Journal of Evolutionary Biochemistry and Physiology 2015 vol.51 N4, pages 296-304

Homocysteine-induced membrane currents, calcium responses and changes in mitochondrial potential in rat cortical neurons

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Abstract

© 2015, Pleiades Publishing, Ltd. Homocysteine, a sulfur-containing amino acid, exerts neurotoxic effects and is involved in the pathogenesis of many neurodegenerative disorders. In contrast to well-studied glutamate excitotoxicity, the mechanism of homocysteine neurotoxicity is not clearly understood. Using wholecell patch-clamp, calcium imaging (fluo-3) and measurements of mitochondrial membrane potential (rhodamine 123), we studied in vitro in cultured rat cortical neurons transmembrane currents, calcium signals and changes in mitochondrial membrane potential induced by homocysteine versus responses induced by NMDA and glutamate. L-homocysteine (50 μM) induced inward currents that were completely blocked by the selective antagonist of NMDA receptors, AP-5. In contrast to NMDA-induced currents, homocysteine-induced currents exhibited a smaller steady-state amplitude. Comparison of calcium responses to homocysteine, NMDA or glutamate demonstrated that in all cortical neurons homocysteine elicited fast oscillatory-type calcium responses, whereas NMDA or glutamate induced a “classical” sustained elevation of intracellular calcium. In contrast to NMDA, homocysteine did not cause a drop in mitochondrial membrane potential at the early stages of its action. However, after its long-term effect, as in cases of NMDA and glutamate, changes in mitochondrial membrane potential arose comparable with its complete drop caused by protonophore FCCP-induced uncoupling of the respiratory chain. Our data suggest that in cultured rat cortical neurons homocysteine at the initial stages of its action induces in vitro neurotoxic effects due to the activation of NMDA-type ionotropic glutamate receptors followed by a massive calcium influx through the channels of these receptors. The long-term effect of homocysteine may lead to mitochondrial dysfuction manifested as a drop in mitochondrial membrane potential.

http://dx.doi.org/10.1134/S0022093015040055

Keywords

calcium, cortical neurons, glutamate, homocysteine, mitochondrial potential