

**THE AGONIST OF METABOTROPIC GLUTAMATE 5 RECEPTORS CHPG INVERTS THE EFFECTS OF DHK (A BLOCKER OF GLIAL GLUTAMATE UPTAKE): AN IN VIVO MICRODIALYSIS STUDY**

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The role of group-I metabotropic glutamate receptors (mGlu1Rs and mGlu5Rs) in neurodegeneration is still unclear, since agonists of these receptors can either amplify or attenuate excitotoxic neuronal death (1). An increase in extracellular glutamate levels (due to an excessive pre-synaptic release or, more importantly, to an inefficient re-uptake), is a crucial step in excitotoxicity. In a previous microdialysis study in the rat striatum, we reported that the mGlu5R agonist CHPG increased extracellular glutamate levels (2), a potentially pro-excitotoxic effect. More recently, however, the activation of mGlu5Rs has been shown to facilitate *in vitro* the astrocytic re-uptake of glutamate (3), which represents a potentially neuroprotective activity. The aim of the present study was to investigate whether the modulation of glial glutamate uptake by mGlu5Rs also occurs *in vivo*. To this end, the influence of the selective mGlu5R agonist CHPG and antagonist MPEP towards the effects induced by didyrokainic acid (DHK), a selective blocker of the glial glutamate transporter GLT-1, was studied by striatal microdialysis. Rats were stereotaxically implanted with a vertical dialysis probe in the striatum (A= + 2.2; L= ± 3.0; V=-6.5 mm from bregma, sagittal suture and dura, respectively). Dialysates were collected every 5 min starting from 24 hours after surgery. The glutamate content of all samples was measured by reverse-phase high performance liquid chromatography coupled to a fluorimetric detector. Probe perfusion with 10 mM DHK significantly increased extracellular glutamate levels (+103.7±20%, N=4, P<0.05 vs basal). CHPG alone (0.5 mM) also increased glutamate outflow (+36.4±20%, N=4, P<0.05 vs basal). Interestingly, when CHPG was administered soon before or co-perfused with DHK, no additive effects were seen but, on the contrary, extracellular glutamate fell below basal levels (-40±8%, N=4, P<0.05 vs basal, P<0.01 vs either DHK and CHPG alone). Such a “paradoxical” effect of CHPG was fully antagonized by MPEP 250µM (N=4). Interestingly, if CHPG perfusion was started after the administration of DHK, CHPG did not influence DHK-induced glutamate outflow. These results show that, while CHPG alone slightly increases glutamate levels, it apparently inverts the effect of the glial uptake blocker DHK. These data, which confirm the dual role exerted by mGlu5Rs on extracellular glutamate levels, may have important implications for neurodegenerative diseases

(1) Nicoletti et al., 1999 38:1477-84.; (2) Pintor et al., 2000 Neuroreport 11:3611-14. ; (3) Vermeiren et al., 2005, J. Neurochem 94:405-416.