Genetics of Childhood Disorders: XIX. ADHD, Part 3: Is ADHD a Noradrenergic Disorder?

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Dysregulation of the central noradrenergic network has long been hypothesized to underlie the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) (Arnsten et al., 1996). This hypothesis is derived largely from pharmacological data documenting that drugs which selectively modulate noradrenergic function show efficacy in treating ADHD. However, a noradrenergic hypothesis of ADHD is compelling in its own right because the noradrenergic system has been intimately associated with the modulation of higher cortical functions including attention, alertness, and vigilance. As recently reviewed by Solanto (1998), preclinical and clinical research has implicated the noradrenergic effects of stimulants in enhancing capacities such as delayed responding, working memory, and attention. Furthermore, executive function and noradrenergic activation are known to profoundly affect the performance of attention, especially the maintenance of arousal, and the ability to sustain attention on a subject, particularly a boring one.

Current neuropsychological, genetic, imaging, and pharmacological data emerging in ADHD research provide compelling support for a noradrenergic hypothesis of ADHD (Arnsten et al., 1996). Attention and vigilance depend on adequate modulation by catecholamine neurotransmitters of prefrontal, cingulate, and parietal cortices, thalamus, striatum, and hippocampus. These brain networks all have a high density of catecholamine terminals.

Perhaps the most compelling evidence for a noradrenergic hypothesis for ADHD derives from psychopharmacological data (Spencer et al., 1996). Preclinical studies have shown that stimulants block the reuptake of dopamine and norepinephrine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Early animal studies used 6-hydroxydopamine to lesion dopamine pathways in developing rats. Because these lesions created hyperactivity, they were thought to provide an animal model of ADHD. Although not entirely sufficient, changes in dopaminergic and noradren-

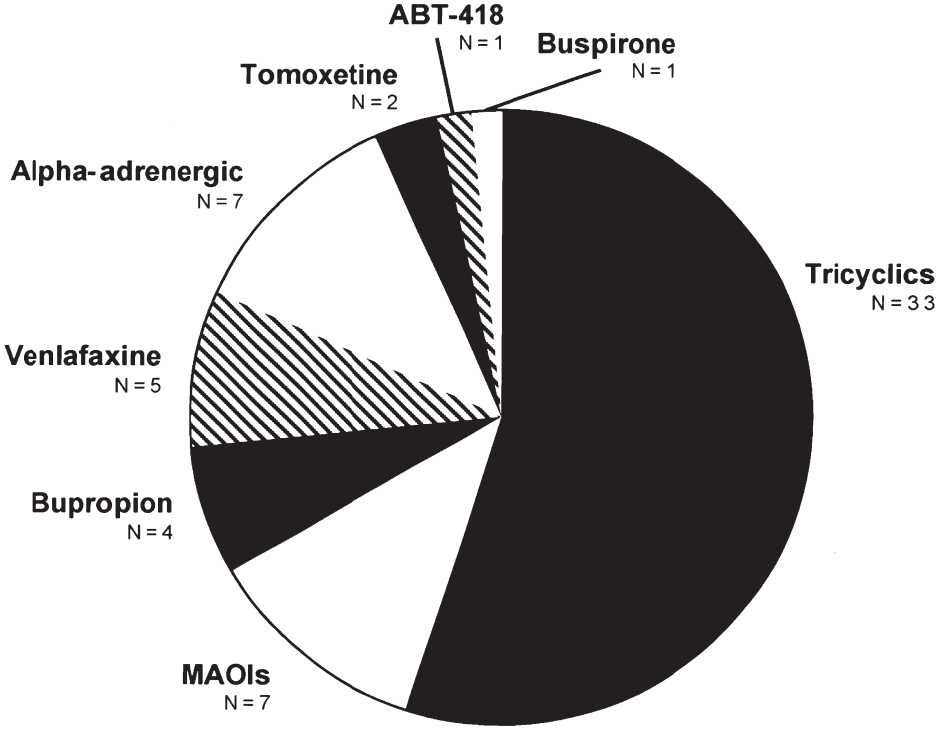

Fig. 1 Studies of nonstimulant treatments in attention-deficit/hyperactivity disorder (ADHD) (controlled and uncontrolled). *N* = 1,829 subjects. MAOIs = monoamine oxidase inhibitors.

ergic function appear necessary for the clinical efficacy of the stimulants. Also, the maximal therapeutic effects of stimulants occur during the absorption phase of the kinetic curve, within 2 hours after ingestion. The absorption phase parallels the acute release of neurotransmitters into synaptic clefts, providing support for the hypothesis that alteration of monoaminergic transmission in critical brain regions may be the pharmacological basis for the effects of stimulants in ADHD. A plausible model is that these medications increase the inhibitory influences of frontal cortical activity on subcortical structures through dopaminergic and noradrenergic pathways (Zametkin and Rapoport, 1987). Indeed, Kuzcenski recently found that low doses of methylphenidate preferentially release norepinephrine. In contrast, effects on serotonin metabolism appear minimally related to the clinical efficacy of the stimulants.

Evidence for noradrenergic actions also comes from studies of antidepressant compounds used to treat ADHD. While the tertiary amines (imipramine and amitriptyline) are more selective for the serotonin transporter than for the norepinephrine transporter, the secondary amines (desipramine, nortriptyline, and protriptyline) are more selective for the norepinephrine transporter. It is assumed that the activity of the tricyclic antidepressants (TCAs) in ADHD stems from their actions on catecholamine reuptake, particularly that of norepinephrine. Advantages of this class of drugs include their relatively long half-lives (approximately 12 hours), obviating the need to administer medication during school hours and lowering the potential for drug abuse or side effects, and their potentially positive effects on mood and anxiety symptoms.

Of 33 studies (21 controlled and 12 open) evaluating TCAs in hyperactive children, adolescents (n = 1,139), and adults (n = 78), 30 reported positive effects on ADHD symptoms. Imipramine and desipramine are the most studied TCAs; there are a handful of studies on the others. The largest controlled study of a TCA in hyperactive children found favorable results with desipramine (DMI) in 62 clinically referred children with ADHD, most of whom had previously failed to respond to psychostimulant treatment (Biederman et al., 1989). The study was a randomized, placebo-controlled, parallel-design, 6-week clinical trial. Clinically and statistically significant differences in behavioral improvement were found for DMI over placebo, at an average daily dose of 5 mg/kg. Specifically, 68% of DMI-treated patients were considered very much or much improved, compared with only 10% of placebo patients (p < .001). Although the presence of comorbidity increased the likelihood of a placebo response, neither comorbidity with conduct disorder, depression, or anxiety nor a family history of ADHD yielded differential responses to DMI treatment. In addition, DMI-treated patients showed a substantial reduction in depressive symptoms compared with placebo-treated patients.

In a similarly designed controlled clinical trial in 41 adults with ADHD, DMI, at an average daily dose of 150 mg (average serum level of 113 ng/mL), was statistically and clinically more effective than placebo. Sixty-eight percent of DMI-treated patients responded compared with none of the placebo-treated patients (p < .0001). Moreover, the average severity of ADHD symptoms at the end of the study was reduced to below the level required to meet diagnostic criteria. Importantly, while the full DMI dose was achieved at week 2, clinical response improved further over the following 4 weeks, indicating a latency of response. Response was independent of dose, serum DMI level, gender, or lifetime psychiatric comorbidity with anxiety or depressive disorders (Wilens et al., 1995).

In a prospective, placebo-controlled discontinuation trial, we recently demonstrated the efficacy of nortriptyline in doses of up to 2 mg/kg daily in 35 school-age youths with ADHD. In that study, 80% of youths responded by week 6 in the open phase. During the discontinuation phase, subjects randomly assigned to placebo lost the anti-ADHD effect compared with those receiving nortriptyline, who maintained a robust anti-ADHD effect. There was again a lag in response to medication and also a lag in loss of response after medication discontinuation. Although the full dose was achieved by week 2, the full effect evolved slowly over the ensuing 4 weeks. ADHD youths receiving nortriptyline also were found to have modest but statistically significant reductions in oppositionality and anxiety. Nortriptyline was well tolerated, with some weight gain. Weight gain is frequently considered to be a desirable side effect in this population. In contrast, a systematic study in 14 treatment-refractory ADHD youths receiving protriptyline (mean dose of 30 mg) reported less favorable results. We found that only 45% of ADHD youths responded or could tolerate protriptyline because of its adverse effects (Wilens et al., 1995).

The potential benefits of TCAs in the treatment of ADHD have been clouded by concerns about their safety stemming from reports of sudden unexplained death in 4 children with ADHD treated with DMI (Biederman et al., 1989), although the causal link between DMI and these deaths remains uncertain. A rather extensive body of literature evaluating cardiovascular parameters in TCA-exposed youths consistently identified mostly minor, asymptomatic, but statistically significant increases in heart rate and electrocardiographic measures of cardiac conduction times associated with TCA treatment. A recent report estimated that the magnitude of DMI-associated risk of sudden death in children may not be much larger than the baseline risk of sudden death in this age group. However, because of this uncertainty, prudence mandates that until more is known, TCAs should be used as second-line treatment for ADHD and only after carefully weighing the risks and benefits of treating or not treating an affected child.

Bupropion hydrochloride is a novel-structured antidepressant of the aminoketone class related to the phenylisopropylamines but pharmacologically distinct from known antidepressants. Bupropion appears to possess both indirect dopamine agonist

and noradrenergic effects. Bupropion has been shown to be effective for ADHD in children in a controlled multisite study (n = 72) and in a comparison with methylphenidate (n = 15). In an open study of adults with ADHD, sustained improvement was documented at 1 year at an average of 360 mg for 6 to 8 weeks. In a placebo-controlled 6-week trial of sustained-release bupropion (up to 200 mg b.i.d.) in adults with ADHD, sustained-release bupropion was well tolerated and effective. Of 38 completers, 76% improved (>30% reduction of symptoms) compared with 37% receiving placebo (p = .012). While bupropion has been associated with a slightly increased risk (0.4%) for drug-induced seizures relative to other antidepressants, this risk has been linked to high doses, a previous history of seizures, and eating disorders.

Although a small number of studies suggested that monoamine oxidase inhibitors (MAOIs) may be effective in treating juvenile and adult ADHD, their potential for hypertensive crisis associated with the irreversible MAOIs (e.g., phenelzine, tranylcypromine), due to dietary transgressions (tyramine-containing foods, i.e., most cheeses) and drug interactions (pressor amines, most cold medicines, amphetamines), seriously limits their use. This "cheese effect" may be obviated with the reversible MAOIs (e.g., moclobemide) that have shown promise in one open trial, although they are not yet available in the United States.

Promising results have been associated with the experimental noradrenergic-specific compound, tomoxetine. One controlled clinical trial in adults documented efficacy and good tolerability. These initial encouraging results, coupled with extensive safety data in adults, fueled efforts at testing this compound in the treatment of pediatric ADHD. An initial open study documented clinical benefits with excellent tolerability, including a safe cardiovascular profile.

Drugs that mimic norepinephrine at the α_2-receptor are also used in the treatment of ADHD. Despite its wide use in children with ADHD, there have been very few studies (n = 4 studies [2 controlled]; n = 122 children) supporting the efficacy of clonidine. Treatment with clonidine appears to have mostly a behavioral effect in disinhibited and agitated youths, with limited impact on cognition. Several cases of sudden death have been reported in children treated with clonidine plus methylphenidate, raising concerns about the safety of this combination. Limited literature exists for guanfacine, a more selective α_{2A}-receptor agonist with fewer side effects. There are 3 small open studies of guanfacine in children and adolescents with ADHD. In these studies, beneficial effects on hyperactive behaviors and attentional abilities were reported. In addition, in a controlled study in normal adults, guanfacine, but not clonidine, improved planning and spatial working memory. In another controlled study in adults with ADHD, guanfacine was reported to improve ADHD symptoms (K. Fletcher, personal communication, 2000). Most recently, a controlled trial in children with ADHD and tics has shown that guanfacine can improve ADHD symptoms and reduce tics (L. Scahill, personal communication, 2000). Thus a variety of noradrenergic agents can improve ADHD symptoms.

In contrast, serotonergic antidepressants are less effective in the treatment of ADHD. While a single, small, open study suggested that fluoxetine may be beneficial in the treatment of children with ADHD, the usefulness of selective serotonin reuptake inhibitors in the treatment of core ADHD symptoms is not supported by clinical experience (NIMH, 1996). Similarly uncertain is the usefulness of the mixed serotonergic/noradrenergic atypical antidepressant venlafaxine in the treatment of ADHD. While a 77% response rate was reported in completers in open studies of adults with ADHD, 21% dropped out because of side effects (n = 4 open studies; n = 61 adults). In addition, a single open study of venlafaxine in 16 children with ADHD found a 50% response rate in completers with a 25% rate of dropout due to side effects, most prominently increased hyperactivity.

In summary, although there is no single pathophysiological profile of ADHD, data implicate dysfunction in the frontosubcortical pathways that control attention and motor behavior. Moreover, the effectiveness of stimulants, along with animal models of hyperactivity, point to catecholamine dysregulation as at least one source of brain dysfunction in persons with ADHD. There is a great need for more research on the role of norepinephrine in ADHD. As most existing research on stimulants has focused on dopamine, it will be important for basic research to examine norepinephrine mechanisms altered by stimulants and other medications. There is also a need for genetic studies to include the norepinephrine transporter, norepinephrine synthetic enzymes, and norepinephrine receptors in ADHD families. Despite their chemical differences, the various compounds with documented anti-ADHD activity share a common noradrenergic/dopaminergic activity. In this regard, it is notable that both noradrenaline as well as dopamine are potent agonists at the D_4 receptor, a gene that has been implicated in the etiology of this disorder (Lanau et al., 1997). It is hoped that advances in the understanding of the underlying neurobiology of ADHD will lead to the development of a new generation of safe and effective treatments for this disorder. Such developments have the promise of revolutionizing the field and improving the quality of life of the millions of affected patients and their families worldwide.

WEB SITES OF INTEREST

http://www.cdc.gov/nceh/programs/cddh/adhd/default.htm
http://neuro-www.mgh.harvard.edu/forum/ADHDMenu.html

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