PRENATAL EXPOSURE TO THE CANNABINOID RECEPTOR AGONIST WIN 55,212-2 REDUCES GLUTAMATE OUTFLOW AND INCREASES GLUTAMATE UPTAKE THROUGH AN OVEREXPRESSION OF GLT1 AND EAAC1 GLUTAMATE TRANSPORTERS IN RAT FRONTAL CEREBRAL CORTEX

[1]Castaldo Pasqualina, [1]Magi Simona, [2]Gaetani Silvana, [3]Cassano Tommaso, [4]Ferraro Luca, [1]Corcione Elisa, [4]Antonelli Tiziana, [2]Cuomo Vincenzo and [1]Amoroso Salvatore.

[1]Sect of Pharmacol, Dept of Neurosci, "University Politecnica delle Marche", Ancona; [2]Dept of Hum Physiol and Pharmacol Univ of Roma "La Sapienza"; [3]Dept of Biomed Sci Univ of Foggia; [4]Sect of Pharmacol, Dept of Clin and Exp Med, Univ of Ferrara

Prenatal exposure to the cannabinoid CB_1 receptor agonist WIN 55212-2 mesylate (WIN) has been shown to induce in offsprings long lasting impairment of cognitive functions associated to a permanent reduction of hippocampal and neocortical glutamate outflow and to an impairment of hippocampal LTP maintenance. Glutamate uptake operated by plasma membrane glutamate transporters (GluTs) is one of the main factors that modulates extracellular glutamate levels.

The aim of the present study was to assess whether prenatal exposure to WIN (0,5mg/kg daily s.c. from the fifth to the twentieth day of gestation), reduced dialysate glutamate levels in frontal cerebral cortex by modulating expression and/or activity of the most prominently expressed GluTs, in adolescent offspring (40 day old) with respect to those born from vehicle-treated mothers.

Results obtained showed that, in frontal cerebral cortex of 40-day old rats, WIN treatment induced a reduction in basal dialysate glutamate levels than those found in control animals. In order to evaluate the GluTs activity, [^{3}H]L-glutamate uptake experiments were performed on prefrontal cortex synaptosome. Results showed a statistically significant time-dependent enhancement of [^{3}H]L-glutamate uptake. Interestingly, kinetic analyses of synaptosomal [^{3}H]L-glutamate uptake revealed a statistically significant enhancement of Vmax, whereas the Km was not modified. In line with these results western blotting analysis, performed either in membrane proteins derived from homogenates or in proteins extracted from synaptosomes of frontal cerebral cortex, revealed that prenatal WIN exposure enhanced the expression of glutamate transporter 1 (GLT1) and excitatory amino acid carrier 1 (EAAC1). Immunocytochemical analyses confirmed an increased immunoreactivity of GLT1 (restricted to perineuronal structures and neuropils) and EAAC1 (detected in pyramidal neurons and neuropil) in adolescent offspring (40 day old) with respect to those born from vehicle-treated mothers. In addition, any alteration was detected in the amount and distribution of glial and neuronal cell population.

Collectively, the results obtained showed that prenatal exposure to the cannabinoid CB1 receptor agonist WIN decreased cortical glutamate outflow in adolescent rats. One of the possible mechanistic events responsible of this impairment seemed to be an increase of expression and functional activity of GLT1 and EAAC1. These findings may contribute to explain the mechanism underlying the cognitive impairment observed in the offspring of mothers who used marijuana during pregnancy.