EFFECTS OF THE FOCAL ADMINISTRATION OF MGLU2/3 RECEPTOR LIGANDS IN SELECTED BRAIN AREAS OF WAG/RIJ RAT, A GENETIC ANIMAL MODEL OF ABSENCE EPILEPSY.

[1]De Sarro Giovambattista, [1]Citrato R., [2]Ngomba R., [1]Russo E., [2]Battaglia G., [2,3]Nicoletti F.

[1]Department of Experimental and Clinical Medicine, Faculty of Medicine and Surgery, University of Catanzaro, Catanzaro, Italy, [2]I.N.M. Neuromed, 86077 Pozzilli, Italy, [3]Department of Human Physiology and Pharmacology, University of Rome "La Sapienza", Italy

Excessive glutamatergic neurotransmission is understood to be one of the primary cause behind the etiology of numerous types of epilepsy(1). In the past few years, attention has been focused on metabotropic glutamate (mGlu) receptors as potential targets for antiepileptic drugs(2). mGlu2/3 receptors are preferentially localized on presynaptic nerve terminals, where they negatively modulate both glutamate and GABA release. WAG/Rij rat, a validated animal model of absence epilepsy, are characterized by the sudden onset of 7-10 Hz spike and wave discharges (SWDs) in the electroencephalogram (EEG), generated by corticothalamic pathways, which primarily involves the reticular thalamic nucleus (NRT), the ventroposteromedial thalamus (VPM) and the cortex (S1po)(3). We have previously demonstrated that i.p. administration of mGlu2/3 receptor agonists and antagonists increased and reduced, respectively, the number of SWDs in WAG/Rij rats(4). The aim of the present study was to investigate the role of mGlu2/3 receptors in selected brain areas of the WAG/Rij rats. In particular, we evaluated the effects of LY379268, a potent and selective agonist of mGlu2/3 receptors and LY341495 a preferential antagonist of mGlu2/3 receptors. Animals were surgically implanted with five cortical electrodes for the EEG recording and two guide cannulae for focal administration of drugs, the number and duration of SWDs were recorded. Injection of LY379268 (5, 10, 20 nmol/0,5 μl) into the NRT increased the number and duration of SWDs, while reduced the number into VPM and S1po and increased their duration in VPM whereas reduced them in S1po. On the other hand, the receptor antagonist, LY341495 (5, 10 20 nmol/0,5 μl) reduced the number of SWDs in all areas, while decreasing significantly SWDs duration only in VPM and S1po. In conclusion, these results indicate either a protective activity by mGlu2/3 receptor antagonist, LY341495 or a pro-convulsive effect of mGlu2/3 receptor agonist LY379268, in thalamic nuclei, in the same animal model. The evidence that LY341495 reduced SWDs suggests that endogenous activation of mGlu2/3 receptors sustains spontaneous absence seizures in WAG/Rij rats. However, the mechanism by which mGlu2/3 receptors modulate absence seizures in WAG/Rij rats remains to be determined.

[1]Meldrum BS., Akbar MT., Chapman AG. (1999). Epilepsy Res. 36: 189-204.
[2]Moldrich RX., Chapman AG., De Sarro G., Meldrum BS. (2003). Eur. J. Pharm. 476:3-16.
[3]Meeren HK., Pijn JP., Van Luijtelaar EL. et al. (2002). J. Neuroscience 22: 1480-1495.
[4]Ngomba RT., Biagioni F., Casciato S. et al. (2005). Neuropharmacology. 49: 89-103.