The Interactions of Cannabinoids with Membranes as Studied by DSC and Solid State NMR

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In an earlier work we have argued that the location of lipophilic ligands in the membrane may play an important role in their ability to effectively interact with their site of action. In support of this postulate, we have provided experimental evidence showing that biologically active cannabinoids align themselves near the polar side of the membrane bilayer, while some inactive analogs segregate near the center of the bilayer leaflet. In the present work the biologically active (-)-Δ^8-tetrahydrocannabinol (Δ^8-THC) and its inactive O-methyl derivative are allowed to interact with model membranes composed of hydrated dipalmitoyl phosphatidylcholine bilayers containing cholesterol. The drug-membrane interactions are studied using differential scanning calorimetry and high resolution solid state NMR. Our experiments allow us to conclude that the two structurally related cannabinoids very differently affect the dynamic properties of the bilayer. Furthermore, our results provide evidence about the location and conformation of the two analogs in the bilayer and the role of cholesterol in these drug-membrane interactions.

Our DSC data indicate that the biologically active Δ^8-THC enhances membrane fluidity more effectively than its O-methyl congener. These data are confirmed by the presence or absence of line widths, and chemical shifts of the observed ^{13}C-NMR frequencies due to the two cannabinoids in the ^{13}C/MAS NMR. The data also suggest that Δ^8- THC resides near the polar face of the bilayer, while O-methyl Δ^8-THC is located deeper in the bilayer. The results support our model according to which lipophilic ligands reach their receptor active sites through rapid lateral diffusion within the membrane bilayer. This drug-receptor interaction is enhanced if the ligand is in the proper location and orientation within the bilayer. The role of cholesterol in these drug membrane interactions will be discussed.