**O-11.6 Short talk**

**Membrane lipid poly-unsaturation selectively affects Dopamine D2 receptor signaling**

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The heterogenous and dynamic constitution of the membrane fine-tunes signal transduction by G-protein coupled receptors (GPCRs). In particular, the polyunsaturated fatty acid (PUFA) tails of phospholipids influence the biophysical properties of the membrane, production of second messengers and membrane partitioning. Few evidence mostly originating from rhodopsin suggest that PUFAs directly modulate the receptor conformational dynamic. Whether such properties translate to other GPCRs remains unclear. The brain is highly enriched in PUFAs and their deficiency has been associated with several neuropsychiatric disorders. We focused on the dopamine D2 receptor (D2R), that is consistently impacted in such disorders and represents the main antipsychotic target. Our results reveal that membrane enrichment in PUFAs potentiates ligand binding to D2R and strongly impairs agonist-induced endocytosis, without affecting the internalization of various other GPCRs. We show that recruitment of β-arrestin 2, that occurs prior to receptor internalization, is strongly impaired and endocytic vesicle formation is slowed down. PUFAs form a corona around the D2R, affecting the exposure of ICL2 as shown by modelling. These results suggest that PUFAs act as allosteric modulators of the D2R and provide a putative mechanism for their potentiating effect on antipsychotic efficacy.