GUANIDINOSUCCINIC ACID, A NEW ENDOGENOUS N-METHYL-D-ASPARTATE RECEPTOR AGONIST.

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Guanidinosuccinic acid (GSA), an endogenous metabolite accumulating in the cerebrospinal fluid (CSF) of patients with renal fallure could play an important role in the pathophysiology of uremic encephalopathy. It is known to induce convulsions in mice. Furthermore GSA and NMDA are closely related chemically.

We studied on rat hippocampal slices, the effects of tonic bath application (40 minutes) of GSA on the glutamate transmission in rat hippocampal slices. We recorded in the CA1 region, with glass extracellular microelectrodes, the postsynaptic field potentials after electrical stimulation of the Schaffer collaterals.

In normal artificial CSF, with no added glycine, the concentrations of 15.625 and 31.25 µM of GSA, encountered in CSF of uremic patients, were inactive. The low concentrations of 62.5 and 125 µM induced a long-term potentiation (LTP) of the AMPA response or GSA-LTP. Higher concentrations (250 and 500 µM) induced a strong membrane depolarization, bringing up a depression of the fEPSP and allowing the expression of the GSA-LTP only during the washout period after membrane repolarisation. During the depolarization step hyperexcitability was observed. Still higher concentrations (1 and 2 mM) induced quickly irreversible toxic cellular lesions due to a large calcium inflow. In every instances, GSA-LTP occluded electrical LTP. All those effects were antagonized by the competitive NMDA receptor antagonist D-2-amino-5-phosphonopentanoic acid (D-AP5) and by the non competitive open channel blocker dizocilpine (MK801).

Afterwards we investigated how magnesium, a channel blocker, glycine and 7-chlorokynurenic acid, respectively agonist and antagonist of the glycine site of the NMDA receptor, could modulate the effects of GSA. The dose response curves were shifted to the right in the presence of 6 mM of MgCl2 and of 50 µM 7-chlorokynurenic acid and to the left in 10 µM of glycine. A strong potentiation of the GSA effect was evidenced at levels found in uremia (15.625 and 31.25 µM). Acute GSA toxicity appears above 125 µM of GSA in the presence of glycine and above 500 µM in the other conditions. Magnesium, glycine and kynurenate modulate the effect of GSA. Magnesium and kynurenic acid reduce neurotoxic effect, glycine enhance the effects of GSA and induces neuronal cytotoxicity.

GSA is a new endogenous agonist of the NMDA receptor. Its effects could explain the encephalopatic symptoms currently observed in the uremic patient: memory loss and hyperexcitability. In clinical conditions, potentiation by glycine should outweigh the effects of magnesium and kynurenic acid. NMDA antagonists could thus prove to be useful in uremic encephalopathy.