Methylphenidate Increased Regional Cerebral Blood Flow in Subjects with Attention Deficit/Hyperactivity Disorder

Boong-Nyun Kim[1]*, Jae-Sung Lee[2], Soo-Churl Cho[1], and Dong-Soo Lee[2]

[1]Division of Child & Adolescent Psychiatry, Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Korea
[2]Department of Nuclear Medicine, Seoul National University Hospital, Seoul, Korea

The regional cerebral blood flow (rCBF) responses to methylphenidate (MPH) treatment were examined in children with attention deficit/hyperactivity disorder (ADHD). Thirty-two male children, diagnosed with ADHD by the DSM-IV diagnostic criteria, other behavioral assessment scales and neuropsychological battery, were studied using ^{99m}Tc-HMPAO-single photon emission computed tomography (SPECT). Subjects were studied before and after MPH treatment. First, using an image subtraction method, we obtained a NDR parametric image of each patient and found increased cerebral blood flow in the frontal lobes, caudate nuclei and thalamic areas after treatment. When the changes in SPECT and clinical response were compared, the matching rate, sensitivity and specificity between them were found to be 77.1, 80.0 and 79.2%, respectively. Second, three transaxial brain slices delineating anatomically defined regions of interest (ROI) at 20, 40, and 60 mm above the orbitomeatal line (OML) were used, with the average number of counts for each region of interest normalized to the area of the cerebellar maximal uptake. The left and right prefrontal areas, and caudate and thalamic areas showed significant increases in rCBF after MPH treatment. These findings suggested MPH could affect the function of the fronto-striato-thalamic circuit, which is known as the pathophysiologic site of ADHD and could be used to correct the underlying brain dysfunction of ADHD.

Key Words: SPECT, ADHD, methylphenidate, pre and post treatment

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is the most frequently diagnosed pediatric behavioral disorder and affects 3-10% of school- age children.[1-3] A recent review of data obtained from numerous studies on ADHD suggested the importance of underlying neurobiological pathophysiology.[4]

Brain imaging techniques have rapidly developed and have been applied in the field of ADHD research, since the late 1980s.[5,6] Converging evidence from structural and functional imaging studies implicates abnormalities in the fronto-striatal network as the likely cause of ADHD.[7-10]

The behavioral symptoms of ADHD, such as inattention, hyperactivity and impulsivity, are effectively managed by psychostimulants.[11] Despite the widespread use of psychostimulants in the management of behavioral symptoms, the precise effect on the brain function is unclear.[12] Efforts to investigate this issue using brain imaging studies have met with mixed success. The first functional imaging study using Xe[133]-SPECT with ADHD children showed increases of blood flow in the striatum after MPH administration.[13] Other studies using FDG-PET with ADHD adults,[14,15] however, failed to reveal significant changes in the regional cerebral metabolic rate of glucose (rCMRglu) after the acute and chronic administration of psychostimulants. The first study,[16] however, had a major limitation because subjects were few and very heterogeneous. To

date, there has been no well-designed study of a larger group of homogeneous school-age subjects that are pure ADHD patients.

To our knowledge, this is the first functional imaging study to examine the effects of psychostimulants on children with pure ADHD. The main purpose of this study was to examine MPH-induced changes of cerebral blood flow for determining the action site of MPH in ADHD, using both SPECT image subtraction and the region of interest (ROI) method.

METHODS

Subjects

Before the study, its nature and purpose were fully explained to the patients and their parents, and a written informed consent was obtained from each child's parent and a written assent from each child for all procedures. The Ethics Committee of the Department of Nuclear Medicine and Neuropsychiatry, Seoul National University, Seoul, Korea, approved the protocol.

A total of 32 male, right-handed ADHD patients participated in this study. All subjects had been living in ordinary family environments and attending regular schools. At least one certified child psychiatrist and child psychologist evaluated each subject. All patients included in this study were clinically diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[1] Patients with any comorbid psychiatric diagnoses, such as depression, anxiety, conduct disorder or learning disorders, were excluded. All ADHD subjects were free from any general medical condition. These were confirmed by medical and neurological examinations and laboratory tests.

Intellectual and learning abilities were assessed using the Korean version of Wechsler Intelligence Scale for Children-Revised (KWISC)[17] and the Luria-Nebraska Neuropsychological Battery (LNNB).[18] ADHD subjects suspected of being afflicted with mental retardation and learning disorders were excluded.

Behavioral and emotional problems were assessed using the Child Behavior Checklist

(CBCL),[19] Yale Children's Inventory (YCI),[20] Conners' Parent Rating Scale (CPRS) and Conners' Teacher Rating Scale (CTRS),[21] which have been standardized in Korea. The clinical characteristics of these subjects are presented in Table 1.

Table 1. Demographic and Psychometric Variables of Subjects

Variable	ADHD (n=32)
Age	
Mean (SD)	10.6 (5.6)
Range	7-14
Grade	
Mean (SD)	5.4 (2.7)
Range	Kindergarten-primary school
WISC-R	
Mean (SD)	105.7 (12.8)
Range	92-124
Degree of achievement	
High	25%
Middle	60%
Low	15%

Data are given as mean (SD). ADHD indicates attention-deficit hyperactivity disorder
SD: Standard Deviation
WISC-R: Wechsler Intelligence Scale for Children-Revised

Procedures

Before MPH treatment, various questionnaires, a psychometric test and neuropsychological battery were applied to the patients and their parents. The patients that had completed the assessments and scales in a drug naive state underwent the first brain SPECT. Patients then received MPH treatment for 8 weeks, at a mean dosage of 0.7 mg/kg. All patients were re-evaluated with a second behavioral assessment and SPECT examination after the 8 week MPH treatment, which is a long enough period to evaluate drug response and the impacts on cerebral blood flow in view of the very short half life and rapid onset of the action of MPH.

Methylphenidate treatment and evaluation of response

The subjects had never been treated with stimulants or other psychiatric medication before

this study. After a baseline SPECT scan, each subject began to take MPH. The dose was individually titrated. The starting dose was a 5 mg bid, and gradually increased, by effect monitoring and particularly adverse effects. The maximum dose did not exceed 1.0 mg/kg/day. On the day of the second scan, MPH was administered 90 minutes before Tc-HMPAO injection.

To differentiate responders from non-responders, we applied three strict criteria. First, total scores in both Conners' Parent and Teacher Rating Scales should decrease 40% after treatment. Second, obvious clinical improvement should be reported by parents or be observed by clinicians at the follow-up session after 8-weeks of treatment. Third, symptom improvement should be maintained until telephone interviews with parents at 12 weeks after the second SPECT scan. Patients fulfilling all three criteria throughout the evaluation process were included in the response group. As a result, 20 patients of 32 (62.5%) were included in the responders group.

Scan acquisition and Image processing

SPECT imaging was performed before and after treatment. All subjects received an intravenous injection of 15 mCi of ^{99m}Tc-HMPAO and were placed in a quiet, dimmed room, in a supine position with eyes closed with head immobilized on a headrest and secured with Velcro straps, to preclude auditory and visual stimulation. SPECT images were obtained with a triple head rotating camera equipped with a high-resolution collimator. Image acquisition began approximately 20 minutes after the injection of ^{99m}Tc-HMPAO. Data was collected in 120 projections, which were produced every three degrees. Processing included normalization, backprojection, filtering, trans-axial reconstruction and attenuation correction. Reconstruction was carried out with a Metz filter on a 120*120 matrix with a slice thickness of 1.67 mm. Resolution of the system was 8.3 mm at full width half maximum.

Analysis of the Image by the imaging subtraction method

After 8-weeks of MPH treatment, each subject

underwent a second SPECT scan. Therefore, two SPECT brain images from the baseline and post-treatment states were obtained in each subject. Using a workstation (Indigo2, Silicon Graphics), we developed software for acquiring subtraction images from two SPECT scans, which has been standardized in the Department of Nuclear Medicine of Seoul National University Hospital. The sequence for making subtraction SPECT images was as follows.

The post-treatment scan was normalized on the pretreatment scan so that each pixel value of the post-treatment scan was related to the corresponding pixel value of the pretreatment scan. A subtraction image was calculated by subtracting the pretreatment scan pixel by pixel from the post-treatment scan. In subtraction SPECT, we used the normalized difference ratio (NDR) of pixel count ((posttreatment-pretreatment)/pretreatment × 100%) parametric image to assess the quantitative change in blood flow. To determine the anatomical position more accurately, we developed a brain contour program, using the same workstation, which automatically differentiates ventricle, cortex and subcortex. Contouring each parametric image, we compared the resulting image with the standard pediatric brain atlas.

The subtraction method used had found to be both valid and reliable in previous studies.[22,23] The reading of the NDR parametric images was conducted by two or more experienced neuroradiologists that were blind to the subjects clinical status.

Analysis of the Image by the Region of interest method

A total of 3 slices were analyzed in each subject. Slices were acquired parallel to the orbitomeatal line (OML) and were of 16 mm thickness. For analysis, 3 planes at 20 mm, 40 mm, and 60 mm above the OML were chosen from slices parallel to the OML. To design the ROI, Count Quantification Tool (CPT) software was developed. This program is executed on workstation (Indigo2, Silicon Graphics) and defines each slice as cortex, subcortex, or ventricle according to the radioactivity count, and further divides the cortex at 30-degree intervals and yields ROIs automatically.

We developed this software to overcome the inaccuracies of the manual ROI method and to improve reliability in defining ROIs. Inter-rater reliability and test-retest reliabilities were 0.96 and 0.98, respectively.

However, ROIs for subcortical structures were drawn manually by experienced neuroradiologists. Inter-rater reliability and test-retest reliability were 0.90 and 0.89, respectively. Cortical and subcortical ROIs were compared to brain structures in the standard pediatric neuroanatomy atlas. At 20 mm above the OML, the inferior and superior temporal cortexes were identified with reference areas in cerebellum. At 40 mm above the OML, lateral/ medial frontal, superior temporal cortex, caudate, thalamus and other basal ganglia in the subcortex were also identified. At 60 mm above the OML, the parietal cortex and occipital cortex were identified. The regional uptake ratio of radiotracer was obtained by calculating the ratio between the average number of counts per voxel in each ROI and the average number of counts per voxel in the two highest cerebellar uptake areas.

Comparison of pretreatment and post-treatment

values was made using the paired t-test with SAS version 6.01

RESULTS

Clinical response

Dramatic improvement in behavior, as indicated by scores on the various rating scales, was noted. Table 2 lists the scores on the rating scales that were significantly changed between the baseline and drug post-treatment condition. All these scales showed improvement in behavioral symptoms, such as, decreased hyperactivity and increased attention span. After 8-weeks of methylphenidate treatment, the number of fulfilled DSM-IV ADHD criteria decreased from 11 at baseline to 4. Symptoms in five of the patients were reported to have completely disappeared, and the attention deficit subcale by CBCL and attention problems, hyperactivity and impulsivity subscales by YCI, and the hyperactivity index by CPS were much improved. Such an improvement was also found in school and hyperactivity scores

Table 2. Behavioral Effects of Methylphenidate Treatment in ADHD Children

Variables	Before Tx (n=32)	After Tx (n=32)	Statistics (paired-T)
DSM-IV criteria*			
CBCL[†]	11.4(4.8)	4.6(2.5)	0.001
Attention problems	6.45(5.8)	3.44(2.2)	0.01
Deliquent behavior	1.05(3.2)	0.55(1.1)	ns[‖]
Aggressive behavior	4.02(5.2)	2.75(1.8)	ns[‖]
YCI[‡]			
Attention problems	13.9(4.0)	4.5(4.3)	0.001
Impulsivity	8.5(2.5)	3.8(2.9)	0.01
Hyperactivity	9.0(2.9)	3.3(2.2)	0.01
Conners scale[§]			
Parent	20.3(4.6)	10.2(3.2)	0.001
Teacher	16.2(4.5)	8.5(2.1)	0.001

Data are given as mean (SD). ADHD indicates attention-deficit hyperactivity disorder
SD: Standard Deviation
*Number of fulfilled criteia in DSM-IV ADHD diagnostic criteria
[†]Child behavior checklist
[‡]Yale childrens inventory
[§]Conners teacher and parent rating scale
[‖]non significant in paired T-test

as CTS significantly decreased.

Results from image subtraction method

The relationship between SPECT change and clinical response

NDR parametric images obtained using subtraction method showed perfusion increase after methylphenidate treatment. Significant increase of perfusion was defined only when the NDR was above 30% (blood flow increased from 100 at baseline to 130 after treatment) and the diameter of the increased area was above 1 cm, which has been used as a threshold in previous studies.[22-24] Out of 32 patients, twenty (62.5%) showed significant perfusion increase. We found 20 drug responders that fulfilled the strict criteria of response which were described in 2.3. Based on this data, we obtained the following results.

The number of cases displaying both significant perfusion increase and clinical improvement (true positive: TP), the number of cases showing clinical response but not perfusion increase (false negative: FN), the number of cases exhibiting neither perfusion increase nor clinical response (true negative: TN), and the number of cases revealing perfusion increase but not clinical improvement (false positive: FP) were 17, 3, 9, and 3, respectively. These results showed the following correlations between SPECT change and clinical response. The overall matching rate was 81.1%, and sensitivity, specificity, positive predictive value, negative predictive value and the Kappa value were 85.3%, 75.2%, 84.7%, 74.8% and 0.67 respectively.

These results indicate that the perfusion changes identified by subtraction SPECT parametric images were compatible with the clinical response.

Neuroanatomical regions showing significant SPECT change after treatment

In seventeen patients that showed significant SPECT changes relevant to clinical improvement (true positives), neuroanatomical localization of SPECT change was searched for in parametric images using brain contours (Fig. 1, Table 3). The most frequent areas of change were the caudate nuclei and the frontal lobes. Eleven ADHD children (64%) showing significant drug response exhibited robust perfusion increase in these areas. In addition, cerebral perfusion increased in the thalamus and the temporal lobe. The changes in these areas were accompanied by changes in the caudate and frontal areas. Eight of seventeen ADHD children (47%) showed perfusion increase in both frontal and caudate areas. To identify the hemispheric localization, the number of changes in the right and left hemispheres was calculated. Changes in the right hemisphere were more prevalent than those in the left or the frontal and caudate lobes. When globally assessed, the total number of perfusion changes was far greater in the right hemisphere than the left (28:10).
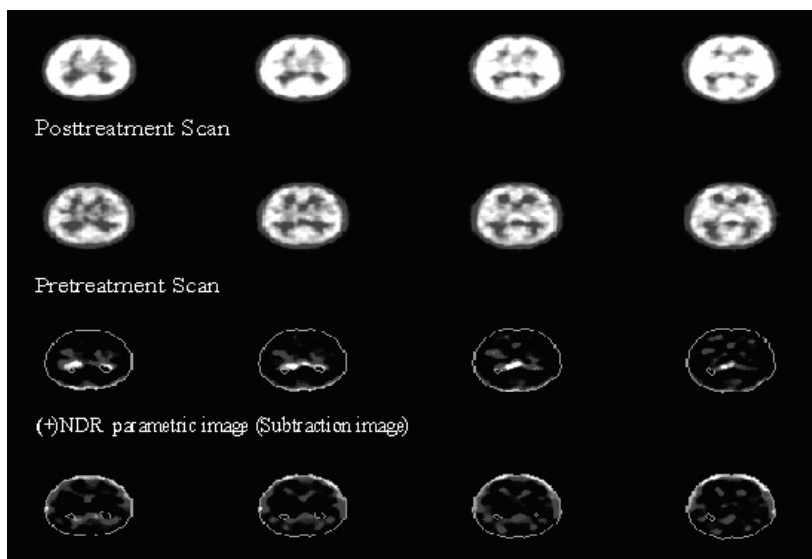
Fig. 1. Example of the image subtraction method in one patient (Significant perfusion increases are shown in the right thalamic area of this figure).

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Results using region of interest method

To validate the neuroanatomical changes identified by image subtraction, the region of interest method, which is another valid method of quantification was applied to all subjects.

Perfusion change at 20 mm above the OML

The perfusion change in the left inferior temporal area was found 20 mm above the OML, but statistical significance was lost after the Bonferroni correction was applied (Table 4).

Perfusion change at 40 mm above OML

Among 12 ROIs, 2 ROIs (left and right lateral

frontal areas) showed significant perfusion increases and this significance persisted after the Bonferroni correction was applied (Table 5)

Perfusion at 60 mm above OML

None of the 12 ROIs exhibited significant perfusion change (Table 6).

Change in subcortical structures

40 mm above the OML, where subcortical structures were best shown, the caudate and thalamic areas in both hemispheres showed significant perfusion increases and this significance persisted after Bonferroni correction (Table 7).

Table 3. Neuroanatomical Localization in SPECT Change

Anatomical localization	Frequency*	Hemispheric loci**
Frontal lobe	64%(11/17)	Rt(8), Lt(3)
Temporal lobe	29%(5/17)	Rt(2), Lt(3)
Caudate lobe	64%(11/17)	Rt(9), Lt(2)
Thalamus	29%(5/17)	Rt(4), Lt(1)
Cingulate	35%(6/17)	Ant(5), Post(1)

* Only patients showing both clinical response and significant SPECT changes are included. Results are given as percentages (No. of patients showing SPECT changes in specific areas/ No. of total patients)
** No. of changes in the right and left hemisphere are calculated. Results are given as hemispheric localization (No. of patients)

Table 4. Uptake Ratio (mean) Pretreatment and Post-treatment at 20 mm Above the Orbitomeatal Line

	Left hemisphere				Right hemisphere		
Region	pre-Tx	post-Tx	P-value	Region	pre-Tx	post-Tx	P-value
1	0.8	0.78	ns	1	0.81	0.8	ns
2	0.77	0.84	0.04	2	0.79	0.81	ns

1: superior temporal cortex, 2: inferior temporal cortex, pre-Tx: pretreatment group, post-Tx: post-treatment group, P-value: Paired t-test, ns: not significant by paired t-test

Table 5. Uptake Ratio (mean) Pretreatment and Post-treatment at 40 mm Above the Orbitomeatal Line

	Left hemisphere				Right hemisphere		
Region	pre-Tx	post-Tx	P-value	Region	pre-Tx	post-Tx	P-value
1	0.8	0.86	ns	1	0.81	0.88	ns
2	0.75	0.94	0.0003*	2	0.79	0.99	0.0004*
3	0.75	0.8	ns	3	0.77	0.81	ns
4	0.78	0.79	ns	4	0.76	0.8	ns
5	0.89	0.9	ns	5	0.83	0.85	ns
6	0.9	0.91	ns	6	0.88	0.91	ns

1: medial frontal cortex, 2: lateral frontal cortex, 3: superior temporal cortex, 4: middle temporal cortex, 5: temporo-occipital cortex, 6: occipital cortex, pre-Tx: pretreatment group, post-Tx: post-treatment group, P-value: Paired t-test
*statistically significant after Bonferroni Correction

Table 6. Uptake Ratio (mean) Pretreatment and Post-treatment at 60 mm Above the Orbitomeatal Line

	Left hemisphere				Right hemisphere		
Region	Pre-Tx	Post-Tx	P-value	Region	pre-Tx	post-Tx	P-value
1	0.74	0.8	ns	1	0.77	0.79	ns
2	0.73	0.78	ns	2	0.75	0.76	ns
3	0.72	0.74	ns	3	0.8	0.82	ns
4	0.8	0.79	ns	4	0.79	0.83	ns
5	0.86	0.89	ns	5	0.83	0.85	ns
6	0.9	0.9	ns	6	0.88	0.89	ns

1: indicate medial frontal cortex, 2: lateral frontal cortex, 3: anterior parietal cortex, 4: middle parietal cortex, 5: posterior parietal cortex, 6: occipital cortex, pre-Tx: pretreatment group, post-Tx: post-treatment group, P-value: Paired t-test

Table 7. Uptake Ratio (mean) in Pretreatment and Post-treatment Subcortical Structure

	Left hemisphere				Right hemisphere		
Region	pre-Tx	post-Tx	P-value	Region	pre-Tx	post-Tx	P-value
Caudate	0.84	1.03	0.0001*	Caudate	0.85	1.07	0.0001*
Thalamus	0.88	0.94	0.003*	Thalamus	0.83	0.98	0.001*
other BG	0.91	0.92	ns	other BG	0.9	0.88	ns

pre-Tx: pretreatment group, post-Tx: post-treatment group, P-value: Paired T-test
*statistically significant after Bonferroni Correction

DISCUSSION

The behavioral data from the parent and teachers rating scales indicated a significant improvement in the symptoms of ADHD (Table 2). The response rate for MPH monotherapy was 62.5% despite the relatively strict criteria of drug-response. These findings confirmed the results of previous studies that general response to MPH in ADHD was sufficiently adequate to control maladaptive behavioral problems.[25-27] The image subtraction method, which is one of the methods used for the quantification of blood flow change in this study, was originally developed to localize cerebral loci in epileptic surgery. This subtraction method has been applied under the name of intervention functional imaging to diverse research and clinical areas, including the evaluation of drug treatment and functional brain mapping after neurostimulation.[28] The validity and reliability of this method has been well established by previous studies.[22-24,29]

The agreement rate between SPECT change and clinical responses was found to be relatively high in our present study. The sensitivity and positive predictive value exceeded 80%, and specificity

and negative predictive value were greater than 70%. Therefore, its is hoped that the subtraction imaging method may have clinical utility in predicting the response to MPH in ADHD patients by replication and extension of these results.

To overcome the poor resolution of SPECT parametric imaging and to localize the precise areas of perfusion changes in the drug responding group, a brain contour program that can discriminate ventricle, cortical and subcortical structures was developed and used in each parametric image. The most robust areas of change were the frontal and caudate areas of both hemispheres. Nearly 50% of drug responders showed perfusion increases in these two areas simultaneously. The frontal and caudate lobes are known as areas associated with pathophysiological process in ADHD. To our knowledge, this is the first functional neuroimaging study that has reported MPH-induced perfusion increases in these areas in ADHD children. Previously, Lou et al.[13,16] in Denmark reported upon MPH action on the striatum, including the caudate lobe, but this study had serious limitations, as it involved a small number of heterogeneous subjects, which included children with gross neurological deficits,

such as, seizure disorder or cerebral palsy.

In terms of the hemispheric localization of drug action, we found that SPECT changes due to MPH were more frequent in the right hemisphere than the left. In particular, the major action sites of MPH were found to be in all likelihood the right fronto-striatal system. This result is compatible with prior structural imaging studies[7,9] and the right fronto-striatal system dysfunction hypothesis.[30-33]

The finding that MPH increased blood flow mainly in the right fronto-caudate areas, which are believed to be the dysfunctional neural system, implied that SPECT changes in parametric images may be directly associated with clinical pharmacological responses in the ADHD group. Using the ROI method, we found that MPH increased cerebral perfusion in six ROIs out of a total of 34. These six ROIs were lateral frontal, caudate and thalamic areas in both hemispheres, but global cerebral perfusion increase was not found and neither did the occipital, parietal, temporal and cerebellar areas show significant perfusion change. This result indicated that MPH improved blood flow in specific cerebral regions and not globally.

Recent neuroimaging data strongly suggested that fronto-striatal network abnormalities are the likely cause of ADHD.[34] The most well known of these were studies that used F18 fluoro-2-deoxy D-glucose (FDG) PET to demonstrate decreased frontal cerebral metabolism in adults with ADHD.[35] Other investigators of brain function have measured local cerebral blood flow, which closely approximates to neuronal activity, using a variety of techniques, including Xe inhalation[13] and Tc99m-HMPAO-SPECT.[36] They have also reported decreased blood flow in the striatum and prefrontal regions of ADHD patients.

Evidence from studies undertaken to identify the neuropsychological deficit in ADHD support the theory of executive dysfunction, which could explain the core symptoms and the related cognitive problems.[37] The fronto-striato-thalamic-frontal circuit is believed to serve as the anatomic substrate for many executive functions. ADHD animal models, like spontaneously hypertensive rats, showed abnormal dopaminergic function in the fronto-striatal network.[38] Therefore, the fronto-

striato-thalamic-frontal areas in which blood flow was increased by MPH treatment were identified as the specific network that serves as the neural substrate of executive function, and the dysfunctional neural system in ADHD. On the basis of past and present studies we might presume that MPH acts on the specific dysfunctional neural networks and might enhance the functions of these sites.

Two pharmagoimaging studies that were similar to the design of our study, but which involved adult ADHD patients, were conducted in the 1990s.[14,15] Both studies reported results which are in conflict with the results of this study, namely, that no significant cerebral perfusion changes occurred after CNS stimulant administration in ADHD. Matochik et al.[15] reported upon a PET study on 18 adult ADHD patients receiving MPH treatment for six months did not detect any significant changes in rCMRglu. They reported increased rCMRglu in only two of 60 ROIs. Another PET study[14] using intravenous bolus infusion of amphetamine to adult ADHD patients revealed increased perfusion in only three areas in 60 ROIs.

Though many factors (i.e., differences in methodology, medication history, or patient selection) are likely to account for the variability of findings of studies, the discrepancy in the ages of subjects could be a major reason for the variance. It is because developmental differences could affect cerebral responsiveness to MPH, and these differences in cerebral responsiveness may result from the developmental changes of the dopamine system in CNS. Of the three monoamines (dopamine, norepinephrine, serotonin), dopamine is the most developmentally active.[4] Previous studies into the ontogenesis of the dopamine system have revealed that dopamine metabolites (HVA, DOPAC) decreased with age from 2-3 to the adult state.[39,40] The number of dopamine containing neurons declines with age from the very early infant period, according to postmortem studies.[41] The dopamine transporter protein is also reported to decrease with age, especially in the globus pallidus and the caudate lobe by PET study. This rate of decrease may be 6.6% per 10 years according to the same study.[42] These findings mean that dopamine neuronal activities

are intended to decline with the aging process from the early infant period, and so cerebral responsiveness to dopamine related drugs (e.g., MPH, amphetamine) may also decrease with age. Such differences in neuronal responsiveness to CNS stimulants (e.g., MPH) in the central nervous system may also explain why the result of our study differ from those of previous studies of adults ADHD patients.

Current functional magnetic resonance imaging (fMRI) studies with school age-children have shown hypoperfusion in the right caudate, which normalized after the administration of the optimal dose of MPH.[10,43] These results directly support the results of our study and the suggestion that the age of the subject can be a crucial factor in the result of studies about MPH-induced changes in brain function.

What then is the putative mechanism of MPH-induced cerebral functional change? This can be directly related to the activation of dopamine neural networks or neural circuits. A PET study using a D2 receptor binding assay revealed that increases in regional rGMRglu induced by MPH are directly related to D2 receptor increase.[44,45] Another neuroimaging study using SPECT confirmed that MPH increased endogenous dopamine release.[46] Moreover, amphetamine increased cerebral dopamine release and synaptic dopamine concentration in another PET study.[47] Therefore, our result of MPH-induced perfusion increase in specific brain regions may be directly related to the MPH-induced activation of specific dopamine neural networks, such as, the frontal lobe, caudate lobe and thalamus. In addition, this MPH-induced activation in the CNS dopamine system may be dependent upon developmental status of the brain.

There are, however, some methodological shortcomings associated with our study. The first is that there was no control group. To determine whether MPH-induced perfusion changes are specific to ADHD patients, we should have applied the same procedure to a normal, healthy, age & sex matched control group, but research ethics do not allow the administration of radiotracers to normal children. The second limitation is that the techniques utilized gave only a rough estimation of cerebral blood flow.

Although HMPAO uptake is roughly proportional to cerebral blood flow, we did not measure absolute global or regional blood flow. Therefore, we must refer to relative cerebral blood flow rather than absolute regional blood flow. Another limitation concerned the poor spatial resolution of the HMPAO SPECT method in measuring regional cerebral blood flow. We did not employ the image overlay technique combining MRI and SPECT data. Therefore, we were unable to determine precisely where the area of functional activity was located in the brain, as our localization was based solely on the knowledge of presumed anatomic relationships between external landmarks and internal brain structures. The fourth limitation is that the data only reflects resting relative regional blood flow, and there is much inherent variability in this measure. Future studies should examine the effect of MPH on mean blood flow in an active state.

In summary, we found that MPH increases relative regional perfusion in fronto-striato-thalamic areas by both the image subtraction method and the region of interest method. This result supports the clinical use of MPH in ADHD children and provides a more powerful academic basis for MPH usage in a clinical setting. Moreover, the MPH-induced SPECT change is completely compatible with observed clinical improvements and the regions of change were related to putative pathophysiological areas of ADHD. This finding also supports the validity of current thinking upon the pathophysiology of ADHD.

Boong Nyun Kim, M.D.
Division of Child & Adolescent Psychiatry,
Department of Neuropsychiatry, Seoul National
University Hospital, 28 Yungun-Dong,
Chongro-Gu, Seoul 110-744, Korea,
Tel: 82-2-760-2928, Fax: 82-2-747-5774,
E-mail: shaywitz@unitel.co.kr

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