Title:	Functional Selectivity in Serotonin Receptor 2A (5-HT2A) Endocytosis, Recycling, and Phosphorylation
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Abstract:	G protein-coupled receptor (GPCR) signaling is modulated by endocytosis and endosomal sorting of receptors between degradation and recycling. Differential regulation of these processes by endogenous ligands and synthetic drugs is a poorly understood area of GPCR signaling. Here, we describe remarkable diversity in the regulation of trafficking of GPCR induced by multiple ligands. We show that the serotonin receptor 2A (5-HT2A), a prototypical GPCR in the study of functional selectivity at a signaling receptor, is functionally selective in endocytosis and recycling in response to five ligands tested: endogenous agonists serotonin (5-HT) and dopamine (DA), synthetic agonist 1-(2,5-dimethoxy-4-iodophenyl)-aminopropane (DOI), antagonist ketanserin, and inverse agonist and antipsychotic drug clozapine. Only four ligands (5-HT, DA, DOI, and clozapine) bring about receptor endocytosis. As we have earlier described with 5-HT and DA, there is ligand-specific requirement for protein kinase C (PKC) in endocytosis. We now show 5-HT2A phosphorylation by PKC is necessary for 5-HT-mediated and DOI-mediated receptor endocytosis, but DA-mediated and clozapine-mediated internalization is not affected if PKC is inhibited. Internalized receptors are recycled to the cell surface, but there is variability in the time course of recycling. 5-HT- and DA-internalized receptors are recycled in 2.5 hours while agonist DOI and antagonist clozapine bring about recycling in 7.5 hours. Recycling in response to those ligands that require PKC activation to effect receptor endocytosis is dependent on receptor dephosphorylation by protein phosphatase 2A (PP2A). Thus, internalization and phosphorylation/dephosphorylation cycles may play a significant role in the regulation of 5-HT2A by functionally and therapeutically important ligands.
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