Chemistry on the Brain: Understanding the Nicotine Receptor

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The human brain is the most complex object known to man. It presents daunting challenges at all levels, from the anatomical, to the cellular, to the molecular. Our work seeks to provide a chemical-scale understanding of the molecules of memory, thought, and sensory perception; of Alzheimer's, Parkinson's, and schizophrenia. An area of particular interest has been the chemistry of nicotine addiction. The initial chemical event of nicotine addiction involves nicotine binding to and activating acetylcholine (ACh) receptors in the brain. Using the mindset and methodologies of physical organic chemistry, we have probed these complex membrane proteins with a precision and subtlety normally associated with small molecule studies. We have established that the cation-π interaction plays a pivotal role in promoting the high potency of nicotine in the brain, leading to its addictive properties. We have also discovered key hydrogen bonding interactions that uniquely contribute to the binding of nicotine to ACh receptors. These chemical studies provide a high-precision structural model for the interaction of potent drugs at brain receptors.