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Amphetamine Activates Protein Kinase C and Calcium/Calmodulin-Dependent Protein Kinase via NMDA Receptor in Primary Cultures of Rat Cortical Neurons

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ABSTRACT

Amphetamine administration may result in long-term changes in behavior. Persistent kinase activation may be a biological mechanism underlying long-term potentiation of synaptic transmission and memory. In the present study, we used primary cultures of rat cortical neurons to investigate whether kinases can be activated by additions of amphetamine and N-methyl-D-aspartate (NMDA). We found that activation of the NMDA receptor resulted in protein kinase C (PKC) translocation in primary culture of cortical neurons. Amphetamine exposure also resulted in PKC translocation and this response was blocked by the NMDA receptor antagonist, D-APV. Both NMDA and amphetamine induced Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) translocation by a significant decrease in the amount of the enzyme in the cytosolic fraction and an increase in the membrane fraction in primary culture of cortical neurons. Similarly, blockade of the NMDA receptor by D-APV diminished the amphetamine effect on CaMK II. Thus CaMK II translocation was induced by both NMDA and amphetamine through the NMDA receptor. The administered amphetamine induced immediate early gene expression through an activation of postsynaptic NMDA receptors and an increase of intracellular calcium. Our results suggest that amphetamine induces long-term behavioral changes by interacting with the NMDA receptor that subsequently activates PKC and/or CaMK II and immediate early gene expression.

INTRODUCTION

Amphetamine administration may result in long-term changes in behavior including sensitization, tolerance, and dependence.[1-3] These long-term changes in behavior are dependent on postsynaptic N-methyl-D-aspartate (NMDA) receptors and Ca^{2+}-mediating immediate early gene expression.[4] Morphine induces the immediate early genes, c-fos and junB, in the neurons of the medial and ventral striatum and nucleus accumbens via D1 and NMDA receptors,[5] a pattern similar to that observed with amphetamine treatment.[6]

NMDA receptor plays a pivotal role in the induction of LTP of synaptic transmission. The induction of LTP requires postsynaptic Ca^{2+} influx and/or PKC activation. Stimulation of NMDA-type glutamate re-

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