Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research

Mary V. Solanto *

Division of Child and Adolescent Psychiatry, Mount Sinai Medical Center, Box 1230, One Gustave L. Levy Place, New York, NY 10029-6574, USA

Received 19 September 2000; accepted 13 August 2001

Abstract

There is strong evidence that the catecholamines dopamine and norepinephrine are both important in the pathophysiology of ADHD, as well as in the mechanism of therapeutic action of stimulant drugs. Due to the known effects of stimulants in blocking reuptake of catecholamines and (in the case of D-amphetamine) facilitating their release, it has traditionally been believed that the stimulants compensate for catecholamine deficiency in ADHD. More recently, however, alternate hypotheses of a hyperdopaminergic and/or hyper-noradrenergic state in ADHD have been suggested. This paper will be limited to a review of the evidence for involvement of dopamine in mediating behavioral and cognitive symptoms and response to stimulants in ADHD, with implications for possible mechanisms. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Attention-deficit hyperactivity disorder (ADHD); Dopamine; Methylphenidate; Amphetamine; Autoreceptors; Prefrontal cortex; Prefrontal–striatal–thalamic–cortical circuit; Striatum; Attention; Impulsivity; MRI; fMRI; PET; Dopamine transporter (DAT); Rate dependency

1. Primary characteristics of ADHD

1.1. Behavioral studies

The primary symptoms of the most commonly recognized, combined-type of ADHD are, (1) motor overactivity; (2) inattention; and (3) impulsivity [2]. Motor overactivity has been documented using truncal accelerometers across a variety of academic and non-academic natural settings as well as sleep [47]. More recently, increased activity was shown using infrared technology in a laboratory setting [69]. Problems with attention, in the form of difficulty focusing, distractibility, and failure to complete tasks, have been documented on well-normed questionnaire ratings by teachers and parents [13], as well as systematic monitoring of academic productivity and accuracy [50,63]. In addition, children with ADHD exhibit worse performance on laboratory measures of vigilance, such as the continuous performance test (CPT) [38], as well as measures of reaction time [18], and focused attention [14]. Also indicative of an attentional dysfunction are smaller amplitude and longer-latency P300 waves on event-related EEG potential recording [32]. Difficulties in inhibitory control are reflected in questionnaire ratings of difficulty waiting, excessive talking, noisiness, intruding on others’ conversations or games [13], and on laboratory measures of response to a stop signal [54], errors of commission on the CPT [38], aversion to delay [58,60], differential response to low-rate reinforcement (DRL) [40,56], interference control on the Stroop Color-Word Naming Test [5] and difficulties, in some studies, in the response organization and execution stages of information-processing [72].

1.2. Neuroimaging studies

Neuroimaging studies are converging in revealing differences in anatomic MRI in children with ADHD, compared with age-matched controls-notably smaller total brain volume (4% decrease from normal), as well as smaller caudate, globus pallidus, anterior frontal cortex, and a subregion of cerebellar vermis [9]. Results
of recent studies of metabolic activity in individuals with ADHD during tests of inhibitory control have been highly inconsistent, however, with one PET study in adolescents finding increased \[^{[18]}F\] F-DOPA uptake in the right midbrain [21] relative to controls. A previous PET study in never-medicated adults with ADHD in this same laboratory reported significantly diminished F-DOPA uptake in left and medial prefrontal cortex (PFC) with no differences in striatum or midbrain regions [20]. The weakness of the signal from \[^{[18]}F\] F-DOPA uptake outside the striatum, the small samples tested, as well as potential differences between adolescents and adults, may all contribute to these disparities among results.

Functional MRI studies have shown reduced striatal activation in children [71] and adolescents [52] with ADHD during performance of response inhibition tasks. The latter study also revealed reduced activation of right mesial PFC during the stop task.

Two recent neuroimaging studies have been consistent in finding increased dopamine transporter (DAT) density in adults with ADHD. In the first of these, PET revealed elevated levels of DAT were found in six patients (who may have received stimulant drugs previously) compared with controls [17]. In the second study of 10 previously untreated adults, SPECT showed that binding to DAT, which was higher than normal control levels at baseline, decreased following 4 weeks of methylphenidate treatment [34]. One possible conclusion from these studies is that increased levels of DAT in ADHD patients produce a reduction in synaptic and extra-synaptic dopamine. An alternative, however, is that the increase in DAT is an adaptive response which evolved over the lifetime of the individual with ADHD to compensate for initially elevated levels of dopamine release. In either case, methylphenidate may normalize these values.

2. Role of dopamine in primary symptomatology of ADHD

2.1. Motor overactivity

The motor dysregulation characteristic of ADHD as well as the neuroimaging data described suggest that dysfunction in striatum or in the cortical regulation of striatum is involved in the pathophysiology of ADHD. It is well-established that the dorsal striatum is importantly involved in the selection, initiation, and execution of voluntary motor responses [70]. Two parallel prefrontal–striatal–thalamic–cortical circuits are involved [8]. One pathway, the ‘direct pathway’, extends from the PFC through the internal segment of the globus pallidus through thalamus, feeding back to exert a net amplification (via disinhibition) of the original cortical output. Depletion of dopamine in this pathway results in difficulty initiating movement, as seen in Parkinson’s patients. The other ‘indirect’ pathway projects through the external segment of the globus pallidus, and synapses on inhibitory projections from the subthalamic nucleus to the internal globus pallidus, producing a net inhibition of cortical output. Insufficient dopaminergic activity in this pathway will result in excessive motor output. Thus, the motor hyperactivity seen in ADHD may reflect a ‘reverse Parkinsonism’, characterized by either excessive dopaminergic activity in the internal segment, or insufficient inhibitory tone in the external segment [8].

2.2. Cognitive dysfunction

The PFC is essential for attentional control, organization and planning. Lesions to the PFC in humans can produce distractibility, hyperactivity, and impulsivity [62]. Studies in primates and normal humans have begun to delineate the roles of the catecholamines in mediating cognitive functions in the PFC. With respect to dopamine, it has been amply demonstrated in primates that D1 agonists enhance, and D1 antagonists impair, working memory function [3]. These studies further reveal that the PFC is extremely sensitive to the neurochemical environment such that both excessive D1 stimulation, as in stress, as well as insufficient stimulation, can lead to working memory deficits [4]. The D2 receptor agonist bromocriptine has been shown to improve spatial (but not non-spatial) working memory as well as measures of executive function in normal adults [42], all of which were impaired by the D2 antagonist sulpiride. Generalizations about differential mediation by dopamine and norepinephrine of specific cognitive functions are premature, however, because of the insufficiency of specific pharmacological probes (e.g. D1 agonists/antagonists) which can be administered to humans. Since the PFC projects to many subcortical regions, including the dorsal and ventral striatum, thalamus, amygdala, substantia nigra, and ventral tegmental area [1], PFC dysfunction may also lead to disinhibition of these regions. This may have particular significance for dysregulation of motor functions mediated by striatum in ADHD.

3. Clinical response to stimulants

Administration of stimulant drugs produces significant reductions in activity level, measured by truncal actometer, in academic and recreational settings in children with ADHD [46]. Stimulants bring about significant improvement on behavioral questionnaire measures of hyperactivity, inattention and impulsivity, as rated by both parents and teachers [25]. In addition,
stimulants produce improvement in cognitive function on the laboratory measures of attention and impulsivity, described above, as well as improvement on measures of paired associate learning [66] and of verbal [67], as well as spatial [30] working memory, and attentional set-shifting [30]. Positive effects have also been shown to occur in normal adults and children [49], as well as in children with ADHD having various comorbidities [25] and thus do not appear to be an effect that is unique or specific to ADHD.

Time–action and dose–response curves for motor and cognitive effects of stimulants appear to be divergent. Whereas careful hourly monitoring has shown that stimulant-induced reduction in motor activity persists as long as 7–8 h, effects on attention last only 2–3 h [45,46,59]. Furthermore, differences in dose–response curves have been documented, such that reduction in locomotor activity has been seen at a sub-clinical dose that produced no improvement in vigilance [55]. A comprehensive literature review concluded that effect sizes are larger for behavioral (0.8–1.0) than for cognitive (0.6–0.8) changes [61] in response to stimulants. In addition, there is evidence that suggests that larger doses are needed to optimize higher-order cognitive functions, such as learning, than simpler, ‘automatic’ functions such as target detection [15,18].

4. Role of dopamine in mediating therapeutic effects of stimulants

The stimulants bind to the dopamine (as well as norepinephrine) transporter, blocking reuptake (D-amphetamine and methylphenidate) and facilitating release (D-amphetamine only). It is relevant in this context that the DAT is expressed in considerably lesser amounts in cortex than in striatum, suggesting that transporter inhibitors would have weaker ability to increase dopamine efflux in cortex than striatum [68]. In cortex, therefore, DA may bind to NE transporter instead, for which, in fact, it has been shown to have greater affinity.

Early studies suggested that the relative effects of stimulants on pre- and post-synaptic dopaminergic receptors are dose-dependent. At low doses, research using single unit recording showed that low doses of D-amphetamine (0.25 mg/kg or less) preferentially stimulated pre-synaptic inhibitory autoreceptors in the nigrostriatal and ventral tegmental pathways, consequently reducing dopamine cell firing rate [6,7,26], whereas higher doses had predominantly post-synaptic effects. The most recent study, however, did not corroborate this result with respect to sensitivity of somatodendritic autoreceptors to low stimulant doses (0.2 mg/kg of D-amphetamine or 1.0 mg/kg of methylphenidate) in the globus pallidus [53]. Terminal autoreceptors and autoreceptors in other regions of striatum were not examined. Even in the absence of differential sensitivity, however, different regional distributions of autoreceptors may have implications for stimulant effects. For example, impulse-regulating and synthesis-regulating autoreceptors, found in the striatum, are lacking in the PFC [41], suggesting the possibility of different mechanisms of stimulant drug effects on motor and cognitive functions mediated by the two regions, respectively.

PET studies of labeled methylphenidate administered orally to primates at doses in the clinical range reveal occupancy of over 50% of total striatal DA transporter sites [64]. PET studies of normal adults have shown increased metabolism in PFC and cerebellum but reduced metabolism in striatum following methylphenidate administration in clinically relevant doses [74]. The only study of fMRI effects of methylphenidate administration in children with ADHD found that the drug increased PFC activation in both ADHD and normal children, but had divergent effects in striatum, increasing activation in ADHD children and reducing it in normal children [71]. Volkow et al. used PET and [3H]raclopride (a D2 receptor radioligand) to index changes in D2 receptor oral availability in striatum in normal adults before and after a clinically relevant oral dose of methylphenidate. Methylphenidate significantly increased extracellular dopamine concentration, as evidenced by a significant reduction in D2 receptor availability [73]. Clearly, further imaging research in adults and children with ADHD and normal adults is necessary to investigate these issues of locus and mechanism of stimulant actions and the functional implications of these changes in regional brain metabolism.

4.1. Rate-dependency

Effects of stimulants on motor activity in adults and children with and without ADHD have been described in terms of the phenomenon of ‘rate-dependency’ [16], such that stimulant-induced change is a negative linear function of the baseline rate. Thus, individuals with high baseline activity show a larger decrease in activity on drug than do those with lower baseline activity [51]. Earlier work with primates revealed that low doses of D-amphetamine (in the clinically relevant range) increased daytime activity in a nocturnally active monkey species but decreased it in a diurnal species [28]. Consistent differences between mouse strains in the direction of amphetamine effects on activity level have also been reported [31,44]. One study reported that those strains responding with a decrease in locomotor activity had higher D2 receptor density than those showing an increase [27]. Interestingly, only increases in activity have been reported in studies with rats, even at stimu-
lant doses as low as 0.2 of d-amphetamine and 0.4 of methylphenidate [29], suggesting that it may not be possible to develop a valid animal model of stimulant effects ADHD in rats. Although the rate-dependency phenomenon has been challenged from mathematical and statistical perspectives [23,65] and requires further empirical documentation in humans treated with stimulants, it may offer a compelling theoretical account of stimulant drug effects on activity level.

4.2. Cognitive effects

A significant literature reviewed by Koelega [33] has documented the positive effects of the psychostimulants on vigilance in adults. Positive effects on memory (e.g., word list learning) have also been shown for both d-amphetamine and methylphenidate [57]. Most recently, Elliott et al. [19] demonstrated that methylphenidate improved performance of normal adults on the same task of self-ordered spatial working memory found sensitive to methylphenidate in children with ADHD [30]. A PET study in adults revealed that d-amphetamine selectively increased activation of the dorsolateral PFC during an attentional set-shifting task (Wisconsin Card Sort) [39] previously shown to engage this region. A pivotal study by Rapoport et al. demonstrated effects of d-amphetamine in normal adults as well as normal children that were qualitatively similar to those in children with ADHD—that is, all three groups responded with decreases in activity, inattention, and impulsivity [48,49]. Thus this data also showed that the enhancing effects of the stimulants on cognitive processes are not unique or specific to ADHD.

A review of clinical drug trials in children with ADHD indicated that agents with some selectivity for dopamine or norepinephrine were less effective than those which, like the stimulants, have effects on both catecholamines [76]. Polypharmacy approaches have been used in studies with children in efforts to delineate the stimulant effects specifically attributable to each neurotransmitter and the mechanisms thereof. Administration of a neuroleptic (dopamine antagonist) enhanced the positive effects of methylphenidate on behavior ratings of the core ADHD symptoms in two studies [22,75], but blocked the facilitative effects of methylphenidate on a cognitive test battery which included the CPT in a third study [37]. In normal adults, methylphenidate reversed the adverse effects of the dopamine antagonist droperidol on divided and focused attention on a dichotic auditory attention task [12]. These studies suggest the possibility that the positive effects of methylphenidate on cognitive function are due to facilitation of dopaminergic activity whereas improvement in behavior ratings of hyperactivity and impulsivity may be mediated by reduction in dopaminergic stimulation, in different brain regions. Rapport compared the effects of methylphenidate with those of desmethylimipramine (DMI) (a norepinephrine reuptake inhibitor), administered separately and together to hospitalized children with mixed features of ADHD and depression. They reported that methylphenidate, but not DMI, improved performance on the CPT (omission errors), suggesting that effects on vigilance are primarily dopaminergically mediated (contrary to results described by Mehta previously in normal adults). Interpretation of these findings, however, is complicated by the atypical comorbidity in this ADHD sample and the possibility that the drug effects on cognition were mediated by alleviation of depression. Nonetheless these studies do highlight the potential utility of systematic comparisons of stimulant effects with those of more selective dopaminergic and noradrenergic agents in delineating stimulant mechanisms.

5. Conclusions

Our understanding of the pathophysiology of ADHD and the mechanisms of therapeutic action of stimulants is clearly still in its infancy. However, a few general conclusions and speculations may be generated that encompass the data available to date, and suggest hypotheses for future research. First, it appears that motor and cognitive symptoms of ADHD are mediated differently. This is based upon: (1) the separability of the attentional and hyperactive-impulsive factors in the presentation of symptoms and delineation of subtypes [35]; (2) the divergence of the two symptom clusters with respect to heritability [43]; and (3) divergence of the time-action and dose-response curves for stimulant effects on motor versus cognitive symptoms. Specifically, hyperactivity may result from dysfunction of subcortical sites, whereas impairment of attentional and working memory may be mediated primarily in the PFC.

Hyperactivity, and possibly poor motor impulse control, in ADHD may result from excess dopaminergic activity in striatum and/or nucleus accumbens. This conclusion is suggested by increased striatal activity on PET in adolescents with ADHD relative to normal controls [21], and also by the finding that among children with ADHD high CSF-HVA was correlated with increased severity as well as a more positive response to stimulants [10,11]. Stimulant drugs may reduce hyperactivity by reducing dopaminergic activation of striatum. There is evidence from work in humans and primates that cognitive symptoms, including reduced capacity for delay and reduced working memory function, are mediated by PFC, and that stimulants may act at D1 and D2 (as well as alpha 2-a noradrenergic receptors) in PFC to optimize or normalize the neuro-
chemical environment. These regional distinctions in stimulant drug effect are supported by behavioral observations that amelioration of the motor symptoms of ADHD occurs at lower stimulant doses and for a longer duration than is true for the cognitive symptoms, in combination with the neuroanatomical facts that the PFC is lacking in impulse-regulating and synthesis-regulating autoreceptors, and has a much lower DAT density than does the striatum. Grace [24] has proposed a model of dopaminergic dysfunction in ADHD at the cellular level that integrates many of the foregoing observations. He suggests that, possibly because of reduced stimulation from PFC, children with ADHD have low tonic dopaminergic activity in limbic regions. Low tonic stimulation of inhibitory autoreceptors leads to high phasic activity in the nucleus accumbens, and possibly other subcortical sites as well, that results in dysregulated motor and impulse control. By blocking dopamine reuptake stimulants increase synaptic dopamine, which diffuses to the extracellular space increasing tonic levels. Higher tonic dopamine increases the stimulation of impulse-regulating and presynaptic autoreceptors, thereby reducing phasic dopamine release. Thus tonic dopamine is increased, and phasic dopamine is decreased, to normal levels. Furthermore, the greater the phasic DA activity at baseline, the greater the decrease produced by the stimulant. This model, which implies that stimulant response is a continuous function of baseline severity, is also consistent with recent clinical research indicating that the core symptoms of ADHD are themselves continuously distributed in the population [36,43]. Unsupportive of this model, however, is the recent failure to find preferential stimulation of somatodendritic autoreceptors (vs. postsynaptic receptors) in globus following low stimulant doses [53].

6. Implications for future research

The understanding of catecholaminergic mechanisms in the pathophysiology of ADHD and in the response to stimulants is likely to be furthered by continued research that bridges the basic and clinical neurosciences. Promising approaches include the use of tasks (such as those in the Cambridge Neuropsychological Test Automated Battery (CANTAB) that assess discrete cognitive functions across age groups and primate species, concomitant neuroimaging, biochemical and behavioral investigations of the effects of low, clinically relevant doses in animal studies, and assessment of behavioral and cognitive effects of drugs with specific catecholamine receptor agonist and antagonist properties. Increased understanding of these mechanisms may lead not only to development of better pharmacological treatments that are targeted to specific symptoms, but may yield increased insight into the neurobiological etiology of the disorder itself.

References


