Nicotinic Receptors: New Targets for Therapeutic Agents

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Neuronal nAChRs are a complex superfamily of pentameric ligand gated ion channels that are activated by acetylcholine (ACh). Nicotine’s association with tobacco consumption has tended to obscure the potential beneficial actions of the alkaloid. In the past decade however, there has been an enhanced understanding of the function of various nAChR subunit combinations with the identification of novel pharmacophores that show selectivity for different subunit combinations and have a reduced incidence of cardiovascular and GI side effects and addiction liability as compared to nicotine.

Epidemiological studies have shown an inverse relationship between smoking and the neurodegenerative disorders Alzheimer's (AD) and Parkinson's Disease. Nicotine has also shown efficacy in two acute trials in AD patients. This has prompted medicinal chemistry and receptor based pharmacology efforts with the identification of compounds like GTS 21, ABT-418, SIB 1508Y and RJR 2403.

The analgesic activity of nicotine was demonstrated in the 1930s. However, the discovery of the potent analgesic frog alkaloid, epibatidine which is 200-times more potent than morphine prompted considerable interest in nAChRs as targets for novel analgesics leading to clinical candidates like ABT-594. Other viable targets for selective neuronal nAChR ligands include anxiety, depression, schizophrenia and disorders of the spinal cord and lower urinary tract.

The challenge for the future is to expand on the understanding of the function of the discrete nAChR pentamers that mediate the molecular events related to these disorders and to continue to develop novel, subtype selective ligands, agonists, partial agonists and antagonists for these. In many respects, therapeutic opportunities for nicotinic based therapeutics at the end of the 1999s are comparable with those for the 5HT receptor (currently around 17 in number) family in the early 1970s.