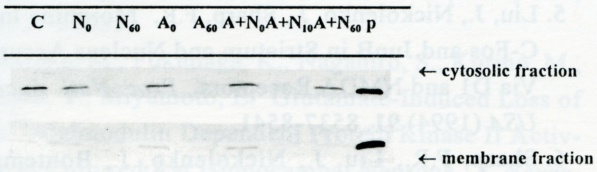
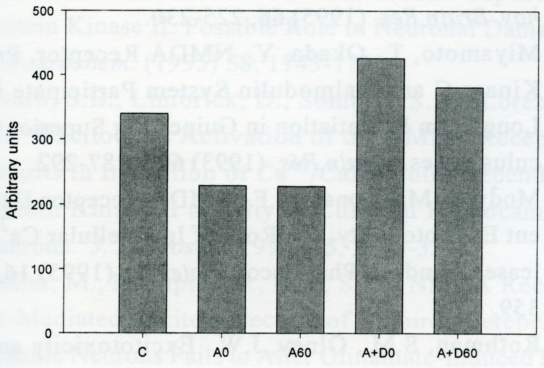
a.



b.

Cytosol



Membrane

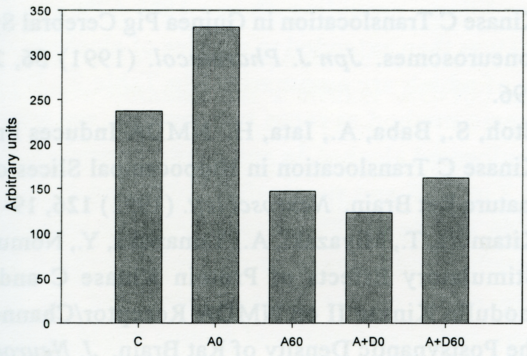


Fig. 4. Acute amphetamine-stimulated Ca^{2+}/CaM kinase II translocation inhibition by D-APV. To further investigate whether amphetamine-induced CaMK II translocation is also mediated through the NMDA receptor, we tested whether acute amphetamine-induced CaMK II translocation in rat cortical neurons can be affected by D-APV treatment. In the membrane and cytosolic fractions of cultured cortical neuronal cells, CaMK II contents were examined by Western blot analysis using anti-CaMK II β-subunit monoclonal antibody (panel a), and then bands were analyzed with a densitometer (panel b). C: control; A: amphetamine; A+D: amphetamine and D-APV co-treatment. Arabic numerals indicate the extra incubation periods at 37 °C after a 15-min treatment with the indicated ligands.

occur remain unclear, it is believed that repetitive addictive drug administration may result in a synaptic plasticity similar to long-term potentiation (LTP). Long-term potentiation is induced by activation of NMDA-type glutamate receptors, postsynaptic Ca^{2+} influx, and activation of PKC and CaMK II. In this report, we demonstrate that both NMDA and amphetamine induce PKC and CaMK II translocations. Most importantly, these effects are blocked by the NMDA receptor-specific antagonist, D-APV, suggesting that amphetamine mediates these effects through NMDA receptors.

It is well established that amphetamine-induced behavioral changes are dependent upon the dopamine receptor.[21] Amphetamine as well as dopamine activates postsynaptic NMDA receptors in striatum neurons.[4] Consistently, amphetamine-induced transient expression of immediate early genes can be blocked by the D1 dopamine receptor antagonist, SCH23390 and by the NMDA receptor antagonist, MK801 in rat striatum neurons, suggesting that both the D1 dopamine and NMDA receptors are required in mediating the expression of immediate early genes prior to behavioral sensitization.[4] Furthermore, amphetamine administration enhances stimulus-induced dopamine release in the rat striatum.[22] Yet, because dopaminergic neurons are absent from primary cultures of cortical neurons, the circuit-based interactions between dopamine and NMDA receptors in rat cortical neurons may not be important in the present studies. However, additional studies are needed to rule out the circuit-based interactions between dopamine and NMDA receptors in rat cortical neurons.

Injection of amphetamine may result in phosphorylation of the neuro-specific calmodulin-binding protein, neuromodulin, that can be mimicked by 12-O-tetradecanoylphorbol 13-acetate (TPA),[24] suggesting that PKC activation contributes to neurochemical events leading to induction of immediate early genes and behavior sensitization. This notion is supported by the fact that both NMDA and amphetamine stimulated PKC translocation and subsequently down-regulated PKC. The effects of amphetamine on PKC and CaMK II kinase activities deserve further discussion. Exposure of cultured cortical neurons to amphetamine for 60 min induced a marked decrease in the total CaMK II activity. These results are consistent with