Attention Deficit Hyperactivity Disorder (ADHD): Methylphenidate (Ritalin) and Dopamine

C J Vaidya, Georgetown University and Children's National Medical Center, Washington, DC, USA
P S Lee, Georgetown University, Washington, DC, USA

Attention deficit hyperactivity disorder (ADHD) is observed in 3–9% of school-aged children and 4% of adults worldwide at higher rates in males than females (2.5:1) and in children older than 9 years relative to younger children. Although family, twin, and adoption studies indicate high heritability (0.76), the mode of transmission is unknown but suspected to be polygenic. Molecular genetic studies suggest that susceptibility to ADHD involves multiple small-effect genes coding for proteins involved in catecholaminergic transmission. Catecholaminergic etiology is consistent with the treatment of choice for ADHD—psychostimulants such as amphetamines and methylphenidate hydrochloride (MPH) that increase synaptic levels of dopamine and norepinephrine by somewhat different mechanisms. Psychostimulants are highly effective for temporary alleviation of symptoms, starting at 30 min and peaking 60–90 min following oral administration of immediate-release formulations. Attempts to elucidate the therapeutic efficacy of MPH for ADHD have shaped current hypotheses about the central role of catecholamines, particularly dopamine (DA), in the neuropathophysiology of ADHD.

Behavioral Profile of ADHD

Clinical Characteristics

Based on the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV), diagnostic criteria for ADHD include parent and teacher reports of symptoms of inattention (e.g., making careless mistakes and difficulty concentrating), hyperactivity (e.g., fidgeting and excessive running or climbing), and/or impulsivity (e.g., difficulty waiting one’s turn and talking excessively). These symptoms must appear prior to age 7 years, persist for at least 6 months in two settings (e.g., school and home), and cannot be explained by other psychiatric or neurological conditions. Symptom presentation varies widely among children and although the definition of subtypes in DSM-IV (e.g., predominantly inattentive, predominantly hyperactive/impulsive, and combined type with both inattention and hyperactivity/impulsivity) recognizes the heterogeneity, it does not fully account for it.

Phenotypic heterogeneity in ADHD stems from a variety of sources. First, assessment of symptoms varies across clinical settings such that primary care physicians rely on parent/teacher reports and direct observation of behaviors but specialty care settings (e.g., neuropsychology services) supplement this information with performance-based measures of cognitive functioning, academic achievement, and symptoms (e.g., Test of Variables of Attention (TOVA)) (Table 1). Performance-based measures alone, however, have limited discriminant validity for diagnostic use. Second, the severity or nature of symptom presentation may depend on gender (e.g., greater motor restlessness in boys but excessive talking in girls), age (e.g., reduced motor restlessness in adolescence relative to childhood), and context (e.g., reduced symptoms in structured environments). Third, ADHD symptoms co-occur with other psychiatric conditions such as mood disorders (e.g., depression and anxiety), conduct disorder, oppositional defiant disorder, obsessive–compulsive disorder, Tourette’s, developmental dyslexia, autism spectrum disorders, as well as nonpsychiatric conditions such as sleep disorders. This complex pattern of comorbidity is difficult to resolve because ADHD symptoms could be primary or secondary or define a distinct phenotype that includes the comorbid disorder.

Cognitive Characteristics

It is commonly believed that the primary cognitive domain impaired in ADHD is executive function, an umbrella term that subsumes multiple dissociable ‘top-down’ operations that control attention and actions in the service of goal-directed behavior. Operations that have been the focus of ADHD research include inhibitory control (e.g., suppressing prepotent or irrelevant responses), working memory (e.g., temporary maintenance and/or manipulation of information), sustained attention or vigilance, and switching of task set (e.g., adapting to changing task demands). Studies using neuropsychological tasks of executive function that involve multiple operations (e.g., Tower of Hanoi, a problem-solving task requiring set maintenance and switching, working memory, and inhibition of inappropriate responses) indicate reduced performance in ADHD relative to control subjects. A meta-analysis of 83 studies involving 6700 subjects reported reductions in all executive operations sampled with effect sizes ranging from 0.4 to 0.7. Furthermore, effect sizes were larger for studies of spatial working memory...
Drawing conclusions from these studies about which executive operations may be core deficits in ADHD is challenging because most neuropsychological tasks do not measure executive operations in a process-pure manner.

An influential theory of ADHD has proposed that a core deficit of response inhibition underlies executive dysfunction in ADHD. Response inhibition can be measured in a relatively process-pure manner using tasks that require subjects to withhold a prepotent response to a cue that occurs unpredictably following initiation of a response on the Stop Signal task or infrequently on the Go/No-go task. A meta-analysis of 17 studies involving 1200 children reported longer Stop Signal reaction times, an index of poor response inhibition, in ADHD relative to control children (effect size, \(d = 0.58\)). Use of response inhibition tasks in frontal lobe-damaged patients and in functional neuroimaging studies of healthy adults and children indicates involvement of dopamine-rich frontal–striatal circuitry. In ADHD children, those frontal–striatal regions are recruited to a lesser extent relative to controls. Thus, converging behavioral and neuroanatomical findings provide evidence for involvement of dopamine-rich regions underlying response inhibition deficits in ADHD.

Three lines of evidence have called into question the view that executive dysfunction is the cardinal cognitive deficit in ADHD. First, effect sizes of group differences in executive task performance are modest \((d = 0.50–1.0)\) and suggest considerable overlap between score distributions of ADHD and control groups. In a study of five executive function measures, only 10% of ADHD children were impaired on all operations, whereas 21% of ADHD and 53% of control children were unimpaired on all operations. Such results have led researchers to conclude that executive dysfunction is neither necessary nor sufficient to account for all cases of ADHD.

Second, a variety of nonexecutive processes show impairments in ADHD subjects. On Go/No-go tasks, responses on Go trials that do not require inhibitory control are slower in ADHD than control children \((d = 0.58)\). Reaction time performance of ADHD children deteriorates over the course of the task, is often slow on initial trials suggesting underarousal, and is more variable from trial to trial. Atypical response characteristics may relate to problems with temporal processing because ADHD children perform poorly on tasks of time estimation, time duration, and motor timing.

Third, motivational deficits have gained attention in ADHD with the observation that ADHD subjects are delay averse – that is, they tend to prefer small immediate rewards than to wait for larger delayed rewards. Delay aversion is posited to reflect atypical functioning of dopaminergic reward systems with motor hyperactivity reflecting compensatory behavior in response to unavoidable delays. Indeed, results of functional imaging study of reward function in ADHD showed that relative to controls, adolescents with ADHD showed reduced ventral striatal activation during anticipation of monetary rewards; furthermore, it was negatively associated with severity of impulsive/hyperactive symptoms. Impaired executive function and delay aversion appear to relate independently to ADHD because when tested in the same group of subjects, the two deficits were uncorrelated but together accounted for 90% of the cases. Thus, executive and motivational dysfunction may represent distinct phenotypes of ADHD.
Summary

The behavioral profile of ADHD suggests considerable phenotypic heterogeneity that is not fully captured by current diagnostic taxonomy and cognitive models of ADHD. At the clinical end, reliance on subjective reports of the child's behavior is unlikely to provide fine-grained symptom profiles unless supplemented by performance-based measures derived from cognitive models of ADHD. At the cognitive end, executive and motivational function appears to be independently affected in ADHD. A unifying factor, however, is that dopaminergic pathways figure centrally in the functional anatomy of both executive and motivational functions.

Evidence for Dopaminergic Dysfunction in ADHD

Whereas convergent lines of evidence suggest abnormal dopaminergic transmission in ADHD, its specific nature is debated. Furthermore, it is believed that the pathophysiology of ADHD is complex, with some interaction between dopaminergic and noradrenergic systems. This view comes from findings showing that pure DA agonists such as levadopa do not attenuate ADHD symptoms. Although the nature of its interaction with the noradrenergic system remains to be specified, strides made in understanding dopaminergic dysfunction in ADHD have been useful for elucidating the neurobiology of ADHD. Sources of evidence suggesting dopaminergic dysfunction in ADHD are discussed next.

Therapeutic Action of MPH

The primary source of evidence for hypothesizing dopaminergic dysfunction in ADHD comes from the mechanism of action of MPH. MPH blocks the dopamine transporter (DAT) that reuptakes DA following release, thereby increasing synaptic levels of DA. Indeed, ligand-based imaging studies in primates and humans showed that MPH bound to DAT in concentrations that were highest in the striatum and lower in thalamus, cortex, and cerebellum, leading to increases in magnitude of extracellular DA. At clinically relevant doses of 0.25–0.5 mg kg\(^{-1}\), MPH blocked 50–60% of DAT in the striatum. MPH-induced (dose, 0.3 mg kg\(^{-1}\)) increases in extracellular DA in the striatum were positively correlated with severity of impulsivity and inattention on a performance-based measure (e.g., TOVA) in ADHD adolescents. Thus, in vivo imaging in humans provides evidence for increased synaptic DA following inhibition of DAT by MPH and its association with ADHD symptom expression.

Hyper- and hypodopaminergic status in ADHD

In light of the pharmacodynamics of MPH, two lines of evidence have been important in shaping current views about dopaminergic dysfunction in ADHD. First, measurements of homovanillic acid (HVA), a metabolite of DA in cerebrospinal fluid (CSF), correlated positively with hyperactivity ratings from parents and teachers, and CSF levels of HVA decreased following MPH (and other stimulants) treatment. This finding suggests that ADHD reflects increased dopaminergic activity. Second, ligand-based imaging studies of DAT, the primary target of MPH, showed increased binding in the striatum in ADHD relative to control subjects in several studies. This finding suggests that ADHD reflects reduced dopaminergic activity due to increased DA reuptake resulting from higher DAT availability.

Both trait- and state-related factors may underlie increased DAT availability in ADHD. Trait-related factors resulting in higher DAT availability include ‘hypertrophy’ of dopaminergic neurons due to insufficient pruning during development and/or genetic differences. Alternately, increased DAT availability in ADHD may be state related, resulting from adaptive processes compensating for greater DA release, reduced vesicular storage, or other differences in DA transmission. In some studies, DAT availability in the striatum did not differ between ADHD and control subjects but, rather, was reduced in the midbrain of ADHD subjects. Differences in sample characteristics (e.g., nicotine use) and properties of ligands (e.g., detection of internalized or external DAT) may have contributed to the inconsistent findings across studies. It is also likely that heterogeneity among individuals may emerge from some combination of trait- and state-related factors.

Working hypothesis of dopaminergic dysfunction in ADHD

Increased DA release and increased DAT availability in ADHD have been reconciled in a model by Seeman and Madras that considers both tonic and phasic dopaminergic activity. Phasic activity reflects acute DA release stimulated by a nerve impulse, whereas tonic activity reflects chronic DA accumulation in synaptic space. The two types of DA activity are reciprocal such that tonic DA activity stimulates autoreceptors on the presynaptic neuron that serve to attenuate phasic DA release. Seeman and Madras posit that tonic DA activity is reduced in ADHD. Findings of elevated DAT in ADHD provide some support for this view because greater reuptake of synaptic DA is likely to result in reduced tonic DA activity. Furthermore, it is posited that low tonic DA activity is unlikely to stimulate presynaptic...
autoreceptors, resulting in higher phasic release of DA. Greater phasic DA release is consistent with findings of greater HVA levels in CSF of hyperactive children. The therapeutic action of MPH in Seeman and Madras’s model is mediated through increased tonic DA and reduced phasic DA. Specifically, they posit that the blockade of DAT reuptake by MPH increases tonic DA activity that leads to increased autoreceptor stimulation, which in turn attenuates phasic DA release. Seeman and Madras’s model, therefore, posits that ADHD is characterized by both hypo- and hyperdopaminergic status that is normalized by MPH.

**Variability in MPH response** Two properties of MPH effects, context dependency and individual variability, should be considered by any model of ADHD pathophysiology. First, anecdotal and clinical reports have emphasized that efficacy of MPH varies across situations. Indeed, in a placebo-controlled study, symptom improvements in ADHD children were greater in a classroom than playground setting. Ligand-based imaging of D2 receptors in healthy adults suggests that context dependency in MPH response is a property of dopaminergic function. Specifically, oral administration of MPH at clinically relevant doses (20 mg) increased extracellular DA in the striatum selectively for a mathematical task with monetary incentives. DA levels were associated with subjects’ reports of greater interest and engagement in the mathematical task following MPH administration. These effects were not observed following MPH and placebo administration for a neutral task (viewing nature scenes without monetary incentives) and were not observed on placebo for the mathematical task. Thus, these results suggest stimulus selectivity in MPH-induced enhancement of attentional performance and interest and associated DA modulation.

Second, a majority (60–70%) but not all ADHD individuals respond favorably to MPH. Whereas responders and nonresponders did not differ in symptom characteristics, nonresponders had lower than normal DAT availability. Furthermore, at similar levels of DAT blockade, the magnitude of extracellular DA increase induced by MPH varied across subjects due to differences in rates of DA cell firing. Thus, it is important to consider etiological factors underlying individual differences in DAT availability and DA cell firing.

**Candidate Dopaminergic Genes**

In light of the molecular targets of stimulant medications and results of transporter imaging studies in ADHD, molecular genetic studies have searched for susceptibility genes relating to catecholamine function. Studies of the dopaminergic system have focused on polymorphisms of D2, D5 receptors – DAT, dopamine beta-hydroxylase (DBH), tyrosine hydroxylase, catechol-O-methyltransferase (COMT), and monoamine oxidase A (MAO-A).

Although findings are not conclusive, the most consistent evidence for association with ADHD comes from polymorphisms of the dopamine transporter gene (DAT1) and D4 receptor gene (DRD4). DAT1, located on chromosome 5p15.3, contains a 40-base pair variable number of tandem repeats ranging from 3 to 13, with 9 and 10 being most common, in the 3’-untranslated region. Greater prevalence of the 10-repeat allele in subjects with ADHD has been reported by many studies but not by all studies. DRD4 contains a 48-base pair variable number of tandem repeats in exon 3, and greater prevalence of the 7-repeat allele in ADHD subjects has been reported by some studies but not by all. Furthermore, some studies have found association of ADHD with other DRD4 alleles (e.g., 2–5 repeat). Mixed findings across studies may result from differences in allelic variability associated with ethnicity of samples, study designs for ascertaining linkage, methods of ADHD diagnosis, and from limited statistical power due to small sample sizes. Examination of odds ratios (a statistic assessing magnitude of association) pooled across studies, a method that circumvents statistical limitations of small samples, showed that polymorphisms of several dopaminergic genes (DRD4, DRD5, DAT, and DBH) confer a statistically significant, albeit small, risk for ADHD.

Genetic polymorphisms have the potential to elucidate dopaminergic pathophysiology of ADHD because allelic variation in DAT1 and DRD4 influences DA transmission. DAT expression was greater for the 10-repeat allele in *in vitro* studies but findings of *in vivo* studies are mixed, reporting higher, lower, and similar striatal DAT expression in homozygous carriers of the 10-repeat allele relative to carriers of the 9-repeat allele. *In vitro* studies of DRD4 alleles indicate that response to DA was reduced for the 7-repeat allele. Selective ligands for D4 receptors are currently unavailable and, therefore, it is unknown whether D4 receptor density differs between carriers of the 7-repeat and other DRD4 alleles.

**Variability in ADHD symptoms and MPH response** Allelic variation in DAT1 and DRD4 relates to ADHD symptoms selectively. Homozygosity of the 10-repeat DAT1 allele was associated with higher hyperactivity symptoms, whereas that of the 7-repeat DRD4 allele was associated with higher inattention symptoms, in ADHD children and their parents. Furthermore, children homozygous for the 10-repeat
DAT1 allele performed worse on performance measures of impulsivity, the Test of Everyday Attention for Children (TEA-Ch) Opposite Worlds task and errors of commission on the Continuous Performance Task, relative to heterozygous ADHD children. Also, homozygous 10-repeat DAT1 children exhibited greater intraindividual response time variability than heterozygous children. It is noteworthy that DAT is primarily expressed in the striatum, whereas D4 is abundant primarily in prefrontal cortex. Thus, selective effects of DAT1 and DRD4 polymorphisms on inattention and impulsivity in ADHD may reflect functional characteristics of the striatum and prefrontal cortex, respectively.

Pharmacogenetic studies suggest that the efficacy of MPH depends on DAT1 and DRD4. Based on in vitro studies indicating that DAT expression was greater for the 10-repeat allele, carriers of that allele should show a better response to MPH. Indeed, homozygosity of the 10-repeat DAT1 allele was associated with a better response to MPH in some studies. Other studies, however, did not replicate this finding. Discrepant findings among studies probably relate to differences in sample selection and characteristics of treatment regimens, such as dosage, duration, and assessment of MPH response. Based on the in vitro observation that DA response is blunted for the 7-repeat allele, carriers of that allele should show a reduced MPH response. Indeed, a study examining variability in dose–response to MPH found that carriers of the 7-repeat allele required higher doses to attain normalization of symptoms relative to noncarriers. Thus, examination of allelic variability in MPH effects is a worthwhile approach to elucidate etiological heterogeneity in DA function in ADHD, but larger well-controlled studies are needed to draw definitive conclusions.

**Functional Brain Imaging of MPH Effects**

Functional magnetic resonance imaging (fMRI) performed with methylphenidate challenge is a noninvasive way to visualize dopaminergic function in vivo. fMRI capitalizes on changes in blood oxygenation secondary to neural activity evoked by a cognitive challenge. Results of several studies indicate that frontal and striatal activation during performance of attentional and inhibitory tasks differs between ADHD and control subjects. Comparison of fMRI measures in the same subjects during performance of a cognitive challenge, once with and once without administration of MPH, provides an index of changes in neural activity induced by alterations in catecholamine levels (generally referred to as pharmacological fMRI). Evidence from animal studies has validated the ability of fMRI to index metabolic changes induced by dopaminergic stimulation. Specifically, fMRI signal in response to amphetamine or its analog, CFT (2B-carboxymethoxy-3B-[4-flurophenyl] tropane, WIN 36 528), was correlated with changes in extracellular DA concentrations in the striatum (confirmed by microdialysis) and was lost following denervation of the striatum by 6-OHDA lesioning. Furthermore, the fMRI signal changes were restricted to regions with high expression of DA receptors, such as striatum and cingulate and frontal cortex (confirmed by receptor-labeled positron emission tomography). Thus, fMRI with MPH challenge provides a noninvasive assay for dopaminergic function relevant to cognitive deficits observed in ADHD.

Findings of pharmacological fMRI studies indicate that MPH has selective effects on brain regions involved in executive function in subjects with ADHD. Results of these studies suggest that MPH normalizes activation in striatal structures but not in other brain regions. Striatal activation was reduced relative to control children and increased following administration of MPH during performance of response inhibition and divided attention tasks. However, other regions with reduced activation in ADHD subjects, such as middle temporal and anterior cingulate gyri, did not change following administration of MPH. Furthermore, effects of MPH on prefrontal activation in ADHD subjects differed across studies such that activation was increased during a difficult response inhibition condition, did not change during an easy response inhibition condition, and was reduced during working memory performance. Thus, effects of MPH on metabolism in circuitry involved in executive function are not uniform across regions.

The influence of MPH on brain metabolism appears to vary by symptom expression. In contrast to increased striatal activation following MPH administration, fMRI imaging during response inhibition in control children showed that MPH reduced striatal activation. These opposite effects of MPH in ADHD and control children were not observed elsewhere in the brain. Furthermore, these opposite effects did not relate to performance differences because MPH improved response inhibition to the same extent in both ADHD and control groups. Results of other studies indicate that MPH increased blood volume in children who were more hyperactive, whereas it decreased blood volume in those who were less hyperactive, in the cerebellar vermis and putamen. In light of evidence relating symptom expression to functional properties of DA transmission, MPH effects on brain metabolism probably reflect differences in baseline dopaminergic function.
Summary

Convergent evidence from studies of MPH effects and *in vivo* imaging suggests that DA transmission is dysfunctional in ADHD and may relate to polymorphisms of dopaminergic genes. The most direct evidence for presynaptic DA dysfunction in ADHD comes from ligand-based imaging studies showing elevated DAT density in subjects with ADHD. Whether this is a trait related to abnormal neuronal pruning or a state reflecting adaptive response to abnormalities in other aspects of DA transmission remains to be resolved. Resolution may come from molecular genetic studies because inheritance of the 10-repeat allele of the DAT gene has been linked to individual differences in DAT expression and susceptibility to ADHD. Polymorphism of D4 receptor genotype also confers some risk for ADHD, suggesting that postsynaptic DA function is also part of the ADHD pathophysiology. The leading model of DA dysfunction in ADHD posits that the disorder involves both lower and higher dopaminergic activity. Specifically, Seeman and Madras hypothesize that ADHD reflects reduced tonic but increased phasic DA activity. Efficacy of MPH in this model is mediated by reduced phasic DA activity via autoreceptor stimulation due to increased tonic DA activity that results from increased synaptic DA following DAT blockade by MPH. However, MPH response varies depending on contextual and subject-related factors, a finding that is not accounted for by current models of ADHD. Use of pharmacological fMRI provides a noninvasive assay of DA function in ADHD. Its use has revealed that changes in neural activity induced by MPH during executive functions serve to ‘normalize’ striatal function in ADHD subjects but depend on symptom severity.

Future Direction: Endophenotypes for ADHD

Researchers agree that phenotypic heterogeneity of ADHD is the primary limiting factor in elucidating the pathophysiology of ADHD. Currently, most researchers endorse an approach that characterizes individual differences in terms of endophenotypes rather than symptom profiles. Endophenotypes refer to cognitive functions that can be specified on performance-based measures that are heritable and draw upon neurophysiology relevant to the disorder. Current research has identified response inhibition measured upon neurophysiology relevant to the disorder. Current performance-based measures that are heritable and draw rather than symptom profiles. Endophenotypes refer to individual differences in terms of endophenotypes researchers endorse an approach that characterizes the pathophysiology of ADHD. Currently, most ADHD is the primary limiting factor in elucidating symptom severity.

Further Reading


