Autoreceptor Regulation of Glutamate and Aspartate Release from Slices of the Hippocampal CA1 Area

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Abstract

Slices of hippocampal area CA1 were employed to test the hypothesis that the release of glutamate and aspartate is regulated by the activation of excitatory amino acid autoreceptors. In the absence of added Mg^{2+}, *N*-methyl-D-aspartate (NMDA)-receptor antagonists depressed the release of glutamate, aspartate, and γ-aminobutyrate evoked by 50 m*M* K^+. Conversely, the agonist NMDA selectively enhanced the release of aspartate. The latter action was observed, however, only when the K^+ stimulus was reduced to 30 m*M.* Actions of the competitive antagonists 3-[(±)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid (CPP) and D-2-amino-5-phosphonovalerate (D-AP5) differed, in that the addition of either 1.2 m*M* Mg^{2+} or 0.1 μ*M* tetrodotoxin to the superfusion medium abolished the depressant effect of CPP without diminishing the effect of D-AP5. These results suggest that the activation of NMDA receptors by endogenous glutamate and aspartate enhances the subsequent release of these amino acids. The cellular mechanism may involve Ca^{2+} influx through presynaptic NMDA receptor channels or liberation of a diffusible neuromodulator linked to the activation of postsynaptic NMDA receptors. (*RS*)-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, a selective quisqualate receptor agonist, and kainate, an agonist active at both kainate and quisqualate receptors, selectively depressed the K^+-evoked release of aspartate. Conversely, 6-cyano-7-nitroquinoxaline-2,3-dione, an antagonist active at both quisqualate and kainate receptors, selectively enhanced aspartate release. These results suggest that glutamate can negatively modulate the release of aspartate by activating autoreceptors of the quisqualate, and possibly also of the kainate, type. Thus, the activation of excitatory amino acid receptors has both presynaptic and postsynaptic effects.