



The impact of lipid polyunsaturation in the activation and signaling of the Dopamine D2 receptor

Keywords: G-protein coupled receptors, lipids, biochemistry, biophysics

Summary:

G-protein coupled receptors (GPCRs) are membrane proteins implicated in several physiological and pathological processes and are the target of about 50% of the drugs in the market. Because they are immersed in the lipid membrane, their function can be greatly impacted by the lipid membrane composition. In addition, several pathologies are associated with dysfunctions in lipid membrane composition as is the case of psychiatric disorders and cancer where altered levels in polyunsaturated fatty acids (PUFAs) and cholesterol, have been respectively associated. The role of lipids in GPCR activation and signaling is far from being understood.

The Dopamine receptor D2 (D2R) is an important target of antipsychotics (APs) used for the treatment of psychiatric disorders such as schizophrenia and depression. Patients suffering from schizophrenia have decreased levels of PUFAs not only in the brain where the D2R is expressed but also in peripheral tissues. Moreover, the use of supplementary PUFA diet in treatments has helped decreased some of the symptoms associated with such disorders. With that in mind, the working hypothesis of our group is that the lipid environment and more specifically the level of lipid polyunsaturation should alter the pharmacology of the D2R.

Preliminary data obtained by the group have revealed that PUFA membrane levels can impact both D2R activation and signaling events and act as allosteric modulators. We would like now to address the question about the molecular mechanisms that are responsible for such PUFA lipid impact. To address this question we are planning to use state of the art biophysical and biochemical approaches.

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Candidate profile: The candidate should be motivated and rigorous and have a master's or engineering degree. The student must be familiar with protein biochemistry or biophysics.