Neurotoxic Effect of Cadmium on Glutamate Uptake by Synaptosomes of Reduced Cholesterol Content.

Borisov A. (1), Krisanova N. (2), Sivko R. (2), Borisova T(2).

(1) National Taras Shevchenko University of Kiev, Ukraine;

(2) Department of Neurochemistry, Palladin Institute of Biochemistry, NAS of Ukraine, Kiev, Ukraine

Chronic exposure to cadmium causes nervous system disorders. To clarify cadmium toxicity, key parameters of synaptic neurotransmission as uptake by Na^+ -dependent glutamate transporters were examined in rat brain synaptosomes. Glutamate transporters terminate glutamatergic neurotransmission keeping the low level of extracellular glutamate, thereby protecting neurons from excitotoxic injury. Proper glutamatergic transmission is essential for basic neuronal communication, synaptic plasticity, learning and memorizing, attention, etc., whereas abnormal glutamate homeostasis contributes to neuronal dysfunction. It was demonstrated that cadmium (200 μM) decreased the initial velocity of transporter-mediated L-[^{14}C]glutamate uptake from 3.0 ± 0.1 nmol x min-1 x mg-1 of proteins to 1.98 ± 0.1 as a result of binding to thiol groups of transporters. Cholesterol is the most prominent component of eukaryotic membranes and certain level of membrane cholesterol is very important for normal functioning of a number of membrane proteins involved in synaptic transmission. To evaluate the role of membrane cholesterol in the development of neurotoxic effect of cadmium, we depleted cholesterol from synaptosomes with cholesterol acceptor methyl-β–cyclodextrin (MβCD) (15 μM) for 30 min. This treatment extracted a quarter of membrane cholesterol content of synaptosomes. Analyzing the effect of cadmium on cholesterol-depleted synaptosomes, we revealed that 200 μM cadmium almost completely abolished glutamate uptake. However, MβCD-treated synaptosomes also showed a decrease in the initial velocity of glutamate uptake that was equal to 3.0 ± 0.3 nmol x min^{-1} x mg^{-1} of proteins in control and 1.77± 0.2 nmol x min^{-1} x mg^{-1} of proteins after cholesterol depletion. The experiments revealed that influence of cadmium on MβCD-treated synaptosomes was more significant than additive effect of Cd^{2+} and MβCD *per se*. The current observation suggested that cadmium could cause more profound neurotoxic effect under conditions of altered cholesterol homeostasis and significantly enhance the neurological symptoms of diseases, which pathogenesis involved changes in the level of membrane cholesterol.