

CAVEOLAE/LIPID RAFTS CONTROL SIGNALING OF CB1 CANNABINOID RECEPTOR IN HUMAN BREAST CANCER CELLS

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The endogenous cannabinoid system, consisting of the cannabinoid CB1 and CB2 receptors, their endogenous ligands (endocannabinoids) and the proteins that regulate endocannabinoid biosynthesis and degradation, is an almost ubiquitous signaling system involved in the control of cell fate. The type-1 cannabinoid receptor (CB1R) is expressed in all cell tissues. It has been previously described that SR141716, a selective CB1 receptor antagonist, besides its antagonist properties, possesses also inverse-agonist characteristics.

Nevertheless, some observations on both the caveolae/lipid rafts-mediated uptake of CB1R ligand anandamide and the intracellular trafficking and regulation of CB1 receptor-mediated signal transduction, suggest that there are connections between CB1R activity and cholesterol enriched lipid rafts. Lipid rafts are specialized membrane microdomains that are enriched in cholesterol and sphingolipids and for their capacity of segregating specific classes of lipids and proteins, rafts perform an important role in protein and lipid sorting and signalling.

We show that CB1R is associated with lipid rafts in MDA-MB-231 cells and that cholesterol depletion by methyl- β -cyclodextrin (MCD) treatment strongly reduces the flotation of the protein on the raft-fractions (DRM) of OptiPREP density gradients suggesting that CB1 raft-association is cholesterol dependent.

We have also shown that the anti-proliferative and anti-migratory effect exhibited by SR141716 treatment in MDA-MB-231 cells is strongly dependent on the integrity of lipid rafts. Indeed, MCD treatment in part prevent anti-proliferative and anti-migratory effect of CB1R antagonist indicating an involvement of rafts integrity in cannabinoid system functioning.

The present findings provide evidence that the molecular mechanism at the basis of SR141716 function might need lipid raft/caveolae integrity to occur. Furthermore, our data support the view that perturbation of lipid rafts/caveolae may represent a useful tool to control CB1R signaling and could provide new insights toward a better understanding of endocannabinoid signaling-regulated malignancy of human breast cancer.