Neuroprotection by Lowering of Membrane Cholesterol Content

T. Borisova, R. Sivko, L. Kasatkina, N. Krisanova

Department of Neurochemistry, Palladin Institute of Biochemistry, NAS of Ukraine; Kiev, Ukraine; E-mail: tborisov@biochem.kiev.ua

In stroke, cerebral hypoxia/ischemia, traumatic brain injury, neurotoxic consequences are evoked by enhanced extracellular concentration of glutamate, which is the major excitatory neurotransmitter in the CNS, and transporter-mediated release of glutamate (glutamate uptake reversal) is the main mechanism of glutamate release. Under these pathological conditions, cholesterol-lowering drugs statins have neuroprotective features. The aim of this study was to assess transporter-mediated release of glutamate from rat brain nerve terminals (synaptosomes) under conditions of cholesterol deficiency. Cholesterol acceptor methyl-β-cyclodextrin (MβCD) reduced the cholesterol concentration in synaptosomes by 25%. Under conditions of cholesterol deficiency: 1) tonic release of endogenous glutamate; 2) stimulated by depolarization of the plasma membrane transporter-dependent glutamate release; 3) release of glutamate by means of heteroexchange with competitive transported inhibitor of glutamate transporters DL-threo-□-hydroxyaspartate; 4) transporter-mediated glutamate release evoked by protonophore FCCP; 5) glutamate release in low-Na medium; was decreased, whereas the endogenous extracellular level of glutamate was increased. Decrease in the level of membrane cholesterol may be used for neuroprotection under pathological conditions including stroke, cerebral hypoxia/ischemia, traumatic brain injury that were associated with an increase in glutamate uptake reversal. Visa versa in norm, a decrease in the concentration of membrane cholesterol may cause neurotoxic consequences resulted from the enhancement of the extracellular glutamate level because of a decrease in glutamate uptake.