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MEMBRANE LIPID RAFTS ARE REQUIRED FOR D2 DOPAMINE RECEPTOR SIGNALING

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Introduction: Lipid rafts are specialized membrane microdomains enriched in cholesterol and sphingolipids and are important in the organization of receptor-protein complexes and the regulation of signaling.

Objective/aims: Given the emerging significance of lipids with respect to receptor structure and activation, we investigated the role of lipid rafts and membrane cholesterol on D2 dopamine receptor (DAR) signaling. As the D2 DAR is the molecular target for all antipsychotic drugs, more information about its signaling may help refine therapeutics for schizophrenia.

Methods: D2 DAR constructs were expressed in HEK293T cells. Sucrose density fractionation resolved lipid rafts from other membrane components. Methyl-β-cyclodextrin (MCD) was used to deplete membrane cholesterol and to disrupt lipid rafts.

Results: Detergent solubilization followed by sucrose gradient centrifugation resolved lipid rafts from heavier membrane fractions. The D2 DAR was equally distributed amongst both the lipid raft and heavier membrane fractions. Pretreatment with MCD, however, eliminated both lipid raft markers and the D2 DAR from lipid raft fractions, although the receptor was still found in heavier membrane fractions. We also found that MCD treatment abolished D2 DAR-mediated inhibition of cAMP accumulation. In contrast D1 DAR-stimulated cAMP accumulation was unaffected by MCD treatment.

Conclusions: Our current results show that the D2 DAR is distributed in multiple membrane microdomains, including cholesterol-rich lipid rafts. We found that extraction of cholesterol disrupted lipid rafts and also an eliminated D2 DAR-mediated signaling . Thus, we hypothesize that lipid rafts are critical for D2 DAR signaling to occur.

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