against not instigated animals, without affecting motor behaviors. Likewise, JNJ16259685 (0.5 mg/kg) administration significantly reduced aggressive behaviors in both cases. Taken together, this study shows that social instigation is an useful experimental procedure that increases significantly the levels of aggression observed in an isolated-induced aggression model, also demonstrating the involvement of mGlu1 receptors in the modulation of normal and heightened aggression in male mice.

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