[S1-5] [4/17/2003(Thur) 16:25-17:00/Grand Hall]

Synthesis of Novel Nicotinic Ligands as Potential Therapeutic Agents for Alzheimer's Disease

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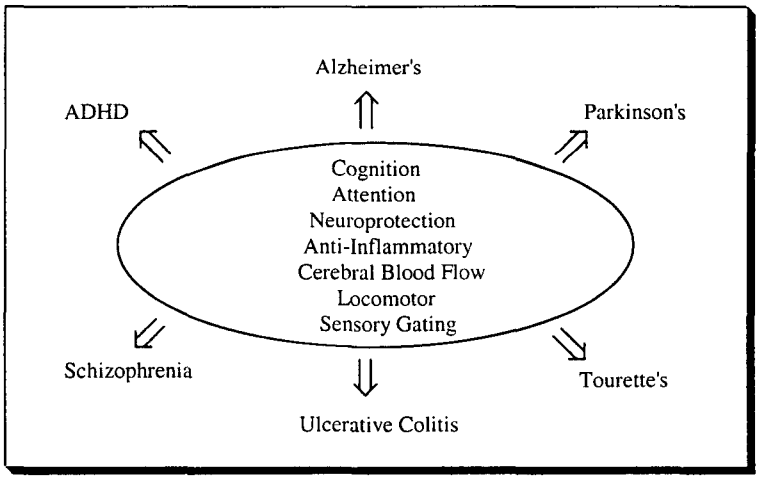
Much of the recent increase in research on nicotinic ligands has been motivated by a growing body of evidence that nicotinic cholinergic pharmacology plays a role in disorder associated with deficits of cognitive function in humans. The importance of developing novel nicotinic ligands as potential therapeutics is emphasized by studies with nicotine itself that have demonstrated many useful CNS and cognitive effects in various disorders such as dementia. However, its side effects at peripheral sites such as neuromuscular and cardiovascular limits its usefulness as a therapeutic tool.



Recent advance in molecular biology enables us to understand that nicotinic receptor exists in multiple receptor subtypes and among them α 4β 2 subtype mediates the cognitive

effects. In this regard, we have been interested in synthesis of novel nicotinic ligands that have CNS selectivity, especially to α 4β 2 subtype, and may offer the potential beneficial effects of nicotine without the accompanying undesirable peripheral side effects, particularly those at neuromuscular and cardiovascular sites.

This presentation will report the synthesis and biological evaluation of several pyridine analogues which have nitrogen containing bicyclic, tricyclic and spiro ring systems as substituents for the *N*-methyl pyrrolidine ring of nicotine to elucidate the steric effects. Also we introduce synthetic pathways of novel *trans*-metanicotine analogues since *trans*-metanicotine has a great selectivity to the subtype what we are targeted, however, it was reported to have a moderate binding affinity and be metabolized *in vivo* experiment. The analogues, which have a substituent at the α -position of the methylamino group in the side chain of *trans*-metanicotine, are designed since *trans*-metanicotine expect to be biotransformed by MAO to several metabolites *in vivo* test. We expect that the substituents would play a role to prevent the molecules from metabolic reactions by inducing steric hindrance as well as modulate biological profiles by changing electronic environment.