Control of aberrant circuit activity by positive modulation of mGlu2 receptors

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Excessive glutamatergic neurotransmission has been attributed to aberrant circuit function in psychiatric indications such as major depressive and anxiety disorders. Normalization of cortico-limbic hyperactivity provides a plausible therapeutic strategy to reduce sensitivity to aversive stimuli and improve emotional control. Besides failure in clinical trials the activation of metabotropic glutamate 2 receptors (mGluR2) by positive allosteric modulation provides an attractive opportunity to tune hyperactive synapses while preserving the temporal pattern of glutamatergic transmission. In the current study, we have investigated the activity of a selective and centrally available mGluR2 positive allosteric modulator (PAM) to reduce hyper-glutamatergic response in brain circuits relevant for mood regulation. Compound 1 exhibited PAM activity at recombinant human and rat mGlu2 receptors, without considerable effect on other mGluRs or unrelated receptors. Activity on native receptors was assessed in rat brain slices by recording of EPSPs and EPSCs in the prefrontal cortex and amygdala, respectively. Application of the mGluR2 PAM led to potentiation of mGluR2/3 agonist-induced suppression of glutamatergic transmission confirming the proposed mode of action at functional synapses. Efficacy of the mGluR2 PAM at hyper-glutamatergic circuits was assessed in rats acutely administered with an NMDA receptor antagonist. We demonstrated dose-dependent reversal of ketamine-induced locomotor hyperactivity indicative of the modulation of hyper-glutamatergic response in vivo. To confirm the modulation of particular brain circuits we monitored changes in brain regional cerebral blood volume in anesthetized rats by pharmacological MRI. Ketamine was administered to induce a substantial elevation of brain activity in cortico-limbic regions, which could be reversed by the mGluR2 PAM. Moreover, in vivo activity has been shown in the mouse forced swim test. In line with literature for the mGluR2/3 agonist acute administration was not found to be effective. Interestingly, efficacy of the mGluR2/3 agonist and mGluR2 PAM could be revealed by repeated administration possibly linked to plasticity mechanisms driving the efficacy in this stress-related task. In conclusion, the mGluR2 PAM has been shown to normalize hyper-glutamatergic activity in brain regions responsible for emotional processing which may contribute to the potential therapeutic benefit in psychiatric indications associated with aberrant cortico-limbic activity.