Imaging the Effects of Methylphenidate on Brain Dopamine: New Model on Its Therapeutic Actions for Attention-Deficit/Hyperactivity Disorder

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Methylphenidate hydrochloride (MP) is an effective treatment for attention-deficit/hyperactivity disorder (ADHD), a common neurobehavioral disorder of childhood onset characterized by inattention, hyperactivity, and distractibility. Methylphenidate hydrochloride blocks the dopamine transporters (DAT), the main mechanism for removing dopamine (DA) from the synapse, is believed to be involved in its therapeutic properties. However, the mechanism(s) by which increases in DA improve symptomatology in ADHD are not completely understood. Our studies of the dopaminergic effects of MP in the human brain using positron emission tomography (PET) have shown that MP blocks DAT, and that extracellular DA increases in proportion to the level of blockade and the rate of DA release (modulated by DA cell firing). These DA increases are greater when MP is given concomitantly with a salient stimulus than with a neutral stimulus, documenting the context dependency of MP effects. Additionally, MP-induced increases in DA are associated with an enhanced perception of the stimulus as salient. We postulate the MP's therapeutic effects are due in part to its ability to enhance the magnitude of DA increases induced by stimuli that by themselves generate weak responses, enhancing their saliency and the attention and interest they elicit. We postulate that these effects would improve school performance.

Key Words: Methylphenidate, attention-deficit/hyperactivity disorder, dopamine, dopamine transporter, saliency

For more than 50 years, methylphenidate hydrochloride (MP) has been used as an effective treatment for attention-deficit/hyperactivity disorder (ADHD), a neurobehavioral disorder that affects an estimated 3% to 9% of school-aged children and approximately 4% of adults worldwide (Faraone et al 2003; Heiligenstein et al 1998; Swanson et al 1998b). Methylphenidate hydrochloride is one of the most frequently prescribed treatments for ADHD, effectively reducing symptoms–inattention, hyperactivity, and impulsivity–in up to 70% of children (Greenhill et al 2002; Swanson et al 1991). The pharmacologic properties of MP have been well characterized in several preclinical studies; however, its mechanism of action is not completely understood (Solanto 1998). Research suggests that MP works by increasing the level of extracellular dopamine (DA) in the brain (Castellanos et al 1996; Volkow et al 1994). This theory has been supported, in part, by preclinical studies that found MP blockades of DA transporters (DATs) as well as norepinephrine transporters (Dougherty et al 1999; Krause et al 2000; Solanto 1998). Dysfunction of the dopaminergic as well as the noradrenergic systems, which have self-regulatory functions such as mediating selective attention (noradrenergic neurons) and motivation (dopaminergic neurons), are implicated in the pathogenesis of ADHD (Dougherty et al 1999; Solanto 1998).

The DAT is the main mechanism by which the DA terminal removes DA released in response to a salient stimulus. By regulating the concentration of DA in the synapse, the DAT regulates both the magnitude as well as the duration of the dopaminergic signal. Therefore, an MP blockade of the DAT should increase DA in the synapse and in the extracellular space and lead to amplification of the signal elicited in response to environmental stimuli. This article will review the imaging studies that have been done to investigate the pharmacokinetics and distribution of MP in the human brain and the ways that MP's effects in the dopaminergic system impact its mechanism(s) of action. Since there are currently no ligands to image the norepinephrine transporter, the relevance of MP's noradrenergic effects has not been investigated with imaging.

Pharmacokinetics and Distribution of Methylphenidate in the Human Brain

Enantiomers of Methylphenidate

Methylphenidate is a chiral drug marketed in the *dl-threo* racemic form. The pharmacologic specificity of MP has been shown to reside entirely in the *d-threo* enantiomer (Ding et al 1997; Patrick et al 1987). In the human brain, *d-threo*-MP binds to the DAT, whereas *l-threo*-MP does not (Ding et al 1997). The distribution of *d-threo*-MP in both baboon and human brains is greatest in the basal ganglia, whereas *l-threo*-MP is found homogeneously throughout the brain. Both enantiomers have similar rates of uptake with peak concentrations reached within 10 minutes of administration; however, *d-threo*-MP has a significantly slower clearance rate than *l-threo*-MP. At 74 minutes, *l-threo*-MP was shown to clear 50% of peak uptake, whereas *d-threo*-MP cleared only 10% to 15% (Ding et al 1997).

Pharmacokinetics of Methylphenidate

The pharmacokinetics of MP in the human brain were investigated using positron emission tomography (PET) and carbon-11 ([^{11}C]MP) (Volkow et al 1995). Labeling MP with ^{11}C allows for the determination of its concentration in the human brain without changing the pharmacologic properties of the drug. When administered intravenously (i.v.), the uptake of [^{11}C]MP in brain was high (7.5% ± 1.5%) and fast; peak concentration was reached in 4 to 10 minutes. The pharmacokinetics of orally administered MP in plasma were significantly slower than those of intravenous administration, and peak concentration in brain did not occur until 60 minutes after administration (Volkow

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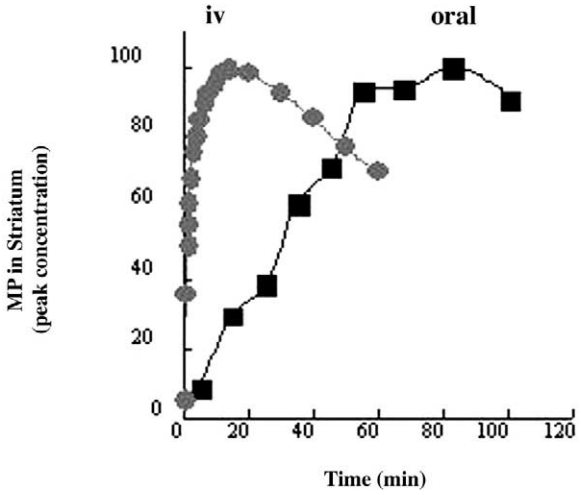


Figure 1. Time activity curves for the uptake and clearance of [^{11}C]methylphenidate (MP) in the nonhuman primate brain after intravenous and oral administration. Each curve has been normalized for its peak uptake.

et al 1995). The clearance of MP estimated after its intravenous administration showed a time to half-peak concentration that ranged from 50 to 90 minutes (Volkow et al 1995). Figure 1 shows the time activity curves for the uptake and clearance of MP in the nonhuman primate brain when given intravenously versus when given orally (a comparison between oral and i.v. could not be done in humans because of the relatively high radiation doses to the esophagus with oral [^{11}C]MP).

The distribution of MP in brain was heterogeneous, and the maximum concentration occurred in the striatum with lower levels in thalamus, cortex, and cerebellum. Specific binding of MP could only be documented to striatum where MP bound predominantly to DAT.

Imaging Studies of Methylphenidate in the Human Brain

Potency of Methylphenidate-Induced Dopamine Transporter Blockade

Imaging studies of the human brain have shown that MP dose dependently blocks the DAT in striatum. These studies showed that for intravenous administration, the MP required to block 50% of DAT (median effective dose [ED_{50}]) was estimated to be .075 mg/kg, and for oral administration, the ED_{50} was estimated to be .25 mg/kg (Volkow et al 1998). Thus, a standard therapeutic dose of .5 mg/kg is expected to block more than 60% of DAT. Although MP has been considered a weak psychostimulant due to the rapid metabolism of oral doses into ritalinic acid, which has a weak affinity for DAT, these results indicate that at the doses used, therapeutic MP blocks a large percentage of the DAT (Volkow et al 1998).

Relevance of Dopamine Blockade by Methylphenidate

Two hypotheses have been proposed to explain the relevance of DAT blockade by MP. The first hypothesis considers that as MP blocks the DAT, the extracellular DA activates autoreceptors in the presynaptic site, leading to an attenuation of DA release in response to phasic DA cell firing (Seeman and Madras 1998). The second hypothesis suggests that the blocked DAT overcomes the inhibitory effects for activation of the autoreceptors, leading to a net effect of DA accumulation in the synapse and amplification of DA signals that result from tonic as well as phasic DA cell firing.

To test these hypotheses, a placebo-controlled study of carbon-11-labeled raclopride ([^{11}C]raclopride), a DA D2 receptor radioligand that competes with endogenous DA for occupancy of the D2 receptors, was undertaken in healthy men (Volkow et al 2001). The [^{11}C]raclopride was administered to subjects before placebo or 60 mg of oral MP. Following treatments, PET images detected reduced binding of [^{11}C]raclopride in the striatum due to competition with DA for DA D2 receptors (Figure 2). The D2 receptor availability, indicated by B_{max}/K_d measures, was significantly reduced in the striatum (20 ± 12%; $p < .0005$) at oral doses of .8 ± .11 mg/kg (estimated for an average 70 kg adult).

Although MP blocks DAT, the increases in extracellular DA that it induces are likely due to both the blockade of DAT

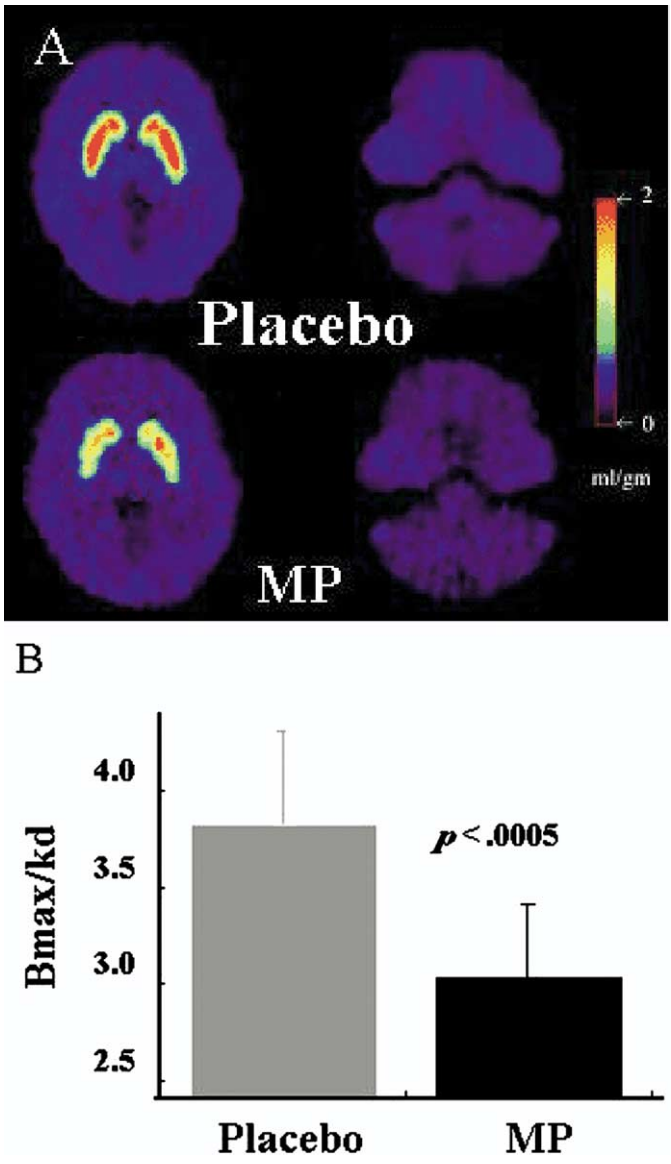


Figure 2. (A) Images of [^{11}C]raclopride in striatum and cerebellum after placebo and after oral MP (60 mg). **(B)** Measures of dopamine D2 (DA D2) receptor availability (B_{max}/K_d) in striatum after placebo and after oral MP. The decreases in B_{max}/K_d in striatum with oral MP reflect the increases in extracellular DA. MP, methylphenidate hydrochloride; DA, dopamine.

(Kuczenski et al 1997) and the rate of DA released, which is regulated by individual differences in DA cell firing and by environmental stimulation (Pucak and Grace 1994). This could explain the large intersubject variability in the magnitude of the increase in extracellular DA induced by MP despite similar levels of DAT blockade (Volkow et al 2001). We have hypothesized that the large variability in MP-induced DA increases may be responsible for the range of doses necessary to elicit a therapeutic response to MP among individuals with ADHD (Swanson et al 1991). We also hypothesize that low levels of DA cell activity may account for nonresponse to MP treatment in some individuals with ADHD.

Therapeutic Relevance of Increased Dopamine in ADHD

Treatment with MP leads to amplified DA signals by blocking DAT. Because DA is known to decrease background firing of striatal neurons while strengthening corticostriatal signals in striatal cells, its amplification increases the signal-to-noise ratio in target neurons (Kiyatkin and Rebec 1996). Thus, one could speculate that in individuals with ADHD, the MP-induced amplification of the striatal DA signal would lead to improved attention and decreased distractibility. Additionally, DA is a neurotransmitter that signals the saliency of stimuli and drives the motivation to perform goal-directed behaviors (Berridge and Robinson 1998; Hollerman and Schultz 1998; Koob 1996). Thus, it could also be speculated that the enhancement of DA signals by MP would cause an increased perception of saliency for the task, motivating the individual to engage in the task and improving attention and performance.

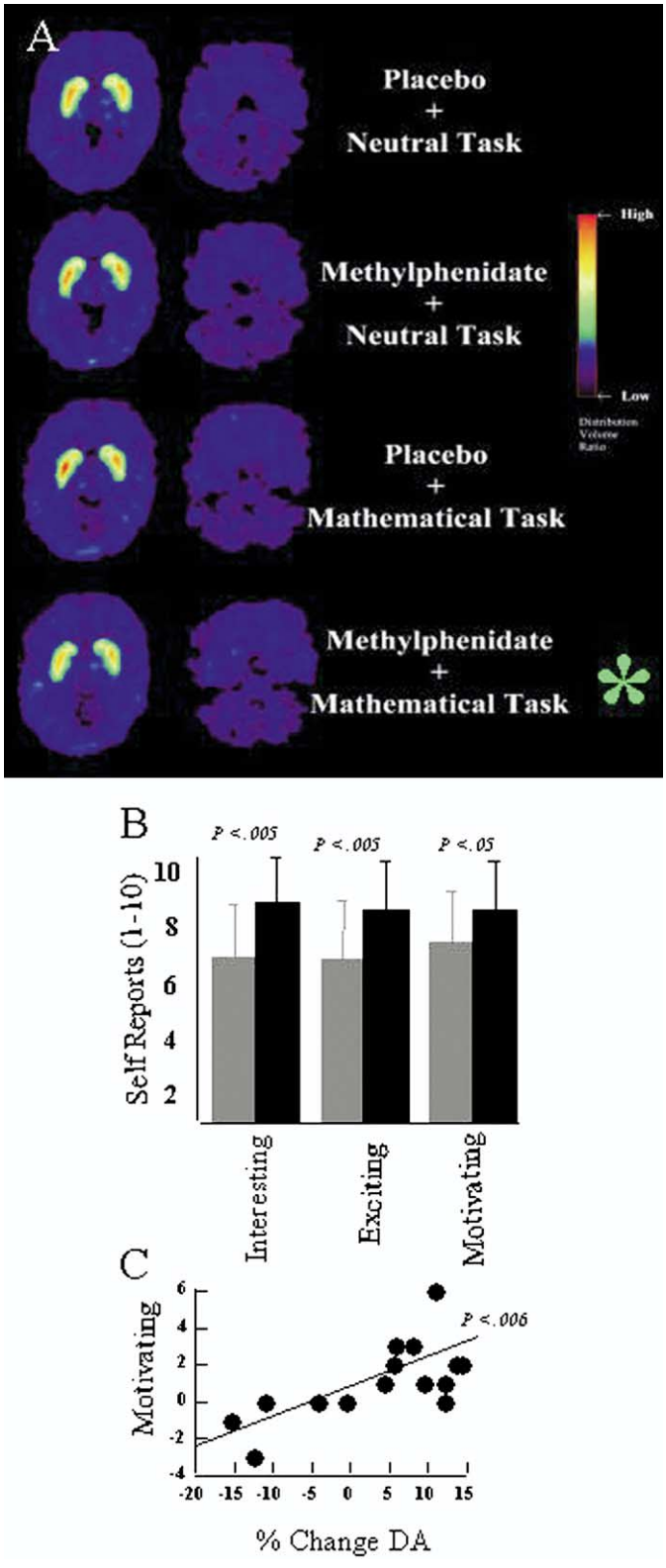
Methylphenidate as a Mechanism for Enhancing the Saliency of Stimuli

Because DA cells fire in response to salient events, which is a mechanism by which the brain signals that a stimulus is relevant and should be attended to, we reasoned that this could contribute to the therapeutic effects of MP. To determine if indeed increases in DA induced by MP were linked to an enhanced perception of events as salient, we conducted experiments involving appetitive stimuli and cognitive tasks. The study that evaluated the effects of MP on appetitive stimuli used PET and [^{11}C]raclopride to compare the changes in DA induced by food stimuli (visual and olfactory presentation of food items) versus neutral stimuli (description of family genealogy) when given with placebo or with MP (20 mg by mouth [PO]) and in parallel evaluated the self-reports for the "desire for the food" and for "hunger" (Volkow et al 2002). This study showed that MP induced significant increases in DA in dorsal striatum when given with food stimuli but not when given with the neutral stimuli. In contrast, no differences in DA were found among placebo-treated subjects exposed to food stimuli, suggesting that stimulus presentation alone was not strong enough to induce a DA change large enough to be detected by PET. Methylphenidate hydrochloride also increased the ratings in self-reports for "desire for food" and for "hunger" when exposed to the food stimuli as compared with placebo. The increases in the perception of hunger and desire for food were correlated with MP-induced increases in extracellular DA in dorsal striatum. These findings support the role of MP in enhancing DA signal saliency for appetitive stimuli. Although MP is traditionally considered an anorexigenic drug (Efron et al 1997; Golinko 1984), under these experimental conditions (food-deprived subjects exposed to food-conditioned stimuli they could not eat), it acted to increase the desire for the food. This result is consistent with preclinical studies that have shown that stimulant drugs enhance the incentive salience of food-conditioned stimuli (Files et al 1989; Wyvell and Berridge 2000), and when given in conjunction with conditioned food stimuli can increase food consumption (Konopacki et al 1985). These preclinical experiments as well as these PET data are consistent with the notion that DA increases the incentive salience of a conditioned cue (e.g., the sight, smell, and taste of food), causing the cue to increase the motivational state of "wanting" for the reward without necessarily enhancing its hedonic properties (Berridge and Robinson 1998; Richardson and Grafton 1996).

In the study of the cognitive task (Volkow et al 2004), we compared the DA increase induced by MP (20 mg PO) when given with an academic task (working mathematical problems with monetary reinforcement) and a neutral task (passively viewing nature cards with no remuneration). We used a mathematical task because this is frequently used as a measure to assess treatment efficacy in ADHD, and although in a classroom setting performance is not monetarily remunerated, it is often reinforced by grading (Swanson et al 1998a). We chose as a neutral task the passive view of scenery pictures rather than a mathematical task with no remuneration, because we wanted to optimize the contrast between a task that might maximize DA increases (mathematical task) and a task that would minimize DA increases (viewing pictures). Changes in DA levels were assessed with PET and [^{11}C]raclopride. Imaging results demonstrated that MP significantly increased DA only when given with the academic task but not when given with the neutral task (Figure 3). Moreover, the salient task when given with placebo failed to increase DA as assessed by changes in raclopride binding. In the evaluation of self-reports of saliency, significantly more MP-treated subjects rated the salient task as interesting and exciting or motivating compared with placebo-treated subjects (Figure 3). More placebo-treated subjects rated the task boring and tiresome compared with the MP-treated subjects. Methylphenidate hydrochloride induced increases in DA were significantly correlated with the increases in self-reports for interesting, exciting, and motivating (Figure 3). The significant association between MP-induced DA increases and the interest and motivation for the task confirms the prediction that MP enhances the saliency of an academic task by increasing DA. The enhanced interest for the task could increase attention and improve performance and could be one of the mechanisms underlying MP therapeutic effects. This study also demonstrated the context-dependency of MP's ability to increase extracellular DA, which was larger when the drug was given coupled to a task that was monetarily remunerated than when given with a nonremunerated task. Taken together, these two studies confirm in humans the context dependency of the pharmacologic effects of MP.

The context dependency of stimulant-induced DA increases has also been demonstrated in laboratory animals where it was shown that MP-induced increases in DA in the prefrontal cortex were significantly greater when rats were restrained at the time of administration than when they were not (Marsteller et al 2002). In clinical studies, the context dependency of stimulant medication was one of the first effects noted in early studies of "hyperactivity" (Conners 1966) and has been replicated in subsequent studies in children with ADHD (Porrino et al 1983). Recently, context dependency was documented in a laboratory school setting, in which children with ADHD treated with MP showed larger reductions in placebo-adjusted activity level in the classroom than in the playground setting (Swanson et al 2002). For these two studies, we chose a 20 mg dose, since it is one that is

regularly used in the treatment of ADHD; it is also a dose that would block > 50% of DAT. However, future studies evaluating dose response in ADHD subjects will help determine the optimal doses to enhance saliency for a stimulus in ADHD subjects. Nonetheless, results from these two PET studies support the notion of an amplification of DA increases by oral MP. They also confirm our hypothesis that MP will operate to amplify the saliency value of stimuli to which the subject may be exposed during everyday routines. These stimuli by themselves may have been insufficient to elicit DA responses that are strong enough and last long enough to signal saliency and drive and maintain interest and attention for the period required to complete the relevant task.



Evidence of Abnormalities in Brain DA Function in ADHD

A prominent theory of ADHD is that there is a dysfunction of DA neurotransmission, with a consequent dysregulation of DA-modulated circuits. These include frontal (prefrontal, motor frontal, cingulate gyrus), subcortical (striatum, mediodorsal thalamus), and limbic brain regions (nucleus accumbens [NAc], amygdala, and hippocampus). The striatum (including NAc) appears to play a prominent role in ADHD symptoms: Symptoms of inattention have been mainly linked with striatum and cingulate gyrus (Bush et al 1999), those of hyperactivity with striatum (Teicher et al 2000), and those of impulsivity with NAc (Cardinal et al 2001). Impairment in executive tasks has been linked with dorsolateral prefrontal cortex (Castellanos 1997; Dinn et al 2001). Involvement of these regions does not exclude the participation of regions that are not connected with the DA system (e.g., parietal cortex, cerebellum) (Aman et al 1998).

Evidence of DA dysfunction in ADHD is supported by: 1) pharmacological studies, which show that DA agonists ameliorate ADHD symptoms (Ebstein et al 1997; Greenhill et al 1999; Shenker 1992); 2) genetic studies, which show that the strongest candidate genes associated with ADHD are the DA D4 receptor (Ebstein et al 1997; LaHoste et al 1996; Rowe et al 1998; Swanson et al 1998c) and the DAT genes (Cook et al 1995; Gill et al 1997; Waldman et al 1998); 3) imaging studies, which show abnormalities in DA metabolism (Ernst et al 1998, 1999), DAT (Dougherty et al 1999; Krause et al 2000), and in DA D2 receptors in ADHD (Ilgin et al 2001); 4) brain anatomical studies, which show morphological changes in targets areas of DA neurons (frontal lobes and striatum) in subjects with ADHD (review Giedd et al 2001; Overmeyer and Taylor 2000); and 5) functional imaging studies, which show involvement of frontal-striatal circuitry and of the anterior cingulate gyrus (Bush et al 1999) in ADHD. However, it should be noted that the imaging studies are still not definitive because of the discrepancies in the findings. For example, while studies with [^{18}F]fluorodopa ([^{18}F]DOPA) to assess DA synthesis and metabolism have reported lower binding in prefrontal cortex in ADHD adults than in control subjects (Ernst et al 1998), they have reported higher binding in right midbrain in ADHD children than in control subjects (Ernst et al 1999). Also, studies measuring DAT in ADHD adults have reported DAT increases (Dougherty et al 1999; Krause et al 2000)

Figure 3. (A) Images of [^{11}C]raclopride in striatum and cerebellum for four conditions: neutral task with placebo, neutral task with oral MP (20 mg), mathematical task with placebo, and mathematical task with oral MP. Binding of [^{11}C]raclopride in the striatum was lowest for the mathematical task with MP condition. **(B)** Comparison of the self-reports for the descriptors of the mathematical task when given with placebo versus when given with oral MP. MP significantly increased the perception of the task as interesting, exciting, and motivating. **(C)** Relationship between the changes in extracellular DA during the mathematical task when given with MP and the changes in the perception of the mathematical task as motivating (when compared with placebo). MP, methylphenidate hydrochloride; DA, dopamine.

or no changes (van Dyck et al 2002). The reasons for the discrepancies are unclear but may reflect differences in ADHD patients studied (gender, medication histories, subtypes), methodologies, or high D2 receptors secondary to genetic or other factors that regulate D2 receptor expression.

Conclusions

Methylphenidate is one of the most frequently prescribed treatments for the neurobehavioral disorder ADHD. Dopamine deficiency has been implicated in the pathogenesis of ADHD, and this could explain why stimulant drugs such as MP that increase DA could temporarily relieve the symptoms of the disorder. Although it had been previously hypothesized that therapeutic effects of MP are due to increased tonic DA levels that stimulate DA autoreceptors and attenuate phasic DA increases (Seeman and Madras 1998), imaging studies have demonstrated that the long-lasting blockade of DAT by MP actually amplifies stimulus-induced DA increases (their magnitude and duration). They also showed that MP-induced increases of DA were associated with an enhanced perception of the stimuli as salient. Thus, we postulate that MP at therapeutic doses will operate to amplify the saliency value of stimuli to which the subject may be exposed during everyday routines and which by themselves may be insufficient to elicit DA responses that signal saliency and drive interest and attention. Future studies comparing the effects of MP in ADHD versus control subjects are required to directly test this "saliency enhancing" model for MP's therapeutic effects in ADHD.

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