Amphetamine-Induced Dopamine Release and Post-Synaptic Specific Binding in Patients with Mild Tardive Dyskinesia

Caleb M. Adler, M.D., Anil K. Malhotra, M.D., Igor Elman, M.D., David Pickar, M.D., and Alan Breier, M.D.

Several lines of evidence suggest that changes in dopamine release and/or post-synaptic sensitivity may be involved in the pathogenesis of tardive dyskinesia (TD). Preclinically, increased D_2 receptor sensitivity and dopamine turnover are associated with D_2 receptor antagonism. Clinically, development of TD is associated with D_2 receptor antagonist administration. Eight patients with mild evidence of TD (AIMS ratings ≥ 14) and six without (AIMS = 10), underwent [^{11}C]raclopride PET scans. Baseline and amphetamine-induced decrements in striatal specific binding were assessed. Baseline and amphetamine-induced decrements in specific binding did not differ between patients with and without evidence of mild TD (p = .53). AIMS ratings did not significantly correlate with baseline (p = .76) or decrements in specific binding (p = .45). This study provides evidence that TD is not associated with increased amphetamine-induced presynaptic dopamine release and/or D_2 receptor binding as measured by [^{11}C]raclopride PET. More research is needed to unravel the neurobiology of this debilitating disorder.
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Tardive dyskinesia (TD) is a debilitating and frequently progressive movement disorder of unclear provenance (Jimenez-Jimenez et al. 1997; Cardoso and Jankovic 1997) that occurs in approximately 20% of schizophrenic patients treated with neuroleptics (Kane and Smith 1982; Morgenstern and Glazer 1993; Jeste and Caligiuri 1993) but may occur in any population receiving medications that antagonize the D_2 receptor (Jeste and Caligiuri 1993). Manifestations of TD may include orofacial movements, axial movement, and limb flexion/extension, as well as opisthotonos and tardive tremors (Cardoso and Jankovik 1997).

Despite the significant clinical impact of TD, the etiology of the phenomenon has not been substantially elucidated. Several lines of evidence suggest that TD is related to increased receptor binding sensitivity in the basal ganglia, stemming from long-term D_2 receptor blockade by neuroleptics (Klawans 1973). Administration of D_2 blocking agents induces an increase in striatal D_2 receptor density (Burt et al. 1977; Clow et al. 1979; Owen et al. 1980) and dopamine turnover in rodents (Clow et al. 1978, 1979), as well as an increase in D_2 re-

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ceptor sensitivity to indirect dopamine agonists (Tarsy and Baldessarini 1974; Gianutsos and Moore 1977; Clow et al. 1978, 1979; Owen et al. 1980). Clinical observations also support suggestions that neuroleptic-related increases in D_2 binding sensitivity may be involved in TD.

Manifestations of movement disorders in schizophrenic patients resembling TD may occur in the absence of neuroleptic medication, but are quite uncommon. Moreover, atypical antipsychotic medications with relatively little D_2 blockade are generally associated with a lower incidence of TD (Meltzer et al. 1989; Meltzer and Gudelsky 1992; Casey 1997). In patients, acute withdrawal of neuroleptic medications may increase or unmask TD-like movements and addition of D_2 receptor antagonists may temporarily blunt TD symptomatology, possibly by respectively exposing or blocking sensitized D_2 receptors (Crane and Naranjo 1971; Cardoso and Jankovic 1997). Consistent with this model of TD, Silvestri et al. (2000) found increased D_2 binding potential with long-term exposure to antipsychotic medication. Further, on both post-mortem exam and structural imaging, TD has been associated with the presence of pathology of the basal ganglia (Campbell et al. 1985; Mion et al. 1991; Granholm et al. 1993).

Studies directly examining D_2 receptor density in patients with TD however, have failed to support hypotheses that increased dopamine binding sensitivity is responsible for TD. Brains of schizophrenic patients with TD examined post-mortem have not demonstrated an increase in striatal D_2 receptor density (Cross et al. 1985; Kornhuber et al. 1989). Similarly, two *in vivo* positron emission tomography (PET) studies using N-[^{11}C]-methylspiperone and [^{76}Br]-bromospiperone failed to demonstrate increased D_2 receptor density in individuals with TD, both compared with individuals exposed to neuroleptics without TD, and in a cohort of age matched controls (Blin et al. 1989; Andersson et al. 1990). A PET study examining patients with Parkinson's Disease also failed to find any difference in D_2 receptor binding in patients who had developed dyskinesias (Turjanski et al. 1997). Moreover, although Blin et al. (1989) observed correlation between orofacial dyskinesia and D_2 receptor density, no correlation between global dyskinesia and D_2 binding was found.

Previous PET studies however, were not primarily constituted of schizophrenic or schizoaffective patients, raising issues of generalizability to these illnesses, particularly given the important role dopamine dysregulation is thought to play in schizophrenia and schizoaffective disorder. In addition, these studies examined only post-synaptic binding data. Schizophrenic patients have been hypothesized to exhibit decreased tonic striatal dopamine release and increased sensitivity to stimuli (Grace 1991), both of which may play a role in the pathogenesis of TD. Examining pharmacologically in-

duced presynaptic dopamine release as well as baseline, post-synaptic binding is necessary to address this potential confound. Furthermore, previous studies have examined individuals with relatively advanced TD. Given the lack of understanding of the pathophysiology of TD, it may be important to study specific binding in subjects with milder symptomatology.

Others and we have previously used [^{11}C]raclopride, a D_2/D_3 receptor ligand to measure striatal dopamine binding at baseline and with administration of pharmacological agents (Breier et al. 1997, 1998; Smith et al. 1998; Adler et al. 2000). Baseline [^{11}C]raclopride binding provides a measure of relative baseline D_2 receptor binding sensitivity. Decreases in [^{11}C]raclopride binding following administration of amphetamine, an indirect dopamine agonist, are proportional to striatal dopamine release. In this study we utilized [^{11}C]raclopride PET to examine baseline and amphetamine-induced striatal D_2 receptor binding in patients with early evidence of TD, and compared this group to a matched cohort of patients without evidence of movement disorder.

METHODS

Subjects

Fourteen patients (mean ± SD) (age = 33.6 ± 9.6, 12 males, three females) participated in this [^{11}C]raclopride study. Patients were diagnosed with schizophrenia ($n = 10$) schizoaffective disorder ($n = 2$), major depression ($n = 1$), or bipolar affective disorder ($n = 1$). Patients were admitted to the 4E inpatient unit of the Clinical Center at the National Institutes of Health and, after evaluation to determine competency to provide informed consent, agreed to participate in this IRB-approved protocol. Patients participated in a weekly group meeting, which reviewed and addressed questions pertaining to the science and methodology of the current study and other studies being conducted on the unit.

DSM-III and IV diagnoses were made in a best estimate meeting and were based on clinical interview, the SCID-IIIR and SCID-IV (Spitzer et al 1990; First et al. 1997), past medical and psychiatric records, and informant interviews. Patients were in good health as determined by physical exam, screening blood work and ECG. Three patients were medication naive or had not received medication for greater than five years. The remainder was free of antipsychotic medications for a minimum of ten days (20.1 ± 10.9 days). In the event that patients exhibited signs of clinical instability during the drug-free interval, prompt reinstitution of medication was initiated and these patients were not eligible for participation in this study. Data from eight of the subjects was previously reported (Breier et al. 1997).

Eight patients (age = 34.9 ± 9.8 years; seven males, one female) (length of illness = 10.8 ± 8.8 years) had

evidence of mild TD, defined as Abnormal Involuntary Movement Scale (AIMS) (US Dept of Health 1976) scores greater than or equal to 14 (mean ± SD: 15.5 ± 1.3). Six patients (age = 29.5 ± 7.7 years; four males, two females) (length of illness = 4.2 ± 4.3 years) showed no evidence of TD on AIMS ratings.

Movement Ratings

TD was assessed with the AIMS during the week of the PET scan, by a research psychiatrist (IE, CA). Interrater reliability coefficient was > 0.90.

Pharmacological Infusion Protocol

Fifty minutes after commencement of raclopride administration (see below), a bolus of 0.2 mg/kg of amphetamine was administered as previously reported (Breier et al. 1997).

PET Scanning Protocol

Studies were conducted on a General Electric Advance scanner at the NIH Clinical Center as previously reported (Breier et al. 1997, 1998). 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 reconstructed images was 6 mm both axially and in-plane. Transmission scans were performed using two rotating ^{68}Ge sources and were 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. Patches were applied over the orbits to reduce incoming light. [^{11}C]raclopride (2.5 to 8.0 mCi) was administered as a bolus followed by a constant infusion over 100 minutes. The bolus dose was 57% of the total amount administered. Beginning with the raclopride bolus, 27 scans were acquired over the 100 minute period. By infusing the [^{11}C]raclopride, near-equilibrium conditions can be reached before administration of a pharmacologic agent, allowing a direct measurement of the binding potential from the ratio of striatum/cerebellum-1. In previous studies in monkeys, equivalent specific binding values were found using the conventional bolus methods and the bolus/infusion technique (Carson et al. 1997). Use of this bolus/infusion paradigm allows the measurement of baseline binding and change in dopamine concentration during a single scan without intrascan blood sampling (Carson et al. 1997). In addition, this paradigm facilitates interpretation of post-amphetamine changes in the curve (Endres et al. 1997).

Image Data Processing and Analysis

Image processing was performed with MIRAGE software developed by the NIH PET center and a single individual in a blinded fashion did all analyses. Images corresponding to 0–5 minutes of raclopride infusion were added together to form a single "sum" image. Volumes of interest (VOIs) were drawn over the cerebellum and on the left and right striatum (caudate and putamen combined). After visual inspection, these VOI's were 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 VOI's were averaged to a single striatal value. Specific binding was calculated as follows: striatum/cerebellum − 1.

Ratio data from five consecutive scans 30–50 minutes after the [^{11}C]raclopride bolus injection and immediately prior to amphetamine administration ("baseline"), and five consecutive scans 75 to 100 minutes post-[^{11}C]raclopride bolus injection ("post-amphetamine") were calculated for all subjects ("change in specific binding").

Data Analysis

Baseline specific binding was compared between patients with an AIMS score of 10 (no TD) versus patients with an AIMS score of 14, using unpaired t-test. Change in specific binding with amphetamine administration was compared between groups using a one-way ANOVA. A follow-up unpaired t-test was also performed. Pearson's correlation coefficients were calculated between AIMS scores of 14 and both baseline specific binding and amphetamine-induced changes in specific binding. All comparisons were two-tailed.

RESULTS

Patients with AIMS scores of 14 demonstrated no significant difference versus patients without evidence of tardive dyskinesia in baseline binding (t = − 0.64, df = 12, $p = .53$). The effect size of the comparison was small to moderate (d = 0.35). Including only schizophrenic and schizoaffective patients did not significantly alter these results (t = − 0.88, df = 10, $p = .40$, df = 0.51).

Change in specific binding showed a significant effect for time, as expected (F = 18.49, df = 13, $p < .001$) but not for either group (F = 0.11, df = 13, $p = .75$) or group × time (F = 0.04, df = 13, $p = .85$). The follow-up t-test also showed no significant difference between cohorts (t = 0.65, df = 12, $p = .53$). Effect size was small to moderate (d = 0.35). Including only schizophrenic or schizoaffective patients did not significantly alter these results (t = 0.71, df = 10, $p = .49$, d = 0.42) (Figure 1).
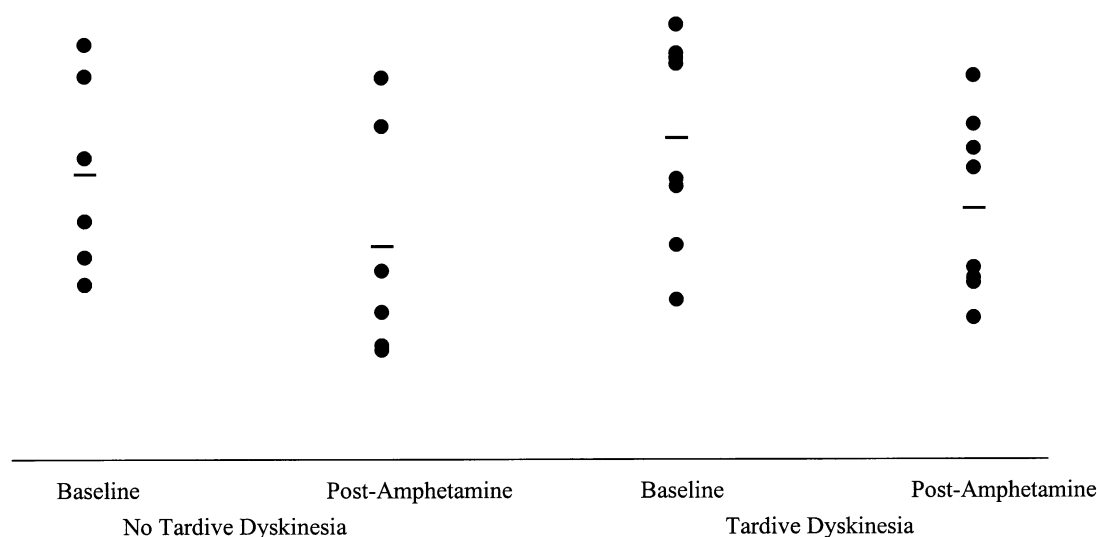
Figure 1. The effects of d-amphetamine on [^{11}C]raclopride striatal specific binding (striatum/cerebellum-1) in patients without evidence of tardive dyskinesia ($n = 6$) and patients with mild tardive dyskinesia ($n = 8$).

No significant correlations were found between AIMS scores of patients with TD and either baseline binding ($r = 0.13, p = .76$) or change in specific binding ($r = -0.31, p = .45$). Excluding patients without diagnoses of schizophrenia or schizoaffective disorder did not significantly affect correlation coefficients for baseline binding ($r = 0.09, p = .85$) or change in specific binding ($r = -0.28, p = .55$).

DISCUSSION

This study did not demonstrate an association between elevated AIMS scores and either increased striatal D$_2$ receptor binding or altered sensitivity to amphetamine-induced dopamine release. Neither baseline striatal D$_2$ receptor binding or the degree of change in specific binding significantly correlated with individual AIMS scores.

The results of this study are consistent with other PET and post-mortem studies that failed to observe an association between TD and striatal dopamine binding. Other studies of similar dyskinesias, such as that observed in patients with Parkinson's disease, have also failed to observe differences in striatal dopamine binding (Brooks et al. 2000). While several studies have observed evidence of basal ganglia pathology, our findings, as well as previous studies, fail to demonstrate any differences in endogenous dopamine concentrations or D$_2$ specific binding that might underlie the pathogenesis of TD.

Similarly, preclinical studies demonstrating increased D$_2$ binding sensitivity with exposure to D$_2$ receptor antagonists are not fully consistent with clinical observations of TD. Increased dopamine sensitivity

manifests rapidly in animals receiving dopamine-blocking agents (Tarsy and Baldessarini 1974; Gianutsos and Moore 1977; Burt et al. 1977). In contrast, TD rarely appears without a considerably longer period of neuroleptic exposure (Jimenez-Jimenez et al. 1997). In addition, although dopamine sensitivity drops off rapidly after discontinuation of dopamine blocking agents in animals, TD may persist indefinitely even after administration of neuroleptic medications has been discontinued.

Several caveats need to be considered in interpreting our data. Sample sizes were relatively small, an issue with regard to interpreting our negative data. Nonetheless, effect sizes with and without inclusion of non-schizophrenic or schizoaffective patients were small to moderate, suggesting that larger cohorts would be unlikely to significantly alter our findings.

While the AIMS ratings of the patient group with TD were fairly low, all subjects in this group met at minimum the criteria of Schooler and Kane (1982) for "probable tardive dyskinesia." A diagnosis of "persistent tardive dyskinesia" could not be made in some cases because the patient was not evaluated over a full three months. Moreover, while mild, the movement symptoms observed in our affected group were clearly pathological.

Subjects in our study without evidence of TD tended to be both younger and to have been diagnosed with illness for a shorter period of time. While in neither instance are the differences statistically significant, age related changes in specific binding might partially obscure group differences (Wong et al. 1997; Volkow et al. 1998). While the lack of difference in baseline and change in specific binding we observed is sufficiently robust to make significant effects of subject age or years

of illness unlikely, more age-matched cohorts will be recruited in future studies.

The data from this study adds further evidence to suggestions that hypotheses linking TD to increased dopamine binding sensitivity constitute an oversimplification, and by extension lend support to hypotheses suggesting other possible etiologies (Casey 2000). By not demonstrating any connection between D$_2$ receptor binding and elevations in AIMS scores, this study suggests that further focus on related pathways and receptor systems might be necessary to yield a clearer understanding of the link between D$_2$ receptor antagonists and TD.

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