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GluN2A subunit-containing NMDA receptors are the preferential neuronal targets of homocysteine

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Abstract

© 2016 Sibarov, Abushik, Giniatullin and Antonov.Homocysteine (HCY) is an endogenous redox active amino acid, best known as contributor to various neurodegenerative disorders. Although it is known that HCY can activate NMDA receptors (NMDARs), the mechanisms of its action on receptors composed of different NMDA receptor subunits remains almost unknown. In this study, using imaging and patch clamp technique in cultured cortical neurons and heterologous expression in HEK293T cells we tested the agonist activity of HCY on NMDARs composed of GluN1 and GluN2A subunits (GluN1/2A receptors) and GluN1 and GluN2B subunits (GluN1/2B receptors). We demonstrate that the time courses of Ca2+ transients and membrane currents activated by HCY and NMDA in cortical neurons are drastically different. Application of HCY to cortical neurons induced responses, which in contrast to currents induced by NMDA (both in the presence of glycine) considerably decreased to steady state of small amplitude. In contrast to NMDA, HCY-activated currents at steady state were resistant to the selective GluN2B subunit inhibitor ifenprodil. In calcium-free external solution the decrease of NMDA evoked currents was abolished, suggesting the Ca2+-dependent NMDAR desensitization. Under these conditions HCY evoked currents still declined almost to the baseline suggesting Ca2+- independent desensitization. In HEK293T cells HCY activated NMDARs of GluN1/2A and GluN1/2B subunit compositions with EC50s of 9.7 ± 1.8 and 61.8 ± 8.9 mM, respectively. Recombinant GluN1/2A receptors, however, did not desensitize by HCY, whereas GluN1/2B receptors were almost fully desensitized by HCY. Thus, HCY is a high affinity agonist of NMDARs preferring the GluN1/2A subunit composition. Our data suggest that HCY induced native NMDAR currents in neurons are mainly mediated by the “synaptic type” GluN1/2A NMDARs. This implies that in hyperhomocysteinemia, a disorder with enlarged level of HCY in plasma, HCY may persistently contribute to post-synaptic responses mediated by GluN2A-containing NMDA receptors. On the other hand, HCY toxicity may be limited by desensitization typical for HCY-induced activation of GluN2B-containing extrasynaptic receptors. Our findings, therefore, provide an evidence for the physiological relevance of endogenous HCY, which may represent an effective endogenous modulator of the central excitatory neurotransmission.

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Keywords

Desensitization, GluN2A, GluN2B, Glutamate, Homocysteine, Neurons, NMDA receptor, Primary culture