Medical Hypotheses (2006) **66,** 985–990

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medical hypotheses

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Nicotinic cholinergic antagonists: A novel approach for the treatment of autism

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Received 2 November 2005; accepted 8 November 2005

Summary 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.
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doi:10.1016/j.mehy.2005.11.015

Overview

An emerging role for cholinergic systems in autism

Autism is part of a spectrum of disorders characterized by a triad of core symptoms, including: deficits in all aspects of social reciprocity; pragmatic communication deficits and language delays; and an assortment of behavioral problems such as restricted interests, sensory sensitivities and repetitive behaviors [1]. In addition, a high percentage of autistic individuals exhibit so-called associated features such as hyperactivity, obsessive-compulsive phenomena, morbid preoccupations, anxiety/depression and self-injury [2]. The basis of autism appears to be multi-factorial, involving complex developmental changes in the brain that occur during the first few years of life. At the anatomical level, abnormalities in the limbic system (hippocampus; amygdala), cerebellum, cortex, basal ganglia and brainstem have been described (reviewed in [3]). At the neurochemical level, abnormalities in a number of key neurotransmitters and/or receptors have been implicated, most notably GABA, serotonin, the neuropeptides oxytocin and vasopressin, the amino acid neurotransmitters, and most recently nicotinic acetylcholine receptors (reviewed in [4]). The implication of acetylcholine is particularly noteworthy since nicotinic cholinergic systems in the brain are known to play a central role in modulating most major neurotransmitter systems [5,6]. They appear to do so through global control of the signal-to-noise ratio in brain pathways and thus can be thought of as the 'volume knobs' of the nervous system. Since aberrant control over signal-to-noise in the brain has been suggested as a unifying theme in autism [7], the newly discovered cholinergic abnormalities offer a potentially fruitful area for exploring novel therapies to treat autism.

Autism, ADHD and the attentional spectrum

Autism appears to be part of a spectrum of variations in attentional tone that range from autistic symptomatology on one end to attentional deficits on the other (Fig. 1). Autism is generally seen as a disorder of *over-focusing* with an increase in the stimulus barrier [8]. Similarly, Aspergers syndrome represents a more mild form of impairment, also characterized by over-focused attention (i.e., scattered focus). Interestingly, this milder impairment is not always detrimental and can actually lead to superior cognitive function, albeit in narrow domains (e.g., savants). By comparison, people diagnosed as having ADHD are described as easily distracted and having *under-focused* attention [9]. They are easily sidetracked and find it hard to focus. Concentration is hard to maintain. However, the usual problem is not a deficit of attending, but an inability to focus attention on task. The individual is attending to too many things at once.

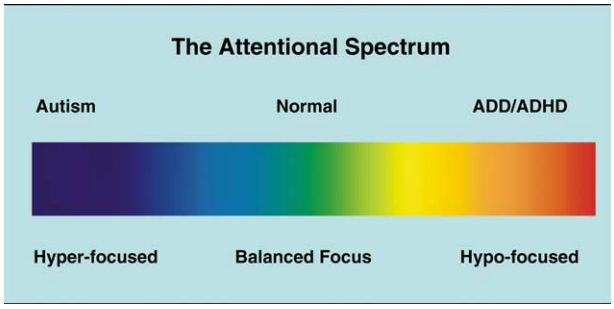

Figure 1 Autism viewed as part of a spectrum of variations in attentional tone that range from autistic (hyper-focused tone) symptomatology on one end to attentional deficits (hypo-focused tone) on the other.

Nicotinic acetylcholine receptors as therapeutic targets

It is important to understand that ADHD and autism lie on two ends of an attentional spectrum because, as will be seen in the following sections, we have learned much from the history of tobacco use as well as from an extensive literature on nicotine pharmacology that may explain why nicotinic cholinergic agonists ameliorate the symptoms of ADHD while nicotinic antagonists may have the potential to ameliorate the symptoms of autism. A nicotinic cholinergic basis for the treatment of multiple diseases and disorders has emerged, based on over two decades of research on the structure and function of neuronal nicotinic acetylcholine receptors (NNRs) as well as on numerous clinical studies with nicotine [10,11]. Examples of therapeutic indications for which NNR-based therapies may have application include Alzheimer's disease, Parkinson's disease, attention deficit disorder, schizophrenia, pain and depression/anxiety. Depending on the specific pharmacological deficits involved, either nicotinic agonists or antagonists may have greater utility. In this regard both the epidemiology of tobacco use and direct clinical studies with nicotine (patch, gum, nasal) have guided the direction of development of novel nicotinic therapies. For example, it is now clear that NNR agonists have greater potential for efficacy

in cognitive dysfunction [12] and attention deficit disorder [13]. On the other hand, evidence suggests greater potential for nicotinic antagonists for the treatment of major depression [14]. The following discussion, based on several different lines of evidence, suggests that the latter may be the preferred approach in autism.

Hypothesis

Normalization of cholinergic tone by selective antagonism of neuronal nicotinic acetylcholine receptors (NNRs) may ameliorate the core symptoms of autism.

Epidemiology — a look at both ends of the spectrum

ADHD. A number of prospective studies have documented a relationship between ADHD or ADD symptomatology and tobacco use. Many of these studies have been with clinical samples of boys, although the relationship has been found for boys and girls in community samples as well. ADHD is associated with more frequent tobacco use and an earlier age of initiation. Adolescents scoring in the clinical range on a self-report of ADHD inattention symptoms were three times as likely to initiate smoking and to be current smokers than their non-affected peers [15]. These findings indicate that smoking may serve another function — to normalize cognitive processes for adolescents with ADHD. It also suggests why young adolescents with ADHD start smoking at earlier ages than unaffected youth. This relationship led to studies at Duke University with the nicotine patch [13] that demonstrated attentional effects in ADD patients comparable to those of Ritalin, providing evidence that NNR pharmacology plays a key role in attentional processes and that an NNR agonist effect may ameliorate attentional deficits.

Autism. Psychiatric patients are significantly more often smokers than the general population, the only known exceptions being obsessive-compulsive disorder (OCD), catatonic schizophrenia and interestingly, autism [16]. Recent studies investigated nicotine use in subjects with autism spectrum disorders (ASD). Only 12.6% were smokers, compared with 19—26% (depending on socioeconomic status) in the general population and 47% in a control group of 161 outpatients diagnosed with schizophrenia or a schizophreniform disorder [17]. These results suggest that smoking is comparatively rare among subjects with ASD, while the opposite is true for schizophrenia. In this regard, there is now emerging interest in development of NNR agonists to treat schizophrenia. More importantly, these results strongly suggest that autistic individuals do not seek to self-medicate with smoking/nicotine, as do those with ADD and schizophrenia. In fact, they may actually be avoiding nicotine because its agonist effects actually exacerbate symptoms (see also 'stimulants' section). Thus, the epidemiological evidence supports the hypothesis that NNR antagonism may be beneficial in autism.

Neuroanatomical evidence

Cholinergic systems in autism

It is well established that cholinergic systems in the brain are intimately involved in regulating and normalizing cognitive processes. The cholinergic hypothesis, which has formed the basis for nearly every marketed therapy developed for Alzheimer's disease, is now being extended to other diseases and disorders of attention and cognitive function ranging from attention deficit disorder to schizophrenia. During the past few years, studies have begun to suggest that cholinergic systems in the brain might also be implicated in autism. The results of several autopsy studies have shown that NNRs are abnormally depleted in certain areas of the cortex, cerebellum and thalamus, which are involved in attentional and sensory processes [18—20]. This raises the possibility that NNRs may represent a novel class of therapeutic targets in autism. Drawing on the cholinergic hypothesis of Alzheimer's, recent clinical studies have explored the use of cholinesterase inhibitors in autism [21—23]. The results indicated modest, and in some cases short-lived, amelioration of some symptoms (see also 'Cholinesterase inhibitor' section). The lack of dramatic effects could be viewed as disappointing. However, the answer may lie in the architecture of cholinergic systems in the autistic brain. For example, cholinergic neurons in the basal forebrain, an area of the brain known to be involved in attention, have been found to be abnormally plentiful, and abnormally large, in children with autism [24]. This raises the possibility that there is actually hypercholinergic tone present, resulting in chronic over-stimulation of cortical and other structures by forebrain projections.This may explain the apparent depletion of NNRs in thalamic and cortical regions, due to compensatory receptor downregulation in response to hypercholinergic stimulation. It also suggests that selective

blockade of NNRs in the basal forebrain with an NNR antagonist may potentially normalize cholinergic tone in the cortex and eventually lead to a re-balancing of receptor levels post-synaptically.

Pain pathways — another clue

Insensitivity to pain is a fairly common symptom in autism. This is a very interesting observation in light of what we know about the role of NNR pathways in pain perception. Pathways originating in the raphe nuclei and locus ceruleus of the brain include descending inhibitory norepinephrine and serotonergic pathways that project to the dorsal horn of the spinal cord. These inhibitory pathways are modulated by cholinergic neurons both in the brain nuclei and in the dorsal horn [25]. Thus activation of the NNRs in these pathways by agonists has been shown to decrease pain perception [26]. If the hypercholinergic tone in the autistic brain were present throughout the CNS then it would predict that inhibitory pain pathways would be chronically over-stimulated, leading to, and consistent with hyposensitivity to pain. Again, all of this is consistent with the hypothesis that selective NNR antagonists may ameliorate the core symptoms of autism.

Pharmacological evidence

Anti-depressants and NNR antagonism

Interestingly, many (but not all) of the symptoms of autism have been treated with anti-depressants for years [27]. This is a key observation because we now know that many marketed anti-depressants actually have NNR antagonist properties and may act in part by normalizing hypercholinergic tone present in depressed states [14]. Thus it is not surprising that bupropion has activity both as an anti-depressant and as a smoking cessation aid, or that the well-known NNR antagonist mecamylamine has been shown to have anti-depressant effects as an adjunct therapy in non-responders to certain anti-depressants alone [28]. These observations suggest that the effects of anti-depressants in autism may actually be related to partial normalization of hypercholinergic tone and further support the hypothesis that selective NNR antagonists may achieve similar, possibly even better results.

Stimulants and autism

Stimulants are the drugs most frequently prescribed to children with Pervasive Developmental Disorders, despite the fact that no studies of stimulant use have been done in this population. The Autism Research Institute's database indicates that many autistic-spectrum patients have bad reactions to stimulants, including increased hyperactivity, aggression, and stereotypic behaviors or tics. Out of 2788 families who replied to a survey question about Ritalin, 45% reported that it made their autistic children's behavior much worse [29]. Because stimulants are basically dopamine agonists, it is not surprising that one therapeutic approach in the treatment of patients with infantile autism involves the use of dopamine antagonists. The dopaminergic system of the brain affects motor behaviors. Its abnormalities involve excess motor activity and stereotypes similar to those observed in autistic patients. Intellectually subnormal autistic children, particularly those with severe hyperactivity and stereotypes, were found to have excess dopaminergic activity as measured by high levels of homovanillic acid in the CSF [30]. Thus it seems sensible that the administration of dopamine antagonists such as haloperidol to autistic patients should result in decreased motor symptoms such as hyperactivity, fidgetiness, and stereotypes thereby facilitating behavior and learning. Chronic haloperidol treatment is in fact able to reduce the stereotypes.

These observations offer another important clue in support of the NNR antagonist hypothesis, especially if viewed in light of the nicotine literature. As mentioned earlier, nicotine has been shown to be as effective as Ritalin in benefiting adults with ADD [13]. This is not surprising since it is well known that one of nicotine's main pharmacological effects as an NNR agonist is to stimulate dopamine release in the brain [31]. This predicts that NNR agonists could actually aggravate the symptoms of autism, as do the (dopaminergic) stimulants. It may also explain the very low incidence of smoking in the autistic population mentioned earlier.

Cholinesterase inhibitors

Three clinical studies have been conducted on the effects of cholinesterase inhibitors in autism, based on the premise that cholinergic stimulation of NNR-depleted areas of the brain may be helpful. The first was an open retrospective trial using adjunctive donepezil in eight children and adolescents [21]. Four of the eight showed some improvement in irritability and hyperactivity; none showed improvement in inappropriate speech, lethargy or stereotypes. The second (open) study reported the effects of galantamine in three adults with autism [22]. Aggressive behavior was diminished in one

adult, and verbal fluency was somewhat improved in the other two. A third (open label) 12-week study with rivastigmine in 32 autistic children showed statistically significant gains in expressive speech and overall autistic behavior over baseline [23]. It is clear that cholinesterase inhibitors have yielded some promising, but variable results. To fully explore a cholinergic therapeutic approach to autism it will be necessary to conduct studies with cholinergic antagonists, especially in light of published studies and anecdotal evidence reported for the NNR antagonist mecamylamine.

Testing the hypothesis

The promise of NNR antagonists

Studies with the classical nicotinic cholinergic antagonist mecamylamine offer some insights into the potential for NNR antagonists in the treatment of autism. Some of the earliest studies of mecamylamine's potential to treat neuropsychiatric disorders were conducted in adolescents with Tourette's syndrome. Inversine® (mecamylamine HCl), originally approved and marketed as an antihypertensive, was found to have minimal effects on motor symptoms (tics) in Tourette's [32]; however, it showed significant improvements in mood and reduction of rage outburst symptoms [33]. In autism, these effects might be expected to manifest as a reduction in some of the least treatable symptoms such as the self-abuse and social belligerence seen in many cases. Other studies have found that low doses of mecamylamine significantly improved cognition and attention in primates [34], suggesting that the drug may help with some of the core symptoms of autism such as social withdrawal, low verbalization and inwardly focused attention. Mecamylamine has some degree of dose-dependent selectivity for different subtypes of NNRs, which may explain why some effects occur at low doses (e.g., cognitive effects) and others at higher doses (e.g., mood normalization) of the drug. This would seem to be supported by anecdotal evidence from at least one physician who has used mecamylamine at doses as low as one-tenth the commercial dose to successfully treat some of the core symptoms of autism, including improvement of verbalization and socialization, and decreased impulsivity and aggression [35]. These observations suggest that there may be a selective, dose-dependent antagonism by mecamylamine at different NNR subtypes associated with various neurological aspects of the autistic spectrum.

Mecamylamine seems to be a very useful tool to explore the efficacy of NNR antagonists in the treatment of autism. However, future studies with this drug should take into account the dose-dependency of effects with respect to which outcomes are targeted. Obviously there is a need for additional clinical studies with mecamylamine, as well as with novel NNR antagonists more selective than mecamylamine, to further test the hypothesis.

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