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Neuronal dopamine internalization and intracellular stimulation of D_5-receptor-dependent CDP-diacylglycerol biosynthesis for phosphoinositide signaling

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Dopamine receptor stimulation facilitates phosphatidylinositol resynthesis, thus amplifying subsequent responses to activation of phospholipase C-coupled receptors. Phosphatidylinositol synthesis critically depends on the nucleolipid CDP-diacylglycerol. Dopamine robustly increases microsomal CDP-diacylglycerol biosynthesis through stimulation of D_1-like receptors, particularly the D_5 subtype the majority of which are intracellularly localized. Here, we explored the mechanism by which extracellular dopamine acts to modulate intracellular CDP-diacylglycerol biosynthesis. Dopamine concentration-dependently stimulated CDP-diacylglycerol synthesis in organotypic and primary neuronal cultures devoid of the presynaptic dopamine transporter. Dopamine was saturably transported into cortical primary neurons or B35 neuroblastoma cells expressing wild-type plasmalemmal monoamine transporter (PMAT), which is known to be the principal component of classical $Uptake_2$ transporters in the forebrain. Dopamine uptake and CDP-diacylglycerol biosynthesis in brain slices or cultured cells were inhibited by microtubule disrupters which block cytoskeletal transport, and by decynium-22 which blocks $Uptake_2$-like transporters. Dopamine effects were selectively mimicked by D_1-like agonists SKF38393 and SKF83959, competitively inhibited by D_1-like antagonist SCH23390, and unaffected by D_2-like agonist or antagonist. These observations indicate that dopamine is actively internalized by $Uptake_2$ into postsynaptic-type cells where the monoamine can stimulate its intracellular D_5-type receptors to increase CDP-diacylglycerol production. This finding counters the conventional notion that postsynaptic-type cells internalize supra-threshold levels of synaptic dopamine only to inactivate the transmitter. Given the critical involvement of CDP-diacylglycerol in phospholipase C and phosphatidylinositol-3-kinase signaling systems, our findings imply that intracellular dopamine could play an important role in cellular responses and adaptation to high levels of extracellular dopamine.

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