

Subjective Effects of AMPT-induced Dopamine Depletion in Schizophrenia: Correlation between Dysphoric Responses and Striatal D₂ Binding Ratios on SPECT Imaging

Lakshmi Voruganti, M.D., M.Sc., Piotr Slomka, Ph.D., Pamela Zabel, M.Sc., Giuseppe Costa, B.Sc., Aaron So, B.Sc., Adel Mattar, M.D. and A. George Awad, M.D., Ph.D.

Approximately one third of schizophrenic patients treated with neuroleptic drugs experience unpleasant subjective responses, that are collectively known as neuroleptic dysphoria. Experimental research in animals indicates that drug induced dopaminergic blockade in mesolimbic circuits, especially the nucleus accumbens, leads to impaired pleasure responsivity and dysphoria. The present study tested this putative mechanism in drug-free schizophrenic patients (n = 12), through inducing dysphoric responses with alphas-methyl paratyrosine (AMPT) and simultaneously quantifying their baseline striatal dopamine (D₂) function with ¹²³IBZM-SPECT imaging. Results showed a wide variability in the occurrence and severity of

dysphoric responses, clearly distinguishing a dysphoric group from non-dysphoric responders. Severity of dysphoric responses, measured by standardized rating scales, correlated inversely with changes in D₂ receptor binding ratios ($r = +0.82, p < .01$). These results support the notion that striatal dopaminergic activity is not uniformly elevated in all schizophrenic patients, and the sub-group of individuals with lower baseline dopamine function are at an increased risk for dysphoric responses during antipsychotic therapy with dopaminergic blocking drugs.

[Neuropsychopharmacology 25:642–650, 2001]

© 2001 American College of Neuropsychopharmacology.
Published by Elsevier Science Inc.

KEY WORDS: *Dysphoria; Dopamine; Schizophrenia; Antipsychotic drugs*

Dopamine carries a distinction of being the most widely studied neurotransmitter, and much of the research has

been focused on studying its role in psychotic disorders and the effects of antipsychotic drugs (Palermo-Neto 1997). This preoccupation has, to some extent, overshadowed the fact that dopamine plays a wide variety of physiological functions within the brain as well as the rest of the body (Le Moal 1995). One such example is the role of dopamine in the regulation of affect; the relationship between altered dopaminergic function and disturbed mood states has been sporadically studied in clinical settings as well as the laboratory (Big-nami 1991; Emerich and Sanberg 1991; Fibiger and Phillips 1986; Sachdev 1995).

In disease states, lowered dopaminergic activity has been associated with depressive symptoms and lack of motivation (e.g., Parkinson's disease and negative syn-

From the Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada (LV, AGA); Department of Psychiatry (LV, GC), and Department of Nuclear Medicine (PS, PZ, AS, AM), University of Western Ontario, London, Ontario, Canada.

Address correspondence to: L. Voruganti, M.D., Schizophrenia Treatment and Research (STAR) Program, 850 Highbury Avenue, London, ON N6A 4H1, Canada, Tel.: 519-455-5110 x 2533; Fax: 519-455-2677; e-mail: lvorugan@julian.uwo.ca

Received December 6, 2000; revised March 22, 2001; accepted April 10, 2001.

Online publication: 4/12/01 at www.acnp.org/citations/Npp0412011031.

drome of schizophrenia) (Bermanzohn and Siris 1995; Markou et al. 1998), while increased dopamine transmission has been linked to euphoria, irritability, hyperarousal and overactivity (e.g., mania and positive symptoms of schizophrenia) (Gerner et al. 1976; Swerdlow and Koob 1987; Diehl and Gershon 1992). However, some of the more convincing examples of the effects of altered dopaminergic function have been derived from studying the subjective effects of drugs, therapeutic as well as illicit. Substances that are known to increase dopaminergic activity (e.g., amphetamines) induce an experience of pleasure or thrill (Koeppe et al. 1998), while those that tend to block dopaminergic activity (e.g., antipsychotics) lead to unpleasant or dysphoric feelings, also known as neuroleptic dysphoria (Van Putten et al. 1981; Awad 1993; Voruganti et al. 1997). Experimental research in animals seems to substantiate the clinical observations, and indicated that nucleus accumbens (NAc) and mesolimbic pathways are the primary neural substrates, and dopamine is the key neurotransmitter involved in the regulation of pleasure responsivity (Fibiger et al. 1990; Taber et al. 1995; Wise 1996; Heimer et al. 1997). An integrated theory suggests that altered dopaminergic activity in the brain reward pathways leads to *drug addiction* in certain situations, and *drug aversiveness* in others (Wise 1988; Koob 1997). Recent developments in the fields of molecular biology and neuroimaging have helped to test these putative mechanisms, through performing *in-vivo* imaging studies, often complemented with various pharmacological challenge tests (Laruelle et al. 1999; Volkow et al. 1997). Imaging striatal dopamine D₂ receptors has emerged as a reliable tool, especially in establishing the link between chemical and therapeutic profiles of antipsychotic drugs (Tamminga and Holcomb 2001).

The focus of the present study was to investigate one aspect of this relationship, i.e. the link between dopaminergic dysfunction and dysphoria, in a clinical population. Using a case controlled study design, we recruited two matched groups of drug free schizophrenic patients—one group with a history of persistent dysphoric responses to previous neuroleptic therapy, and the other without such problems. The specific aims of the investigation were,

1. to induce dopamine depletion with the aid of alpha-methyl paratyrosine (AMPT), and monitor the consequent changes in mental status through carrying out serial measurements of the individual's subjective responses over a 96-hr period,
2. to measure striatal dopamine D₂ receptor binding ratios with ¹²³IBZM, using single photon emission computerized tomography (SPECT), and
3. to examine the association between baseline striatal dopaminergic function and the magnitude of AMPT-induced dysphoric responses.

SUBJECTS

The study participants (n = 12) received a letter of information and provided informed consent, as required by the institutional review board of the University of Western Ontario. The sample consisted of subjects who were previously treated with neuroleptic drugs, but went off their medications (for periods ranging from four weeks to a year) and returned to the clinic, often with a relapse of symptoms. Subjects were screened with structured clinical interview (SCID) to confirm the diagnosis of schizophrenia, and also to rule out other comorbid conditions such as mood disorders, substance abuse and mental retardation. An attempt was made to include equal numbers of "dysphoric" and "non-dysphoric" responders, and form two comparable matched study groups. The dysphoric predisposition was established through reviewing subjects' past treatment history, and their scores on drug attitude inventory (DAI), a rating scale used to identify dysphoric responders. DAI is an established rating scale for quantifying subjective tolerability of antipsychotic drugs, and the cumulative score on the scale ranges between +10 and -10 (Awad 1993). The shorter version of the scale was administered on earlier occasions while the subjects were receiving antipsychotic drugs (Voruganti et al. 2000). For the purpose of this study, subjects who received a negative score (0 to -10) were designated as "dysphoric" responders, and those who received a positive score (0 to +10) were considered as "non-dysphoric" responders. The demographic and clinical characteristics of the two groups are summarized in Table 1.

The dysphoric and non-dysphoric groups were clearly distinct from each other in terms of their past DAI scores, but were not significantly different in age, duration of illness, or the length of drug free interval. These results ensured that the groups were properly matched and comparable, without the confounding effects of age, sex, length of illness, or the duration of drug free interval.

METHODS

Study Procedure

The study procedures described below received approval from the institutional review board, and were carried out in accordance with the declaration of Helsinki. All the consented subjects were hospitalized and comprehensively evaluated with a detailed history, full physical examination, routine blood tests, electrocardiogram and urinary screen for illicit drugs, prior to the initiation of AMPT protocol. The study was planned as a 96-hr clinical experiment, consisting of three phases: an initial 24-hr assessment phase (to carry out the baseline evaluations), followed by a 48-hr AMPT-induced

Table 1. Sample Description (n = 21)

Clinical Variable	Dysphoric responders ¹ (n = 6) mean ± sd	Non-dysphoric responders ¹ (n = 6) mean ± sd	Differences
1. Age (years)	35.33 ± 7.28	38.8 ± 10.6	ns
2. Sex (Males : Females)	4:2	4:2	ns
3. Duration of illness (years)	7.56 ± 4.88	6.66 ± 1.66	ns
3. Duration of drug free interval (months)	4.83 ± 2.92	4.66 ± 3.66	ns
4. Global assessment of functioning (GAF)	44.2 ± 4.5	42.3 ± 6.1	ns
5. Drug attitude Inventory (DAI) score ²	-6.66 ± 1.36	3.33 ± 0.81	p < .001
6. Alpha-methyl-para-tyrosine dose (mg)	1208.33 ± 102.06	1208.33 ± 102.06	ns

p < 0.05, statistically significant.

¹Groups selected based on subjects' pattern of subjective responses to previous neuroleptic therapy.

²Negative score indicates negative subjective responses and positive score indicates favorable subjective responses to antipsychotic drugs.

dopamine depletion procedure, and a final 24-hr observation period. SPECT imaging was performed before and at the end of the AMPT protocol, consisting of the equilibrium method using constant infusion technique (Laruelle et al. 1997). Some of the key procedural aspects are further described below.

Dopamine Depletion Protocol

Alpha-methyl-paratyrosine (AMPT) interferes with dopamine synthesis through competitive inhibition of the enzyme tyrosine hydroxylase. The AMPT-induced dopamine depletion procedure was developed to quantify endogenous dopamine levels, originally in baboons and later in humans including healthy volunteers and subjects with schizophrenia (Laruelle et al. 1997; Kegeles and Mann 1997; Abi-Dargham et al. 1998). The protocol consists of oral administration of AMPT at 6-hr intervals, over a 48-hr period, to induce a temporary depletion of synaptic dopamine without causing an up-regulation of D₂ receptors. The dose of AMPT was determined according to individual's body weight, using a sliding scale regime as following: 50–58 kg—750 mg every 6 hrs; 59–75 kg—1000 mg every 6 hrs; 76–92 kg—1250 mg every 6 hrs; and 93–115 kg—1500 mg every 6 hrs. (Laruelle, personal communication). Subjects were encouraged to drink fluids liberally during the 48-hr period, and sodium bicarbonate was given to alkalize the urine and prevent the formation of crystals. Subjects' urine was tested every morning, for three days during the AMPT protocol, to detect any crystal formation. A fluid intake and urinary output chart was maintained during the study period. Vital observations, especially the blood pressure, were monitored regularly for postural hypotension. Subjects were prescribed lorazepam and benztropine for treating side effects.

SPECT Imaging

Two series of brain SPECT scans were performed on each subject: a baseline scan (B-scan), and another after

dopamine depletion (D-scan). Radio-iodinated Iodobenzimide (¹²³I-IBZM) was the preferred radioligand used for the study of D₂ receptors (Lassen 1996). ¹²³I-IBZM was prepared by direct electrophilic radio-iodination of the phenolic precursor BZM with high purity sodium ¹²³I-iodide in 0.1 M NaOH, maintaining an average radiochemical purity of 95 ± 2% (Kung et al. 1990). Appropriate steps were taken to maintain sterility and apyrogenicity.

Subjects were administered 600 mg of potassium iodide orally to minimize radiation exposure to the thyroid, and were asked to wear reference (fiducial) markers. Intravenous catheter was inserted into the arm, and a total ¹²³I IBZM dose of 5.79 ± 0.76 mCi was given as a bolus, followed by a continuous infusion at a rate of 0.66 ± 0.08 mCi/hr for 250 minutes. Scanning began after 180 minutes of infusion, and continued for 72 minutes, obtaining 6 acquisitions of 12 minutes each, each with 90 projections lasting 16 seconds.

Scans were acquired with MULTISPECT II (Chicago, IL) dual headed camera equipped with high resolution fan beam collimators (focal length 41 cm). The acquisition parameters were: radius of rotation 16.3 cm, 128 × 128 matrix size, pixel size of 3.89 mm/pixel. A typical count rate was 0.8–1.0 kcount/per sec. Data were reconstructed with the uniform attenuation correction (0.12 cm⁻¹) and Butterworth 3D post reconstruction filter with cut-off 0.9 cycles/cm and order 5. The same size of the elliptical outline was used for the attenuation correction for the B-scan and the D-scan for each patient.

MRI Imaging

Anatomical MRI images were acquired to verify the anatomical shape of the basal ganglia on the 4T whole body Varian Unity INOVA (Palo Alto, CA) scanner with a Siemens (Erlangen, Germany) actively shielded (AS25) gradient set. High resolution (256 × 256) 3D T1-weighted anatomical volumes were acquired (TE=6ms, TR=11ms, TI=500ms, flip angle=11deg).

The resulting acquisition produced 128 contiguous structural images each with a slice thickness of 1.5 mm. The field of view was $24 \times 24 \times 19.2$ cm. The total time for the 3D volume acquisition was 10.5 min.

Image Analysis

The SPECT scans were corrected for patient motion by using automated image registration using mutual information technique (Slomka et al. 1997, 2000; Radau et al. 2000). The reconstructed image datasets were re-registered to the first dataset in each 6-scan series adjusting three translations and three rotations. The data was subsequently summed together to create an equivalent to the 72-minute SPECT scan for both the baseline (B-scan) and the dopamine depleted state (D-scan).

Using the same automated image registration technique the B-scans and D-scans were spatially co-registered to each other. Rigid-body parameters (three translations and three rotations) were adjusted on the D-scan to match the B-scan. To eliminate any bias in the image quantification due to the tri-linear interpolation of the data during the alignment, similar image registration was performed in the opposite order; i.e., the D-scans were registered to the B-scans. Also, if MRI datasets were available, the B-scans and D-scans were both co-registered to the MRI scans for the visual verification of the anatomical shape of the basal ganglia.

After the registration, the regions of interest were drawn for left and right basal ganglia and the background region was drawn in the occipital cortex, on the slice containing the image maximum. Since the B-scans and D-scans were co-registered to the same spatial coordinates the ROIs were drawn only once and they were used for the quantification of both scans. The maximum count was then found in the whole 3D region of the left and right basal ganglia, which included up to four contiguous transverse slices. The average count was found in the background region. The binding ratio (BR) was calculated as the ratio of the mean of the left and right maximum divided by the average background counts. The maximum value was chosen instead of the average counts for the basal ganglia region due to the partial volume effect resulting in poor definition of the anatomical boundaries of the basal ganglia on SPECT scan and the possibility of the variation in the image orientation. The maximum count is less affected by these imaging limitations and such a definition is less operator-dependent. This quantification was repeated on the scans registered in the reverse order (B-scan to D-scan) and the mean of both binding ratios was used in the further calculations (Figure 1).

Clinical Measurements

Patients' subjective responses were recorded with two self administered rating scales: the Addiction Research

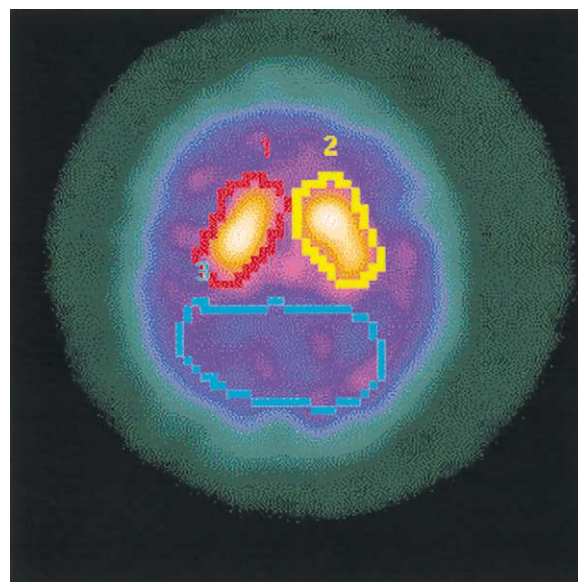


Figure 1. Quantifying D_2 receptor binding ratio (BR) with $^{123}\text{IBZM}$ SPECT imaging—A typical scan from the series showing the regions of interest* and image quality. *1 = Left basal ganglion, 2 = Right basal ganglion, 3 = Background region (occipital cortex).

Center Inventory (ARCI) (Haertzen 1965), and the Drug attitude inventory (short version) (Hogan et al. 1983). ARCI is a self-administered and easy-to-use measure that has been extensively employed in studying the subjective effects of various psychotropic drugs. The ARCI has six subscales (referred as Cole scales), and the summed weighted scores range between -27 and 144 (higher score indicative of increasingly negative subjective responses). Items on the DAI are assigned a score of $+1$ or -1 , and the total scores range between $+10$ and -10 (higher scores are indicative of positive subjective responses). The scales were administered at the baseline, and twice a day during the 48-hr period of AMPT administration.

Symptom severity was established with the Positive and Negative Syndromes Scale (PANSS) (Kay et al. 1987), and side effects were quantified with Barnes akathisia scale (BAS) (Barnes 1989) and Simpson-Angus extrapyramidal side effects rating scale (Simpson and Angus 1970). Clinician's assessments were performed by independent "blinded" raters, at the baseline, 24, 48 and 96 hrs, and the respective rating scales were completed.

Data Analysis

Data were gathered by three researchers "blinded" to each other's ratings: clinical evaluations were carried out by a psychiatrist, self-administration of scales was supervised by a research coordinator, and the SPECT data were analysed independently by the nuclear medi-

cine team. Data was entered into a database, and was further analysed with the statistical program for social sciences (SPSS. v 10.0).

The primary outcomes were the changes in ARCI and DAI scores (differences between the observations at baseline and at the end of 48-hr AMPT administration), and the alterations in D₂ receptor binding ratios between the two SPECT scans. D₂ receptor binding ratios are generally believed to be a surrogate index of synaptic dopamine function (Laruelle et al. 1997). Secondary outcome variables included changes in PANSS, BAS and Simpson-Angus scale. Scores from the serial administration of various rating scales were subjected to repeated measures analysis of variance, with the scores as key dependent variables, and the time (baseline vs. post-test) and group membership (dysphoric vs non-dysphoric) as factors. Changes were considered significant if Pillai trace showed the probability of type 1 error of $\alpha < 0.05$.

The associations between subjective responses to AMPT (changes in ARCI and DAI scores), and changes in D₂ receptor binding ratios (expressed as % increase) were examined using a simple general linear model (correlation and linear regression) with significance set at $\alpha < 0.05$.

RESULTS

All the participants experienced dysphoric symptoms with AMPT, some less and others more, some earlier and others later. The profile of changes in mental status during the study period and the corresponding dopamine receptor binding ratios for the two study groups are summarized in Table 2. The two groups were clearly distinguishable in terms of their responses to AMPT, on key outcome measures. The ANOVAs calculated with ARCI, DAI, BAS and Simpson-Angus scale as the dependent variables showed that both factors (time and the group), as well as their interaction, were significant. The subjects who were identified at the outset as "dysphoric" responders demonstrated a significantly greater changes in scores on both ARCI and DAI during the dopamine depletion, indicative of experiencing a greater degree of dysphoria. They were also noted to be at an increased risk for akathisia and extra-pyramidal effects, as indicated by the significant increases in BAS and Simpson-Angus scale scores.

The ANOVA calculated with the binding ratios showed that, both time and the effect of the group membership were significant. The ANOVA of the PANSS data showed that there was a slight improve-

Table 2. Effects of AMPT Induced Dopamine depletion in Drug Free Schizophrenic Patients: Results of Repeated Measures Analysis of Variance

Outcome measure	Dysphoric responders ¹ (n = 6)			Non-dysphoric responders ¹ (n = 6)			Within subjects effect (Pillai's trace)	
	Baseline	after 48 hrs	Observed difference	Baseline	after 48 hrs	Observed difference	Time	Group*time
Clinical Measures								
Positive & Negative Syndromes Scale (PANSS) total score	66.8 ± 18.6	63.7 ± 7.06	3.14 ± 2.26	65.8 ± 5.64	57.6 ± 4.9	7.33 ± 1.36	0.928, F[4,8]= 25.65, <i>p</i> < .0001	0.643, F[4,8]= 3.59, <i>p</i> < .058
Barnes Akathisia Scale (BAS) score	0.14 ± 0.37	7.42 ± 0.78	7.28 ± 0.95	0.16 ± 0.40	1.66 ± 0.51	1.5 ± 0.54	0.99, F[4,8]= 206.26, <i>p</i> < .0001	0.973, F[4,8]= 71.034, <i>p</i> < .0001
Simpson-Angus Scale (SAS) score	0.00 ± 0.00	19.14 ± 0.89	19.14 ± 0.89	0.00 ± 0.00	7.1 ± 0.89	7.1 ± 0.89	0.99, F[4,8]= 590.378, <i>p</i> < .0001	0.98, F[4,8]= 125.64, <i>p</i> < .0001
Subjective Measures								
Addiction Research Centre Inventory (ARCI)	2.42 ± 2.63	52.42 ± 2.57	50.0 ± 4.08	2.16 ± 1.16	23.6 ± 4.1	21.5 ± 14.46	0.96, F[4,8]= 63.192, <i>p</i> < .0001	0.81, F[4,8]= 8.568, <i>p</i> < .005
Drug Attitude Inventory (DAI) score	3.83 ± 1.32	-7.16 ± 1.94	11.0 ± 1.78	3.50 ± 1.37	0.30 ± 1.83	3.33 ± 1.50	0.91, F[4,8]= 21.781, <i>p</i> < .0001	0.893, F[4,8]= 16.65, <i>p</i> < .001.
Imaging Parameters								
Striatal D ₂ Binding ratio (BR)	1.80 ± 0.12	1.91 ± 0.10	5.13 ± 1.32% ²	1.68 ± 0.11	2.06 ± 0.11	19.16 ± 2.7%	0.87, F[1,10]= 71.59, <i>p</i> < .001	0.79, F[1,10]= 39.75, <i>p</i> < .001.

¹Groups selected based on subjects' pattern of subjective responses to previous neuroleptic therapy.

²Conventionally, changes in binding ratios (BR) are represented as percentage increases.

ment in psychotic symptoms (especially in items on the positive symptoms and general psychopathology subscales), and the change was marginally higher among the subjects in the non-dysphoric group.

The association between subjective responses (increases in dysphoria scores on ARCI and DAI) and the changes in D₂ receptor binding ratios, for the dysphoric and non-dysphoric subjects, are represented in Figures 2 and 3. The two variables were correlated inversely ($r = -0.82$, $p < .01$ with ARCI, and $r = -0.78$, $p < .01$ with DAI) and the association was statistically significant. Results from the analysis of variance revealed that the changes in binding ratios were not only significant over time, but also distinguished dysphoric group from the non-dysphoric responders. It is inferred from this observation that subjects with a greater increase of D₂ receptor binding ratio following AMPT administration (presumably indicative of higher synaptic dopamine activity at the baseline) were less susceptible to experience dysphoric responses and extrapyramidal side effects, and may have even benefited from it. Subjects with relatively smaller increases, on the other hand, were at an increased risk for dysphoria as well as akathisia and EPS.

DISCUSSION

The focus of the investigation was to study the subjective consequences of interfering with dopaminergic function, in an attempt to understand the pathophysiology of neuroleptic dysphoria encountered during antipsychotic drug therapy of schizophrenia. However, creating an experimental paradigm that can mimic the effects of antipsychotic drugs in the clinical setting was a challenge. Standard neuroleptic drugs are ill suited as pharmacological probes for this purpose, since the absorption, metabolism and pharmacodynamic actions of these drugs are notoriously variable and unpredictable

(Keck et al. 1989). The ideal design was to induce a rapid, transient and reversible disruption of dopaminergic activity in a structured experimental setting, and observe the steady and predictable evolution of dysphoric responses in vulnerable individuals. The AMPT-induced transient and reversible disruption of dopaminergic activity was eminently suited to fulfill our goal of linking dysphoric responses with dopamine dysfunction. The AMPT paradigm, originally developed to estimate endogenous dopaminergic activity, was not only helpful in inducing dysphoric responses in predisposed individuals, but also ethically acceptable because of its ability to bring about some symptomatic improvement in untreated, acutely ill individuals.

This preliminary investigation, however, has had some methodological limitations. First, the absence of a healthy control group created a dilemma with regard to the interpretation of imaging data. The magnitude of binding ratios observed in our sample, especially among subjects in the dysphoric sub-group were similar to those observed among healthy controls in a recent study that used identical methodology (Abi-Dargham et al. 2000). Since a healthy control group was not included in our study, it is difficult to conclude if the binding ratios in this sub-group would be higher than normal controls but relatively lower compared to the non-dysphoric subjects; or if they were indeed comparable to those of healthy controls. The latter scenario revives an under-recognized notion that biochemical mechanisms other than dopamine might be involved in the origin of schizophrenic symptoms (Garver et al. 1997, 2000). Second, the failure to monitor serum AMPT levels raised some uncertainty about the extent of dopamine depletion achieved and the consequent rise in the D₂ binding ratios in our subjects, which were comparatively lower in our subjects compared to the other reports (Abi-Dargham et al. 2000). Third, the role of gender in determining the liability to dysphoria, and also the magnitude of the D₂ binding ratios observed, can't

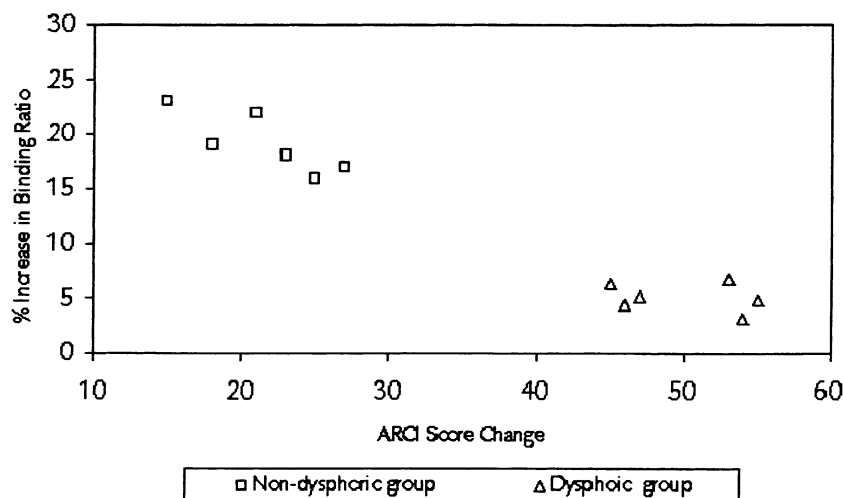


Figure 2. Relationship between AMPT-induced Dysphoria (ARCI score change) and corresponding increases in Striatal IBZM binding ratios ($n = 12$).

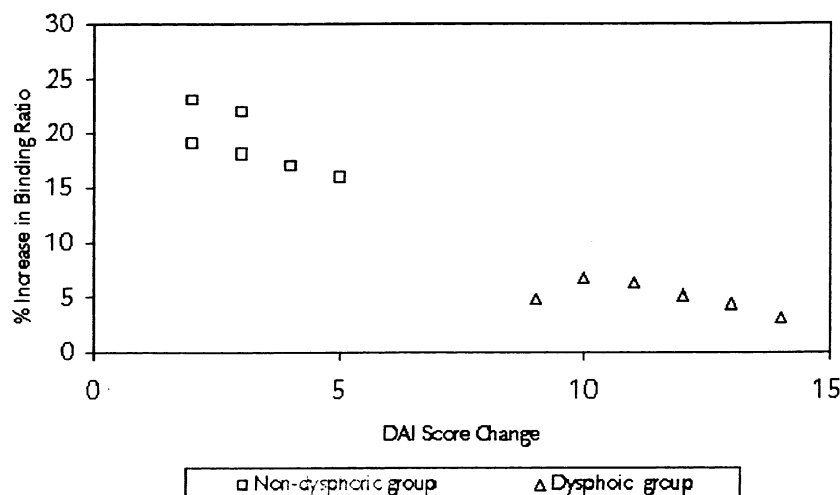


Figure 3. Relationship between AMPT-induced Dysphoria (DAI score change) and corresponding increases in Striatal IBZM binding ratios ($n = 12$).

be delineated clearly because of the smaller sample size (Wong et al. 1988; Pohjalainen et al. 1998).

The results of our study add further momentum to a growing body of evidence linking lowered dopaminergic activity and dysphoria/depression in schizophrenia. Several recent studies have attempted to address the relationship between altered dopaminergic function and disturbed mood in schizophrenia, through employing receptor imaging studies. Fujita et al. used a protocol similar to that of ours, consisting of AMPT administration and SPECT imaging with ^{123}I -epidepride in healthy volunteers, and were able to demonstrate an association between increased D_2 binding potential in the temporal cortex and a corresponding worsening of dysphoric mood (Fujita et al. 2000). Hietala et al., in an exploratory study, examined the striatal dopamine levels of ten drug-naïve first-episode schizophrenic patients with ^{18}F -DOPA PET imaging, and correlated them with clinical symptom clusters. A strong correlation ($r = 0.86\text{--}0.9$) was found between low striatal dopamine, and scores on the depressive items on the PANSS (Hietala et al. 1999). de Haan et al. used ^{123}I -IBZM-SPECT imaging to estimate striatal D_2 occupancy rates in schizophrenic patients treated with olanzepine or risperidone, and found a significant correlation between percentage of D_2 occupancy and dysphoric responses (de Haan et al. 2000). In a more recent study, Martinot et al. demonstrated that hypodopaminergic activity in the left caudate nucleus is associated with depression, affective flattening and psychomotor retardation (Martinot et al. 2001). While many of these studies viewed the depressive spectrum of disorders as a single category, we have been specifically interested in the neuroleptic dysphoria, and used specific rating scales (ARCI and DAI) to capture the subtle variations precisely and in a timely manner. The future challenge lies in identifying the anatomical sites of dopamine dysfunction (e.g., nucleus accumbens) that are crucial for the patho-

physiology of neuroleptic induced dysphoria and depression.

Since our study was more focused, and was "purpose-built" to exclusively study various aspects of dysphoria, there were other notable findings. These include observations that individuals may vary in terms of their vulnerability to develop dysphoric responses, and such individual vulnerability, in turn, could be linked to their low baseline synaptic dopamine status. Clinical research in the past has consistently shown that about one third of all schizophrenic patients experience dysphoric feelings during antipsychotic drug treatment (Weiden et al. 1989; Awad et al. 1995); and *post mortem* studies on the brain dopaminergic receptor status indicated that about one third of schizophrenic patients may not have elevated dopaminergic activity (Zakzanis and Hansen 1998). Is it possible that the one third of schizophrenic patients without elevated dopamine levels are the same one third who tend to develop dysphoric responses during antipsychotic drug therapy? Our study supports a growing notion that dopaminergic function may differ vastly, across different people with schizophrenia (Seeman et al. 1984; Zakzanis and Hansen 1998), and at different stages of illness (Laruelle et al. 1999), but also indicated that schizophrenic patients with little or no elevation of synaptic dopamine at the baseline were indeed at an increased risk to experience dysphoric responses with AMPT.

The relationship between dopamine and dysphoria, however, is likely to be more complex and warrants further exploration. AMPT is also known to interfere with the synthesis of other catecholamines, i.e., epinephrine and nor-epinephrine, and the clinical implications of these additional actions remain unclear at the present time. Recently, there has been a renewed interest in understanding the role of norepinephrine in the pathophysiology of both psychotic and affective disorders; and it is conceivable that AMPT-induced dyspho-

ria in our experiment may have been linked, in part, to an impaired noradrenergic activity. The strong correlation observed between clinical measures of dysphoria and D₂ receptor binding ratio, by itself, suggests that dopamine would be a principal, if not the only factor, involved in the origins of dysphoric responses. Future work in this area should attempt to delineate the differential contribution of dopaminergic and noradrenergic mechanisms, through monitoring biochemical indices that are reliably measurable.

One of the clinical implications of the study is that AMPT-induced dopamine depletion with or without the simultaneous SPECT imaging could provide valuable predictive information in terms of identifying individuals that are prone to develop dysphoria, depression and other side effects during antipsychotic drug therapy. Our results also suggest that individuals with low basal dopamine status not only carry an increased risk of developing side effects, but also respond unfavorably to traditional dopaminergic blocking drugs, suggesting a need to explore strategies for developing non-dopaminergic antipsychotic drugs.

ACKNOWLEDGMENTS

The authors wish to thank Marc Laruelle, MD for his help in successfully implementing the AMPT-SPECT paradigm. The project was supported in part by the Internal Research Fund (IRF) of the London Health Sciences Centre.

REFERENCES

- Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, Charney DS, Innis R, Laruelle M (1998): Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* 155:761–767
- Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M (2000): Increased baseline occupancy of D₂ receptors by dopamine in schizophrenia. *Proc. Natl Acad Sci USA* 97:8104–8109
- Awad AG (1993): Subjective response to neuroleptics in schizophrenia. *Schizophrenia Bulletin* 19:609–618
- Awad A, Voruganti L, Hogan T (1995): Patients' subjective experiences on antipsychotic medications: implications for outcome and quality of life. *International Clinical Psychopharmacology* 10 (suppl. 3):123–132
- Barnes TRE (1989): A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 154:672–676
- Bermanzohn PC, Siris SG (1992): Akinesia: a syndrome common to Parkinsonism, retarded depression, and negative symptoms of schizophrenia. *Comprehensive Psychiatry* 33:221–232
- Bignami G (1991): Neuroleptic dysphoria in animals. *Biological Psychiatry* 30:844
- de Haan L, Lavalaye J, Linszen D, Dingemans PMAJ, Booij J (2000): Subjective experience and striatal dopamine D₂ receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. *Am J Psychiatry* 157:1019–1020
- Diehl DJ, Gershon S (1992): The role of dopamine in mood disorders. *Comprehensive Psychiatry* 33(2):115–120
- Emerich DF, Sanberg PR (1991): Neuroleptic dysphoria. *Biological Psychiatry* 29:201–203
- Fibiger HC, Phillips AG (1986): Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems. In Mountcastle VB, Bloom FE, Geyer SR (eds), *Handbook of Physiology: The Nervous System IV*. Bethesda MD, American Physiological Society, pp 647–675
- Fibiger HC, Phillips AG, Blaha CD (1990): Dopamine and the neural substrates of reward: implications for the mechanisms of action of antidepressant drugs. *Advances in the Biosciences* 77:51–62
- Fujita M, Verhoeff PLG, Varrone A, Zoghbi SS, Baldwin RM, Jatlow PA, Anderson GM, Seibyl JP, Innis RB (2000): Imaging extrastriatal dopamine D₂ receptor occupancy by endogenous dopamine in healthy humans. *European J Pharmacology* 387:179–188
- Garver DL, Steinberg JL, McDermott BE, Yao JK, Ramberg JE, Lewis S, Kingsbury SJ (1997): Etiologic heterogeneity of the psychoses: is there a dopamine psychosis? *Neuropsychopharmacology* 16:191–201
- Garver DL, Holcomb JA, Christensen JD (2000): Heterogeneity of response to antipsychotics from multiple disorders in schizophrenia spectrum. *J Clin Psychiatry* 61:964–972
- Gerner RH, Post RM, Bunney WE (1976): Dopaminergic mechanism in mania. *Am J Psychiatry* 133:1177–1180
- Haertzen CA (1965): Addiction Research Centre Inventory (ARCI): Development of a general drug estimation scale. *Journal of Nervous and Mental disease* 141:300–307
- Heimer L, Alheid G, de Olmos JS, Groenewegen HJ, Haber SN, Harlan RE, Zahm DS (1997): The Accumbens: Beyond the core-shell dichotomy. In Salloway S, Malloy P, Cummings JL (eds), *The Neuropsychiatry of limbic and subcortical disorders*. Washington, American Psychiatric Press,
- Hietala J, Syvalahti E, Vilkmann H, Vuorio K, Rakkolainen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Eronen E, Ruotsalainen U, Salokangas RKR (1999): Depressive symptoms and pre-synaptic dopamine function in neuroleptic naive schizophrenia. *Schizophrenia Research* 35:41–50
- Hogan TP, Awad AG, Eastwood R (1983): A self report scale predictive of drug compliance in schizophrenics: reliability and discriminant validity. *Psychological Medicine* 13:177–183
- Kay S, Fiszbein A, Opler L (1987): The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin* 13:261
- Keck PE, Cohen BM, Baldessarini RJ, McElroy SL (1989): Time course of antipsychotic effects of neuroleptic drugs. *American Journal of Psychiatry* 146:1289–1292
- Kegeles LS, Mann JJ (1997): *In vivo* imaging of neurotransmitter systems using radiolabeled receptor ligands. *Neuropsychopharmacology* 17:293–307

- Koepp MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T, Brooks DJ, Bench CJ, Grasby P (1998): Evidence for striatal dopamine release during a video game. *Nature* 393:266–268
- Koob GF (1997): Drug abuse and alcoholism: overview. *Advances in pharmacology* 42:969–977
- Kung HF, Alavi A, Chang W, Kung MP (1990): *In vivo* SPECT imaging of CNS D2 dopamine receptors: initial studies with 123-I-IBZM in humans. *J Nucl Med* 31: 573–579
- 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, Abi-Dargham A, Gil R, Kegeles L, Innis R (1999): Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biological Psychiatry* 46:56–72
- Lassen NA (1996): A reappraisal of the relative merits of SPECT and PET in the quantification of neuroreceptors: the advantage of a longer half-life! *European Journal of Nuclear Medicine* 23:1–4
- Le Moal M (1995): Mesocorticolimbic dopaminergic neurons: functional and regulatory roles. In Bloom FE, Kupfer DJ (eds), *Psychopharmacology: the fourth generation of progress*. New York, Raven Press, pp 283–296
- Markou A, Kosten TR, Koob GF (1998): Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. *Neuropsychopharmacology* 18:135–174
- Palermo-Neto J (1997): Dopaminergic systems. *The Psychiatric Clinics of North America* 20:705–721
- Martinot M-L P, Bragulat V, Artiges E, Dolle F, Hinnen F, Jouvent R, Martinot J-L (2001): Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *Am J Psychiatry* 158:314–316
- Pohjalainen T, Rinne JO, Nagren K, Syvalahti E, Hietala J (1998): Sex differences in the striatal dopamine D₂ receptor binding characteristics *in vivo*. *Am J Psychiatry* 155:768–773
- Radau P, Linke R, Slomka PJ, Tatsch K (2000): Optimization of the automated quantification of Iodine¹²³IBZM uptake in the striatum applied to Parkinsonism. *J Nucl Med* 41:220–227
- Sachdev P (1995): Neuroleptic dysphoria. In Akathisia and restlessness. London, Cambridge University Press. pp 47–62
- Seeman P, Ulpian C, Riederer P, Jellinger K, Gabriel E, Reynolds GP, Tourtellotte WW (1984): Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science* 225:728–731
- Simpson G, Angus J (1970): A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica* (Suppl.) 212:11–19
- Slomka PJ, Stephenson J, Reid R, Hurwitz GA (1997): Automated template-based quantification of brain SPECT. In De Deyn PP, Dierckx RA, Alavi A, Pickut BA (eds), *SPECT in Neurology and Psychiatry*. London, John Libbey & Company Ltd., pp 507–512
- Slomka PJ, Mandel J, Fenster A, Downey D (2000): Automated 3D registration of magnetic resonance angiography, 3D power doppler, and 3D B-mode ultrasound images of carotid bifurcation. *Proceedings of the International Society for Optical Engineering SPIE symposium. Proc SPIE Medical Imaging* 3979:332–341
- Swerdlow NR, Koob GF (1987): Dopamine, schizophrenia, mania and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behav Brain Sci* 10:197–245
- Taber MT, Das S, Fibiger HC (1995): Cortical regulation of subcortical dopamine release: mediation via the ventral tegmental area. *Journal of Neurochemistry* 65:1407–1410
- Tamminga CA, Holcomb HH (2001): Images in Neuroscience. Neural systems VI: Basal ganglia. *Am J Psychiatry* 158:185
- Van Putten T, May PRA, Marder R, Wittmann LA (1981): Subjective response to antipsychotic drugs. *Archives of General Psychiatry* 38:187–190
- Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzmann R, Shea CE (1997): Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386:827–830
- Voruganti L, Heslegrave R, Awad AG (1997): Neuroleptic dysphoria may be the missing link between substance abuse and schizophrenia. *Journal of Nervous & Mental Disease* 185:463–465
- Voruganti L, Cortese L, Ouyewumi L, Cernovsky Z, Zirul S, Awad AG (2000): Comparative evaluation of conventional and new antipsychotic drugs with reference to their subjective tolerability, side effect profile and impact on quality of life. *Schizophrenia Research* 43:135–145
- Weiden P, Mann JJ, Dixon L, Haas G, DeChillo N, Frances A (1989): Is neuroleptic dysphoria a healthy response? *Comprehensive Psychiatry* 30:543–552
- Wise RA (1988): The neurobiology of craving: implications for the understanding and treatment of addiction. *Journal of Abnormal Psychology* 97(2):118–132
- Wise RA (1996): Addictive drugs and brain stimulation reward. *Annu Rev Neurosci* 19:319–40
- Wong DF, Broussolle EP, Wand G, Villemagne V, Dannals RF, Links JM, Zacur HA, Harris J, Naidu S, Braestrup C, Wagner HN Jr, Gjedde A (1988): *In vivo* measurement of dopamine receptors in human brain by positron emission tomography: age and sex differences. *Ann NY Acad Sci* 515:203–214
- Zakzanis KK, Hansen KT (1998): Dopamine D₂ densities and the schizophrenic brains. *Schizophrenia Research* 32: 201–206