

SELECTIVE ACTIVATION OF METABOTROPIC GLUTAMATE RECEPTORS SUBTYPE 4 ENHANCES SPONTANEOUS AND EVOKED ABSENCE SEIZURES

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We examined the expression of metabotropic glutamate receptors, subtype 4 (mGlu4), in an animal model of absence seizures using genetically epileptic WAG/Rij rats, which develop spontaneous non-convulsive seizures after 2-3 months of age. Analysis by western blotting of various brain regions from six-month old WAG/Rij rats showed an increased expression of mGlu4 receptors in the reticular thalamic nucleus while there were no significant differences in expression in ventrolateral regions of the somatosensory cortex and the ventrobasal thalamic nuclei. To examine whether pharmacological activation or inhibition of mGlu4 receptors affects absence seizures, we recorded spontaneous spike-wave discharges (SWDs) in 8-month old WAG/Rij rats systemically injected with solvent (oil) and PHCCC, a positive allosteric modulator of mGlu4 receptor. Injection of 10 or 3 mg/kg of PHCCC (10 or 3 mg/kg, s.c.) increased the number of SWDs during the first 2-4 hrs post-treatment in a dose dependent manner. To directly address the role of mGlu4 receptors in absence epilepsy, we have used mGlu4 knock-out mice, which are resistant to chemically induced absence epilepsy by low doses (30 mg/kg) of pentylenetetrazole (PTZ). We examined the effect of PHCCC (10 mg/Kg) on seizures induced by PTZ in mGlu4 wildtype SVJ129 mice which confirmed an increase in the epileptiform activity. In contrast, PHCCC-treated mGlu4 knock-out mice (n=10) showed few and insignificant seizure activity in our experimental condition and in at least six out of ten animals were completely devoid of any epileptiform activity. We speculate that the mGlu4 receptor is involved in the modulation of SWDs and that variation of expression patterns of these receptors in specific nuclei might be involved in the pathogenesis of absence epilepsy. Moreover, these results raise the possibility that mGlu4 receptor antagonists are of potential value in the treatment of absence epilepsy.