Effects of NMDA on carbachol-stimulated Phosphatidylinositol Resynthesis in Rat Brain Cortical Slices

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摘要

Abstract

N-methyl-D-aspartate (NMDA) inhibits carbachol-stimulated phosphoinositide breakdown in rat brain cortical slices but not in isolated membranes (1). To gain insight into the mechanisms, we examined the effects of NMDA on carbachol-stimulated [3H]inositol phosphate and intermediates of phosphatidylinositol cycle accumulation in rat cortical slices. The inhibition is primarily on the synthesis of inositol phospholipids subsequent to activation of muscarinic cholinergic receptors. In the absence of lithium, NMDA inhibited carbachol-stimulated [32P]PtdIns but not [32P]PtdOH synthesis. Carbachol-stimulated CDP-DAG formation required trace amount of Ca2+ and the response was inhibited by NMDA at low but not high extracellular Ca2+ concentrations. The inhibition due to NMDA was only seen at millimolar extracellular Mg2+. The inhibition of carbachol-stimulated CDP-DAG formation was not affected by adding tetrodotoxin or cobalt chloride suggesting the inhibitory effect was not due to releasing of neurotransmitters. The inhibitory effects of NMDA could be abolished by MK-801, the specific NMDA receptor associated channel antagonist. When cortical slices were preincubated with ligands and lithium to allow the build up of CDP-DAG, carbachol stimulated the incorporation of [3H]PtdIns. However, this response was not inhibited by NMDA. These results suggest that CDP-DAG synthesis is the primary site of regulation by NMDA. Because CDP-DAG cytidyltransferase requires Mg2+ as cofactor and is sensitive to Ca2+ it is possible that NMDA inhibits ligand-stimulated PtdIns breakdown by blocking the replenish of agonist-sensitive PtdIns pool through changes of divalent cation homeostasis.