STUDY OF DRUG MEMBRANE INTERACTIONS USING SOLID STATE NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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Solid state NMR is the method of choice for the detailed molecular information on the conformational and dynamic properties of membranes. The solid state NMR experiment can be carried out by observing the wide-line spectrum obtained from one or a small number of nuclei in the system under investigation. In such experiments, the sample is stationary and the nucleus under observation is either introduced by isotropic labeling (e.g., ^{2}H, ^{13}C), or is already present in natural abundance in the system (e.g. ^{31}P, ^{14}N). The spectrum from a solid or semisolid sample can be obtained in a high resolution mode using the magic angle sample spinning (MASS) experiment. Such spectra resemble those obtained from solution and can be analyzed using analogous principles.

To study the structural requirements for drug activity we compared the effects of structurally closely related analogs which had a wide range of pharmacological potencies. We studied two pairs of molecules in depth. In the cannabinoid series we have chosen the psychotropically active (-)-Δ^{8}-tetrahydrocannabinol (Δ^{8}-THC) with its inactive O-methyl-ether Me-Δ^{8}-THC analog. This example serves to examine the role of the phenolic hydroxyl group in cannabinoid activity. In the class of anesthetic steroids we have compared alphaxalone, a potent anesthetic, with its D ring to adopt a puckered conformation. The inactive analog Δ^{16}-alphaxalone has a flat conformation with all four rings coplanar because of a double bond in the 16-position. It has been argued that this difference in geometry is responsible for the respective differences in their abilities to perturb membranes and in their pharmacological properties.

The emerging picture for drug molecules which produce their effects by interacting with the cell membrane using solid state NMR spectroscopy is: (1) They must incorporate into membrane bilayer and initiate their perturbation at the membrane interface. These amphipathic interactions are accompanied by reduced chain cooperativity. (2) They must have proper location and orientation in the membrane bilayer in order to reach the active site of the receptor through lateral diffusion.