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Abstract

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Some properties of ionic channels activated by excitatory amino acids in hippocampal neurons.

Yamamoto C, Sato H.

Abstract

Properties of excitation induced by various excitatory amino acids were studied in thin slices of the guinea pig hippocampus in the presence of Mn2+, tetrodotoxin and tetraethylammonium chloride. Depolarizations induced by L-glutamate (Glu), quisqualate (Quis) and D-homocysteate (DH) were accompanied consistently by decreases in neuron input resistance. In the current-voltage function, increases in input resistance were never observed at any membrane potential. The amplitude of Glu, Quis and DH responses decreased during tonic outward currents and increased during tonic inward currents. Although neuron input resistance decreased with depolarizations induced by L-aspartate (Asp) as well, the magnitude of the resistance reduction was significantly smaller than that induced by Glu. Asp responses changed in amplitude as did Glu responses during tonic inward and outward currents. Depolarizations induced by N-Methyl-D-aspartate (NMDA) were accompanied by apparent increases in input resistance, and their amplitudes increased and decreased during tonic depolarization and hyperpolarization, respectively. Mn2+ was almost without effect at the concentration used (2.7 mM) on responses induced by Glu, DH or Asp. These results suggest that Glu, Quis and DH induce depolarizations in hippocampal neurons by activating only Quis receptors, and that Asp activates Quis receptors preferentially though it activates NMDA receptors as well.

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COMPARATIVE AND ONTOGENIC PHYSIOLOGY

Homocysteine-Induced Membrane Currents, Calcium Responses and Changes in Mitochondrial Potential in Rat Cortical Neurons

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Abstract—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 whole-cell 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 dysfunction manifested as a drop in mitochondrial membrane potential.

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Key words: homocysteine, glutamate, calcium, mitochondrial potential, cortical neurons.

Abbreviations: $[Ca^{2+}]_i$—intracellular calcium concentration, $\Delta\varphi_{mit}$—mitochondrial membrane po-