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МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

REDOX EFFECTS OF HOMOCYSTEINE ON NMDA RECEPTORS

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Homocysteine (HC) – an amino acid containing the thiol group, is formed as an intermediate of methionine metabolism. In hyperhomocysteinemia the increase of HC concentration in plasma and cerebrospinal fluid complicates the course of many neurodegenerative diseases. Neurotoxic effect of excessive concentrations of extracellular HC in CNS is associated with its agonist properties of NMDA receptors, primarily of GluN1/2A subunit composition. In recombinant NMDA receptors containing GluN1 subunit in combination with GluN2A, GluN2B or GluN2C subunits for HC the two-phase concentration dependence of ion currents through the receptor channel is shown. In the case of GluN1/2A receptor the EC50 for HC activation was about 10 μM with saturation at 50–100 μM, but an increase in HC concentration above 200 μM caused an additional raise in receptor currents. We assumed that HC in high concentrations can potentiate NMDA receptor currents as a reducing agent acting on the redox sites of the GluN1 subunit. Modification of GluN1/2A, GluN1/2B and GluN1/2C redox sites by dithiotrietol potentiated their response to NMDA. In the case of HC, the dithiotrietol effects were dependent on the subunit composition of the receptors. In control 100 μM, HC activates both GluN1/2A and GluN1/2B receptors, but causes significant desensitization of the latter. Dithiotrietol relieves the desensitization of GluN1/2B by HC receptors, which significantly increases the integral current through them, but suppresses the currents of GluN1/2A. In cortical neurons, HC induced calcium entry to neurons occurred mainly via GluN1/2A receptors in control and via GluN1/2B receptors after dithiotrietol disulfide bonds were reduced. Thus, in hyperhomocysteinemia the thiol status of NMDA receptors significantly changes the degree of their activation by HC, and the effect depends on the subunit composition of the receptors.

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