

Nicotinic cholinergic antagonists: a novel approach for the treatment of autism.

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Evidence supports the hypothesis that normalization of cholinergic tone by selective antagonism of neuronal nicotinic acetylcholine receptors (NNRs) may ameliorate the core symptoms of autism. As often is the case, epidemiology has provided the first important clues. It is well recognized that psychiatric patients are significantly more often smokers than the general population. The only known exceptions are obsessive-compulsive disorder (OCD), catatonic schizophrenia and interestingly, autism. In this regard, clinical studies with nicotine have demonstrated amelioration of symptoms of a number of diseases and disorders, including Alzheimer's disease, Parkinson's disease, ADHD and Tourette's syndrome. Nicotine's agonist properties at CNS NNRs have been implicated in these effects and support the concept of self-medication as a strong motivation for smoking in cognitively compromised individuals. On the other hand, the inverse correlation between autism and smoking suggests that smoking does not provide symptomatic relief and may actually be indicative of an active avoidance of nicotine's agonist effects in this disorder.

Neuroanatomical evidence is consistent with this idea based on the presence of hypercholinergic architecture in the autistic brain, particularly during the first few years of development, making the avoidance of further stimulation of an already hyperactive cholinergic system plausible. This may also explain why stimulants (known to increase dopamine levels as do NNR agonists) appear to aggravate autistic symptoms and why studies with cholinesterase inhibitors that increase acetylcholine levels in the brain have yielded variable effects in autism. Taken together, the evidence suggests the possibility that nicotinic cholinergic antagonism may in fact be palliative. Pharmacological evidence supports this hypothesis. For example, antidepressants, many of which are now known to be non-competitive NNR antagonists, have been used successfully to treat a number of autistic symptoms. More specifically, there is anecdotal evidence from at least one medical practitioner that mecamylamine, a non-selective NNR antagonist, is effective in treating many autistic symptoms, particularly those that are refractory to most other treatments. Clearly there is a need for carefully controlled clinical studies with novel selective NNR antagonists to explore their potential as a new and exciting approach for the treatment of autism.