The Journal of Neuroscience, May 1, 1997, 17(9):3168–3177

PET Measurement of Dopamine D_2 Receptor-Mediated Changes in Striatopallidal Function

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This study was designed to validate an *in vivo* measurement of the functional sensitivity of basal ganglia neuronal circuits containing dopamine D_2 receptors. We hypothesized that a D_2 agonist would decrease striatopallidal neuronal activity, and hence regional cerebral blood flow (rCBF) over the axon terminals in the globus pallidus. Quantitative pallidal blood flow was measured using positron emission tomography (PET) with bolus injections of $H_2{}^{15}O$ and arterial sampling in six baboons before and after intravenous administration of the selective D_2 agonist U91356a. We also tested whether the response to U91356a was modified by previous acute administration of various antagonists. Another baboon had serial measurements of blood flow under identical conditions, but received no dopaminergic drugs. In all animals that received U91356a, pallidal flow decreased in a dose-related manner. Global CBF had a similar response, but the decline in pallidal flow was greater in magnitude and remained significant after accounting for the global effect. A D_2 antagonist, but not antagonists of D_1, serotonin-2, or peripheral D_2 receptors, prevented this decrease. This work demonstrates and validates an *in vivo* measure of the sensitivity of D_2-mediated basal ganglia pathways. It also supports the hypothesis that activation of the indirect striatopallidal pathway, previously demonstrated using nonselective D_2-like agonists, can be mediated specifically by D_2 receptors. We speculate that the U91356a-PET technique may prove useful in detecting functional abnormalities of D_2-mediated dopaminergic function in diseases such as parkinsonism, dystonia, Tourette syndrome, or schizophrenia.

Key words: globus pallidus; dopamine D_2 receptor; positron emission tomography; pharmacological activation; baboon; U91356a

Functional abnormalities of dopaminergic pathways are implicated in a number of syndromes, including parkinsonism, dystonia, chorea, tics, psychosis, and drug addiction (Jankovic and Tolosa, 1993; Knable et al., 1995; Nestler, 1995). However, the pathophysiology and pharmacology of these syndromes remain primarily unknown.

Longitudinal or human studies require an *in vivo* technique for studying these pathways. An *in vivo* method also may prove more relevant than *in vitro* techniques (Perlmutter and Raichle, 1986; Bloch and LeMoine, 1994; Gerfen and Keefe, 1994).

One approach to assess changes in neuronal function is to measure the effects of dopamimetics on regional cerebral metabolism or blood flow (rCBF). *Ex vivo* autoradiography gives precise anatomic detail (von Essen et al., 1980; Jauzac et al., 1982; McCulloch, 1982; McCulloch et al., 1982a,b,c; Palacios and Wiederhold, 1984, 1985; Pizzolato et al., 1984, 1985a,b, 1987; Trugman and Wooten, 1986, 1987; Mori et al., 1989; Engber et al., 1990; Russo et al., 1991; Stein and Fuller, 1992; Tarazi et al., 1993), whereas PET and other imaging techniques allow *in vivo* studies using stimulants (Mathew and Wilson, 1989; Daniel et al., 1991; Pearlson et al., 1993), LDOPA (Rougemont et al., 1984; Henriksen and Boas, 1985; Leenders et al., 1985; Perlmutter and Raichle, 1985; Melamed et al., 1986; Montastruc et al., 1987; Rotrosen 1987; Kobari et al., 1992, 1995), nonspecific dopamine agonists (Cleghorn et al., 1991; Sabatini et al., 1991; Grasby et al., 1993; Rascol et al., 1993; Kapur et al., 1994), and nonselective D_2-like agonists (Celsis et al., 1988; Perlmutter, 1995). D_2-like antagonists, although less relevant to this study, also have been studied extensively (Holcomb et al., 1996).

The main rCBF response to the nonselective D_2-like agonist quinpirole was a decrease in globus pallidus (GP) (Perlmutter et al., 1993). Because neuronal activity is highly correlated with metabolism and rCBF at axonal termini (Raichle, 1987; Jueptner and Weiller, 1995), we interpret this as reflecting decreased activity of striatopallidal neurons mediated by D_2-like receptors (Pizzolato et al., 1985c; Strange, 1990; Harrison et al., 1992; Robertson et al., 1992; Levey et al., 1993; Young and Penney, 1993; Gerfen et al., 1995). This fits other data that D_1-like receptors activate inhibitory striatal neurons that project to internal globus pallidus (GPi) or substantia nigra pars reticulata (SNr), and D_2-like receptors decrease GPi/SNr activity indirectly via decreased striatal inhibition of the external globus pallidus (GPe)

Received Jan. 6, 1997; accepted Feb. 11, 1997.

This work was supported by National Institutes of Health Grants AA07466, NS01898, NS32318, and NS31001; the Charles A. Dana Foundation (The Dana Clinical Hypotheses Research Program); the American Parkinson Disease Association; National Alliance for Research on Schizophrenia and Depression; and the McDonnell Center for Higher Brain Function. We gratefully acknowledge helpful discussions with Professor P. J. Bédard (Centre de Recherche en Neurobiologie, Hôpital de l'Enfant-Jésus, Québec, Canada), and Drs. M. F. Piercey and M. W. Moon (CNS Research, Pharmacía-Upjohn). U91356a was a generous gift of the Upjohn Company.

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(Gerfen et al., 1990; Levey et al., 1993). The two pathways have important behavioral correlates (Young and Penney, 1993) and complex interactions (Bédard et al., 1992; Jackson and Westlind-Danielsson, 1994; Gerfen et al., 1995).

The discovery of numerous dopamine receptor subtypes and selective drugs (Jackson and Westlind-Danielsson, 1994) makes possible more precise characterization of pharmacological responses. Because D_2 receptors are the most numerous D_2-like receptor in striatum, we hypothesized that rCBF in the GP would decline after systemic administration of a specific D_2 agonist, as it had after quinpirole, and that the dose–response would be biologically meaningful and pharmacologically specific.

MATERIALS AND METHODS

Subjects. These studies conformed to the Society for Neuroscience's Policy on the Use of Animals in Neuroscience Research, including previous approval by the Washington University Animal Studies Committee. Subjects were five normal baboons (three male, two female; ages 3–10 years; 10.5–25.9 kg), and two male baboons (ages 4–8 years; 14.1–28.5 kg) that had had previous unilateral intracarotid administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), in one case resulting in marked hemiparkinsonism and in the other case producing only mild rigidity of the contralateral upper extremity. The normal baboons were used to establish the presence of the hypothesized rCBF response. To avoid exposing the normal baboons to dopamine antagonists, the untreated control hemispheres of the MPTP-treated baboons were used to test the pharmacological specificity of the hypothesized response (except for one experiment using domperidone pretreatment in a normal animal).

PET scan conditions. Subjects were given intramuscular atropine (in 4 cases; 0.2 mg, median 13 μg/kg) or glycopyrrolate (in 10 cases; 0.07–0.10 mg, median 0.08 mg or 5 μg/kg) to control pharyngeal secretions, and intramuscular ketamine (225–500 mg, median 250 mg or 17.2 mg/kg) for sedation. We placed a 20 gauge catheter into a limb vein for drug and radiopharmaceutical administration and a soft-cuffed endotracheal tube to permit ventilation with 70% nitrous oxide and 30% oxygen to maintain sedation throughout the study. The animal was paralyzed with gallamine or pancuronium to control pCO_2 throughout the studies. The choice of chemical sedation is complex, but our experience and review of the literature suggests that N_2O has less effects on rCBF responses than other general anesthetics and provides adequate sedation for the neuromuscular blockade. A similar anesthetic technique has been used for comparable studies (McCulloch and Teasdale, 1979; Ingvar et al., 1983; Akeson et al., 1993).

Arterial access was established with a 20 gauge catheter placed in the femoral artery by direct puncture after local anesthesia with 1% lidocaine. Arterial samples were obtained at intervals throughout the study, and pO_2 and pCO_2 were measured using a pH/blood gas analyzer and a CO-oximeter (System 1306 and IL-482, Instrumentation Laboratory, Lexington, MA). Arterial blood pressure, pulse, ventilatory rate, and temperature were also monitored continually throughout the study.

All PET scans were performed at least 3 hr after the ketamine and atropine or glycopyrrolate administration, to allow the acute effects of these agents on rCBF to dissipate. A 3 hr interval was chosen for the following reasons. On the one hand, NMDA antagonists clearly affect D_2-like neuronal function 5–15 min after administration (Engber et al., 1993), ketamine affects accumulation of a D_2-5HT2 ligand measured 30–80 min after intramuscular injection (Onoe et al., 1994), and ketamine alters regional cerebral metabolism and blood flow for 5–90 min (Hougaard et al., 1974; Nelson et al., 1980; Crosby et al., 1982; Oguchi et al., 1982; Hammer and Herkenham, 1983; Dhasmana et al., 1984; Cavazzuti et al., 1987; Lahti et al., 1995). On the other hand, some studies have detected no effects of ketamine on dopamine metabolism (Bacopoulos et al., 1979; Koshikawa et al., 1988). Ketamine-specific binding in the brain is virtually gone 30 min after intravenous administration (Björkman et al., 1992), and changes in CBF attributable to intravenous ketamine are gone at 90 min (the metabolite norketamine has negligible effects on global CBF) (Akeson et al., 1993; Hartvig et al., 1995; Lahti et al., 1996). The peak clinical effect of intramuscular ketamine is at 20 min, compared with 1 min after intravenous ketamine (Reves and Glass, 1990). To test the duration of ketamine effects using our protocol, we had previously measured CBF repeatedly in baboons given intramuscular ketamine and then kept sedated with N_2O for up to 6 hr without other interventions. Ketamine caused an initial rapid decline in global CBF, which then gradually *increased* ~25% during the first 1–2 hr followed by either a stable baseline or a slight further increase in CBF over the next 2 hr. The only notable regional effect on CBF was in the cortex (J. S. Perlmutter, unpublished observations).

After the 3 hr had elapsed, several baseline measurements of rCBF were obtained (described below). In some experiments, an antagonist was given intravenously at this point and several rCBF scans were repeated (described below). Then at approximately hourly intervals, we gave various doses of U91356a intravenously over 2–5 min, while continuously monitoring pulse and blood pressure. After each dose, several rCBF PET scans were obtained at 15 min intervals. Each successive dose of U91356a was ~10-fold higher than the last. The number of doses used in a given study varied from one to three. PET scans were performed in a quiet room, with lights on to facilitate observation of the animal. The animal's eyes were closed and covered to prevent drying. The data reported represent 179 PET rCBF scans.

PET methods. All PET images were acquired on a Siemens/CTI 953B scanner [Erlangen, Germany (Mazoyer et al., 1991; Spinks et al., 1993)] using the two-dimensional wobble sampling mode yielding 31 slices with a center-to-center spacing of 3.375 mm and a reconstructed resolution of 5 mm (full-width, half-maximum). CBF images were acquired using a 40 sec acquisition beginning with the arrival of isotope in the head, after a bolus injection of 30–50 mCi of $H_2{}^{15}O$. Scans were reconstructed using a ramp filter and a measured attenuation factors for each subject. Continuous arterial sampling during each scan with an automated blood sampler and scintillation counter, calibrated daily against a well counter, allowed quantitative determination of rCBF. This method has been validated in our laboratory using baboons (Raichle et al., 1983; Videen et al., 1987).

Pharmacological agents. U91356a is a specific dopamine D_2-receptor agonist. Its affinity (K_i) for various receptors has been reported as dopamine D_1, >1000 nM; D_2, 1.3 nM; D_3, 32 nM; D_4, 195 nM; and serotonin 5HT1A, 58 nM; with no submicromolar affinities for any other adrenergic, cholinergic, or serotonergic receptors tested (Piercey et al., 1995). U91356a was effective in treating MPTP-induced parkinsonism, but consistent with the *in vitro* specificity data, it did not affect striatal D_1-like receptor density, as l-DOPA did (Martel et al., 1993). Some evidence suggests that 10–30 $\mu g^{-1} \cdot kg^{-1} \cdot d$ might be a clinically relevant subcutaneous dose for treatment of MPTP-induced parkinsonism in monkeys (M. F. Piercey et al., unpublished observations). Additionally, the ED_{50} in rats for U91356a-induced inhibition of substantia nigra pars compacta neuronal firing is 32 μg/kg (Piercey et al., 1995). This evidence guided selection of the doses used in this study, which were grouped as low (1–2 μg/kg), medium (10–22 μg/kg), and high (100–220 μg/kg) doses.

Antagonists included SCH23390 (a dopamine D_1 antagonist), 1 mg/kg; eticlopride (a dopamine D_2 antagonist), 4 mg/kg; ketanserin (serotonin 5HT2 antagonist), 0.6 mg/kg; and domperidone (a dopamine D_2 antagonist that penetrates the blood-brain barrier relatively poorly), 0.1 mg/kg.

Identification of anatomic locations in PET images. The head of the sedated animal was fixed in position with a headholder system that bolted to a acrylic "cap" surgically implanted in the skull and also to the PET scanning table (Perlmutter et al., 1991a). This ensured no movement of the head throughout the scan (Black et al., 1996a).

Anatomic regions were identified on a magnetic resonance image (MRI) of each animal's brain, acquired on a different day from the PET studies, and then transferred to the PET image using an automated routine. The steps used in this process were as follows.

Three-dimensional MPRAGE images were acquired sagittally with a 1.5T Siemens Magnetom scanner using the same headholder as for PET studies. The magnet was shimmed before each study. A three-dimensional acquisition (TR = 9.7 msec, TE = 4 msec, and flip angle = 12°) used a slab thickness of 200 mm with 160 partitions and a 200 mm square field of view in a 256 × 256 matrix, giving 0.78 × 0.78 × 1.25 mm voxels. For convenience, a single interpolation step then resampled the MR images to 0.5 mm cubic voxels and rotated the brain to the same orientation as that of the Davis and Huffman (1968) stereotactic atlas of baboon brain, under visual guidance. A histogram method allowed uniform scaling of signal intensity. Specifically, the mean signal from a volume of interest (VOI) placed in air in the original image was mapped to 0 in the new image, the mean signal plus two standard deviations from pixels in a brain VOI centered on the splenium of the corpus callosum

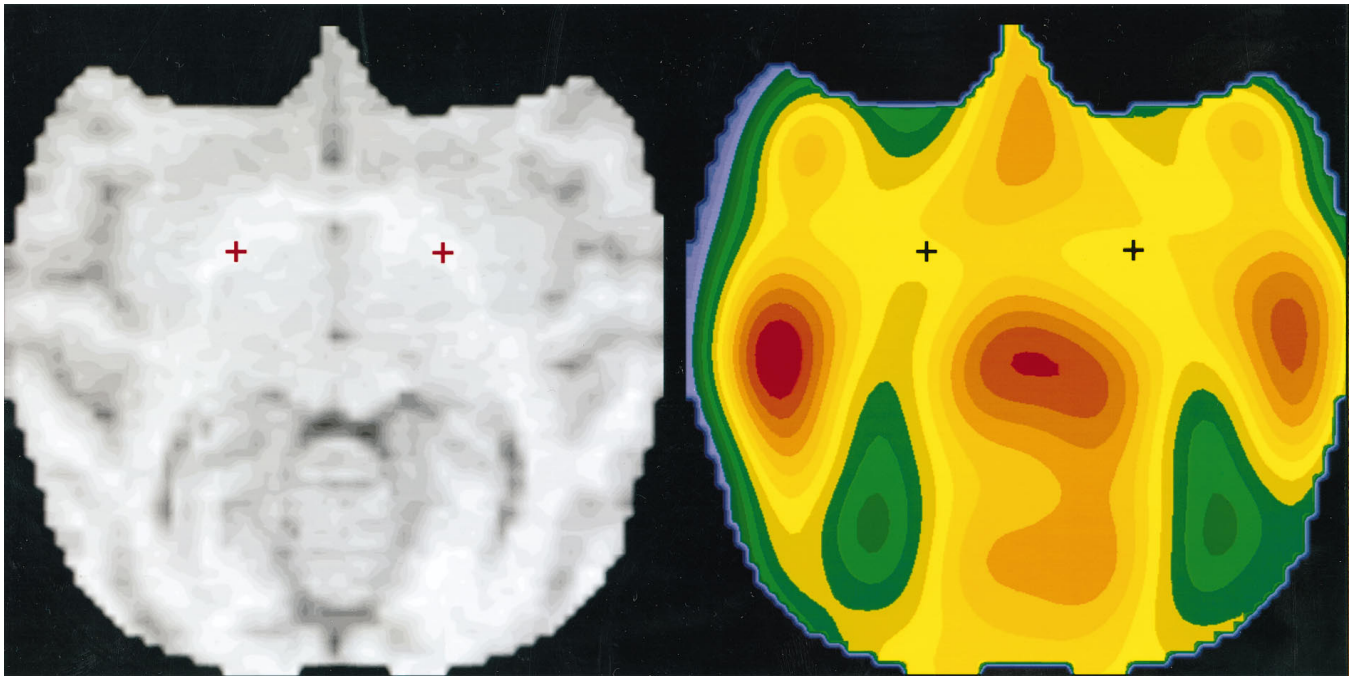


Figure 1. The Davis and Huffman (1968) atlas points used for GP, as transferred to a representative MRI and matching PET image. Each PET image was sampled using a ball-shaped volume of interest with radius 5 mm, centered on the points indicated. (See Materials and Methods).

was mapped to 255, and pixels of intermediate signal intensity were linearly scaled between 0 and 255.

Anatomic locations in the MRI were identified as follows. The center of the anterior commissure (AC) and the superior border of the posterior commissure (PC) defined a transverse reference plane in the orientation of the Davis and Huffman atlas (1968). For a given atlas point, corresponding points in each animal's MRI were computed by linear scaling in three orthogonal dimensions. The scaling in each dimension was determined by the distance between the AC and the PC (anterior-posterior, y), and two distances measured on the coronal plane passing through the AC: namely, the interputaminal distance (left-right, x), and the average vertical distance between the superior border of the caudate nuclei and the inferior border of the optic tracts (superior-inferior, z). All anatomical landmarks were chosen by a single observer (K.J.B.), blind to PET data, after review with a neuroradiologist with extensive experience in primate neuroanatomy (M.H.G.).

The atlas "center" of each GP was taken as $(x, y, z) = (\pm 10.5, A17.0, +6.6)$. A midline point in the cerebellum (0.0, P4.5, +1.0) was also chosen. The cerebellum has negligible D_2 receptor density (Palacios and Pazos, 1987; Levey et al., 1993), but unfortunately remains susceptible to indirect dopaminergic effects on metabolism and blood flow (Jauzac et al., 1982; McCulloch et al., 1982c; Ingvar et al., 1983; Azuma et al., 1988; Celsis et al., 1988).

These three points on each animal's MRI were transferred to the corresponding PET images using the Automated Image Registration (AIR) software of Woods et al. (1993) (Fig. 1). We have previously validated this method in baboons by reference to external fiducials attached to the headholder system and visible in both modalities; the maximum residual error at the GP after AIR alignment was 2.4 mm (mean error, 2.0 mm) (Black et al., 1996a).

Sampling of PET images. Ball-shaped VOIs 10 mm in diameter (67 PET voxels, or 0.86 cm^3) were centered on the left and right globus pallidus and midline cerebellum as described above, and the average rCBF within each of these VOIs was computed for each rCBF scan. Global CBF for each scan was computed as the average CBF within brain over the middle 5 axial PET planes showing the brain. "Within brain" was defined by a 40% intensity threshold on a baseline rCBF image after filtering to a resolution of 11 mm using a three-dimensional Gaussian filter.

Data analysis: dose–response studies. To minimize statistical noise, the rCBF from left and right GP were averaged before further analysis. The results were analyzed using an ANCOVA with GP rCBF as the dependent variable. This variable was hypothesized to depend primarily on three independent variables: dose, animal, and global flow. Specifically, similar doses were lumped together to minimize the number of dose levels, as described above. A categorical animal variable, each subject being a different "level," was included to account for differences in rCBF between animals (an approach advocated by McCulloch et al., 1982a). Global blood flow was included as a covariate to test whether the effect in the GP was simply a reflection of global shifts in CBF. No other main or interaction effects were added because this model explained >99% of the variance in observed GP rCBF (model, $R^2 = 0.997$; $F_{(8,45)} = 1991.8$; $p < 0.0001$). The p values reported below correspond to the partial F statistic for the independent variable named.

Effects of U91356a on global or cerebellar CBF were tested with an ANOVA using dose and animal effects and a dose by animal interaction. To rule out systematic differences in pCO_2 across different doses of U91356a, we computed a one-factor ANOVA with pCO_2 as the dependent variable and dose as the grouping factor.

Data analysis: antagonist pretreatment studies. In the MPTP-treated animals used for these studies, only the rCBF in the control hemisphere GP was analyzed. For each antagonist, an ANCOVA was performed as for the dose–response studies, with the addition to the model of a categorical pretreatment drug variable and a pretreatment drug by dose level interaction. This interaction term, which reflects differences in the response to U91356a depending on whether the antagonist was administered, is the variable of interest. (A similar approach to statistical analysis of drug effects was taken by Grasby et al., 1993.) The control experiments included in each ANCOVA overlapped, but were not identical, because for some antagonists only one MPTP-treated animal was studied.

RESULTS

Dose–response experiments

Pallidal rCBF decreased substantially after U91356a, in a dose-related manner (Fig. 2). This decrease remained significant after

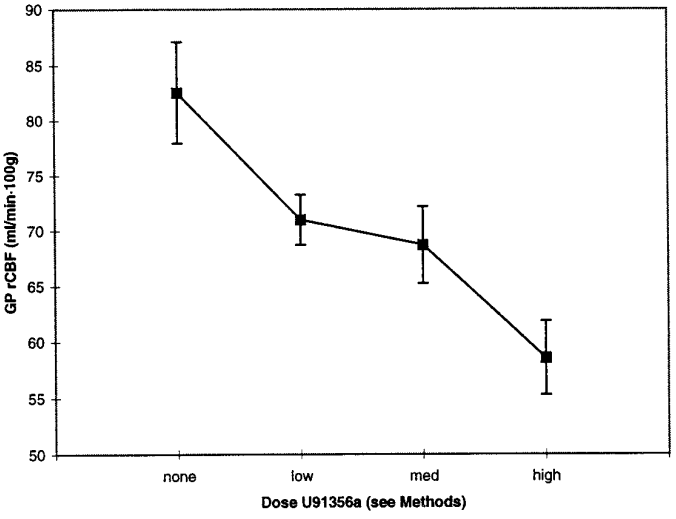
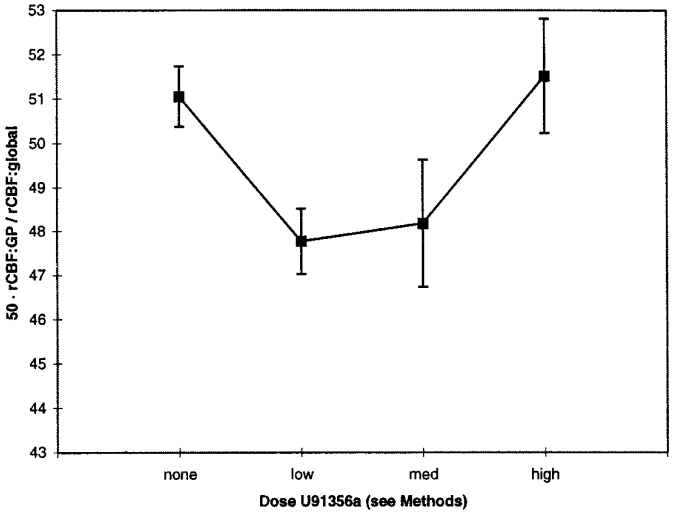


Figure 2. U91356a causes a dose-dependent decrease in GP rCBF. Mean (± SEM) values for blood flow in the GP are shown at baseline and after acute intravenous administration of low, medium, and high doses of the D_2 agonist U91356a. Key to doses: low = 1 to 2 μg/kg, medium = 10 to 22 μg/kg, and high = 100 to 220 μg/kg.



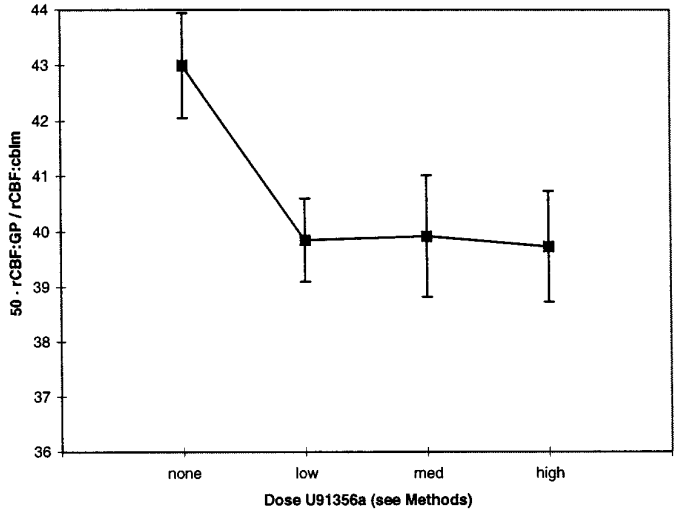


Figure 3. GP rCBF response to U91356a relative to global or cerebellar rCBF. Mean values for *relative* GP blood flow are graphed at baseline and after different doses of the D_2 agonist U91356a. In the *top graph*, absolute GP rCBF was normalized by setting global CBF to 50. In the *bottom graph*, cerebellum CBF was used rather than global CBF.

accounting for differences across animals and global changes in CBF (ANCOVA dose effect, $p < 0.01$). As expected, between-animal differences and global CBF also contributed significantly to total variance in this model ($p < 0.0001$ for each variable).

There was also a dose-dependent decrease in global blood flow, with a substantial decrease of 29% at the highest dose (mean flows 80.8, 74.3, 71.2, and 57.1 ml/100 mg·min at baseline, low, medium, and high doses, respectively; dose effect, $p < 0.0001$; high dose significantly different from all other doses by *post hoc* Scheffé test). This was not attributable to systematic changes in arterial pCO_2, as pCO_2 did not vary with dose of U91356a (dose effect, $p = 0.78$).

After noting the marked fall in global flow in this planned analysis, we reconsidered our use of global blood flow as a covariate, because our "global" region was largely composed of cerebral cortex, which contains D_2-like and 5HT receptors and also receives thalamocortical output influenced by the basal ganglia. We compared "global" blood flow with flow in the cerebellum (see Materials and Methods). Cerebellar flow did decline after U91356a (mean flows, 96.4, 89.6, 85.9, and 74.9 ml/100 mg·min at baseline, low, medium, and high doses, respectively; dose effect, $p = 0.001$; high dose significantly different from baseline by *post hoc* Scheffé test). However, at the highest dose of U91356a, rCBF declined more in the "global," primarily cortical region, than in cerebellum (one-factor ANOVA, global:cblm ratio as dependent variable; dose effect $p = 0.03$). When cerebellar rCBF was substituted for "global" CBF as the covariate in the original ANCOVA, GP rCBF was even more strongly related to doses of U91356a (dose effect, $p = 0.0001$).

In the control animal that received no U91356a, there was no decline at corresponding time points. GP rCBF increased from 73.1 (3–4 hr after ketamine) to 87.0 $ml^{-1} \cdot 100\ mg^{-1} \cdot min$ (6–7 hr after ketamine), with similar increases in global and cerebellar flow and an increase in pCO_2 (35.5 to 39.9). When normalized to global or cerebellar flow (Fig. 3), GP changed from 56.6 to 57.3 (global; dimensionless) and from 44.1 to 44.6 (cerebellar) during the same intervals.

For practical reasons, lower doses of U91356a always preceded higher doses during a single study, raising the possibility that our results could be attributable to "priming" effects of lower doses, the passage of time, or diminishing effects of the preanesthetic ketamine. To examine these concerns, we administered a single dose of U91356a (200 μg/kg) after baseline rCBF measurements to one animal not previously exposed to dopamimetics (i.e., bypassing "low" and "medium" doses). Pallidal rCBF declined by

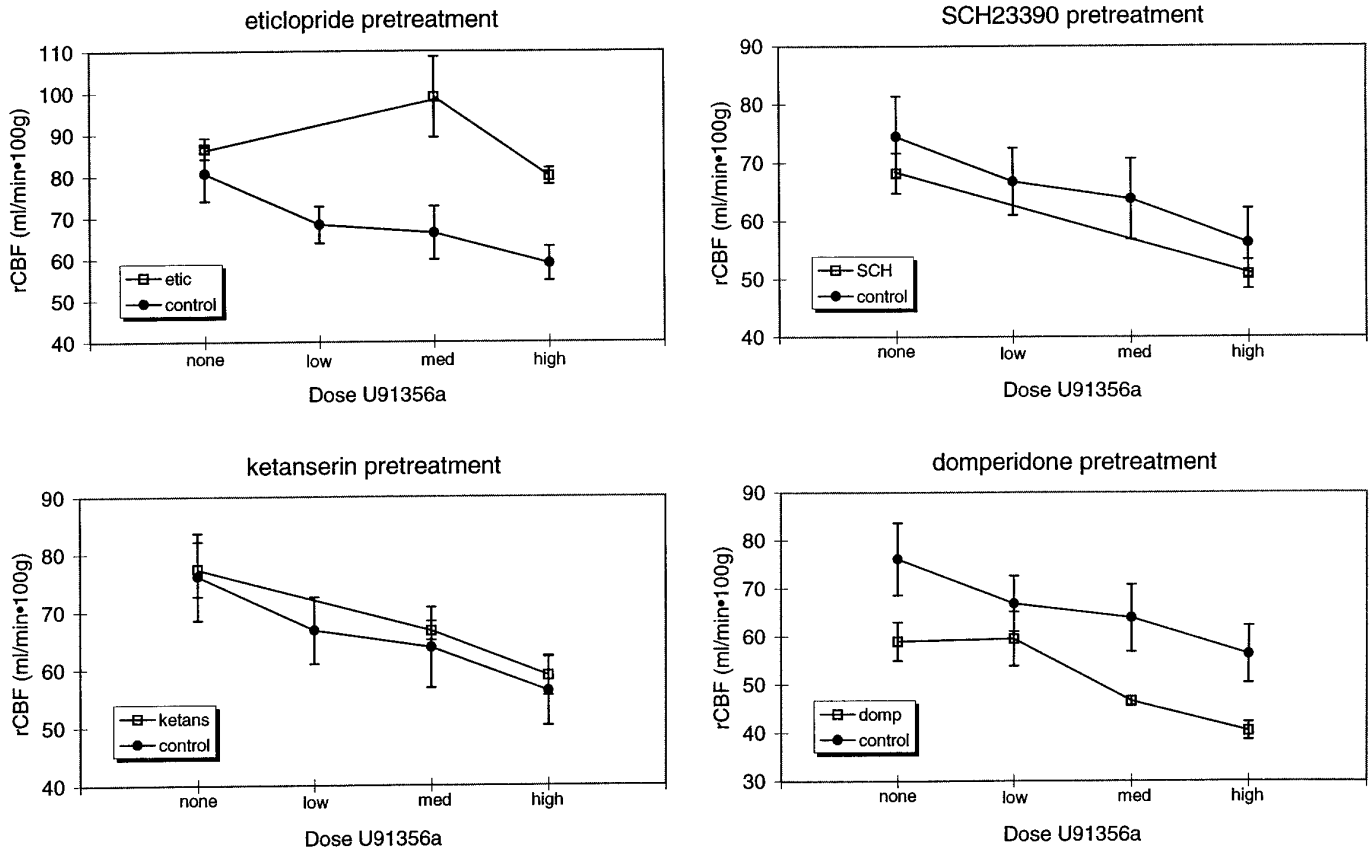


Figure 4. Effect of pretreatment with various antagonists on the GP rCBF response to U91356a. In each graph, control experiments (mean ± SEM) are represented by *filled circles* and antagonist pretreatment experiments are represented by *hollow squares*. *Top left*, eticlopride (D_2 antagonist, 4 mg/kg); *top right*, SCH23390 (D_1 antagonist, 1 mg/kg); *bottom left*, ketanserin (5HT2 antagonist, 0.6 mg/kg); *bottom right*, domperidone (peripheral D_2 antagonist, 0.1 mg/kg).

27.4%, the ratio (GP rCBF:global CBF) declined by 2.5%, and the ratio (GP rCBF:cblm CBF) declined by 5.6%, all similar to the overall results. Thus, these possible effects do not explain our results.

Because atropine, which might be expected to affect dopaminergic neurons, was used in a few cases as a preanesthetic, we compared results from two U91356a challenge experiments performed in the same animal, one using atropine and the other using glycopyrrolate (which is essentially devoid of central anticholinergic activity). The maximal decrease in relative GP flow normalized to cerebellum occurred at the medium dose of U91356a and was 9.4% (atropine) and 9.8% (glycopyrrolate). This suggests that atropine's effect on our results was negligible.

Pharmacological specificity experiments

In the control hemisphere of the unilaterally MPTP-lesioned animals, we were able to replicate the dose-related effect of systemic U91356a on GP rCBF, with decreases of 15%, 18%, and 27% at low, medium, and high doses, respectively (dose effect, $p = 0.0001$; *post hoc t* tests, $p < 0.02$, 0.06, 0.0005, respectively; see *filled circles*, Fig. 3, *top left graph*). This suggests that the control hemisphere of these animals is a reasonable model for testing the pharmacological specificity of the nearly identical response seen in normal animals.

Eticlopride prevented this response to U91356a (pretreatment drug by dose interaction, $p < 0.003$), with *post hoc t* tests showing significant effects of eticlopride at each dose of U91356a (open squares, Fig. 4, *top left graph*).

The other antagonists tested, however, did not prevent the response to U91356a. The significance of the pretreatment drug by dose interaction was: domperidone, $p = 0.56$; ketanserin, $p = 0.89$; and SCH23390, $p < 0.03$. The comparison using SCH23390 reached significance because this D_1 antagonist slightly augmented, rather than blocked, the U91356a-induced decrease in GP rCBF by least-squared means. The GP rCBF response to U91356a after pretreatment with various antagonists is depicted in Figure 4.

DISCUSSION

The selective dopamine D_2 agonist U91356a induced a pharmacologically specific decline in pallidal rCBF at biologically relevant

doses. Although global CBF also declined, the decrease in GP rCBF remained significant after accounting for this effect. We first examine technical concerns about our results and then their implications.

The comparison of atropine and glycopyrrolate as preanesthetics shows that atropine does not explain our findings. We minimized ketamine effects by waiting 3 hr after its administration before the first CBF measurement. Ketamine did not produce our results (see Results), although we cannot exclude a long-lasting synergistic effect on the response to dopamine agonists. Importantly, ketamine does not seem to disrupt coupling of metabolism to flow (Cavazzuti et al., 1987).

Inhaled N_2O may affect rCBF directly but does not affect our results, because N_2O concentration was constant. Under N_2O anesthesia, rCBF responses to pCO_2 changes or behavioral or pharmacological stimuli remain intact (Fox et al., 1992; Yaster et al., 1994). N_2O was chosen because other anesthetics affect metabolic or flow responses to dopaminergics (Grome and McCulloch, 1981, 1983). However, in analogous studies with the D_2-like agonist quinpirole, we showed identical pallidal rCBF responses in N_2O-sedated baboons and in awake nemestrina monkeys (Perlmutter et al., 1993). Studying sedated animals has the advantage that rCBF changes in awake animals could reflect not only direct drug effects, but also secondary effects from drug-altered behavior.

For practical reasons, the pharmacological specificity studies were performed in animals given intracerebroventricular MPTP. Although our observations were confined to the "control" hemisphere, that hemisphere is not normal (Trugman and Wooten, 1986; Robinson, 1991; Todd et al., 1996). However, the response we found in normal animals was replicated in the control GP of the MPTP animals, so this concern is moot.

U91356a has only a 25- to 150-fold preference for D_2 over D_3, D_4, and serotonin 1A receptors. Although U91356a has little efficacy at central 5HT1A receptors (Piercey et al., 1992), it is possible that some of the effects at higher doses may be attributable to these receptors. We are investigating a D_3-preferring agonist for comparison (Black et al., 1996b).

PET images suffer from volume averaging, so that the apparent rCBF in GP includes contributions from adjacent regions. We minimized this by centering the VOI on the GP, using a small VOI (similar to the dimensions of GP, with a radius similar to the image resolution), and using a high-resolution PET and reconstruction filter.

Dopamine agonists modify cerebral vascular resistance, raising the question of whether U91356a uncouples rCBF and metabolism. rCBF remains proportional to regional cerebral metabolic rate (rCMR) under various conditions (McCulloch et al., 1982a; Beck et al., 1986; Tuor et al., 1986); thus, quantitative images of rCBF only need to be scaled to reflect rCMR. Dopaminergics usually do not affect the global CBF/CMR ratio (Berntman et al., 1976, 1978; McCulloch and Harper, 1977; McCulloch et al., 1978, 1982a; McCulloch and Edvinsson, 1980; Azuma et al., 1988; Sharkey et al., 1991), but certain drugs can change it (Ingvar et al., 1983; Leenders et al., 1985; Tuor et al., 1986; Beck et al., 1988; Sabatini et al., 1991). This raises the question of whether U91356a alters the vasculature to decrease global CBF or whether it decreases neuronal activity in large areas of brain. Several lines of evidence suggest the latter. The most direct evidence is that U91356a globally reduces cerebral metabolism in awake rats (Piercey et al., 1995). Also, in our study domperidone did not prevent the global fall in CBF. Domperidone does not affect central metabolism (Palacios and Wiederhold, 1987), but can block a disproportionate, presumably vascular, change in rCBF after apomorphine (Sabatini et al., 1991).

Qualitative PET images of relative flow often are normalized to global counts because many such studies are not performed quantitatively. This may be reasonable in behavioral activation studies in normals because activation does not produce appreciable global effects. However, this assumption may not hold for pharmacological studies, as we demonstrate. Because the purpose of the rCBF measurements is to indicate local neuronal activity that may lead to behavorial responses, it is important to consider whether neuronal activity corresponds best to absolute changes in rCBF or to relative changes compared with the rest of the brain. The definitive answer to this question is unknown. However, we assume that neuronal activity correlates with absolute flow or metabolism and demonstrate a dose–response curve for absolute flow in GP (Fig. 2). This dose response corresponds reasonably to previous physiological studies with U91356a (see Materials and Methods). Absolute flow also changes in other regions, so the effect is not limited to pallidum. However, we demonstrate (Fig. 3 and ANCOVA) that lower doses preferentially affect the pallidum. This does not imply that these lower doses must correspond to the maximal behavioral effect, because a further decrease in absolute pallidal activity at higher doses of U91356a may produce additional behavioral responses despite changes in other brain regions. This local versus global issue could not be addressed without our absolute flow measurements.

We now turn to the implications of our findings. U91356a decreased pallidal rCBF, consistent with the prediction that D_2 agonists inhibit the activity of striatopallidal neurons. Although this finding is consistent with previous studies of D_2-like agonists, we extend this to a D_2-selective agonist. In the only previous metabolic study of U91356a, regional effects were not reported (Piercey et al., 1995).

GP was more affected than other regions of the brain. The data are consistent with a relatively specific striatal effect at low-to-intermediate doses equaled by effects on cortex at higher doses that did not cause equivalent effects on cerebellum. These results may be caused by cortical D_3, D_4, or 5HT1 receptors at the highest dose.

We centered our volume of interest on the entire GP, rather just GPe, to which D_2-receptor-bearing striatopallidal neurons preferentially project. A D_2 agonist might be expected to decrease rCBF in GPe and GPi because of a decrease in the firing rate of subthalamic neurons projecting to GPi (via disinhibition of inhibitory pallidosubthalamic neurons). Alternatively, U91356a may affect pallidal rCBF via dopaminergic nigropallidal neurons (Parent et al., 1990). Although innervation of GPi by GPe might counteract this effect, the hypothesized decrease in GP rCBF was still observed.

An acute dose of LDOPA produced a nonsignificant 15% decrease in 2DG uptake in GP and enteropeduncular nucleus (EPN) (corresponding to primate GPe and GPi, respectively) in normal rats (Trugman and Wooten, 1986). On the other hand, in unilateral 6OHDA-lesioned rats a D_2-like agonist caused bilateral metabolic increases in GP and EPN (Trugman and Wooten, 1987). However, these rats were circling rapidly during the time of 2DG uptake, and the increased metabolism may reflect this dramatic change in motor behavior.

The synergistic decrease in GP rCBF after the D_1 antagonist SCH23390 is also consistent with the proposed model of dopaminergic pathways in basal ganglia. The lack of effect of the

serotonin 5HT2 antagonist ketanserin on GP rCBF or on the pallidal response to U91356a suggests that blockade of these receptors produces minimal change in pallidal activity despite the known interactions between 5HT2 receptors and dopaminergic neurons (Kapur and Remington, 1996).

The methods used here have several potential advantages. First, we show that an *in vivo* PET technique is sensitive to the effects of U91356a. Advantages of PET over *ex vivo* studies include its minimally invasive nature and the possibility of repeated measurements in the same subject, including within-subject studies before and after lesions or treatment. Second, the D_2 selectivity of U91356a allows for more specific conclusions regarding D_2 receptors. This may provide better specificity for a given effect and may also better clarify the effects of disease or interventions on D_2-specific pathways. Third, pharmacological activation of rCBF provides complementary information to other PET methods for studying dopaminergic pathways. This provides less specific information about receptor binding than radioligand studies (Perlmutter et al., 1986, 1989, 1991b, 1997; Farde et al., 1989; Sadzot et al., 1991), but may be more sensitive to changes in postsynaptic neurons that affect D_2 signal transduction (Breece et al., 1987). Another complementary technique is to study the pharmacological effects of dopaminergic agents on other neurotransmitter receptors (Dewey et al., 1990, 1993), a method that may provide more detail on dopaminergic output to neurons with cholinergic receptors, for example, but may miss effects on other circuits.

We are developing a baboon PET atlas and methods for combining data across animals. This will permit us to analyze the response to U91356a in other brain regions.

With a tool for measuring specific effects of D_2-mediated pathways, we can explore several interesting questions. For instance, combined with our analogous study with a D_1 agonist (Black et al., 1997), we can investigate *in vivo* how chronic L-DOPA affects D_1- and D_2-mediated neuronal pathways in MPTP-hemiparkinsonsian monkeys, or inpatients with Parkinson's disease. We also can investigate the sensitivity of D_2 (specific)-influenced pathways in diseases such as dystonia, Tourette syndrome, schizophrenia, and drug addiction.

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