Effects of Methylphenidate on Regional Brain Glucose Metabolism in Humans: Relationship to Dopamine D_2 Receptors

Nora D. Volkow, M.D., Gene-Jack Wang, M.D., Joanna S. Fowler, Ph.D., Jean Logan, Ph.D., Burton Angrist, M.D., Robert Hitzemann, Ph.D., Jeffrey Lieberman, Ph.D., and Naomi Pappas, M.S.

Objective: *The authors' goals were to determine whether baseline dopamine activity contributes to response to methylphenidate and to assess the pattern of metabolic responses associated with enhanced dopamine activity.* *Method:* *They used positron emission tomography with 2-deoxy-2[18F]fluoro-D-glucose to evaluate the effects of two sequential doses of methylphenidate on brain metabolism in 15 healthy subjects. Dopamine D_2 receptor availability was measured with [11C]raclopride to evaluate its relation to methylphenidate-induced metabolic changes.* *Results:* *Methylphenidate increased brain metabolism in six subjects, decreased it in two, and did not change it in seven; however, it consistently increased cerebellar metabolism. Methylphenidate significantly increased "relative" (region relative to the whole brain) metabolism in the cerebellum and decreased it in the basal ganglia. Regional metabolic changes in the cerebellum and the frontal and temporal cortices were significantly correlated with D_2 availability. Frontal and temporal metabolism were increased in subjects with high D_2 receptors and decreased in subjects with low D_2 receptors.* *Conclusions:* *Methylphenidate induced variable changes in brain metabolism, but it consistently increased cerebellar metabolism. It also induced a significant reduction in relative metabolism in the basal ganglia. The significant association between metabolic changes in the frontal and temporal cortices and in the cerebellum and D_2 receptors suggests that methylphenidate's metabolic effects in these brain regions are due in part to dopamine changes and that differences in D_2 receptors may be one of the mechanisms accounting for the variability in response to methylphenidate.*

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Dopamine is a neurotransmitter that plays a pivotal role in the regulation of movement, motivation, reward, and cognition (1). Abnormalities in brain dopamine are associated with specific neuropsychiatric disorders (i.e., Parkinson's disease, schizophrenia, and substance abuse). Understanding the role of dopamine in brain function, therefore, is a topic of major importance. Neuroimaging techniques have recently made possible the investigation of the role of dopamine in the function and organization of the living human brain (2). One strategy has been to evaluate the effects of drugs that enhance or antagonize dopamine function in regional brain metabolism or cerebral blood flow (2). Although not always consistent with regard to the direction of the metabolic changes, most studies investigating the effects of dopamine agonists or antagonists have shown changes predominantly located in the basal ganglia, frontal cortex, and temporal cortex (these studies have been reviewed by Wolkin et al. [3]). However, interpretation of these changes is confounded by the inability to determine whether such changes reflect effects on the dopamine system or nonspecific effects.

The present study used positron emission tomography (PET) with [11C]raclopride to measure D_2 receptors at baseline (2) and PET with 2-deoxy-2[18F]-fluoro-D-glucose (FDG) to evaluate regional brain metabolism (4) at baseline and after administration of two sequential doses of methylphenidate given 90 minutes apart. This paradigm allowed us to evaluate which

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of the regional metabolic changes induced by methylphenidate correlated with baseline D_2 measures and to assess whether the variability in response to methylphenidate (5–7) was mediated in part by differences in D_2 receptors between subjects. Methylphenidate was used because it induces a sustained and long-lasting inhibition of dopamine transporters in the brain (half-life >90 minutes) (8). We chose a two-sequential-dose strategy rather than an acute administration procedure to minimize the immediate responses that might follow an abrupt disruption in dopamine concentration. We hypothesized that dopamine-enhancing drugs would change activity in the basal ganglia and in the frontal and temporal cortices and that an individual's D_2 receptor measures would predict the magnitude of methylphenidate-induced metabolic changes in these brain regions.

METHOD

Subjects

We studied 15 healthy right-handed male subjects (mean age=35 years, SD=7, range=24–45) who were screened for absence of medical, psychiatric, and neurological disease. Special attention was given to ensure that subjects did not abuse addictive substances, and urine toxicology studies were performed to ensure lack of psychoactive drug use. The study was approved by the Human Protection Committees at Brookhaven National Laboratory and the Department of Veterans Affairs Hospital at Northport, N.Y. Written informed consent was obtained from each subject after each had been given a complete description of the study. The behavioral responses to methylphenidate of these subjects were described in a study that compared behavioral responses to methylphenidate between normal subjects and cocaine abusers (9).

Scans

Each subject underwent two FDG studies done on separate days and a [11C]raclopride study, all within a 10-day period. The first FDG scan was done 7 minutes after two sequential doses of placebo (baseline), and the second FDG scan was done 7 minutes after the second of two sequential intravenous doses of methylphenidate. The first dose was 0.5 mg/kg and was administered 90 minutes prior to the second dose, which was 0.25 mg/kg. The order of administration (placebo versus methylphenidate) was fixed to avoid possible long-lasting effects of methylphenidate on brain metabolism. [11C]Raclopride studies were conducted 7 minutes after administration of placebo and were always done prior to the baseline metabolic scan. Subjects were blind to the drugs received. Prior to the administration of placebo or methylphenidate and 27 minutes after the first and the second methylphenidate dose and at the end of the study (157 minutes after the first methylphenidate dose), subjects recorded their subjective emotional experience for "high," anxiety, restlessness, distrust, alertness, sexual desire, and mood, using analog scales ranging from 0 to 10 (9). Methylphenidate concentration in plasma was measured 27, 67, 97, and 127 minutes after administration of the first methylphenidate dose by using capillary gas chromatography-mass spectrometry.

PET scans were done on a CTI 931 tomograph (6.5 mm×5.9 mm×5.9 mm full width at half maximum, 15 slices). For FDG, one emission scan was taken 35 minutes after intravenous injection of 4–6 mCi of FDG for a total of 20 minutes. For [11C]raclopride, sequential emission scans were obtained immediately after intravenous injection of 4–10 mCi of [11C]raclopride (specific activity=0.5–1.5 Ci/mM at end of bombardment) and were continued for a total of 60 minutes as described elsewhere (10). Details on the synthesis of FDG and [11C]raclopride, venous and arterial catheter placement, subject positioning and repositioning, transmission and emission scans, blood sampling procedures, quantification and metabolite analyses ([11C]-raclopride), and procedures for calculation of metabolic rates have been described elsewhere (10, 11).

Image Analysis

For the metabolic images, we used a template that we have described elsewhere (11) to locate 72 regions of interest, which were then individually fitted to each subject's images. Weighted averages of the regions of interest from different slices corresponding to the same anatomical areas were computed into 15 "composite" brain regions. A measure of "whole brain" metabolism was obtained by averaging the metabolisms of the 15 brain slices. For the [11C]raclopride images, regions of interest were obtained in the basal ganglia and in the cerebellum as described elsewhere (10). The time activity curves for [11C]raclopride in the basal ganglia and in the cerebellum and the time activity curves for unchanged tracer in plasma were used to obtain distribution volumes (12). The ratio of the distribution volume in the basal ganglia to that in the cerebellum, which corresponds to B_{max}/K_d plus 1 and is insensitive to changes in cerebral blood flow, was our measure of D_2 receptor availability (13).

Effects of methylphenidate on regional brain metabolism were tested with both parametric (repeated measures analysis of variance [ANOVA]) and nonparametric (Wilcoxon signed ranks test) measures to account for possible deviations in the statistical assumptions of ANOVA. To assess the significance of the differences in variability for the regional metabolic measures between placebo and methylphenidate, we used a test for equality of variances for dependent samples (14). The significance of individual changes after methylphenidate administration was evaluated by performing separate ANOVAs for each subject. Pearson product-moment correlation analyses were performed between the regional changes in the metabolic values (placebo compared with methylphenidate) and the estimates for B_{max}/K_d. We also assessed the effects of methylphenidate on "relative" (region of interest relative to the whole brain) metabolism with repeated measures ANOVA.

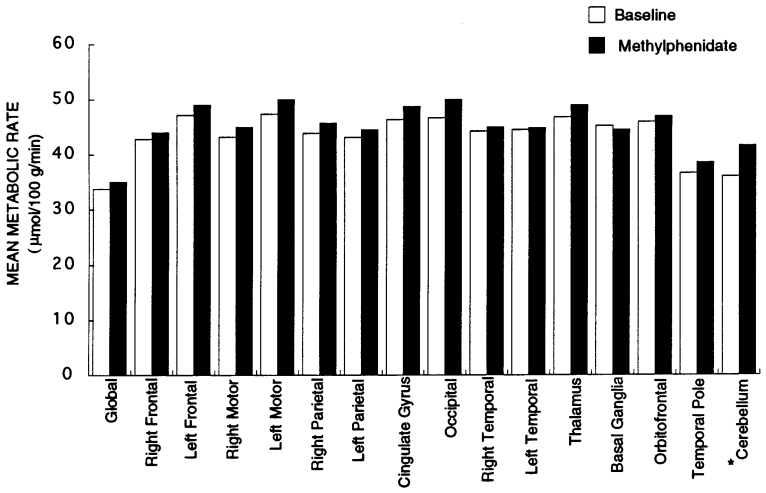
To correct for multiple comparisons in the group effects, we set the level of significance at $p>0.01$; values between $p>0.01$ and $p<0.05$ are reported as trends. We did not use Bonferroni corrections because they assume independence of variables and the measurements are highly correlated with one another (15). The individual analyses are corrected with Bonferroni ($p<0.003$).

RESULTS

Mean serum concentrations of methylphenidate were 122 ng/ml (SD=12) at 27 minutes; 78 ng/ml (SD=15) at 67 minutes, and 58 ng/ml (SD=9) at 90 minutes after administration of the first methylphenidate dose and 130 ng/ml (SD=21) at 37 minutes and 99 ng/ml (SD=14) at 67 minutes after the second dose. Some subjects described methylphenidate as feeling pleasurable, but others described intense feelings of anxiety and restlessness. The effects of methylphenidate on the behavioral measures were significantly higher ratings for "high" ($F=29.4$, $df=3, 43$, $p<0.0001$), restlessness ($F=24.4$, $df=3, 43$, $p<0.0001$), alertness ($F=6.24$, $df=3, 43$, $p<0.001$), and anxiety ($F=4.7$, $df=3, 43$, $p<0.007$).

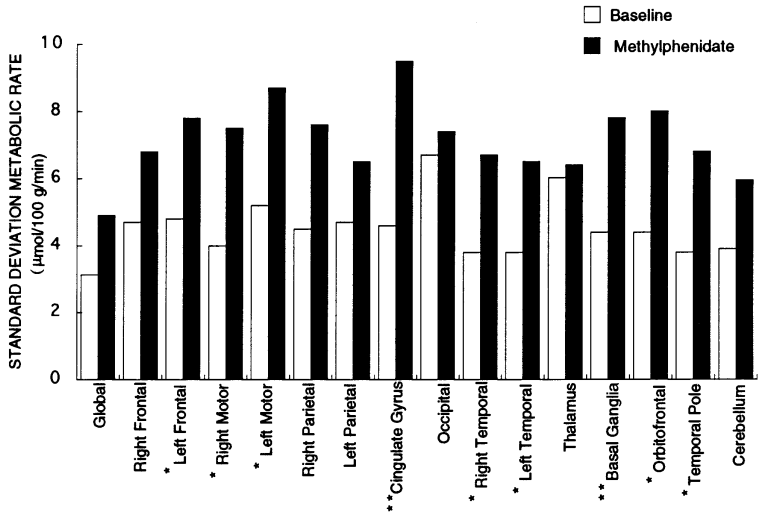
The metabolic changes induced by methylphenidate varied among subjects: methylphenidate significantly increased metabolism in six subjects, decreased it in two, and did not change it in seven. Repeated measures were significant for methylphenidate-induced increases

FIGURE 1. Mean Values for Regional Brain Metabolic Measures in 15 Normal Subjects After Placebo Administration (Baseline) and After Methylphenidate Administration[a]



[a]Analysis of variance and Wilcoxon signed ranks test were used to determine the significance of differences between baseline and postmethylphenidate values.
*p<0.001.

FIGURE 2. Standard Deviations for Regional Metabolic Measures in 15 Normal Subjects After Placebo Administration (Baseline) and After Methylphenidate Administration[a]



[a]t tests were used to determine the significance of differences between baseline and postmethylphenidate values.
*p<0.05. **p<0.01.

only in cerebellar metabolism (F=14.2, df=1, 14, p<0.003; Wilcoxon z=–2.987, p<0.003) (figure 1). The variability of the regional metabolic measures was increased by methylphenidate (figure 2). Differences in variability were significant in the cingulate gyrus (t=3.53, df=13, p<0.01) and orbitofrontal cortex (t=3.16, df=13, p<0.01) and showed a trend in the left prefrontal cortex, left and right motor cortex, right and left temporal cortex, basal ganglia, and temporal poles (t values >2.2, df=13, p<0.05).

Regional metabolic changes induced by methylphenidate in the cerebellum and frontal and temporal cortices were significantly correlated with B_{max}/K_d (table 1). In the cerebellum, the higher the B_{max}/K_d values the larger the increases in metabolism; in the frontal and temporal cortices, low B_{max}/K_d values were associated with reductions in metabolism, whereas high B_{max}/K_d values were associated with increases in metabolism (figure 3). The metabolic changes were not correlated with subjects' age, plasma methylphenidate concentration, or behavioral measures.

Methylphenidate induced significant increases in relative metabolism in the cerebellum (placebo mean=1.08, SD=0.07, methylphenidate mean=1.19, SD=0.10) (F=18, df=1, 14, p<0.001) and significant decreases in relative metabolism in the basal ganglia (placebo mean=1.34, SD=0.06; methylphenidate mean=1.26, SD=0.08) (F>19.3, df=1, 14, p<0.001) and a trend for a decrease in the left temporal cortex (placebo mean=1.32, SD=0.08; methylphenidate mean=1.27, SD=0.05) (F>5.6, df=1, 14, p<0.05) and orbitofrontal cortex (placebo mean=1.39, SD=0.09; methylphenidate mean=1.34, SD=0.12) (F>4.5, df=1, 14, p<0.05).

DISCUSSION

The findings from this study can be summarized as follows: 1) In some subjects, methylphenidate increased and in others it decreased regional brain metabolism, except for the cerebellum, where methylphenidate consistently increased metabolism. 2) The metabolic changes in frontal, temporal, and cerebellar metabolism in response to methylphenidate were associated with measures of dopamine D_2 receptor availability. 3) The variability of regional metabolic measures was increased by methylphenidate. 4) Changes in metabolic activity with two sequential doses of methylphenidate differ markedly from the results previously reported after acute psychostimulant administration. 5) methylphenidate decreased relative metabolic activity in the basal ganglia.

These results show that changes in brain dopamine concentration can lead to either increases or decreases in cortical and subcortical metabolism. Therefore, the effects of dopamine cannot be conceptualized as simply excitatory or inhibitory on metabolic activity. This corresponds to the well-recognized role of dopamine as a neurotransmitter that modulates the activity of brain

regions enabling both excitatory as well as inhibitory signals (16). It also explains the seemingly paradoxical reports of the same regional brain metabolic changes in schizophrenic patients when given a dopamine agonist (amphetamine) and when given a dopamine antagonist (haloperidol) (3).

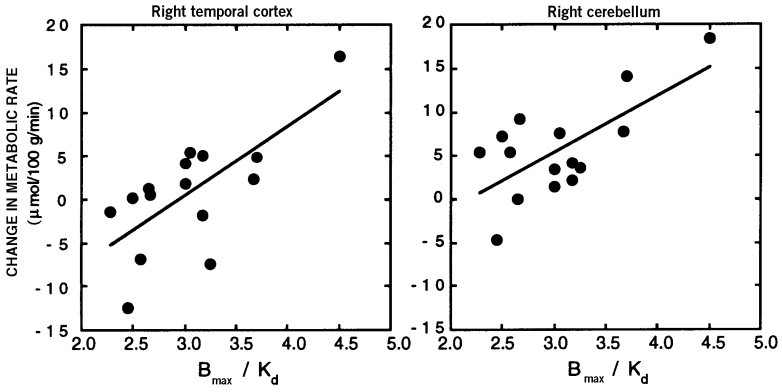
The significant correlation between methylphenidate-induced changes in metabolism and D_2 receptors would suggest that the effects of dopamine on brain activity depend in part on the state of the dopamine system. This corresponds well with animal studies, which have consistently shown that responses to psychostimulants are determined in part by the state of the dopamine system (17, 18). The dependency of responses to methylphenidate on the state of the dopamine system could provide an explanation for the seemingly paradoxical effect that methylphenidate has on the symptoms of children with attention-deficit/hyperactivity disorder (ADHD) (19). In fact, previous studies had shown that the therapeutic response to methylphenidate in ADHD could be predicted on the basis of the individual's levels of homovanillic acid in CSF: higher concentrations were associated with better drug responses (20). Future studies evaluating D_2 receptors in ADHD will enable a determination of whether there are changes that could help predict response to psychostimulants. The dependency of responses to methylphenidate on the state of the dopamine system could also account for the heterogeneous responses to psychostimulants observed in schizophrenic patients. For example, some schizophrenic patients develop psychotic symptoms but others improve with psychostimulant drugs (this issue was reviewed by van Kammen et al. [21]). Future studies assessing the relation between D_2 receptor measures in schizophrenic patients and their response to amphetamine may enable us to determine whether the predictive value of the psychostimulant challenge in schizophrenic patients (22) relates to differences in dopamine D_2 receptors.

TABLE 1. Correlations Between Regional B_{max}/K_d Estimates and Metabolic Changes Induced by Methylphenidate[a] for 15 Normal Subjects

Region	r	p
Right prefrontal	0.60	0.05
Left prefrontal	0.68	0.006
Right motor frontal	0.54	0.04
Left motor frontal	0.52	0.05
Right parietal	0.64	0.005
Left parietal	0.50	0.06
Cingulate gyrus	0.64	0.01
Occipital	0.52	0.05
Right temporal	0.70	0.005
Left temporal	0.74	0.002
Thalamus	0.49	0.06
Basal ganglia	0.55	0.03
Orbitofrontal	0.71	0.003
Temporal pole	0.64	0.01
Cerebellum	0.68	0.005

[a]Difference between values after placebo administration and values after methylphenidate administration.

FIGURE 3. Regression Slopes for Association Between B_{max}/K_d Estimates and Metabolic Changes Induced by Methylphenidate[a] in the Right Temporal Cortex and Right Cerebellum for 15 Normal Subjects



[a]Difference between values after placebo administration and values after methylphenidate administration.

The association between D_2 and changes in metabolic activity in the frontal and temporal cortices serves to corroborate a role of dopamine in the metabolic activity of these brain regions. Metabolism in the frontal and temporal cortices (in addition to the basal ganglia) has been shown to be consistently affected by dopamine agonists and dopamine antagonists (this issue was reviewed by Wolkin et al. [3]). Our failure in this study to show an association between changes in basal ganglia metabolism and D_2 receptors may reflect the predominant influence of nerve terminals in the metabolic signal (23).

The increased cerebellar metabolism induced by methylphenidate is intriguing because this region is almost devoid of D_2 receptors (24). Although it could be argued that it represents the effects of methylphenidate on the norepinephrine transporter (25), the fact that the metabolic changes in the cerebellum were significantly associated with D_2 receptors suggests that they are mediated in part by dopamine. This interpretation is supported by studies showing that dopamine agonists increase (26, 27) and dopamine antagonists decrease (3, 28) cerebellar metabolism. These apparently discrepant findings can be accounted for by the fact that metabolism predominantly reflects activity in nerve terminals (23) and hence could reflect the effects of methylphenidate on striatal projections into the cerebellum (24). This finding is also intriguing vis à vis the therapeutic properties of methylphenidate. Although the cerebellum has been classically identified as a region involved in motor coordination, there is increasing evidence that it plays an important role in higher cognitive functions, including memory, learning, and attention (29, 30)—

processes that are disrupted in ADHD (31) and have been shown to be improved by methylphenidate (32). It is also noteworthy that cerebellar pathology has been documented in children with learning disabilities (33). Thus, one should evaluate the possibility that methylphenidate could exert its beneficial effects in part by its activation of cerebello-thalamo-frontal circuits (29).

Variability in regional brain metabolic measures between individuals increased after methylphenidate administration. Similar findings were reported for the behavioral effects of amphetamines in schizophrenic patients (21). Because the dopamine system has been shown to display wide variability between individuals (34), one could speculate that enhancing dopamine activity by methylphenidate accentuates this variability. However, further studies are required to determine the significance of this finding.

Although the results from this study are similar to those reported after oral administration of methylphenidate (35), they differ from those reported with other psychostimulants: decreases in metabolism have been found after administration of amphetamine (3) and cocaine (36). We do not believe that this discrepancy indicates a fundamental difference between methylphenidate and other psychostimulants because animal studies have shown that regional brain metabolic responses to acute administration of equivalent doses of psychostimulant drugs, including methylphenidate, are quite similar (37, 38). It is more likely to reflect differences in the experimental conditions, subjects, or pharmacological variables (doses, route of administration, timing). In particular, we believe that the dosing paradigm in this study (two sequential methylphenidate doses) is a major contributor to the differences. Studies that documented decrements in metabolism administered a single acute dose at the time when peak behavioral effects were observed, whereas the current study evaluated methylphenidate-induced changes under conditions that maintained drug effects for a sustained time. Because the dopamine system adapts differently to fast tonic changes than to slower phasic ones (39), one should not necessarily expect the same metabolic responses to an abrupt increase in dopamine concentration as to a sustained longer-lasting increase. The steady and relatively long-lasting plasma concentrations achieved by oral administration of methylphenidate (40) could explain the similarities between results obtained in this study and those obtained after oral administration of methylphenidate. Because drugs are rarely taken as single doses, either for therapeutic or for abuse purposes, studies should be done to evaluate differences in metabolic responses between single and repeated doses and between oral and intravenous routes of administration.

The decrease in relative metabolic activity in the basal ganglia after administration of methylphenidate is in agreement with the literature on the sensitivity of this brain region to the effects of dopamine agents (3). Failure to observe an effect for the analysis with the "absolute" metabolic measures highlights the relevance of separately assessing both normalized and absolute measures.

The findings in this report need to be considered in the light of a potential drug interaction effect because the repeated metabolic measures in general tend to be lower on the second study than on the first (41; E.D. London, personal communication). The results also highlight the relevance of an individual subject's analysis as well as average group effects. Lack of a correlation in this study between behavioral and metabolic effects of methylphenidate may reflect the fact that behavioral states are likely to implicate activation or deactivation of several brain regions.

Several leads for future studies arise from the current results: 1) investigation of the differences between the metabolic response to psychostimulant drugs when administered after a single acute dose and after repeated doses, 2) evaluation of the role that methylphenidate-induced cerebellar activation has on its therapeutic actions, and the 3) evaluation of the relation between D_2 receptor measures in schizophrenic patients and their psychotogenic response to psychostimulant drugs.

In summary, this study shows that methylphenidate significantly and consistently increased cerebellar metabolism and that its effects in other brain regions varied markedly between subjects. The fact that methylphenidate-induced metabolic changes in the frontal and temporal cortices and in the cerebellum were correlated with D_2 measures indicates that they reflect in part changes in dopamine concentration and that the variability in responses to methylphenidate is in part related to differences in D_2 receptor availability. However, because associations do not prove causality links, future studies are required to delineate the role of dopamine on the function of these brain regions.

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