Glutamatergic neurotransmission has been strongly implicated in the pathophysiology of affective disorders such as major depression and anxiety (Stewart and Reid, 2002). Of all glutamate receptors, the role of group III metabotropic glutamate receptors (mGluR4; mGluR6; mGluR7; mGluR8) in such disorders is the least investigated because of the lack of specific pharmacological tools. We have generated mice with a targeted deletion of the gene for mGluR7 (mGluR7−/−) and investigated the effects in animal models of depression and anxiety.

We examined the behavioral effects of (sex matched, 25-35g) mGluR7−/− mice and their wildtype counterparts (bred onto C57BL/6 background for 14 generations; 10-14 weeks old) in animal models of depression (forced swim test; tail suspension test; see Cryan et al., 2002) and anxiety (elevated plus maze; staircase test; light-dark box and stress-induced hyperthermia test see Holmes 2001). Housing was at room temperature, in a 12 hr light/dark cycle with lights on at 8 A.M. All experiments were conducted during the light cycle. All data are expressed as mean ± SEM and are analysed using one way ANOVA. The level of significance was set at p <0.05.

mGluR7−/− mice had a significantly lower immobility score (57 ± 10 sec; n = 24) than mGluR7+/+ mice (113 ± 12 sec; n = 24) in the forced swim test which indicates an antidepressant-like effect. Similarly, mGluR7−/− mice had a significantly lower immobility score (98 ± 6 sec; n = 19) than mGluR7+/+ mice (176 ± 8 sec; n = 13) in the tail suspension test which is also indicative of an antidepressant-like effect.

In all four anxiety tests employed mGluR7−/− mice were significantly less anxious than mGluR7+/+ mice. mGluR7−/− mice had a significantly higher number of transitions between the dark and light compartments throughout the 10 minutes of the light-dark test (43 ± 8 transitions; n = 12) when compared with mGluR7+/+ animals (16 ± 3 transitions; n= 16). mGluR7−/− mice had significantly more entries into the open arms of the elevated plus maze (5.5 ± 1.1 entries; n = 24) compared with mGluR7+/+ animals (2.6 ± 0.5 entries; n = 24). In the staircase test mGluR7−/− mice had a significant increase in the ratio of steps:rears (2.6 ± 0.31; n = 16) as compared with mGluR7+/+ mice (1.4 ± 0.12; n = 16) which is the primary indicator of reduced anxiety in this test. mGluR7−/− mice had a significantly lower stress–induced hyperthermia (0.57 ± 0.17; n = 10), a physiological test of anticipatory anxiety, than mGluR7+/+ (1.1 ± 0.1; n = 10) mice which is indicative of a reduced anxiety.

These data, showing robust antidepressant and anxiolytic-like effects in mGluR7−/− mice, strongly suggest that mGluR7 plays a pivotal role in mechanisms that regulate behavioral responses to aversive states. Therefore, drugs acting at mGluR7 may provide novel treatments for psychiatric disorders such as depression and anxiety.