

Smoke 'em if you got 'em: Nicotine receptors in Health and Disease

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Nicotinic acetylcholine receptors are prototypes of the Cys-loop superfamily of ligand-gated ion channels. These receptors mediate much of the fast synaptic neurotransmission within the central and peripheral nervous systems and are targets of intense study for drug development for treating diseases ranging from smoking cessation to Alzheimer's and Tourette's Syndrome, Myasthenia Gravis, and Schizophrenia. Nicotinic receptors are activated by the tobacco alkaloid nicotine, which distinguishes them from their muscarinic counterparts which are G-protein coupled receptors activated by the mushroom alkaloid muscarine.

Our laboratory is interested in the molecular mechanisms by which nicotine and other drugs exert their effects on these receptors. We are particularly interested in the structural features that determine the selectivity of nicotinic ligands for the 15 known subtypes of nicotinic receptors as well as what distinguishes agonists from partial agonists from antagonists at these receptors. Both of these goals are important for drug design and for separating desirable (e.g. analgesia) from undesirable (e.g. addiction) effects. Our work is multifaceted, ranging from the discovery of natural products that serve as ligands for nicotinic receptors, to the development of fluorescent ligands for labeling receptors in-vitro, to designing scaffolds to facilitate crystallization of nicotinic receptors for x-ray structural analysis. This talk will touch on each of these topics and describe our progress to date.

