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Assessment of endogenous dopamine release by methylphenidate challenge using iodine-123 iodobenzamide single-photon emission tomography

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Abstract. This double-blind, placebo-controlled study assessed pharmacologically induced endogenous dopamine (DA) release in healthy male volunteers ($n=12$). Changes in endogenous DA release after injection of the psychostimulant drug methylphenidate were evaluated by single-photon emission tomography (SPET) and constant infusion of iodine-123 iodobenzamide ($[^{123}\text{I}]\text{IBZM}$), a D_2 receptor radioligand that is sensitive to endogenous DA release. Methylphenidate induced displacement of striatal $[^{123}\text{I}]\text{IBZM}$ binding, resulting in a significantly decrease in the specific to non-specific $[^{123}\text{I}]\text{IBZM}$ uptake ratio (average: 8.6%) in comparison with placebo (average: -1.9%). Moreover, injection of methylphenidate induced significant behavioural responses on the following items: excitement, anxiety, tension, and mannerisms and posturing. The results of this study demonstrate the feasibility of using constant infusion of $[^{123}\text{I}]\text{IBZM}$ and SPET imaging to measure endogenous DA release after methylphenidate challenge and to investigate neurochemical aspects of behaviour.

Key words: Single-photon emission tomography – D_2 receptors – Iodine-123 iodobenzamide – Methylphenidate – Constant infusion

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Introduction

The positron emission tomography (PET) and single-photon emission tomography (SPET) techniques can now be used to study dopaminergic receptors and transporters in the human brain in vivo [1, 2]. Recent studies have suggested the additional potential of both techniques for the study of endogenous dopamine (DA) release [3–5]. In these studies, the pharmacologically in-

duced DA release was measured by the in vivo competition between endogenous DA and dopaminergic radioligands for binding to DA receptors. This approach is of interest since differences in the response of the dopaminergic system may be associated with neuropsychiatric illnesses, e.g. schizophrenia [4–6].

Interestingly, two recent SPET studies from Laruelle and co-workers [5, 6] have reported the feasibility of using a constant infusion technique with $[^{123}\text{I}]\text{iodobenzamide}$ ($[^{123}\text{I}]\text{IBZM}$, a D_2 receptor radioligand) to evaluate the *d*-amphetamine induced DA release in the human brain. Although these studies clearly showed the feasibility of using a $[^{123}\text{I}]\text{IBZM}$ constant infusion programme to measure endogenous DA release and behavioural effects after pharmacological challenge, the studies were not placebo controlled. Moreover, *d*-amphetamine is not a registered drug in Europe. The aim of this study, therefore, was to investigate the feasibility of the constant infusion SPET technique for imaging of the endogenous DA release induced by the DA uptake blocker methylphenidate [4, 7] and to measure behavioural responses in a double-blind, placebo-controlled design.

Materials and methods

Subjects. Twelve volunteers participated in this randomized, double-blind, placebo-controlled study (mean age 24, range 21–27 years). Inclusion criteria were: (a) male aged between 18 and 30 years, (b) absence of any prior exposure to methylphenidate or *d*-amphetamine, and (c) absence of past or present medical, neurological and psychiatric conditions (including alcohol and drug abuse). All subjects gave their written informed consent. This study was approved by the Medical Ethical Committee of the Academic Medical Center. Subjects received potassium iodide prior to the SPET scanning.

SPET protocol. $[^{123}\text{I}]\text{IBZM}$ (specific activity of $>200 \text{ MBq/nmol}$), was prepared by Amersham Cygne (Eindhoven, The Netherlands) as previously described [8], and injected via a permanent cannula

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in a forearm vein as a bolus followed by a constant infusion, according to the following scheme (data represent average $\pm$ SD, $n=12$): bolus 68.4 ± 3.9 MBq; rate of infusion, 15.8 ± 1.5 MBq h^{-1} ; duration of the study 300 min.

Subjects were scanned on the high-resolution tomographic neuroSPET system, the SME 810 X (Strichman Medical Equipment Inc., Medfield, Mass., USA) using the settings previously described [9].

Each subject was scanned during three sessions. Session 1 (which took place from 30 to 60 min after the onset of the experiment) started after positioning of the subject in the camera with a fixed light source oriented along the canthomeatal (CM) line, by multiSPET acquisition (150 s/slice) from the CM line up to the vertex to locate the slice demonstrating best visualization of the striatum (typically +3 cm from the CM line). Sessions 2 (120–180 min) and 3 (240–300 min) consisted of dynamic SPET scans (10–12 consecutive acquisitions of 300 s per slice) performed at the level of the reference slice as identified in session 1. Images were attenuation corrected and reconstructed as previously described [2]. Methylphenidate (0.5 mg/kg) or an identical volume of placebo (saline 0.9%) was injected intravenously at 180 min (directly after the end of session 2).

Evaluation of behavioural response. Behavioural responses to methylphenidate or placebo were measured by the Positive and Negative Syndrome Scale (PANSS) interview [10]. The interview consisted of 30 items, and responses were rated from 1 (symptom not present) to 7 (symptom extremely severe). Factors covered by the interview included a positive (7 items), a negative (7 items), and a general psychopathology scale (16 items). This interview proved to have high inter-rater reliability [10]. Two interviews were undertaken per subject, one at the onset of the study (0–30 min) and one after intervention (185–230 min). Both interviews were video-taped. The video-tapes were evaluated blind to methylphenidate or placebo injection. To quantify behavioural changes due to methylphenidate or placebo, the “baseline” scores for each item were subtracted from the scores after intervention. Due to logistical problems, the pre- and post-intervention interviews could only be obtained in 10 of the 12 volunteers.

Data analysis. SPET data were also analysed blind to methylphenidate or placebo injection. A standard template with regions of interest of constant size and shape for the striatum and occipital cortex was positioned on the images, as previously described [9]. The occipital cortex was selected as the background region because the density of D_2 receptors is negligible in this brain area. Striatal specific binding was calculated as striatal (average of left and right striatum) minus occipital cortex activity [in Strichman Medical Units (SMUs)]. For scanning sessions 2 and 3, the ratio of specific to non-specific striatal uptake was calculated by dividing the specific striatal uptake by the occipital uptake. The difference in the average ratio of specific to non-specific binding in sessions 2 and 3 was expressed as a percentage of this ratio in session 2. The applied quantification of striatal uptake is insensitive to changes in cerebral blood flow caused by methylphenidate during equilibrium and does not require plasma measurement of the radioligand [5].

The stability of regional brain activity over time was assessed by linear regression. The slope of these regressions was expressed as the percentage of the average value in this time interval. Average change over time was calculated as the average value of the slope [5].

Differences between groups were analysed by non-parametric testing (Wilcoxon rank sum).

Results

In the placebo group ($n=7$), the striatal and occipital cortex activities and the specific to non-specific [123 I]IBZM uptake ratio were stable from 120 min to the end of the experiment (Fig. 1). Changes in striatal activity over time ranged from -2.6% h^{-1} to 5.6% h^{-1} , with an average of 0.5% h^{-1} . Changes in occipital cortex activity over time ranged from -2.0% h^{-1} to 1.7% h^{-1} , with an average of 0.4% h^{-1} . Changes in the specific to non-specific ratio over time ranged from -3.6% h^{-1} to 4.1% h^{-1} (average change, 0.2% h^{-1}).

In the methylphenidate group ($n=5$) the occipital cortex activity was also stable from 120 min to the end of

Fig. 1. Time course of striatal and occipital cortex uptake activity (SMU) during constant infusion of [123 I]IBZM. Left part of the figure: a typical placebo experiment. The bolus plus constant infusion administration schedule allowed achievement of stable levels of striatal and occipital activity from the beginning of session 2 (120 min) to the end of session 3 (300 min). Right part of the figure: a typical methylphenidate experiment. Injection of methylphenidate (0.5 mg/kg intravenously at 180 min) induced loss of striatal activity, whereas the activity in the occipital cortex remains stable between 120 and 300 min

Fig. 2. Individual differences in the specific to non-specific striatal [123 I]IBZM uptake ratio in sessions 2 and 3, expressed as a percentage of this ratio in session 2, for the placebo- and methylphenidate (*methylph*)-treated groups. Methylphenidate induced a statistically significant decrease in the [123 I]IBZM binding potential ($P=0.019$)

Table 1. Behavioural effects of methylphenidate and placebo as assessed by PANSS interviews

	Placebo (n=6)	Methylphenidate (n=4)
Positive scale	0.0 ±0.3	2.3±0.3*
Excitement	0.0 ±0.6	2.0±0.0*
Negative scale	0.5 ±0.8	0.0±0.0
General psychopathology scale	0.2 ±1.3	5.3±3.8*
Anxiety	-0.2±0.4	1.5±1.0*
Tension	0.0 ±0.6	1.5±1.3*
Mannerisms and posturing	0.0 ±0.0	1.5±1.3*

Data are given as the difference between "intervention" and "pre-intervention" scores and represent the mean±SD.

* Statistically significant different from placebo ($P<0.05$)

the experiment (Fig. 1; average change, $-1.3\pm 2.0\%$ h^{-1}). Methylphenidate induced displacement of striatal [^{123}I]IBZM binding, resulting in a significant decrease in the specific to non-specific [^{123}I]IBZM uptake ratio ($8.6\pm 5.6\%$) in comparison with placebo ($-1.9\pm 6.0\%$; Fig. 2).

Injection of methylphenidate induced significant behavioural responses. Total scores on the positive and general psychopathology scales, but not on the negative scale, were increased. Methylphenidate induced a significant increase on the following items: excitement, anxiety, tension, and mannerisms and posturing (Table 1).

Discussion

In this study a [^{123}I]IBZM constant infusion technique was used to create optimal conditions for within-experiment quantification of endogenous DA release by methylphenidate in volunteers [5]. Methylphenidate induced a small but significant reduction in the specific to non-specific striatal [^{123}I]IBZM uptake ratio. Similar results have been reported with human carbon-11 raclopride PET and [^{123}I]IBZM SPET studies. Volkow and co-workers [4] observed an average decrease of 23% in the [^{11}C]raclopride distribution volume after intravenous administration of 0.5 mg/kg methylphenidate. Moreover, Farde and co-workers [3] observed an average decrease of 10% in [^{11}C]raclopride specific striatal binding after oral administration of 30 mg *d*-amphetamine. Recently, Laruelle et al. [5], using a [^{123}I]IBZM constant infusion schedule, showed an average decrease of 15% in D_2 receptor availability after *d*-amphetamine (0.3 mg/kg) injection. Interestingly, using the same technique, they also showed that the decrease in D_2 receptor availability was greater in patients with schizophrenia than in controls [6].

Methylphenidate is a psychostimulant drug commonly prescribed for attention-deficit hyperactivity disorder

and narcolepsy. Its main pharmacological mechanism of action has been suggested to involve increased synaptic DA levels as a consequence of blockade of the DA transporter [11]. Methylphenidate has been found to exhibit significant affinity to DA transporters, but no significant affinity to D_2 receptors [7, 11].

Recently, Wang and co-workers reported that methylphenidate decreases cerebral blood flow in human subjects [12]. Therefore, one might argue that the results of the present study are related to changes in blood flow induced by methylphenidate. To study the influence of methylphenidate on the availability of striatal D_2 receptors, we therefore used the [^{123}I]IBZM equilibrium method as described by Laruelle and co-workers [5]. They reported that during equilibrium the quantification of specific striatal [^{123}I]IBZM uptake is insensitive to changes in cerebral blood flow induced by psychostimulants [5].

The present placebo-controlled study showed a significant increase in excitement after injection of methylphenidate. Interestingly, other studies have reported a comparable increase in restlessness after injection of amphetamine-like drugs [4, 5]. Moreover, our study reported an increase in anxiety after injection of methylphenidate. This phenomenon was not observed in the study of Volkow et al. [4]. However, Laruelle et al. [5] reported an increase in anxiety just several minutes after injection of *d*-amphetamine, with a decline thereafter. The onset of the interview in our study was several minutes after intervention, which might explain the discrepancy between the result of our study compared to that of the study of Volkow et al. [4].

In conclusion, the results of this study showed the feasibility of using [^{123}I]IBZM constant infusion and SPET imaging to measure the endogenous DA release after methylphenidate challenge and to investigate neurochemical aspects of behaviour.

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