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Impact of membrane lipid polyunsaturation on dopamine D2 receptor ligand binding and signaling

G-protein coupled receptors (GPCRs) are an important class of membrane proteins, with almost 1000 different proteins in the human genome, that are target of about 50% of the drugs in the market. Being composed of 7 transmembrane helices these receptors establish important lipid contacts and their structure and function is expected to be impacted by the properties of the surrounding lipids. Moreover, certain GPCRs are major pharmacological targets regarding pathologies where a lipid imbalance has been identified. Establishing a link between the lipid pathological imbalance and the receptor functioning in such environment is thus essential. The dopamine D2 receptor (D2R) – which belongs to the GPCR family – has been implicated in the etiology of several psychiatric disorders such as schizophrenia, depression or bipolar disorders, and is a main target of most antipsychotics. Interestingly, a "whole-body" decrease in long-chain polyunsaturated fatty acids (PUFA) levels – n-3 PUFAs such as docosahexaenoic acid (DHA) in particular - has been consistently described in these psychiatric disorders. However, the mechanisms by which alteration in PUFA levels may contribute to pathogeneses and could alter the functionality and pharmacology of the D2R are unknown. In recent years and together with collaborators we have aimed at unraveling the impact of membrane PUFAs on D2R pharmacological properties and conformational states through biochemical and biophysical studies in both PUFA enriched cells and membrane model systems of controlled lipid composition. To this aim, we have investigated the impact of membrane PUFAs in the first stages of receptor activation, that is in the receptor/ligand interaction using plasmon waveguide resonance (PWR) in both cell membrane fragments and reconstituted model systems. Moreover, PUFAs impact on the recruitment and activity of D2R signaling effectors was investigated by energy transfer approaches and confocal and TIRF microscopy.
The data shows that membrane enrichment in n-3 PUFA potentiates ligand binding to the receptor, suggesting that DHA acts as an allosteric modulator of this receptor. Molecular dynamics simulations confirm that DHA has a high preference for the interaction with the D2R and show that membrane unsaturation selectively enhances the conformational dynamics of the receptor around its second intracellular loop. Membrane unsaturation spares G protein activity but potentiates the recruitment of β-arrestin in cells. Furthermore, in vivo n-3 PUFA deficiency blunts the behavioral effects of D2R ligands. These results highlight the importance of membrane unsaturation for D2R activity and provide a putative mechanism for the potentiating effect of PUFAs on antipsychotic efficacy.
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