



Effect of DL-Methylephedrine on Dopamine Transporter Using Positron Emission Tomography With [¹⁸F]FE-PE2I

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Rationale: Since ephedrine has a dopamine transporter (DAT) inhibitory effect similar to amphetamine, dl-methylephedrine, a derivative of ephedrine, is considered to have the characteristics of a central nervous system stimulant due to the DAT inhibitory effect. For example, the World Anti-Doping Agency categorizes dl-methylephedrine as a stimulant in the prohibited list for competitions. Assuming to have the same effect as ephedrine, the urinary concentration of dl-methylephedrine is regulated below 10 μg/mL, as is ephedrine. However, the extent to which dl-methylephedrine affects brain function is not yet fully understood.

Objectives: The purpose of this study was to evaluate DAT occupancy by a single oral administration of a daily dose of dl-methylephedrine using positron emission tomography (PET) with [¹⁸F]FE-PE2I to characterize its stimulatory effect on the central nervous system.

Methods: Nine healthy male volunteers were enrolled in the study. The experiments were designed as a placebo-controlled randomized double-blind crossover comparative study. After the first PET scan in a drug-free state, the second and third PET scans were performed with randomized dosing at 60 mg of dl-methylephedrine or placebo. The plasma and urine concentrations of dl-methylephedrine were measured just before and after the PET scans, respectively.

Results: Mean urine and plasma concentrations of dl-methylephedrine were 13.9 μg/mL and 215.2 ng/mL, respectively. Mean DAT occupancy in the caudate was 4.4% for dl-methylephedrine and 1.2% for placebo. Mean DAT occupancy in the putamen was 3.6% for dl-methylephedrine and 0.5% for placebo. There was no significant difference of DAT occupancies between the groups.

Conclusion: In this study, the urinary concentration of dl-methylephedrine (13.9 μg/mL) was higher than the prohibited reference value (10.0 μg/mL), and there was no significant difference in DAT occupancy between dl-methylephedrine and placebo. These findings suggest that a clinical daily dose of dl-methylephedrine may exceed the doping regulation

value according to urine concentration; however, it was considered that at least the central excitatory effect mediated by DAT inhibition was not observed at the daily dose of dl-methylphenidate.

Keywords: dl-methylphenidate, dopamine transporter, positron emission tomography, [^{18}F]FE-PE2I, doping

INTRODUCTION

Drug doping in athletics is increasing and diversifying, using drugs that improve not only pure motor function, but also brain functions such as concentration during competition, and such drug usage has become a new problem (1). A wide range of drugs, from prescribed drugs to luxury foods and health foods, which aim to improve brain function, are called nootropic drugs. It is known that modafinil enhances wakefulness and cognitive performance (2, 3), and in recent years nootropic drugs have been used in sports for the purpose of improving competitive ability (4). However, the effects of nootropic drugs on central nervous system function have not been sufficiently investigated in terms of either efficacy or adverse effects.

Ephedrine, dl-methylphenidate, and pseudoephedrine, which are used to treat cough and rhinitis, are classified as stimulants in the World Anti-Doping Agency (WADA) list of prohibited drugs (5). Ephedrine and pseudoephedrine are precursors of methamphetamine, and it is thought that they act as a mechanism of central action in the dopamine system. In addition, since ephedrine has a dopamine transporter (DAT) inhibitory effect similar to amphetamine, dl-methylphenidate, a derivative of ephedrine, is considered to have the characteristics of a central nervous system stimulant due to the DAT inhibitory effect.

DAT controls the spatial and temporal dynamics of dopamine neurotransmission by promoting the reuptake of extracellular transmitter into presynaptic neurons (6). Many of stimulants prohibited by WADA possess DAT inhibition, thus increasing extracellular dopamine. However, it is reported that ephedrine has a weaker, a little <40 times DAT inhibitory action, compared to amphetamine (7), and that pseudoephedrine has a weaker, about 150 times DAT inhibitory action, than amphetamine (8). On the other hand, there is no data regarding any DAT inhibitory action with dl-methylphenidate.

Brain imaging studies are useful to see how psychotropics affect psychiatric disorders (9–11), but there have not been many studies that demonstrate how nootropic drugs affect competitive ability or higher brain function. Some of the nootropic drugs, as well as stimulants, are thought to improve competition ability with effects on neurotransmitters such as choline, dopamine, and serotonin (5). Research with stimulants, such as amphetamine, methylphenidate and ephedrine, showed improved performance (12–14). As these stimulants are thought to improve cognitive function by increasing extracellular dopamine via DAT, it is important to investigate the relation between stimulants and DAT inhibition. DAT inhibition can be evaluated by positron emission tomography (PET) by measuring occupancy. When evaluating drugs in PET study, binding property of drugs administered to the target molecules such as receptors and transporters is estimated. Binding potentials (BP_{ND}) is a

quantitative representation of the target combining the density of target molecules to the affinity of a ligand to that target. Occupancy is defined as the treatment-induced change in BP_{ND} following a drug administration. The BP_{ND} value of the PET radioligand decreases when the drug increasingly occupies the target receptor and competes with PET radioligand (15). The advantage of using PET is that it enables intracerebral evaluation with small numbers. For example, in a clinical trial with dose setting of the antipsychotic drug blonanserin, the optimal dose was determined from about 150 participants, but we showed equivalent results with about one-tenth of the participant numbers using PET (16). Several radioligands for imaging DAT have been developed for PET, such as [^{11}C]cocaine, [^{11}C] β -CIT, and [^{11}C]PE2I (17–20). Furthermore, [^{18}F]FE-PE2I with high affinity and selectivity for DAT has been developed (21), with kinetics favorable compared to other radioligands, and quantification of DAT is less biased (22, 23). Using this ligand [^{18}F]FE-PE2I, several DAT occupancies by stimulants were reported (24, 25).

Some of the stimulants listed by WADA are regulated by urinary concentration levels. For example, cathine is regulated below 5 $\mu\text{g}/\text{mL}$ and pseudoephedrine below 150 $\mu\text{g}/\text{mL}$. It is known that pseudoephedrine has a dose-dependent effect on improving athletic ability, and the regulation criteria for pseudoephedrine have been revised based on scientific evidence from research results. Pseudoephedrine was regulated below 25 $\mu\text{g}/\text{mL}$ until 2003, was removed from the prohibited drug list between 2004 and 2009, and was then re-entered as a prohibited drug from 2010 (26, 27). Assuming to have the same effect as ephedrine, the urinary concentration of dl-methylphenidate is regulated below 10 $\mu\text{g}/\text{mL}$, the same as ephedrine. However, the extent to which dl-methylphenidate affects brain function is not yet fully understood.

We conducted a DAT occupancy study with dl-methylphenidate using PET with [^{18}F]FE-PE2I to characterize its stimulatory effects on the central nervous system.

MATERIALS AND METHODS

Subjects

Ten healthy male volunteers (age range 21–36 years; mean age \pm S.D = 27.2 \pm 5.2 years; 60 mg) participated in the study. None of the volunteers were excluded due to drug usage. None had a history of present or past psychiatric, neurological or somatic disorders, or alcohol-related problems. All subjects were non-smokers and stopped caffeine intake 48 h prior to the PET scans. The study was approved by the review board of Nippon Medical School Hospital, Japan. After thorough explanation of the study, written informed consent was obtained from all participants.

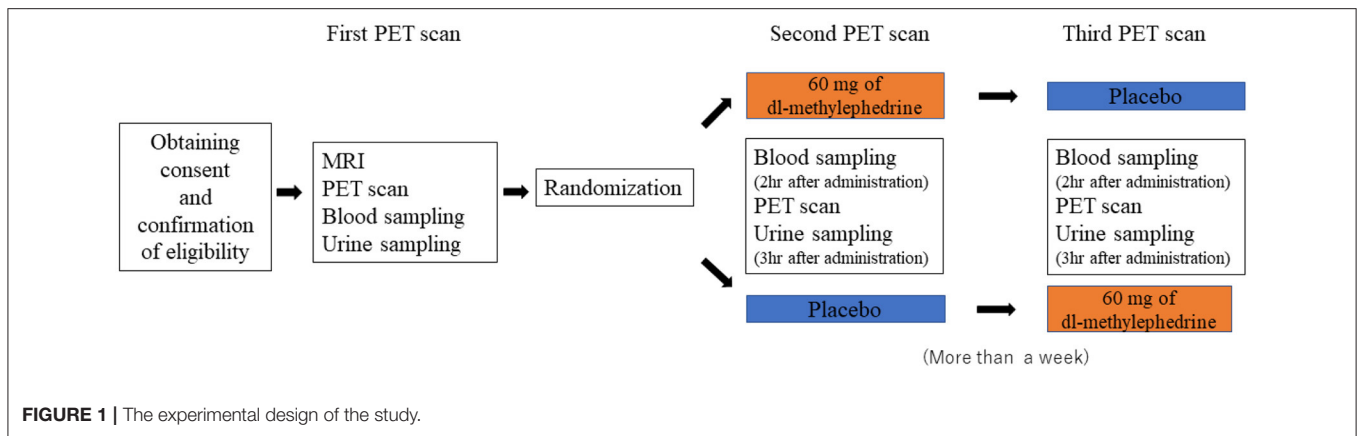


FIGURE 1 | The experimental design of the study.

Study Design

The experiment was designed as a placebo-controlled randomized double-blind crossover comparative study. Three PET scans were conducted for each subject, with the scans all separated by intervals of more than 1 week. After the first PET scan with drug-free condition, the second and third PET scans were performed with randomized dosing with 60 mg of dl-methylphenidrine or placebo (60 mg of lactose). We planned the second and third scans to aim for the T_{max} of dl-methylphenidrine, 2 h, which is the time interval after the drug administration to reach the maximum plasma concentration. The plasma and urine concentrations of dl-methylphenidrine were measured just before and after the PET scans, respectively (see **Figure 1**).

PET Procedures

An Eminence SET-3000GCT-X (Shimadzu Corp., Japan) scanner system was used for all measurements, with a head fixation device to minimize head movement. A 10-min transmission scan was performed to correct for attenuation. Dynamic PET scan was performed for 60 min after intravenous bolus injection of [^{18}F]FE-PE2I. Injected radioactivity was 182.9–191.1 (mean \pm S.D = 188.2 \pm 2.3) MBq at baseline condition, 180.5–189.7 (186.0 \pm 2.6) MBq for placebo, and 182.3–190.8 (188.1 \pm 2.4) MBq for dl-methylphenidrine. Specific radioactivity was 566.8–728.0 (641.7 \pm 77.4) GBq/ μmol at baseline condition, 581.5–1072.7 (960.4 \pm 171.6) GBq/ μmol for placebo and 544.0–1072.73 (894.2 \pm 313.6) GBq/ μmol for dl-methylphenidrine.

MRI Procedure

Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Intera 1.5 T Achieva Nova (Philips Medical Systems, Best, Netherlands). T1-weighted MR images were obtained at 1-mm slices. The MRI results revealed no apparent structural abnormalities.

Plasma and Urine Concentration

Venous blood samples were collected in tubes containing EDTA-2Na, and centrifuged at 3,000 rpm for 10 min at 4°C. Separated plasma samples were stored at -80°C until analysis. Plasma concentration of dl-methylphenidrine was

measured by a validated method using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a target lower quantification limit of 1 ng/mL (LSI Medience Corp., Japan). Urine samples were collected after the PET scans and were stored at -80°C until analysis. The urine concentration of dl-methylphenidrine was measured by gas chromatography (LSI Medience Corp., Japan) with a target of lower quantification limit of 0.03 $\mu\text{g/mL}$.

Data Analysis

All MR images were co-registered to the PET images using the software package PMOD (version 3.17; PMOD Technologies Ltd, Switzerland). Regions of interest (ROIs) were drawn manually on summed PET images with reference to co-registered MR images and defined for the striatum (caudate and putamen) and cerebellum. The average values of right and left ROIs were used for analysis. DAT bindings were quantified using a simplified reference tissue model (28, 29). The cerebellum was used as reference region because of its negligible DAT density (23). This model allows the estimation of binding potentials (BP_{ND}), which were defined as $f_{ND} \times B_{max}/K_d$, where f_{ND} is the free fraction of ligand in the nondisplaceable tissue compartment, B_{max} is the transporter or receptor density, and K_d is the dissociation constant (30).

DAT occupancies by dl-methylphenidrine and placebo were calculated by the following equation: Occupancy (%) = $(BP_{baseline} - BP_{drug})/BP_{baseline} \times 100$, where Occupancy is DAT occupancy, $BP_{baseline}$ is BP_{ND} in the drug-free state, and BP_{drug} is BP_{ND} after administration of dl-methylphenidrine or placebo. Difference of DAT occupancies between dl-methylphenidrine and placebo in caudate and putamen were tested by Wilcoxon signed-rank test. The relationship between DAT occupancy of striatum (average of caudate and putamen) and urine concentration with dl-methylphenidrine was also estimated by Spearman's rank correlation coefficient.

RESULTS

We excluded one volunteer whose BP_{ND} of DAT in the drug-free state was extremely low, as we could not rule

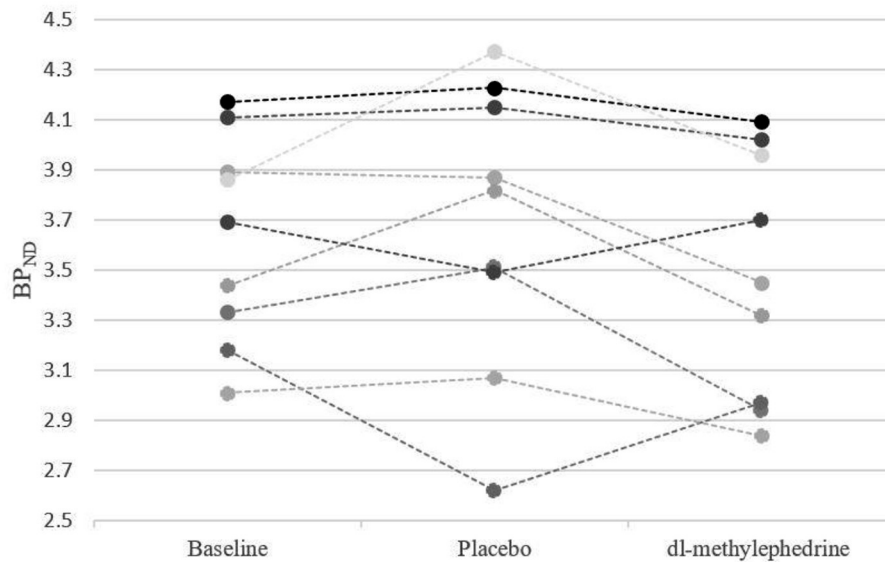


FIGURE 2 | BP_{ND} in caudate for each subject at baseline, placebo, and 60 mg of dl-methylphenidrine.

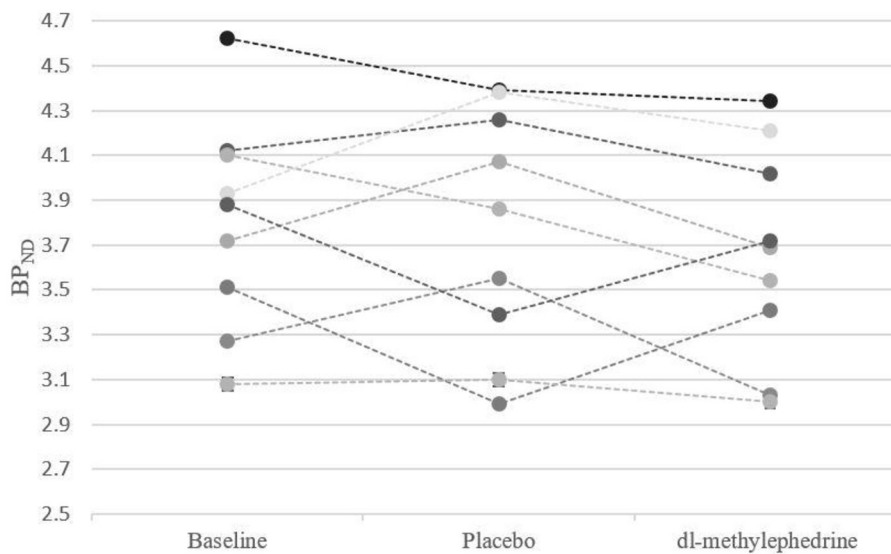


FIGURE 3 | BP_{ND} in putamen for each subject at baseline, placebo, and 60 mg of dl-methylphenidrine.

out a pre-disease state of neurodegenerative disorders. The remaining 9 were analyzed. BP_{ND} in caudate and putamen are shown in **Figures 2, 3**. The mean plasma concentration with a single administration of 60 mg dl-methylphenidrine was 215.2 ± 97.5 ng/mL (two hours post administration, mean \pm S.D; range 73.7–404.9), and mean urine concentration was 13.9 ± 17.5 μ g/mL (three hours post administration, mean \pm S.D; range 3.86–58.75). Mean \pm S.D DAT occupancies in the caudate and putamen measured with [¹⁸F]FE-PE2I were 4.4 ± 4.9 % and 3.6 ± 5.6 % with 60 mg of dl-methylphenidrine and -1.2 ± 9.1 % and 0.5 ± 9.6 % with placebo (**Table 1**). There was no significant difference between

the groups with dl-methylphenidrine and placebo [caudate: $z = 1.48$, $p = 0.14$, putamen: $z = 1.01$, $p = 0.31$ (Wilcoxon signed-rank test)]. There was no correlation between DAT occupancy in striatum and urine concentration with dl-methylphenidrine ($r_s = 0.13$, $P > 0.05$: Spearman’s rank correlation coefficient) (**Figure 4**).

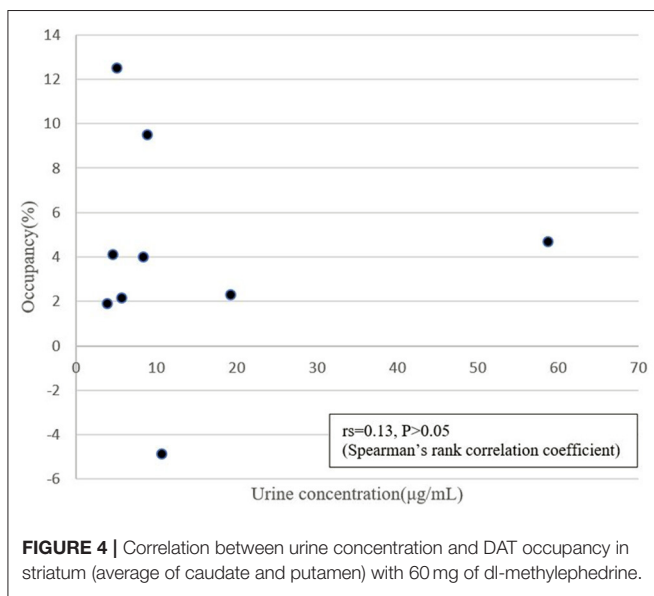
DISCUSSION

To the best of our knowledge, this is the first PET study to evaluate the effect of dl-methylphenidrine on DAT in the striatum *in vivo*. Mean DAT occupancy was approximately

TABLE 1 | DAT occupancy in the striatum with placebo and dl-methylphenidate, and blood and urine concentrations of dl-methylphenidate.

No.	Age (yr)	BW (Kg)	BMI (Kg/m ²)	Occupancy (%)				Blood concentration (ng/mL)	Urine concentration (μg/mL)
				Placebo		dl-methylphenidate 60 mg			
				Caudate	Putamen	Caudate	Putamen		
1	36	62	21.5	-1	-3.4	2.2	2.4	167.4	19.25
2	22	63	22.9	0.5	5.9	11.3	13.7	245.7	5.09
3	21	60	19.6	-5.4	-8.6	11.7	7.3	264.4	8.89
4	28	66	21.6	-1.4	5	1.9	6.1	189.2	8.33
5	26	59	20.4	-13.2	-11.5	-2.6	-7.1	237.3	10.66
6	27	72	24.9	-11	-9.4	3.5	0.8	249.5	5.7
7	33	58	21.3	17.6	14.8	6.6	2.8	105.2	58.75
8	32	54	19.4	5.4	12.6	-0.3	4.1	73.7	3.86
9	25	50	18.8	-2	-0.6	5.6	2.6	404.9	4.59
Mean	27.8	60.4	21.2	-1.2	0.5	4.4	3.6	215.26	13.9
S.D	5.0	6.4	1.9	9.1	9.6	4.9	5.6	97.5	17.5

There was no significant difference between the groups with dl-methylphenidate and placebo [caudate: $z = 1.48, p = 0.14$, putamen: $z = 1.01, p = 0.31$ (Wilcoxon signed-rank test)]. Blood sample was taken 2 h after administration, and urine sample was taken 3 h after administration BW, body weight; BMI, body mass index.



4% (4.4% in caudate and 3.6% in putamen) after a single administration of 60 mg dl-methylphenidate. This is remarkably low compared with the results of other prohibited central nervous system stimulants by WADA, such as modafinil, methylphenidate and mazindol. In our previous study, we reported that the DAT occupancy of modafinil with [¹⁸F]FE-PE2I was 51.4% and 56.9% in the striatum at 200 mg and 300 mg (24). DAT occupancy of methylphenidate with [¹¹C]cocaine was reported as 40–74% in the striatum at clinical doses of 10–60 mg (31). As for mazindol, DAT occupancy in the striatum was approximately 25% with 1.5 mg (25). Compared to those results, DAT occupancy by dl-methylphenidate was quite low, approximately 4% in the present study, and there

was no significant difference compared with placebo. The test-retest reproducibility of BP_{ND} value estimated by [¹⁸F]FE-PE2I for the striatum in the previous research was approximately 5% (32). Although the occupancy of the individuals in this study vary to some extent, the average occupancy with placebo was smaller (approximately 1%) than the previous research. Thus, the variety of the results in this study were considered insignificant.

Striatum was evaluated in this study, since DAT density is not high enough to evaluate with PET in other brain regions. Central nervous system stimulants pharmacologically exert their effect by blocking DAT, thereby causing an increase in extracellular dopamine concentrations (33, 34). Dopamine is related to motivation, learning ability, motor ability, memory and reward system (35, 36), and central nervous system stimulants are thought to improve those abilities by increasing extracellular dopamine. There are also some arguments regarding the relationship between abuse liability and dopamine increase by blocking DAT. Cocaine and related compounds bind to DAT increase the extracellular dopamine levels in limbic area, initiates the sequence of events that ultimately cause the rewarding effect. It is well known that the higher binding affinity to the DAT induce the higher rewarding effect (37, 38). Since dl-methylphenidate is a derivative of ephedrine and methamphetamine is synthesized from ephedrine, dl-methylphenidate is also considered to act on the central nervous system via DAT. For this reason, dl-methylphenidate is classified as prohibited drug by WADA.

For the improvement of cognitive function, the brain region other than striatum is also considered to be important. Methylphenidate, used for treatment of attention deficit hyperactivity disorder (ADHD), is also used for the enhancement of cognitive performance (39). Dopamine in prefrontal cortex (PFC) plays a very important role for cognitive functions (40), and it is hypothesized that the improvement of cognitive function

by methylphenidate is due to an increase of dopamine in the PFC. However, in a monkey study, methylphenidate showed improvement in various cognitive tasks, with a marked increase in the striatum but no significant difference in PFC, which indicate that improvement of cognitive function is contributed by dopamine increase in striatum or the accompanying change in the PFC-striatal network (41).

To protect the health of athletes and provide them with the opportunity to pursue human excellence without the use of prohibited substances and methods, WADA has issued a prohibited drug list, in which some of the drugs are regulated according to urine concentration. The urine concentration of dl-methylephedrine is regulated at below 10 $\mu\text{g}/\text{mL}$, the same as for ephedrine, whereas pseudoephedrine, an isomer of ephedrine, has a regulated urinary concentration of 150 $\mu\text{g}/\text{mL}$. Pseudoephedrine is widely used as a nonprescription drug in Europe, and investigation was conducted on the regulation values that cause doping effects, resulting in daily administration of doses that did not show changes in performance. Thus, the upper limit of urinary concentration (150 $\mu\text{g}/\text{mL}$) was set as the cutoff value when taken at regular dose (26, 27). In Japan, dl-methylephedrine is included in nonprescription drugs such as cold, rhinitis, and antitussive medications, and the maximal daily dose is 60 to 110 mg. It is cited as one of the causes of inadvertent doping that athletes take to treat cold symptoms. In the present study, the urine concentration 3 h after a single administration of 60 mg dl-methylephedrine was 13.9 $\mu\text{g}/\text{mL}$. Thus, by taking a daily dose of dl-methylephedrine included in the nonprescription medication, the urine concentration may exceed the regulated value. On the other hand, the DAT inhibitory effect by 60 mg of dl-methylephedrine as evaluated by PET and [^{18}F]FE-PE2I did not show a significant difference from the placebo. Also, the degree of inhibition was approximately 4%, much lower than the 25–74% of inhibition by other prohibited drugs (24, 25, 31). It is considered that there is no significant dopamine release at this level of DAT occupancy, because in the mazindol study, even with a single administration of 1.5 mg, DAT occupancy was about 25%, but a decrease of BP_{ND} , which reflects dopamine release, was only about 2.8 to 4.6% (25).

The results of this study showed that there was no significant DAT inhibition with a single dose of 60 mg of dl-methylephedrine and a urinary concentration over 10 $\mu\text{g}/\text{mL}$. Therefore, the regulated value should be reviewed, as with the current regulation value, the effect on DAT does not differ from that of placebo, with the probability that there is no dopamine release that enhances cognitive ability.

Limitations and Future Directions

There were some limitations to this study. First, 60 mg of dl-methylephedrine was administered in this study, which is about half of the maximum daily dose, and therefore a study with a higher dose of dl-methylephedrine would be preferred. Second, the sample size participated in this study was small. From the past study, it is unclear how much occupancy makes meaning or is enough to prove doping. Accordingly, in this

study, we only calculated the occupancy and evaluated its value without estimating the required sample size using a power analysis. Third, only male volunteers participated in this study. Urine concentration is expected to show higher value with female because of their smaller size. Therefore, the further study with female is needed to evaluate the gender difference.

As the regulation criteria of urine concentration with pseudoephedrine had been revised based on scientific evidence from research results, a direct comparison study with pseudoephedrine to assess the DAT inhibitory effect is needed. We evaluated DAT occupancy in this study, but the effect on other portions of the central nervous system or the relation with cognitive function has not been elucidated; therefore, it is necessary to investigate other neurotransmitters and effects on cognitive function with dl-methylephedrine is beneficial to determine revision of the regulation.

CONCLUSION

Dl-methylephedrine is thought to have the feature of a central nervous system stimulant via DAT, but our data suggest that with daily administration, DAT inhibition was quite low in comparison with other prohibited drugs. It was considered that at least the central excitatory effect mediated by DAT inhibition was not observed with a daily dose of dl-methylephedrine. The result indicates that there is room for reconsideration with the regulation for urine concentration of dl-methylephedrine.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Review Board of Nippon Medical School Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TN, RA, TS, YI, and AT designed the study, wrote the protocol, and collected the data. YO commented on the protocol. TN and AT analyzed the data. TN wrote the first draft of the manuscript. All authors commented on the manuscript and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpsy.2022.799319/full#supplementary-material>

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