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Amphetamine actions rely on the availability of phosphatidylinositol-4,5-bisphosphate

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Background

Neuronal functions, such as excitability or endo- and exocytosis, require phosphatidylinositol-4,5-bisphosphate (PIP_2) since ion channels and other proteins involved in these processes are regulated by PIP_2. Monoamine transporters control neurotransmission by removing monoamines from the extracellular space. They also display channel properties, but their regulation by PIP_2 has not been reported. The psychostimulant amphetamine acts on monoamine transporters to stimulate transportermediated currents and efflux and thereby increases the levels of extracellular monoamines.

Methods and results

Direct or receptor-mediated activation of phospholipase C (PLC) reduced membrane PIP_2 and amphetamine-evoked currents through recombinant serotonin transporters; extracellular application of a PIP_2-scavenging peptide mimicked this effect. PLC activation also diminished amphetamine-induced reverse transport without altering transmitter uptake. Inhibition of reverse transport by PLC activation was also observed in brain slices and with recombinant dopamine and noradrenaline, but not GABA transporters; rises in intracellular Ca^{2+} or activation of protein kinase C were not involved in these effects.

Conclusions

These data demonstrate for the first time PIP_2 dependence of reverse transport and current in monoamine transporters.

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