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ORIGINAL INVESTIGATION

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Assessment of methylphenidate-induced changes in binding of continuously infused [^{11}C]-raclopride in healthy human subjects: correlation with subjective effects

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Abstract *Rationale:* The dopaminergic system has been implicated in the pathogenesis and treatment of a variety of neuropsychiatric disorders. It has been shown that information on endogenous dopamine (DA) release can be obtained noninvasively by combining positron emission tomography with a dopaminergic challenge. This approach is based on the assumption that an injected radiolabeled ligand competes with the neurotransmitter for the same receptor. Increases in DA release will therefore result in a decreased binding of the radioligand. *Objectives:* We investigated the effect of the DA reuptake blocker methylphenidate (MP) on the binding of the D_2 receptor ligand [^{11}C]-raclopride (RAC). *Methods:* The effect of a 0.25 mg/kg intravenous dose of MP was studied in six healthy volunteers. RAC was administered as a bolus followed by constant infusion, and subjective effects were assessed using verbal rating scales. *Results:* Control scans without MP administration showed that the mean RAC binding reached stable values approximately 30 min after start of the infusion. MP administration induced a 24% decrease in RAC binding in the total striatum. Correlations were found between the MP-induced change in euphoria and the percent change in binding potential (ΔBP) in the dorsal striatum and between baseline anxiety and ΔBP in the dorsal and middle striatum. We also found a negative correlation between baseline BP in the dorsal striatum and change in euphoria. *Conclusions:* Our results comply with previous findings, indicating the feasibility of the bolus infusion design combined with a relatively low MP dose to study dopaminergic (dys)function.

Keywords PET · Reward · Striatum · D_2 · Receptor binding · Neurotransmitter release

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Introduction

The dopaminergic system has been implicated in the pathogenesis and treatment of a variety of neurological and psychiatric disorders, such as schizophrenia, Parkinson's disease, depression, and addiction (Kapur and Mamo 2003; Leenders 2002; Naranjo et al. 2001; Volkow et al. 2002a). The involvement of dopamine (DA) in these disorders may be related to its function in reward processing (Kapur 2003; Kunig et al. 2000; Schmidt et al. 2001). However, the exact role of DA in these processes is not completely known yet. It is important to quantify changes in DA levels in the living brain to study the (dys)function of the dopaminergic system.

Over the last decade, it has been shown that information on endogenous DA release can be obtained noninvasively by using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). This approach is based on the assumption that an injected radiolabeled ligand competes with the endogenous neurotransmitter for the same receptor. Increases in DA release

will result in a decreased binding of the radioligand and vice versa (Dewey et al. 1993; Laruelle 2000). The exact mechanism for these changes in receptor availability is not known. The changes may be a result of true competition between the DA and the injected ligand, but may also be due to DA-induced internalization of the receptor (Sun et al. 2003). Nevertheless, it is generally assumed that the changes in radioligand binding can be used as a measure for the alterations in neurotransmitter release (Laruelle 2000). Using this method, correlations between DA function and behavioral or physiological scores have been found, providing information on the possible role of this neurotransmitter in pathological or physiological processes (Drevets et al. 2001; Laruelle et al. 1995; Leyton et al. 2002; Martinez et al. 2003; Pruessner et al. 2004; Volkow et al. 1994, 1999a, 2003).

Previous studies that investigated changes in DA levels have primarily assessed changes in striatal binding using D_2 receptor antagonists such as [^{11}C]-raclopride (RAC) or [^{123}I]-IBZM. In most studies, a paired bolus protocol was used, with two separate scans: A dopaminergic challenge is administered during one of the scans, while the other scan serves as a control. Alternatively, the ligand may be administered as a bolus followed by a constant infusion, leading to sustained equilibrium of radioligand levels in the blood and brain (Carson 2000). A challenge can then be administered during the equilibrium period, enabling measurement of baseline and drug-induced changes in ligand binding in the same experiment. During equilibrium, there is no net transfer of the radioligand across the blood-brain barrier, thereby minimizing possible effects of changes in drug-induced blood flow on ligand binding (Laruelle 2000). This aspect is an important advantage of the bolus with infusion paradigm, as compared to the double-bolus protocols.

Previous studies using RAC as a bolus followed by infusion have used amphetamine (AMPH) to assess pharmacologically induced changes in dopaminergic transmission (Breier et al. 1997; Carson et al. 1997; Martinez et al. 2003; Tsukada et al. 2002). Since AMPH is not a registered drug in The Netherlands, we aimed to investigate the effect of the DA reuptake blocker methylphenidate (MP). Microdialysis studies have shown that both compounds induce large increases in DA levels (Breier et al. 1997; Hernandez et al. 1987; Hurd and Ungerstedt 1989; Kuczenski and Segal 1997), which resulted in 15–25% reductions in RAC binding in human subjects after intravenous administration (Breier et al. 1997; Drevets et al. 2001; Martinez et al. 2003; Piccini et al. 2003; Volkow et al. 1994). The effect of MP on RAC binding has only been investigated using the double-bolus method. Using this method, Volkow et al. (1999a) studied the effect of a wide range of MP doses and found significant changes in specific binding after intravenous doses of 0.25 and 0.5 mg/kg. The effect of MP on RAC binding has not yet been investigated using a bolus with constant infusion protocol. In our study, we used this protocol to investigate the effect of MP in healthy volunteers. In future studies, we intend to use this method to study the dopaminergic system in psychiatric patients. We used an intravenous MP dose of 0.25 mg/kg, because in previous studies, comparable doses were used in psychiatric patients (Janowsky and Davis 1976; Joyce et al. 1986). To check the equilibrium state of the ligand, we also investigated the protocol without MP administration. We assessed the subjective state of the subject before and after MP administration since previous studies reported correlations between subjective effects and changes in ligand binding (Drevets et al. 2001; Laruelle et al. 1995; Leyton et al. 2002; Martinez et al. 2003; Volkow et al. 1994, 1999a). Finally, studies using AMPH have found a larger effect on ligand binding more in the ventral than in the dorsal regions of the striatum. Therefore, we studied the effect of MP in different striatal regions.

The aim of our study is to investigate if the results from the combined use of a relatively low dose of MP with a RAC constant infusion protocol comply with results from previous studies that used different dopaminergic challenges or double-bolus injections.

Methods

Subjects

Six healthy volunteers participated in the study (five men, one woman, mean age 24 years, range 18–32 years). All subjects gave written informed consent after written and oral explanation of the study. Suitability to participate in the study was determined by an independent physician after a medical examination including an electrocardiogram (ECG), routine blood hematology, and biochemistry tests. Exclusion criteria were current or past psychiatric, neurological, or other diseases that could interfere with the study, dependence on any substance other than nicotine or caffeine, and exposure to psychoactive drugs during the past 3 months. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen (UMCG).

[^{11}C]-raclopride synthesis

The tracer RAC was prepared from [^{11}C]-methyl iodide as previously described by Ehrin et al. (1987). It was dissolved in a volume of 20 mL sterile saline and was taken to the subject in the PET scanner. The specific radioactivity was >10.000 GBq/mmol at the time of injection.

PET scan protocol

The subjects were instructed to refrain from alcohol- and caffeine-containing products 24 h prior to each scan. Before the start of the PET scan, an intravenous catheter was inserted in each arm for blood sampling and MP injection and for ligand administration. The volunteers were positioned for scanning, and their heads were fixed using a head restraint. The subjects were scanned in 3D acquisition

mode using a Siemens ECAT Exact HR+ camera, giving 63 slices with a center-to-center distance of 2.425 mm. During the scans, RAC was administered as a fast bolus (1 min) followed by a constant infusion for 90 min with a bolus to infusion rate ratio (K_{bol}) of 100 min. The K_{bol} was based on a previous study, in which a K_{bol} of 105 min was associated with a slight overshoot in RAC binding (Mawlawi et al. 2001). The mean (±SD) activity at the start of the experiment was 220 (±99) MBq. Thirty-six consecutive frames were acquired for a duration of 2.5 min. Each subject was scanned twice. One of the scans served as a control scan to check the equilibrium state of the ligand. During the other scan, 0.25 mg/kg MP was injected intravenously for 1 min, 40 min after start of the RAC infusion. Three of the subjects received their control scan first, in the other three subjects, the treatment order was reversed. The two scans were separated by 2–7 months [the average test-retest variability in baseline binding potential (BP) was less than 11%]. During both scans, plasma samples were taken for metabolite analysis at 5, 30, 60, and 90 min after the start of the RAC infusion. During the MP scan, subjective and behavioral effects were evaluated using a verbal analog rating scale at 10 min before and 10 min after MP injection. The subjects were asked to respond to the following descriptors using a whole number between 0 (no effects) and 10 (maximal effects): euphoria, anxiety, happiness, sexual desire, desire for MP, alertness, annoyance, distrust, loss of control, restlessness, depression (Volkow et al. 1999a,b; Wang et al. 1997). Blood pressure, heart rate, and ECG were continuously monitored during the MP scans.

Metabolite analysis

Plasma samples from only five subjects were analyzed due to sampling problems in one of the volunteers. After centrifugation with acetonitrile, the liquid phase of the samples was injected into the high-performance liquid chromatography (HPLC) system, which contained a 300×7.9 mm μBondapak C18 semipreparative column. The column was eluted with a mixture of acetonitrile/water/85% phosphoric acid (500:500:1) at a flow rate of 2 mL/min. Fractions of the eluate were collected at 0.5-min intervals, and radioactivity in the fractions was determined using a gamma counter. The relative contributions of parent and metabolites were calculated.

Image analysis

Attenuation correction was performed by drawing ellipses on the brain images assuming uniform attenuation (Bergstrom et al. 1980; Zaidi et al. 2004). Statistical Parametric Mapping (SPM) 99 (Friston et al. 1995) was used for spatial normalization of the RAC image. A summation of the first ten RAC frames was normalized to the SPM [^{15}O]–H_2O template, giving 68 horizontal planes. The normalization parameters were thereafter used to normalize the other frames of the RAC scan. A predetermined standard region of interest (ROI) template localized in stereotactic Montreal Neurological Institute (MNI) space was applied to determine the ROIs, including left and right dorsal, middle and ventral caudate nucleus, dorsal and ventral putamen, cerebellum, and occipital cortex (see Fig. 1 for an example of the striatal ROIs). For further analyses, we defined the following three striatal subregions: dorsal (mean of six horizontal slices containing the dorsal caudate and putamen), middle (mean of four horizontal slices containing the middle caudate and ventral putamen), and ventral (mean of three horizontal slices containing the ventral caudate, including the nucleus accumbens). An activity threshold of 30% was used to extract stable peak values from the ROIs (Rottenberg et al. 1991). Time-activity curves from striatal and occipital regions were obtained. Estimates of the mean BP were calculated with $(C_t - C_{ref})/C_{ref}$ (Ito et al. 1998), where C_t is the mean activity over a time interval (T) in the ROI, and C_{ref} is the mean activity over T in a reference region. Intervals were T_1 (32.5–40 min) and T_2 (65–80 min). During T_1, RAC binding was relatively stable, as assessed by visual inspection of the time-activity curves. T_2 was chosen as a compromise between effect size and signal-to-noise ratio.

In our study, we selected the occipital cortex as reference region since the activity in the cerebellum was relatively noisy, probably due to low injected activity. The density of D_2 receptors is negligible in the occipital region compared with the striatum (Camps et al. 1989; Lidow et al. 1989) and has been used before as a reference region for D_2 binding (Booij et al. 1997; Kegeles et al. 1999; Laruelle

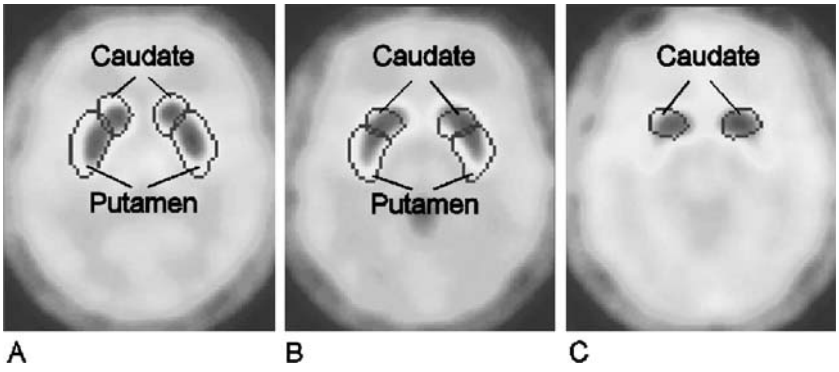

Fig. 1 Region of interest (ROI) placement examples of the dorsal (**a**), middle (**b**), and ventral (**c**) striatum

et al. 1995; Laruelle et al. 1997). The baseline subjective scores and the scores after MP minus baseline score were used as outcome measures for the behavioral effects.

Statistical analysis

Differences between BP(T_1) and BP(T_2) were calculated for the control and MP scans using a paired *t* test. Percent change in BP (ΔBP) was calculated as follows: [BP(T_2)−BP(T_1)/BP(T_1)]×100. ΔBP was assessed for the control and MP scans for the total striatum and the striatal subregions (dorsal, middle, and central), and differences in ΔBP between the control and MP conditions were calculated using paired *t* tests. The effect of MP on the subjective scores was assessed using paired *t* test. Pearson product moment correlations were calculated between the behavioral changes and ΔBP (difference between ΔBP in the control and MP conditions) in the striatal subregions. Based on previous studies, we investigated the following correlations: ΔBP with MP-induced change in euphoria, anxiety at baseline with ΔBP, and baseline BP with change in euphoria (Drevets et al. 2001; Laruelle et al. 1995; Martinez et al. 2003; Volkow et al. 1994, 1999a,b, 2002b). It was assumed that baseline D_2 receptor measurements are stable across experiments (Volkow et al. 2002b). Baseline BP was therefore averaged over control and MP scans. The effect of MP on blood pressure and heart rate was tested with a paired *t* test. The four values measured during an interval of 30 min before start of the PET scan were compared with the six values obtained between 4 and 18 min after MP administration, which was the time period when peak effects occurred. Bonferroni corrections were applied to all tests involving multiple comparisons.

Drugs

Methylphenidate was obtained from Fagron Farma BV, The Netherlands, and infusions were prepared and provided by the pharmacy of the UMCG.

Results

Metabolite analysis

As in previous studies, raclopride metabolism was not significantly altered by MP (Fig. 2; Drevets et al. 2001; Martinez et al. 2003; Volkow et al. 1994).

Cardiovascular measurements

MP significantly increased heart rate ($p<0.001$) and systolic ($p<0.001$) and diastolic blood pressure ($p<0.001$). Increases ranged from 40 to 70% (heart rate), from 20 to 40% (systolic blood pressure), and from 20 to 30% (diastolic blood pressure). The effects on heart rate and blood pressure are in agreement with results from previous studies (Volkow et al. 2003). No significant changes were observed in the ECG, apart from the increases in heart rate.

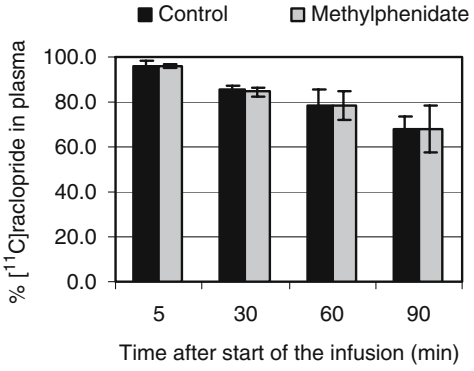

Fig. 2 Percent unchanged [^{11}C]-raclopride (RAC) in plasma at 5, 30, 60, and 90 min after start of the RAC infusion in control and methylphenidate (MP) scans. Methylphenidate (0.25 mg/kg) was injected at 40 min after start of the infusion

PET measurements

Mean time-activity curves for the control and MP scans (total binding and ratio to the occipital cortex) are shown in Fig. 3. In the control condition, the mean RAC BP reached relatively stable values approximately 30 min after the start of the infusion. MP administration induced a decrease in RAC binding in the striatum, whereas binding in the occipital cortex was not affected. Fig. 4 shows the BP values before and after MP administration for each striatal subregion. A paired *t* test showed a significant difference between BP before [BP(T_1)] and after [BP(T_2)] MP administration in the total striatum ($p<0.001$), whereas in the control condition, no difference was found between BP (T_1) and BP(T_2) ($p=0.57$). Mean ΔBP in the total striatum after MP injection was −24% (range −14 to −40%), whereas the mean ΔBP in the control condition was 0% (range +33 to −21%). Since not all individual time-activity curves in the control situation were in equilibrium, we used the difference in ΔBP between the MP and control scans for further analyses. The mean difference in ΔBP between the MP and control conditions was −24% (range 0 to −48%). The difference in ΔBP between the control and MP conditions was larger in the ventral striatum (−43%, range +19 to −128%) compared with the middle (−27%, range −1 to −46%) and dorsal striatum (−13%, range −5 to −18%). A paired *t* test showed a significant difference in ΔBP between the control and MP conditions in the whole striatum ($p=0.029$), the dorsal ($p=0.001$) and middle striatum ($p=0.026$), but not in the ventral striatum ($p=0.122$).

Subjective effects

MP significantly increased the scores for euphoria ($p=0.01$), restlessness ($p=0.003$), and desire for MP ($p<0.001$). After Bonferroni correction, only the change in restlessness and

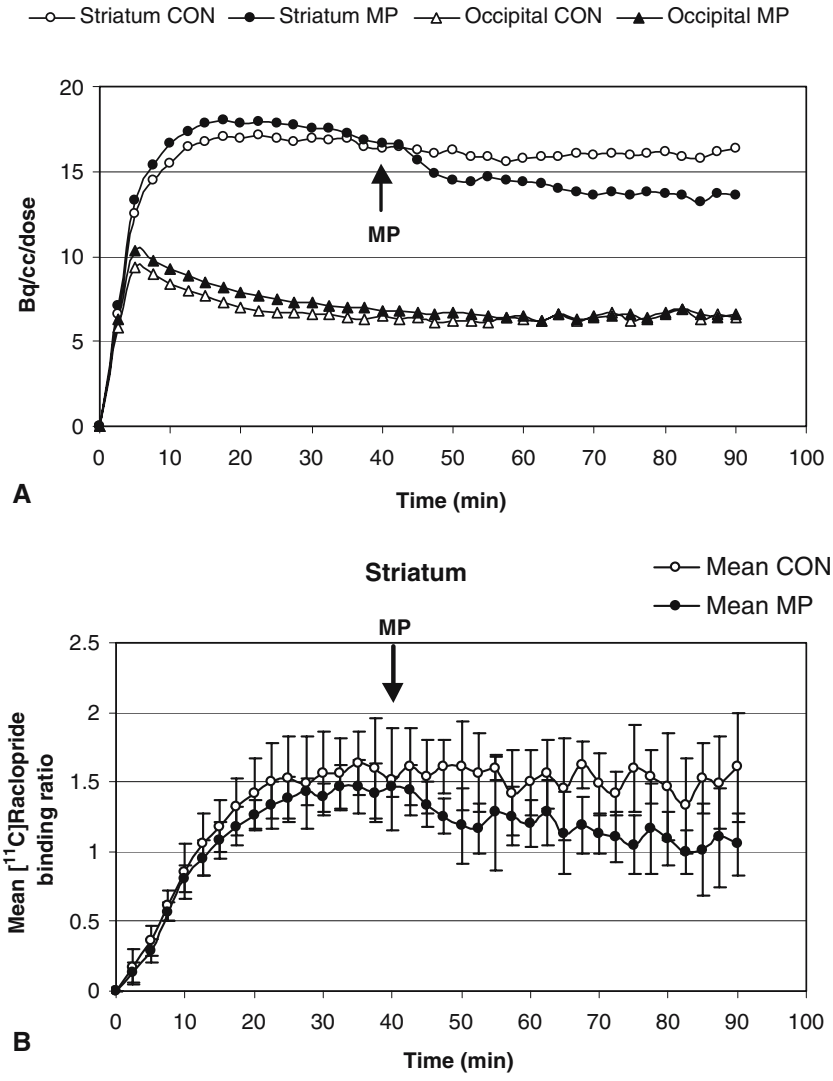

Fig. 3 **a** Mean time-activity curves of total RAC uptake for the control (*CON*) and methylphenidate (*MP*) scans. **b** Mean (±SD) time-activity curves of the binding ratio to the occipital cortex $(C_t - C_{ref})/C_{ref}$ for the control scans and MP scans

desire for MP were significant. The behavioral response differed between subjects. Most subjects described the experience as pleasurable, only one of the subjects described the effect as partly unpleasurable. Correlations were found between change in euphoria and ΔBP in the dorsal striatum (p=0.006) and between baseline anxiety and ΔBP in the dorsal (p=0.037) and middle striatum (p=0.005). We found a negative correlation between baseline BP in the dorsal striatum and change in euphoria (p=0.037) (Fig. 5). When applying Bonferroni correction (α_{crit}=0.0055), which is considered rather conservative at nine comparisons, only the correlation between baseline anxiety and ΔBP in the middle striatum was significant. However, the other correlations were also considered genuine on the

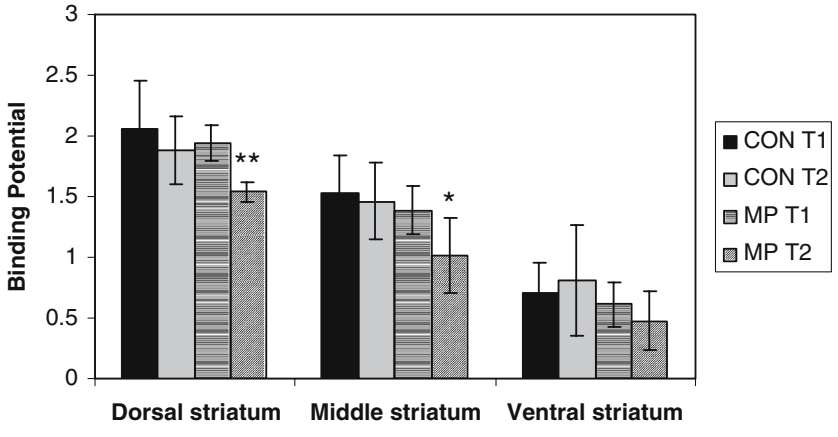

Fig. 4 Mean (±SD) binding potential (BP) values for T_1 (32.5–40 min) and T_2 (65–80 min) in the control and MP condition for each striatal subregion. *Indicates significant difference between T_1 and T_2 (p<0.05). **Indicates significant difference between T_1 and T_2 (p<0.01)

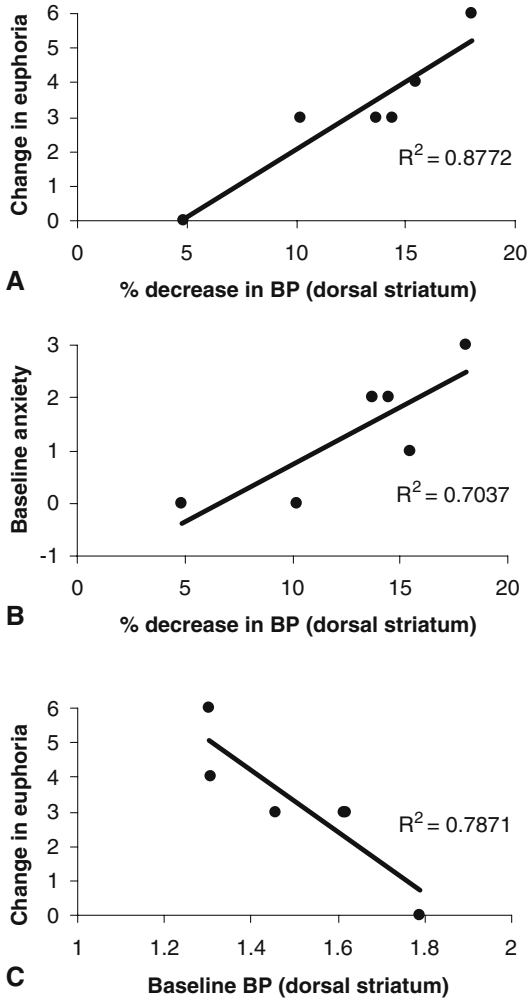

Fig. 5 Correlations between percent decrease in BP (*MP-CON*) and change in euphoria (**a**), percent decrease in BP (*MP-CON*) and baseline anxiety (**b**), and between baseline BP and change in euphoria (**c**)

basis of results from previous studies (Drevets et al. 2001; Laruelle et al. 1995; Martinez et al. 2003; Volkow et al. 1994, 1999a,b, 2002b).

Discussion

In the present study, we investigated the effect of a relatively low dose of MP on RAC binding. This is the first study that investigated the effect of MP using a bolus with infusion protocol. The mean RAC BP reached relatively stable values approximately 30 min after the start of the infusion. Immediately after MP administration, a clear reduction in striatal RAC binding was seen, suggesting increased DA levels.

Previous human studies have shown that MP- or AMPH-induced changes in RAC binding usually ranged between 15 and 25% in double-bolus or bolus with infusion studies (Breier et al. 1997; Drevets et al. 2001; Martinez et al. 2003; Piccini et al. 2003; Volkow et al. 1994). These studies also reported large differences between the individual subjects. Using a double-bolus design, Volkow et al. (1999a) showed that MP (0.25 mg/kg) induced a change in RAC binding that ranged from approximately +5 to −30%. It has been suggested that the double-bolus and bolus with infusion methods may differ in sensitivity due to differences in timing of the drug with respect to tracer delivery (Carson et al. 1997). In our bolus with infusion study, however, the MP-induced changes in BP were comparable to the changes in the double-bolus study by Volkow et al. (1999a).

In our and previous studies, correlations were found between changes in DA release and subjective effects. DA release, especially in the striatum, has been implicated in the process of rewarding or reinforcing effects of certain stimuli (Ikemoto and Panksepp 1999; McClure et al. 2004; Spanagel and Weiss 1999; Ungless 2004; Wise 2004). Data indicate that DA is released after unexpected rewards, during expectation of a reward and desire for a reward, and also after novel stimuli (Berridge and Robinson 1998; De la Fuente Fernandez et al. 2002; Leyton et al. 2002; Schultz 1998). DA increases have been found both in the dorsal and in the ventral striatum. In our study, we have found a correlation between the MP-induced change in euphoria and BP change in the dorsal striatum, which agrees with findings from previous studies with MP and studies using nondrug challenges (Barrett et al. 2004; De la Fuente Fernandez et al. 2001; Small et al. 2003; Volkow et al. 1999a; Zald et al. 2004). In contrast, previous studies using AMPH have found correlations with BP changes in the ventral but not the dorsal striatum (Drevets et al. 2001; Martinez et al. 2003). The underlying mechanisms that cause the dissociation between these striatal subregions are currently unknown but may depend on the nature of the reward or the behavioral response (Dagher 2005; De la Fuente Fernandez et al. 2001, 2002; Leyton et al. 2002).

In our study, the reduction in RAC was larger in the ventral striatum compared with the dorsal striatum, although not significant. The lack of significance may be due to the high variability in this region. Some previous studies using AMPH have shown larger changes in the ventral striatum (Drevets et al. 2001; Leyton et al. 2002; Martinez et al. 2003), which is in agreement with animal studies that have shown that drugs of abuse preferentially increase DA release in the nucleus accumbens (Di Chiara and Imperato 1988). It is however not known if this also applies to MP.

We found correlations between MP-induced BP changes and baseline anxiety. Since MP only blocks reuptake, it is dependent on the extent of physiologically released DA, and therefore on the subjective state of the subject during the experiment (Volkow et al. 1994). Volkow et al. (1994) has also found correlations between baseline anxiety and MP-induced changes in BP. They postulate that higher anxiety scores may reflect a higher responsiveness of the subjects to novel stimuli and/or unfamiliar situations, which could be linked with a more responsive DA system. In agreement with these findings are studies which show an effect of stress and cortisol on MP- and AMPH-induced increases in DA levels (Marsteller et al. 2002; Oswald et al. 2005).

In addition, in our study, a negative correlation between baseline BP and change in euphoria was seen. This is also in agreement with studies by Volkow et al. (1999b, 2002b). As Volkow et al. (2002b) suggest, it is possible that in subjects with a high D_2 receptor density, a smaller dose of MP may have been perceived as pleasant. The low D_2 density could have been caused by high baseline DA levels. However, Volkow et al. (2002b) showed that the measurements were stable over different experiments, suggesting that they were not influenced by differences in DA concentration, which, in contrast to D_2 density, may fluctuate rapidly between measurements.

There are several methodological limitations that should be considered for this study. Equilibrium was not always achieved in the individual scans; therefore, we used the difference between the MP and control scans for further analyses. Optimally, the control and drug measurements should be made within the same scan. This would need an increase in scan duration to attain equilibrium before and after drug administration and would require higher injected activity. In situations of nonequilibrium, the estimation of BP may be biased due to effects of ligand distribution or clearance (Carson et al. 1993). In addition, ΔBP may be underestimated if the equilibrium is not established postchallenge (Slifstein et al. 2004). It is currently unknown to what extent these effects may have influenced our results. The power of the study was limited due to the relatively small number of subjects. No magnetic resonance imaging (MRI) scans were made in our study, which would have enabled individual ROI delineation. Unfortunately, this study was not placebo controlled, and we did not assess the subjective state during the control condition. Therefore, we were unable to distinguish expectation-induced changes in the DA from the experience of MP effects. In future studies, it is important to control for such variables. In addition, correction for patient motion will help to increase the sensitivity of the measurements, and coregistration with individual MRI scans would enable partial volume correction.

Despite these methodological limitations, our results comply with previous findings, indicating the feasibility of the bolus infusion design combined with a relatively low MP dose to study dopaminergic (dys)function in psychiatric patients.

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References

Barrett SP, Boileau I, Okker J, Pihl RO, Dagher A (2004) The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [11C]raclopride. Synapse 54:65–71

Bergström M, Bohm C, Ericson K, Eriksson L, Litton J (1980) Corrections for attenuation, scattered radiation and random coincidences in a ring detector positron emission transaxial tomograph. IEEE Trans Nucl Sci 27:549–554

Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28:309–369

Booij J, Korn P, Linszen DH, van-Royen EA (1997) Assessment of endogenous dopamine release by methylphenidate challenge using iodine-123 iodobenzamide single-photon emission tomography. Eur J Nucl Med 24:674–677

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de-Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci U S A 94:2569–2574

Camps M, Cortes R, Gueye B, Probst A, Palacios JM (1989) Dopamine receptors in human brain: autoradiographic distribution of D2 sites. Neuroscience 28:275–290

Carson RE, Channing MA, Blasberg RG, Dunn BB, Cohen RM, Rice KC, Herscovitch P (1993) Comparison of bolus and infusion methods for receptor quantitation: application to [18F]cyclofoxy and positron emission tomography. J Cereb Blood Flow Metab 13:24–42

Carson RE, Breier A, de-Bartolomeis A, Saunders RC, Su TP, Schmall B, Der MG, Pickar D, Eckelman WC (1997) Quantification of amphetamine-induced changes in [11C] raclopride binding with continuous infusion. J Cereb Blood Flow Metab 17:437–447

Carson RE (2000) PET physiological measurements using constant infusion. Nucl Med Biol 27:657–660

Dagher A (2005) Human dopamine response to drugs and natural rewards. In: Abstract INV37 Brain '05, Vrije Universiteit, Amsterdam, 7–11 June 2005

De la Fuente Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ (2001) Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293:1164–1166

De la Fuente Fernandez R, Phillips AG, Zamburlini M, Sossi V, Calne DB, Ruth TJ, Stoessl AJ (2002) Dopamine release in human ventral striatum and expectation of reward. Behav Brain Res 136:359–363

Dewey SL, Smith GS, Logan J, Brodie JD, Fowler JS, Wolf AP (1993) Striatal binding of the PET ligand 11C-raclopride is altered by drugs that modify synaptic dopamine levels. Synapse 13:350–356

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274–5278

Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biol Psychiatry 49:81–96

Ehrin E, Gawell L, Högberg T, de Paulis T, Ström P (1987) Synthesis of (methoxy-^{3}H)- and (methoxy-^{11}C)-labelled raclopride, specific dopamine D-2 receptor ligands. J Label Compd Radiopharm 24:931–939

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 2:189–210

Hernandez L, Lee F, Hoebel BG (1987) Simultaneous microdialysis and amphetamine infusion in the nucleus accumbens and striatum of freely moving rats: increase in extracellular dopamine and serotonin. Brain Res Bull 19:623–628

Hurd YL, Ungerstedt U (1989) In vivo neurochemical profile of dopamine uptake inhibitors and releasers in rat caudate-putamen. Eur J Pharmacol 166:251–260

Ikemoto S, Panksepp J (1999) The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. Brain Res Brain Res Rev 31:6–41

Ito H, Hietala J, Blomqvist G, Halldin C, Farde L (1998) Comparison of the transient equilibrium and continuous infusion method for quantitative PET analysis of [11C]raclopride binding. J Cereb Blood Flow Metab 18:941–950

Janowsky DS, Davis JM (1976) Methylphenidate, dextroamphetamine, and levamfetamine. Effects on schizophrenic symptoms. Arch Gen Psychiatry 33:304–308

Joyce PR, Donald RA, Nicholls MG, Livesey JH, Abbott RM (1986) Endocrine and behavioural responses to methylphenidate in depression. Psychol Med 16:531–540

Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23

Kapur S, Mamo D (2003) Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 27:1081–1090

Kegeles LS, Zea-Ponce Y, Abi-Dargham A, Rodenhiser J, Wang T, Weiss R, Van-Heertum RL, Mann JJ, Laruelle M (1999) Stability of [123I]IBZM SPECT measurement of amphetamine-induced striatal dopamine release in humans. Synapse 31:302–308

Kuczenski R, Segal DS (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 68:2032–2037

Kunig G, Leenders KL, Martin-Solch C, Missimer J, Magyar S, Schultz W (2000) Reduced reward processing in the brains of parkinsonian patients. Neuroreport 11:3681–3687

Laruelle M, Abi-Dargham A, van-Dyck CH, Rosenblatt W, Zea-Ponce Y, Zoghbi SS, Baldwin RM, Charney DS, Hoffer PB, Kung HF, Innis RB (1995) SPECT imaging of striatal dopamine release after amphetamine challenge. J Nucl Med 36: 1182–1190

Laruelle M, D'Souza CD, Baldwin RM, Abi-Dargham A, Kanes SJ, Fingado CL, Seibyl JP, Zoghbi SS, Bowers MB, Jatlow P, Charney DS, Innis RB (1997) Imaging D2 receptor occupancy by endogenous dopamine in humans. Neuropsychopharmacology 17:162–174

Laruelle M (2000) Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. J Cereb Blood Flow Metab 20:423–451

Leenders KL (2002) Disease process and drug treatments in Parkinson's disease. Eur Neuropsychopharmacol 12:575–580

Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A (2002) Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology 27:1027–1035

Lidow MS, Goldman-Rakic PS, Rakic P, Innis RB (1989) Dopamine D2 receptors in the cerebral cortex: distribution and pharmacological characterization with [3H]raclopride. Proc Natl Acad Sci U S A 86:6412–6416

Marsteller DA, Gerasimov MR, Schiffer WK, Geiger JM, Barnett CR, Borg JS, Scott S, Ceccarelli J, Volkow ND, Molina PE, Alexoff DL, Dewey SL (2002) Acute handling stress modulates methylphenidate-induced catecholamine overflow in the medial prefrontal cortex. Neuropsychopharmacology 27:163–170

Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y, Cooper T, Kegeles L, Zarahn E, Abi-Dargham A, Haber SN, Laruelle M (2003) Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metab 23:285–300

Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang Y, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D (2) receptor parameter measurements in ventral striatum. J Cereb Blood Flow Metab 21:1034–1057

McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004) Separate neural systems value immediate and delayed monetary rewards. Science 306:503–507

Naranjo CA, Tremblay LK, Busto UE (2001) The role of the brain reward system in depression. Prog Neuropsychopharmacol Biol Psychiatry 25:781–823

Oswald LM, Wong DF, McCaul M, Zhou Y, Kuwabara H, Choi L, Brasic J, Wand GS (2005) Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. Neuropsychopharmacol (in press)

Piccini P, Pavese N, Brooks DJ (2003) Endogenous dopamine release after pharmacological challenges in Parkinson's disease. Ann Neurol 53:647–653

Pruessner JC, Champagne F, Meaney MJ, Dagher A (2004) Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J Neurosci 24:2825–2831

Rottenberg DA, Moeller JR, Strother SC, Dhawan V, Sergi ML (1991) Effects of percent thresholding on the extraction of [18F]fluorodeoxyglucose positron emission tomographic region-of-interest data. J Cereb Blood Flow Metab 11:A83–A88

Schmidt K, Nolte-Zenker B, Patzer J, Bauer M, Schmidt LG, Heinz A (2001) Psychopathological correlates of reduced dopamine receptor sensitivity in depression, schizophrenia, and opiate and alcohol dependence. Pharmacopsychiatry 34:66–72

Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurophysiol 80:1–27

Slifstein M, Narendran R, Hwang DR, Sudo Y, Talbot PS, Huang Y, Laruelle M (2004) Effect of amphetamine on [(18)F]fallypride in vivo binding to D(2) receptors in striatal and extrastriatal regions of the primate brain: single bolus and bolus plus constant infusion studies. Synapse 54:46–63

Small DM, Jones-Gotman M, Dagher A (2003) Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage 19: 1709–1715

Spanagel R, Weiss F (1999) The dopamine hypothesis of reward: past and current status. Trends Neurosci 22:521–527

Sun W, Ginovart N, Ko F, Seeman P, Kapur S (2003) In vivo evidence for dopamine-mediated internalization of D2-receptors after amphetamine: differential findings with [3H]raclopride versus [3H]spiperone. Mol Pharmacol 63:456–462

Tsukada H, Miyasato K, Kakiuchi T, Nishiyama S, Harada N, Domino EF (2002) Comparative effects of methamphetamine and nicotine on the striatal [(11)C]raclopride binding in unanesthetized monkeys. Synapse 45:207–212

Ungless MA (2004) Dopamine: the salient issue. Trends Neurosci 27:702–706

Volkow ND, Wang GJ, Fowler JS, Logan J, Schlyer D, Hitzemann R, Lieberman J, Angrist B, Pappas N, MacGregor R, Burr G, Cooper T, Wolf A (1994) Imaging endogenous dopamine competition with [11C]raclopride in the human brain. Synapse 16:255–262

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, Hitzemann R, Pappas NR (1999a) Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. J Pharmacol Exp Ther 291:409–415

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Gifford A, Hitzemann R, Ding YS, Pappas N (1999b) Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. Am J Psychiatry 156:1440–1443

Volkow ND, Fowler JS, Wang GJ (2002a) Role of dopamine in drug reinforcement and addiction in humans: results from imaging studies. Behav Pharmacol 13:355–366

Volkow ND, Wang GJ, Fowler JS, Thanos PP, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas N (2002b) Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. Synapse 46:79–82

Volkow ND, Wang GJ, Fowler JS, Molina PE, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas NR, Zhu W, Swanson JM (2003) Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacology (Berl) 166:264–270

Wang G-J, Volkow ND, Hitzemann RJ, Wong C, Angrist B, Burr G, Pascani K, Pappas N, Lu A, Cooper T, Lieberman JA (1997) Behavioral and cardiovascular effects of intravenous methylphenidate in normal subjects and cocaine abusers. Eur Addict Res 3:49–54

Wise RA (2004) Dopamine, learning and motivation. Nat Rev Neurosci 5:483–494

Zaidi H, Montandon ML, Slosman DO (2004) Attenuation compensation in cerebral 3D PET: effect of the attenuation map on absolute and relative quantitation. Eur J Nucl Med Mol Imaging 31:52–63

Zald DH, Boileau I, El-Dearedy W, Gunn R, McGlone F, Dichter GS, Dagher A (2004) Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 24:4105–4112