Neuropsychopharmacology (2005) 30, 2283–2289

www.neuropsychopharmacology.org

Occupancy of Striatal and Extrastriatal Dopamine D_2/D_3 Receptors by Olanzapine and Haloperidol

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There have been conflicting reports as to whether olanzapine produces lower occupancy of striatal dopamine D_2/D_3 receptor than typical antipsychotic drugs and preferential occupancy of extrastriatal dopamine D_2/D_3 receptors. We performed [^{18}F] fallypride PET studies in six schizophrenic subjects treated with olanzapine and six schizophrenic subjects treated with haloperidol to examine the occupancy of striatal and extrastriatal dopamine receptors by these antipsychotic drugs. [^{18}F] setoperone PET studies were performed in seven olanzapine-treated subjects to determine 5-HT_{2A} receptor occupancy. Occupancy of dopamine D_2/D_3 receptors by olanzapine was not significantly different from that seen with haloperidol in the putamen, ventral striatum, medial thalamus, amygdala, or temporal cortex, that is, 67.5–78.2% occupancy; olanzapine produced no preferential occupancy of dopamine D_2/D_3 receptors in the ventral striatum, medial thalamus, amygdala, or temporal cortex. There was, however, significantly lower occupancy of substantia nigra/VTA dopamine D_2/D_3 receptors in olanzapine-treated compared to haloperidol-treated subjects, that is, 40.2 *vs* 59.3% ($p = 0.0014$, corrected for multiple comparisons); in olanzapine-treated subjects, the substantia nigra/VTA was the only region with significantly lower dopamine D_2/D_3 receptor occupancy than the putamen, that is, 40.2 *vs* 69.2% ($p < 0.001$, corrected for multiple comparison). Occupancy of 5-HT_{2A} receptors was 85–93% in the olanzapine- treated subjects. The results of this study demonstrated that olanzapine does not produce preferential occupancy of extrastriatal dopamine D_2/D_3 receptors but does spare substantia nigra/VTA receptors. Sparing of substantia nigra/VTA dopamine D_2/D_3 receptor occupancy may contribute to the low incidence of extrapyramidal side effects in olanzapine-treated patients.

Neuropsychopharmacology (2005) **30,** 2283–2289. doi:10.1038/sj.npp.1300836; published online 3 August 2005

Keywords: dopamine D_2/D_3 receptor; olanzapine; haloperidol; atypical antipsychotic drug; substantia nigra; PET

INTRODUCTION

Olanzapine is an atypical antipsychotic drug (APD), that is, therapeutically efficacious with a significantly lower incidence of extrapyramidal side effects (EPS) than typical APDs such as haloperidol at clinically effective doses (Beasley *et al*, 1996). Olanzapine is chemically closely related to clozapine (Bymaster *et al*, 1996; Schotte *et al*, 1996). A number of animal studies have suggested that the atypical antipsychotic profiles of olanzapine and clozapine are related to their selective effects on cortical and limbic regions and lesser effects on the dorsolateral striatum. Both clozapine and olanzapine produce c-fos induction in the medial prefrontal cortex, which is not seen with haloperidol, and greater induction of c-fos in the nucleus accumbens and lateral septal nucleus than in dorsolateral striatum, whereas haloperidol produces similar levels in the dorsolateral striatum and nucleus accumbens (Robertson and Fibiger, 1992; Robertson *et al*, 1994; Robertson and Fibiger, 1996). Chronic administration of both clozapine and olanzapine produce greater upregulation of the medial frontal cortical than dorsolateral striatal DA D_2/D_3 receptors (Janowsky *et al*, 1992; Tarazi *et al*, 2001). Consistent with the above hypothesis, [^{123}I] epidepride SPECT (Bigliani *et al*, 2000) and [^{76}Br] FLB457 PET (Xiberas *et al*, 2000) studies have reported preferential occupancy of temporal cortical DA D_2/D_3 receptors by olanzapine. This was not confirmed by a recent PET study using [^{11}C] raclopride and [^{11}C] FLB457, which failed to find preferential occupancy of extrastriatal DA D_2/D_3 receptors by olanzapine (Tauscher *et al*, 2002). In addition, some PET (Kapur *et al*, 1998;

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Received 8 November 2004; revised 25 March 2005; accepted 9 June 2005
Online publication: 21 June 2005 at http://www.acnp.org/citations/Npp06210505001l/default.pdf

Nordstrom *et al*, 1998) and SPECT (Raedler *et al*, 1999; Tauscher *et al*, 1999) studies have reported that therapeutic doses of olanzapine occupy levels of striatal DA D_2/D_3 receptors similar to that seen with typical APDs, that is, 65–75%, while other PET (Xiberas *et al*, 2000) and SPECT (Bigliani *et al*, 2000; Pilowsky *et al*, 1996) studies report that therapeutic doses of olanzapine occupy less than 50% of striatal DA D_2/D_3 receptors. Given these discordant results, we undertook a study of the occupancy of striatal and extrastriatal DA D_2/D_3 receptors in olanzapine and haloperidol-treated schizophrenic subjects using [^{18}F] fallypride PET studies (Kessler *et al*, 2000; Mukherjee *et al*, 2002). As atypical APDs have been distinguished from typical APDs by a high 5-HT_{2A}/DA D_2/D_3 receptor affinity ratio (Meltzer *et al*, 1989, 2003) and olanzapine has a high 5-HT_{2A}/DA D_2/D_3 affinity ratio (Bymaster *et al*, 1996; Schotte *et al*, 1996), we also performed [^{18}F] setoperone (Trichard *et al*, 1998; Kessler *et al*, 2002) PET studies of cortical 5-HT_{2A} receptor occupancy by olanzapine. Preliminary results from this study have been previously presented (Kessler *et al*, 2002).

METHODS

This study was conducted with the approval of the Vanderbilt University School of Medicine Intramural Research Board. All subjects were evaluated to assure that subjects met DSM IV criteria for schizophrenia, had a medical history, and a physical examination was performed. A CBC with differential, plasma electrolytes, BUN, Cr, plasma glucose, cholesterol, triglycerides, total protein, bilirubin, urine analysis, and urinary drug screen were obtained. Subjects were free of current substance dependence—other than tobacco and caffeine, major medical illness, history of major trauma, or other psychiatric or neurological disorders.

PET [^{18}F] fallypride studies were performed in six subjects receiving olanzapine monotherapy (5 M, 1 F, mean age = 29.8 years, age range of 20–45 years) and six subjects receiving haloperidol monotherapy (4 M, 2 F, mean age of 34.3 years, age range of 21–45 years). Four of the six olanzapine-treated subjects were studied off-medication and following 3–6 weeks of olanzapine therapy (doses of 10 mg, $N=1$; or 20 mg, $N=3$). Regional receptor occupancies for these subjects were computed using their individual regional off-medication values. Two of the olanzapine-treated subjects were studied only while on medication (doses of 15 mg). Haloperidol-treated subjects received either depot haloperidol every 4 weeks ($N=4$; doses of 75 mg, $N=1$; 100 mg, $N=1$; or 150 mg, $N=2$), oral haloperidol ($N=1$, daily dose of 10 mg), or a combination of depot and oral haloperidol ($N=1$, 50 mg depot and alternating oral daily doses of 2 and 5 mg). Subjects receiving depot haloperidol were studied 3.5 weeks following their last dose. For the subjects studied only on medication, regional receptor occupancies were calculated using mean regional values of 10 off-medication schizophrenic subjects (5 M, 5 F, mean age of 33.0 years, age range of 20–45 years). Off-medication subjects were either previously unmedicated ($N=4$) or self-withdrawn from all medications for at least 3 weeks. Off-medication subjects received no medications during their off-medication period except for one subject who received 1 mg lorazepam p.o. during the later portion of the PET study.

PET [^{18}F] setoperone studies (Petit-Taboue *et al*, 1996) were performed in seven olanzapine-treated schizophrenic subjects (7 M, mean age of 33.1, age range 19–47 years); all subjects were studied off medication initially and following 3–6 weeks of olanzapine therapy (doses of 5 mg, $N=2$; 10 mg, $N=3$; 20 mg, $N=2$).

For studies of dopamine D_2/D_3 receptor occupancy, PET [^{18}F] fallypride scans were performed using a GE Advance PET Scanner (resolution of 5–6 mm) in the 3D mode. [^{18}F] fallypride (3.8–5.2 mCi, specific activity $\geqslant$3500 Ci/mmol) was administered as a slow bolus over a 20 s period and serial PET scans of the brain were obtained over a period of from 180 to 250 min as previous modeling studies have shown demonstrated stable fits using the reference region method (Lammertsma *et al*, 1996) in all brain regions from 180 min onward (Kessler *et al*, 2000). MRI scans of the brain were performed using a GE Signa LXi echospeed 1.5 T MRI scanner using sagittal and coronal T1-weighted thin section gradient echo acquisitions (IR SPGR, TE = 3.6, TR = 19, TR = 400, slice thickness of 1.2–1.5 mm), an axial spin density weighted FSE acquisition ($T=19$, TR = 5000, slice thickness of 3 mm), and an axial T2-weighted FSE acquisition (TE = 10.6, TR = 5000, slice thickness of 3 mm). PET scans were coregistered to each other and to the MRI scans using a mutual information rigid body algorithm (Maes *et al*, 1997; Wells *et al*, 1996) Regions of interest, that is, the putamen, caudate, ventral striatum, medial thalamus, amygdala, temporal cortex, and ventral midbrain/region of substantia nigra, were manually drawn by a neuroradiologist experienced in PET data analysis (RMK) on the MRI studies and transferred to the corresponding PET images. The ventral striatum was delineated using the criteria of Mawlawi *et al* (2001). Regional binding potentials were estimated using the reference region method (Lammertsma *et al*, 1996).

For studies of 5-HT_{2A} receptor occupancy, PET [^{18}F] setoperone (Kapur *et al*, 1997; Petit-Taboue *et al*, 1996) studies were performed using an ECAT 933/08/16 PET scanner following the injection of 2.6–7.55 mCi (specific activity greater than 2000 Ci/mmol) of [^{18}F] setoperone. Serial PET scans were obtained for up to 70 min following injection. Cortical regions of interest were manually delineated for planes above the level of the lateral ventricles, corresponding to levels 28–40 mm above the ACPC line in the Talairach atlas (Talairach and Tournoux, 1988). Binding potentials were calculated using the reference region method (Lammertsma *et al*, 1996; Bonab *et al*, 1998). Cortical 5-HT_{2A} receptor occupancies were calculated for each subject using their individual off-medication binding potential.

Regional 5-HT_{2A} or D_2/D_3 receptor occupancies were calculated using the following formula:

$$\textit{Percent occupancy in region } i = 1 - \left[\frac{Ri\,(medicated)}{Ri\,(off-medication)}\right] \times 100$$

where *Ri* refers to the binding potential in region '*i*' in the indicated state.

The differences in DA D_2/D_3 receptor occupancy in brain regions during treatment with olanzapine or haloperidol were evaluated using analysis of variance with drug and region as factors.

RESULTS

Regional occupancies of DA D_2/D_3 receptors for haloperidol and olanzapine are shown in Table 1 and Figure 1. Representative time–activity curves for an olanzapine-treated subject studied off-medication and following olanzapine therapy (20 mg/day) are shown in Figure 2. Analysis of variance for regional dopamine DA D_2/D_3 receptor occupancies with region and drug as factors, corrected for multiple comparisons, demonstrates no significant differences between the olanzapine- and haloperidol-treated subjects in the putamen, ventral striatum, medial thalamus, amygdala, or temporal cortex. For olanzapine-treated subjects, comparison of occupancies in the putamen, ventral striatum, medial thalamus, amygdala, and temporal cortex demonstrated no significant differences in indicating that olanzapine did not produce preferential occupancy in extrastriatal regions at clinically therapeutic doses, that is, 10–20 mg. Similarly for haloperidol-treated subjects, no preferential occupancy of the ventral striatal, thalamic, amygdalar, or temporal cortical receptors was observed. The occupancy in the substantia

Table 1 Occupancy of Striatal and Extrastriatal DA D_2/D_3 Receptors Haloperidol and Olanzapine

	Percent occupancy	
Region	**Haloperidol ($n=6$)**	**Olanzapine ($n=6$)**
Putamen	76.5±8.2	69.2±10.2
Ventral striatum	75.5±8.2	70.9±6.9
Medial thalamus	78.2±6.2	71.0±9.0
Amygdala	75.6±8.1	72.4±6.7
Temporal cortex	70.9±5.5	67.5±7.1
Substantia nigra/VTA	59.3±9.2	40.2±12.2*

*Significantly different from regional occupancy for haloperidol, $p=0.0014$ corrected for multiple comparisons using ANOVA with drug and region as factors.

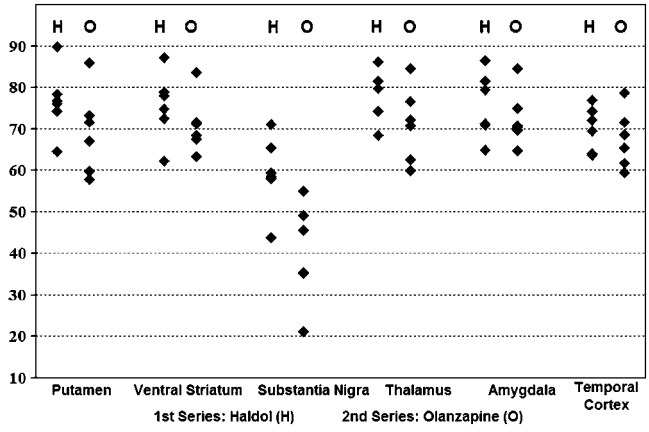

Figure 1 Plots of regional DA D2/D3 receptor occupancy for haloperidol (left hand column) and olanzapine (right hand column)-treated subjects in the putamen, ventral striatum, substantia nigra, medial thalamus, amygdala, and temporal cortex.

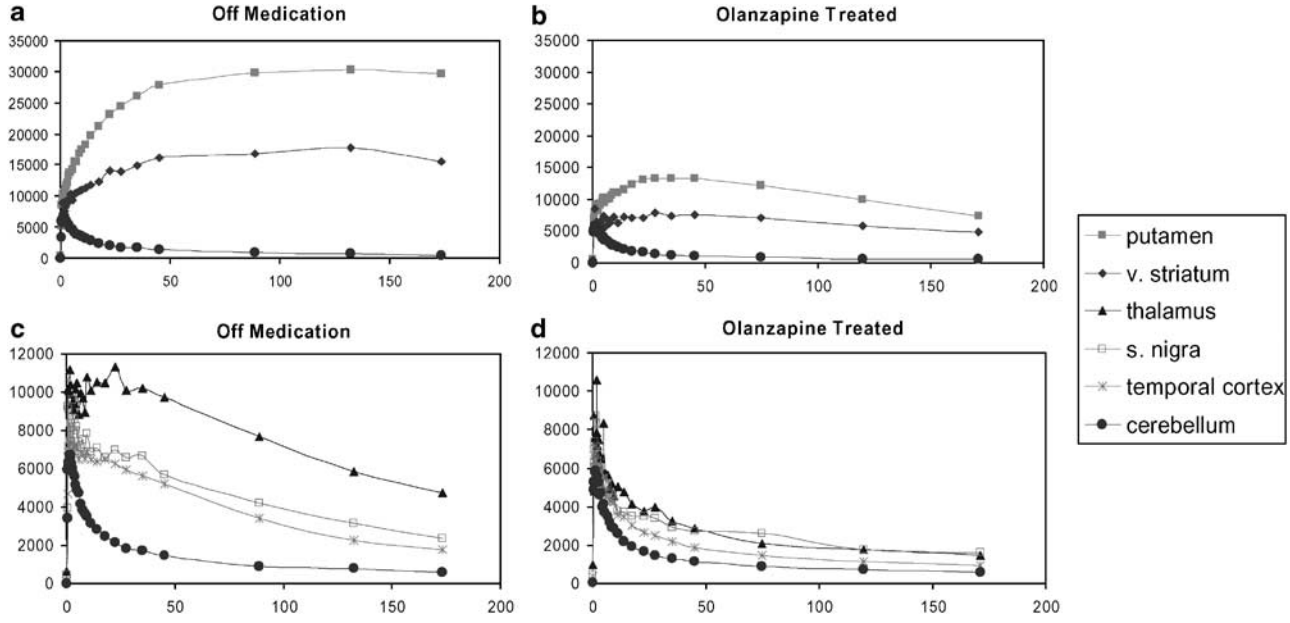

Figure 2 Time–activity curves of regional [^{18}F] fallypride uptake in a schizophrenic subject studied off-medication, that is, never medicated, and following 6 weeks of olanzapine therapy (20 mg/day). (a) and (b) show the putamenal, ventral striatal, and cerebellar time–activity curves prior to and following olanzapine treatment. (c) and (d) show time–activity curves for the thalamus, substantia nigra, temporal cortex, and cerebellum prior to and following olanzapine therapy. The time–activity curve of the substantia nigra shows a lesser decrement in uptake after olanzapine treatment than other extrastriatal regions.

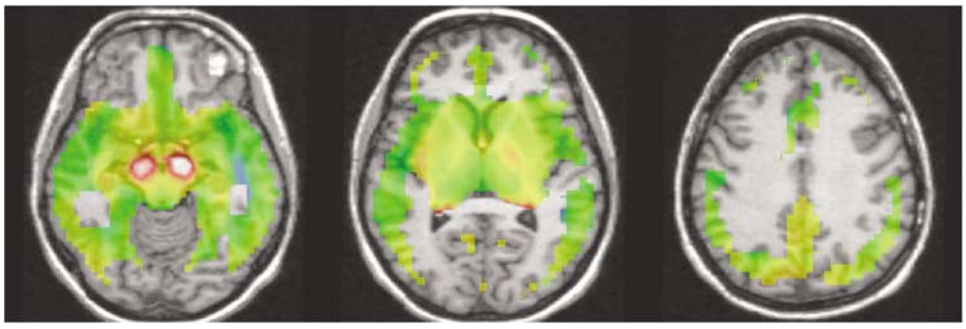

Figure 3 Summed parametric images of dopamine D_2/D_3 receptor occupancy for olanzapine-treated subjects studied off-medication and after 3–6 weeks of olanzapine therapy ($N = 4$) which demonstrate different, that is, lower occupancy—40%, in the substantia nigra/VTA in comparison to the putamen and other brain regions—about 70%. The color scale has been adjusted to show lower occupancies in white and red while higher occupancies are shown in yellow and green.

nigra/VTA for olanzapine-treated subjects was significantly lower than in all other brain regions sampled for both olanzapine ($p < 0.001$ corrected for multiple comparisons) and for haloperidol treated subjects ($p \geqslant 0.0014$, corrected for multiple comparisons) including the substantia nigra/VTA in haloperidol-treated subjects (see Table 1 and Figure 1). Only one haloperidol-treated subject had a DA D_2/D_3 receptor occupancy in the substantia nigra, which fell in the range seen in olanzapine-treated subjects. In contrast, the olanzapine subjects with the highest putamenal occupancy, 86%, had a nigral/VTA occupancy of 55%, lower than all but one haloperidol-treated subject. Olanzapine appears to spare DA D_2/D_3 receptor occupancy in the substantia nigra (see Figure 3).

[^{18}F] setoperone PET studies of cortical 5-HT_{2A} occupancy indicate very high levels of cortical 5-HT_{2A} receptor occupancy at all doses studied, that is, a 5 mg dose of olanzapine produced a mean occupancy of 85%, a 10 mg dose 88%, and a 20 mg dose 93%.

DISCUSSION

The main findings of this study are: (1) similar levels of occupancy of DA D_2/D_3 receptors in the putamen, ventral striatum, medial thalamus, amygdala, and temporal cortex with therapeutic doses of haloperidol and olanzapine in patients with schizophrenia; (2) significantly lower levels of DA D_2/D_3 receptor occupancy in the ventral midbrain/substantia nigra in olanzapine than haloperidol-treated subjects; and (3) over 80% occupancy of 5-HT_{2A} receptors in the cortex with olanzapine at doses from 5 to 20 mg/day.

This study is consistent with a number of previous [^{11}C] raclopride PET and [^{123}I] IBZM SPECT studies in showing similar levels of striatal DA D_2/D_3 receptor occupancy by haloperidol and olanzapine at typical therapeutic doses, that is, 68–84% at doses of 10–20 mg of olanzapine (Kapur *et al*, 1998; Nordstrom *et al*, 1998; Raedler *et al*, 1999; Tauscher *et al*, 1999). Tauscher *et al* (2002) using [^{11}C] FLB457 has recently reported similar levels of DA D_2/D_3 receptor occupancy in the thalamus and striatum in normal subjects receiving a single 15 mg dose of olanzapine, that is, peak occupancies of 70 and 81% occupancies, respectively. In contrast, both Bigliani *et al* (2000) and Xiberas *et al* (2000) have reported preferential occupancy of thalamic and temporal cortical receptors by olanzapine using [^{123}I] epidepride SPECT and [^{76}Br] FLB457 PET studies. For doses of 10–20 mg the mean DA D_2/D_3 receptor occupancies reported in these studies were 41.3% (Bigliani *et al*, 2000) and 44.0% (Xiberas *et al*, 2000) in the striatum, 66.4% (Xiberas *et al*, 2000) in the thalamus, and 82.8% (Bigliani *et al*, 2000) and 81.4% (Xiberas *et al*, 2000) in the temporal cortex. The results in the present study are consistent with those of Tauscher *et al* (2002), who calculated regional receptor levels in the thalamus using the simplified reference region method (Gunn *et al*, 1997). Both Bigliani *et al* (2000) and Xiberas *et al* (2000) utilized ratio methods to estimate available regional DA D_2/D_3 receptor levels. The lower striatal DA D_2/D_3 receptor occupancy reported by Bigliani and Xiberas for olanzapine compared to [^{11}C] raclopride studies (Kapur *et al*, 1998; Nordstrom *et al*, 1998) and the current study suggests that these ratios were calculated at a time prior to the attainment of a transient equilibrium in the striatum, resulting in an underestimation of striatal DA D_2/D_3 receptor occupancy (Olsson and Farde, 2001; Erlandsson *et al*, 2003). Previous modeling studies of [^{123}I] epidepride have produced conflicting findings regarding whether temporal cortical : cerebellar ratios obtained at 3 or 4 h, the time used in the [^{123}I] epidepride SPECT study of olanzapine (Bigliani *et al*, 2000), are significantly correlated with modeled estimates of the striatal and temporal cortical receptor density (Fujita *et al*, 1999; Erlandsson *et al*, 2003). The results of the current study do not support preferential occupancy of DA D_2/D_3 receptors in the ventral striatum, thalamus, amygdala, or temporal cortex by olanzapine. The level of DA D_2/D_3 receptor occupancies in the putamen, thalamus, amygdala, and temporal cortex were not significantly different for olanzapine- and haloperidol-treated subjects.

In olanzapine-treated subjects, only the ventral midbrain/substantia nigra demonstrated significantly different, that is, lower, DA D_2/D_3 receptor occupancy than that seen in haloperidol-treated subjects. Some of the difference between DA D_2/D_3 receptor occupancy in the ventral midbrain/substantia nigra and other brain regions may be due to the small size of this brain region, with a loss of quantitation due to the limited resolution of the scanner utilized (5–6 mm) and a resulting lowering of apparent occupancy

(Kessler *et al*, 1984). While a partial volume correction would be desirable for the substantia nigra, its exact borders are difficult to trace on high-resolution T1-weighted scans, making definition of a partial volume correction difficult. Partial voluming would affect ventral midbrain/substantia nigra occupancies in haloperidol and olanzapine-treated subjects in an identical fashion. The results of this study suggest that olanzapine produces lower occupancy of ventral midbrain/substantia nigra DA D_2/D_3 receptors than is seen with haloperidol.

There are a number of observations that suggest that DA D_2/D_3 receptor-mediated neurotransmission within the substantia nigra and/or VTA may be involved in mediating the atypical profile of olanzapine. These include the ability of olanzapine (Stockton and Rasmussen, 1996), like clozapine (Chiodo and Bunney, 1983), but unlike haloperidol (Chiodo and Bunney, 1983), to produce a selective depolarization of DA neurons in the VTA, but not in the substantia nigra, and the role of dopaminergic neurotransmission in the substantia nigra in motor behaviors (Gerhardt *et al*, 1999, 2002; Robertson and Robertson, 1989). Studies in animals have demonstrated that a number of motor behaviors require normal nigral as well as normal striatal dopaminergic function. Motor dysfunction in middle-aged and elderly monkeys compared to young monkeys was most closely correlated with declines in DA release in the substantia nigra as opposed to putamen (Gerhardt *et al*, 2002). In unilaterally MPTP-lesioned rhesus monkeys, a single intraventricular injection of GDNF produced improvement in motor function, which was correlated with DOPAC and HVA levels in the lesioned nigra but not in the striatum (Gerhardt *et al*, 1999). In unilaterally 6-OH-dopamine-lesioned rats, l-DOPA-induced rotational behavior was temporally correlated to the duration of increased DA levels in the substantia nigra rather than the striatum (Robertson and Robertson, 1989). In rats, neuroleptic-induced increases in hind limb muscle tone, a measure of rigidity, requires blockade of nigral DA D_2/D_3 receptors (Double and Crocker, 1995). It has been suggested that EPS requires blockade of both striatal and nigral DA D_2/D_3 receptors (Crocker and Hemsley, 2001; Hemsley and Crocker, 1999). It is of interest that amisulpride, a substituted benzamide-type atypical APD produced a wide range of occupancies of caudate and putamenal D_2/D_3 receptors including occupancy levels greater than 80% in 2/9 schizophrenia subjects (Vernaleken *et al*, 2004). No linear relationship could be found between D_2/D_3 receptor occupancy and EPS, suggesting that factors other than striatal D_2 occupancy are important with regard to EPS. The lower incidence of motor side effects seen with olanzapine may relate to the sparing of ventral midbrain/nigral DA D_2/D_3 receptor occupancy, which may confer a conditional freedom from EPS. In order for EPS to occur, higher levels of striatal DA D_2/D_3 receptor occupancy may be needed with olanzapine compared to haloperidol. If sparing of DA D_2/D_3 receptor occupancy occurs in the VTA as well as in the substantia nigra, this may have significant effect on cortical DA release, which may be important to the improvement in cognition produced by olanzapine and other related atypical APDs (Meltzer and McGurk, 1999).

The current study utilized off-medication schizophrenic subjects to compute occupancies for subjects studied only on medication. A potential confound of using off-medication schizophrenic subjects is residual medication effects. While a comparison of schizophrenic and normal subjects will be published in a separate communication, it is noteworthy that putamenal binding potentials were nearly identical for off-medication schizophrenic subjects and normal controls, that is, 36.08 ± 4.53 for the 10 schizophrenic subjects and 37.34 ± 2.53 for the 10 matched normal control subjects, indicating no residual medication effects. Unlike the striatum where most studies indicate no changes in DA D_2/D_3 receptor levels in schizophrenics, there are now studies indicating lower levels of DA D_2/D_3 levels in the thalamus (Talvik *et al*, 2003; Yasuno *et al*, 2004) and temporal cortex (Tuppurainen *et al*, 2003; Buchsbaum *et al*, 2004). Using normal subjects may not be appropriate in studies of DA D_2/D_3 occupancy in these regions. The use of the reference tissue method with [^{18}F] fallypride may be criticized due to the presence of low levels of DA D_2/D_3 receptors in the cerebellum. Comparison of regional binding potentials calculated using Logan plots with a metabolite corrected plasma input function with those calculated using the reference region method demonstrated a correlation coefficient greater than 0.99 with a slope of 1.0 (Kessler *et al*, 2000). To examine the fraction of cerebellar uptake due to binding to DA D_2/D_3 receptors, ratios of the uptake in the cerebellar reference region to white matter were calculated for the four subjects studied off-medication and following olanzapine therapy; post-mortem studies have shown no specific binding in white matter (unpublished data, R.M. Kessler). Ratios at 90 min after injection were 1.128 ± 0.046 in the off-medication state and 1.103 ± 0.042 in the medicated state. These observations indicate that for [^{18}F] fallypride, the reference region method is an appropriate method for estimating regional DA D_2/D_3 receptor levels.

The high occupancy of 5-HT_{2A} receptors seen in this study, 88% or greater at therapeutic doses, 10 or 20 mg of olanzapine, is consistent with the results from previous studies (Kapur *et al*, 1998, 1999). Our results suggest that this occupancy is dose-dependent but more subjects need to be studied to establish this. A number of findings support the role of 5-HT_{2A} receptor blockade in producing an atypical APD profile. These include the ability of 5-HT_{2A} receptor blockade to decrease the effect of haloperidol to increase DA efflux in the ventral striatum (Liegeois *et al*, 2002), to reverse haloperidol induced catalepsy in animals (Lucas *et al*, 1997), to decrease the incidence of EPS effects in subjects receiving typical APDs (Bersani *et al*, 1990), and studies of binding profiles of APDs demonstrating that a high ratio of 5-HT_{2A}/D_2 affinities distinguishes atypical from typical APDs (Meltzer *et al*, 1989; Roth *et al*, 1995). 5-HT_{2A} receptor antagonists can ameliorate haloperidol induced catalepsy even without affecting striatal DA release (Lucas *et al*, 1997) and modulate nigral dopaminergic neurotransmission (Sorenson *et al*, 1993; Bruggeman *et al*, 2000; Timmerman *et al*, 1999; Andersson *et al*, 1995). This modulation of nigral dopaminergic function may be a factor in producing an atypical profile.

In conclusion, the principal findings in this study are the lack of preferential occupancy of cortical and other extrastriatal regions by olanzapine and the relative sparing of ventral midbrain/substantia nigra DA D_2/D_3 receptor

occupancy in olanzapine-treated subjects, and the high $5HT_{2A}$ receptor blockade seen with therapeutic doses of olanzapine. The lower incidence of EPS seen with olanzapine may be related to sparing of ventral midbrain/substantia nigra DA D_2/D_3 receptor occupancy. Further studies are needed to confirm these conclusions and to elucidate the role of the substantia nigra and VTA and $5\text{-}HT_{2A}$ receptor blockade in mediating an atypical antipsychotic profile.

ACKNOWLEDGEMENTS

This work was supported by Eli Lilly, Indianapolis, a grant—NIMH R01MH660890, The William T Warren Foundation, The Ritter Foundation, and a gift of Mr Donald Test.

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