Head-to head comparison between mGlu1 and mGlu5 receptor enhancement in the chronic treatment of absence epilepsy in WAG/Rij rats

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Spike-wave discharges (SWDs), the electroclinical hallmark of clinical absence epilepsy, are generated within cortico-thalamo-cortical circuit. mGluRs located within this network are potential targets for SWD modulatory drugs. Symptomatic WAG/Rij rats endowed with spontaneous occurring absence seizures showed that the acute administration of positive allosteric modulators (PAMs) of mGlu1 and mGlu5 receptors (RO0711401 and VU0360172, respectively) reduced the incidence of SWDs dose dependently without affecting motor behaviour (Ngomba et al., 2011; D'Amore et al., 2013). As a follow up of these previous studies it was investigated whether tolerance during a 10 day chronic treatment occurred and whether the sensitivity for the drugs changed after treatment. mGlu receptor expression by immunoblotting and brain concentrations of both compound during the treatment were additionally determined. The mGlu5 receptor PAM, VU0360172 (3 mg/kg, s.c., daily for 10 days) reduced the incidence of SWDs without signs of tolerance and without affecting motor behaviour during chronic administration. In contrast, tolerance developed after 2 days of treatment with the mGlu1 receptor PAM, RO0711401 (10 mg/kg, s.c., daily for 10 days). Western blot analysis data showed alteration of expression of both mGlu1 and mGlu5 receptors in the cerebral cortex and thalamus of WAG/Rij and control rats in response to RO0711401 administration. Intriguingly, only the mGlu5 receptor expression was altered in the above-mentioned regions of WAG/Rij and control rats in response to VU0360172 treatment. Preliminary data in control animals showed that brain levels of RO0711401 decreased with time during treatment, whereas VU0360172 levels remained constant. These data confirm the efficacy of mGlu1 and mGlu5 PAMs in the treatment of absence epilepsy. Further investigations are required to dissect the mechanisms underlying any development of tolerance to chronic activation of the group I mGlu receptors.

D'Amore et al. (2013). *Neuropharmacology*. 66, 330-8.
Ngomba et al. (2011). *Neuropharmacology.* 60, 281-91.