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Effects of Atypical Antipsychotic Drug Treatment on Amphetamine-Induced Striatal Dopamine Release in Patients with Psychotic Disorders

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Clozapine, risperidone, and other new "atypical" antipsychotic agents are distinguished from traditional neuroleptic drugs by having clinical efficacy with either no or low levels of extrapyramidal symptoms (EPS). Preclinical models have focused on striatal dopamine systems to account for their atypical profile. In this study, we examined the effects of clozapine and risperidone on amphetamine-induced striatal dopamine release in patients with psychotic disorders. A novel ^{11}C-raclopride/PET paradigm was used to derive estimates of amphetamine-induced changes in striatal synaptic dopamine concentrations and patients were scanned while antipsychotic drug-free and during chronic treatment with either clozapine or risperidone. We found that amphetamine produced significant reductions in striatal ^{11}C-raclopride binding during the drug-free and antipsychotic drug treatment phases of the study which reflects enhanced dopamine release in both conditions. There were no significant differences in % ^{11}C-raclopride changes between the two conditions indicating that these atypical agents do not effect amphetamine-related striatal dopamine release. The implications for these data for antipsychotic drug action are discussed.
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Clozapine, risperidone, and other new "atypical" antipsychotic agents (e.g., olanzapine, sertindole) are distinguished from traditional neuroleptic drugs by having clinical efficacy with either no or low levels of extrapyramidal symptoms (EPS) (Meltzer 1991, Deutch et al. 1991). Preclinical models have focused on striatal dopamine systems to account for the favorable EPS profile (Chiodo 1988). Both atypical and typical neuroleptics inhibit firing rates of ventral tegmental area (VTA) neurons (i.e., A-10 neurons) that innervate limbic and cortical regions (Skarsfeldt 1992; Stockton and Rasmussen 1996a; Chiodo and Bunney 1983, 1985; White and Wang 1983; Chiodo 1988), an action hypothesized to account for antipsychotic efficacy (Bunney 1992). In contrast, typical but not atypical agents inhibit firing rates of substantia nigra pars compacta (SNC) dopamine neurons (i.e., A-9 neurons) that innervate dorsal striatum, and action suggested to account for the differential EPS profile of these agents (Chiodo and Bunney 1983, 1985; White and Wang 1983; Chiodo 1988). Also, traditional antipsychotics induce greater early gene expres-

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sion (i.e., C-FOS) is dorsal striatum than atypical drugs which is suggestive of differential EPS effects (Deutch et al. 1992; Nguyen et al. 1992; Robertson and Fibiger 1992). Moreover, the new antipsychotic agents reverse amphetamine-induced effects on A-10 dopamine neurons to a greater degree than A-9 neurons (Stockton and Rasmussen, 1996b), whereas traditional neuroleptics reverse amphetamine effects on both A-9 and A-10 neurons (Bunney and Aghajanian 1973, 1976; Goldstein et al. 1986; Skarsfeldt 1992). Furthermore, previous brain imaging studies have shown that traditional neuroleptics have higher striatal dopamine D-2 receptor occupancy levels than the atypical agents (Pickar et al. 1996; Nyberg et al. 1997; Farde et al. 1988, 1989; Kerwin et al. 1993; Nordstrom et al. 1993; Wiesel et al. 1990). Taken together, these data suggest that the relative lack of effects on dorsal striatal dopamine neurons may contribute to the atypical profile of the new antipsychotic agents.

There is comparatively little information about the effects of antipsychotic drugs on striatal dopamine function in clinical populations because of the methodological limitations in examining *in vivo* dopamine physiology in human studies. A relatively new application of *in vivo* brain imaging, however, provides a method to derive estimates of striatal synaptic dopamine concentrations following changes in dopamine release. This approach determines the change in striatal radiotracer binding levels following administration of pharmacologic agents that affect dopamine outflow but do not themselves bind to dopamine receptors (Dewey et al. 1993; Innis et al. 1992). The change in striatal radiotracer binding levels is attributable to changes in the concentration of synaptic dopamine that competes with the radiotracer for receptor binding. Using this approach, we (Breier et al. 1997) and others (Laruelle et al. 1996) have reported that amphetamine produced greater D-2 tracer binding reductions in schizophrenic patients than healthy controls suggesting enhanced synaptic dopamine concentrations in this illness.

In this study, we examined the effects of risperidone and clozapine on amphetamine-induced striatal dopamine release in patients with psychotic illnesses. Our brain imaging method, which has been previously validated (Breier et al. 1997; Carson et al. 1997; Endres et al. 1997), involves determining changes in the specific binding of the D-2/D-3 PET ligand ^{11}C-raclopride following administration of amphetamine (0.2 mg/kg). Patients were studied with this method during antipsychotic drug-free and atypical antipsychotic drug treatment conditions. We predict that clozapine and risperidone will not effect amphetamine-induced changes in ^{11}C-raclopride specific binding.

METHODS

Subjects

Six patients admitted to the 4 East Inpatient Unit of the NIH Clinical Center gave informed written consent to an institutional review board approved protocol and participated in the study. Psychiatric diagnoses was determined by a diagnostic conference utilizing data from a structured diagnostic interview (SCID), clinical interview by a research psychiatrist, past psychiatric and medical records, and informant interviews. Five patients fulfilled DSM IV diagnostic criteria for schizophrenia disorder, chronic type, and one patient's diagnoses was major affective disorder with psychotic features. Five patients had chronic antipsychotic drug exposure prior to admission and one patient was naive to antipsychotic drug treatment. Demographic and illness related variables are contained in Table 1.

Treatment Protocol

Each subject participated in two raclopride studies: one while free of antipsychotic drugs (drug-free scan) and the other while taking either risperidone or clozapine (on-drug scan). The number of antipsychotic drug-free days prior to scanning are listed in Table 1. One patient (Subject #2) had their on-drug scan first and drug-free scan second, while the other patients had the drug-free

Table 1. Demographic and Illness-Related Characteristics of the Patients Participating in Drug-Free and Antipsychotic Drug ^{11}C-Raclopride PET Studies

Subject	Age (yr)	Gender	Weight (kg)	Years Ill	Days Drug-Free[a]	Medication Daily Dose[b]
1	33	F	96	1	Naive	Risperidone 3 mg
2	33	M	89	9	15	Risperidone 3 mg
3	28	M	105	14	14	Risperidone 3 mg
4	48	M	112	23	11	Risperidone 3 mg
5	23	M	117	5	14	Clozapine 200 mg
6	50	F	72	9	36	Clozapine 400 mg

[a] Days antipsychotic drug-free prior to the drug-free PET scan.
[b] Daily dose of antipsychotic medication for the on-drug PET scan.

scan first and on-drug scan second. All on-drug scans were conducted after a minimum of 14 days of antipsychotic drug treatment. Clozapine and risperidone doses for each patient were based on optimal efficacy and no EPS as determined by clinical observation (see Table 1 for doses).

PET Scanning Protocol

PET studies were conducted on a General Electric Advance scanner at the NIH Clinical Center. Acquisitions were done with the interplane septa retracted and a wide axial acceptance angle. Each scan yielded 35 planes 4.25 mm apart. The effective resolution of the reconstruction was 6 mm both axially and in-plane. A transmission scan was performed using two rotating ^{68}Ge sources and was used for attenuation correction.

Subjects were positioned in the scanner such that acquired planes would be parallel to the orbital-meatal line. Head movement was minimized with individually fitted thermoplastic masks and patches were applied over the orbits to reduce incoming light. ^{11}C-raclopride (2 to 8 mCi) was administered as bolus/constant infusion over 2 hours. The bolus dose was 57% of the total amount administered. Beginning with the raclopride bolus, 29 scans were acquired over the two hour period every three to five minutes. Fifty minutes after commencement of raclopride administration, amphetamine (0.2 mg/kg IV) was infused over 60 seconds. Plasma samples for amphetamine levels were drawn 40 minutes after amphetamine administration.

Data Processing and Analysis

Image processing was performed with MIRAGe software developed by the NIH PET Center. The images corresponding to 0 to 5 minutes of raclopride infusion were added together to form a single "sum" image. Volumes of interest (VOIs) were drawn in the cerebellum and on the left and right striatum (consisting of caudate and putamen combined). After visual inspection, these VOIs were then overlaid onto their corresponding position in each of the 31 individual scans and samples (mean pixel values) were generated for each VOI. Left and right striatal VOIs were averaged to a single striatal value. The specific binding was computed as follows: striatum/cerebellum - 1 (Carson et al. 1993). Ratio data from five consecutive scans 30 to 50 minutes after raclopride bolus injection and immediately before amphetamine administration ("baseline") and five consecutive scans 75 to 100 minutes post raclopride bolus injection ("post-amphetamine") were averaged.

Individual group comparisons were conducted with paired t-tests. Plasma amphetamine levels were correlated with change in % ^{11}C-raclopride striatal binding ratios using a Pearson's correlation coefficient. All comparisons were two-tailed and group data were presented as mean ± standard deviations.

RESULTS

Amphetamine produced significant reductions in striatal ^{11}C-raclopride binding from baseline levels during both the drug-free and antipsychotic drug treatment phases of the study (Table 2) which reflects enhanced dopamine release in both conditions. Drug-free baseline striatal ^{11}C-raclopride binding ratios (2.6 ± 0.9) were significantly greater than on-drug binding ratios (1.7 ± 0.7; $t = 2.6$, $df = 5$, $p = .05$) because of decreased receptor availability during the on-drug scan secondary to antipsychotic drug occupancy. There were no significant group mean differences in % striatal ^{11}C-raclopride binding changes between drug-free and antipsychotic drug scans (Figure 1). Amphetamine plasma levels (mean ± SD) for the drug-free scan were 49.3 ± 12.8 ng/ml and for the on-drug scan were 48.3 ± 15.6 ng/ml and they were not related to % striatal ^{11}C-raclopride

Table 2. The Effects of Amphetamine (0.2 mg/kg) on Specific ^{11}C-Raclopride Binding (Striatum/cerebelum -1) Conducted While Patients Were Antipsychotic Drug-Free (Drug-Free Scan) and Treated with Risperidone or Clozapine (On-Drug Scan)

	Drug-Free Scan		On-Drug Scan	
Subjects	**Baseline**	**Post-Amphetamine**	**Baseline**	**Post-Amphetamine**
1	2.13	1.52	2.21	1.55
2	1.58	1.32	1.00	0.63
3	3.35	2.13	1.36	1.03
4	1.72	1.41	1.10	0.84
5	3.32	2.99	3.01	2.68
6	3.84	3.31	2.01	1.65
Mean ± SD	2.65 ± 0.96	2.11 ± 0.85[a]	1.78 ± 0.78	1.39 ± 0.74[b]

[a] Baseline vs. Post-Amphetamine: $t = 3.7$, df = 5, $p = .01$.
[b] Baseline vs. Post-Amphetamine: $t = 6.5$, df = 5, $p = .001$.

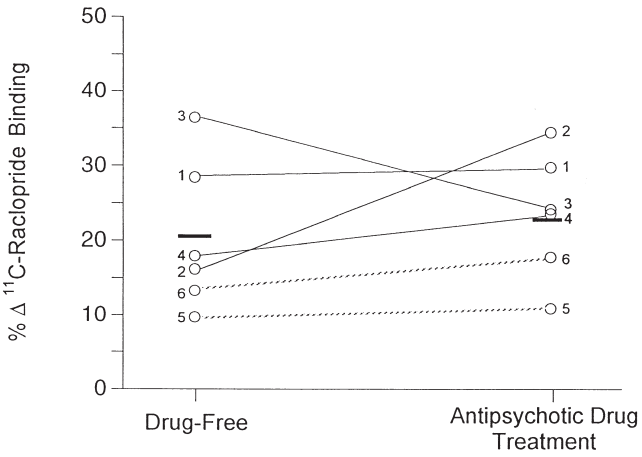

Figure 1. Effects of amphetamine (0.2 mg/kg) on ^{11}C-raclopride binding (striatum/cerebellum -1) during anti-psychotic drug-free and drug treatment periods. Numbers next to each datapoint identify individual patients. Risperidone (connected by solid lines), clozapine (connected by dashed line), $t = 0.8$, $p = .5$.

binding changes ($r = .05$, $p = .9$ and $r = .5$, $p = .2$, respectively).

DISCUSSION

The results of this study indicate that treatment with clozapine and risperidone did not effect amphetamine-related striatal ^{11}C-raclopride binding changes. The data suggest that these atypical antipsychotic agents did not antagonize amphetamine-induced striatal dopamine release. The amphetamine-induced raclopride changes reported here were all greater than our previously reported control (i.e., saline administration) levels of 1.9 ± 3.7% change in ^{11}C-raclopride striatal binding (Breier et al. 1998). We have assessed the relationship between simultaneously derived extracellular dopamine concentrations with *in vivo* microdialysis and ^{11}C-raclopride striatal binding changes in nonhuman primates with the same amphetamine dose reported here (0.2 mg/kg) and discovered a ratio of extracellular dopamine to raclopride changes of 40 to 1 (Breier et al. 1997). Extrapolating from these data, it appears amphetamine produced substantial increases in synaptic dopamine concentrations in both drug-free and atypical antipsychotic drug treatment conditions.

It is important to consider the mechanism by which amphetamine enhances synaptic dopamine concentrations in assessing the implications of these data for antipsychotic drug action. Amphetamine, particularly in low doses, is thought to selectively release cytoplasmic dopamine through a process of Ca^{2+} independent accelerative exchange-diffusion involving expression of dopamine into the extracellular space via the dopamine transporter (Fischer and Cho 1979). Thus, our data indicates that clozapine and risperidone appear not to interfere with this mechanism. We cannot, however, extrapolate to other mechanisms, such as Ca^{2+} dependent electophysiologic events, that may be relevant in understanding atypical antipsychotic drug effects on striatal dopamine function.

Clozapine and risperidone have important differences in their neurochemical and clinical profiles. Risperidone is more potent than clozapine at dopamine D-2 and serotonergic 5HT-2 receptors, and less potent at muscarinic receptors (Leysen et al. 1988; Janssen et al. 1988). In doses higher than used in this study (i.e., >6 mg/day), risperidone causes EPS at levels comparable to neuroleptic drugs (Marder and Meibach 1994) whereas clozapine does not cause EPS even in high dosage ranges (Kane et al. 1988). Although our sample was too small to assess clozapine versus risperidone differences, it would be interesting to determine if there are differential effects of these agents on amphetamine-induced dopamine release.

Several caveats should be considered in interpreting these data. We did not examine the effects of traditional neuroleptic treatment on amphetamine-induced raclopride binding to determine if classical antipsychotic agents and atypical drugs have differential striatal dopamine effects. Therapeutic doses of traditional antipsychotic agents show a steep dose-occupancy curve with apparent near-maximal binding of striatal D-2 receptors (i.e., ⩾80% estimated occupancy) (Farde et al. 1988, 1992; Wiesel et al. 1990; Pilowsky et al. 1993; Wolkin et al. 1989; Coppens et al. 1991; Karbe et al. 1991) which could lead to baseline raclopride binding ratios that are too low to adequately assess amphetamine-related reductions in ligand binding. Another important issue is the lack of dopamine release data from A-10 dopamine neurons in limbic and cortical areas. These neurons have been hypothesized to mediate clinical efficacy for typical and atypical antipsychotic drugs (Bunney 1992). Raclopride does not have adequate signal-to noise to detect D-2 receptor binding in these regions (Halldin et al. 1995). However, there are new PET ligands with very high D-2 affinity and good signal-to-noise in extrastriate regions under investigation (Halldin et al. 1995; Kessler et al. 1992), and theoretically that could be applied to address the issue of drug effects on dopamine A-10 neuronal systems. Lastly, these findings should be considered preliminary pending replication with a larger sample.

In summary, we found that in this sample of six patients amphetamine-induced striatal ^{11}C-raclopride binding changes were not affected by treatment with clozapine or risperidone. Future studies are needed to examine the effects of these and other atypical agents on a broad spectrum of central dopamine functions, including interactions with other neurotransmitters (e.g., serotoner-

gic, cholinergic, glutamatergic), cotransmitter modulation and differential dopamine receptor subtype effects in clinical populations.

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