

**P010** Comparative models of GABA<sub>A</sub> receptor transmembrane domains  
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GABA<sub>A</sub> receptors are a large group of closely related inhibitory ligand-gated ion channels that are important drug targets. Many different classes of drugs act on GABA<sub>A</sub> receptors, but the structural basis of action is unknown for the majority of compounds. Rational drug design will greatly benefit from an understanding of structural determinants of drug binding and action. Based on the recently published structures of the nicotinic acetylcholine receptor transmembrane domain and the acetylcholine binding protein, we present comparative (homology) models of GABA<sub>A</sub> receptor transmembrane domains, as well as of combined extracellular and transmembrane domains, for different receptor subtypes. The models provide evidence for a conserved binding pocket, that is present in each subunit and is located at the border between the extracellular compartment and the lipid bilayer. The pocket exhibits strong variability in volume, hydrophobicity and electrostatic properties among the different classes of receptor subunits. A large body of published mutagenesis and cysteine mapping data can be interpreted in the context of these structural models, providing a basis for mechanistic hypotheses concerning the binding and action of several important classes of ligands.