Extrastriatal and striatal D_2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia*

X. XIBERAS, J. L. MARTINOT, L. MALLET, E. ARTIGES, C. LOC'H, B. MAZIÈRE and M. L. PAILLÈRE-MARTINOT

Background Both traditional and atypical antipsychotics have been hypothesised to be effective in schizophrenia through limbic and cortical D_2 dopamine receptor blockade.

Aims To investigate this hypothesis with the D_2/D_3-selective positron emission tomography (PET) probe [^{76}Br]-FLB457.

Method PET scans were performed on 6 controls and 18 patients with schizophrenia treated with haloperidol or with risperidone, clozapine, amisulpride or olanzapine.

Results The D_2 dopamine receptor blockade was high in the temporal cortex with both haloperidol and atypical antipsychotics. The atypicals, however, induced a significantly lower D_2 binding index than haloperidol in the thalamus and in the striatum.

Conclusions Results suggest that cortical D_2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D_2 receptors in the cortex than in the basal ganglia is suggested as an indicator of favourable profile for a putative antipsychotic compound.

Declaration of interest The Fondation pour la Recherche Médicale and the Fondation Lilly France supported X.X. in part during the study.

Dopamine D_2 receptor blockade is thought to mediate antipsychotic action. *In vivo* studies in medicated patients have shown that treatments with traditional antipsychotic compounds such as haloperidol consistently induce 70–80% occupancy of the striatal D_2 receptors (Martinot *et al*, 1990; Nordström *et al*, 1993). Furthermore, high levels of D_2 receptor occupancy in the striatum are associated with higher risk of extrapyramidal side-effects (Farde *et al*, 1992). At variance with traditional compounds, atypical antipsychotics such as clozapine have a low tendency to induce extrapyramidal side-effects (Moller, 2000). This may be consistent with the lower *in vivo* D_2 striatal blockade reported with the usual doses of clozapine (Farde *et al*, 1992). Whereas the nigro-striatal dopaminergic pathways appear to be involved in extrapyramidal side-effects, models of the antipsychotic mechanism of action involve extrastriatal cerebral structures such as the meso-cortico-limbic pathways (Moore *et al*, 1999). Therefore, the D_2 receptor blockade by antipsychotic drugs in extrastriatal structures may be one of the mechanisms that account for the antipsychotic effect, as suggested by earlier single photon emission tomography studies (Bigliani *et al*, 2000; Stephenson *et al*, 2000). This hypothesis requires substantiation with the more sensitive and quantitative positron emission tomography (PET) technique. However, in the extrastriatal structures such as thalamus, limbic and temporal cortices, the D_2 dopamine receptor density is 5- to 25-fold lower than in the striatal structures, where they exist in nanomolar concentrations (Kessler *et al*, 1993). The development of [^{76}Br]-FLB457, a bromine-labelled benzamide radioligand for PET with picomolar affinity and a high selectivity for D_2 and D_3 receptors (dissociation constant $K_{i(D_2)}=0.018$ nM) (Loc'h *et al*, 1996), has made possible the comparison of the binding of various antipsychotic compounds to extrastriatal and striatal structures. In order to compare four atypical antipsychotics with a traditional molecule at the recommended dose ranges for therapeutic antipsychotic effect, we studied the binding of the reference compound haloperidol ($K_{i(D_2)}=1$ nM) and that of four atypical antipsychotics – risperidone ($K_{i(D_2)}=3$ nM), clozapine ($K_{i(D_2)}=125$ nM), amisulpride ($K_{i(D_2)}=3.4$ nM and $K_{i(D_2)}=3.5$ nM) and olanzapine ($K_{i(D_2)}=11$ nM) (Chivers *et al*, 1988) – in patients with schizophrenia treated with these compounds.

METHOD

Subjects

Nineteen patients with DSM–IV (American Psychiatric Association, 1994) schizophrenia (16 males, 3 females, mean age=32 years, s.d.=7) treated with haloperidol (n=4), risperidone (n=3), clozapine (n=3), amisulpride (n=5) or olanzapine (n=4) were included (Table 1). They were treated with daily dosages matching the recommended ranges for antipsychotic effect. For haloperidol this range was 3–20 mg/day (Editions du Vidal, 1993; Zimbroff *et al*, 1997); for risperidone, 6–12 mg/day (Kasper, 1998; Nyberg *et al*, 1999); for clozapine, 200–400 mg/day (Fitton & Heel, 1990); for amisulpride, 200–1200 mg/day (Coukell *et al*, 1996); and for olanzapine, 5–20 mg/day (Kasper, 1998). Patients were scanned 18–20 h after the last evening dose of the antipsychotic, in order to avoid the peak plasma concentration following the drug dose intake. All patients were medicated for at least 15 days, which is much longer than the five half-lives necessary to reach the steady state for plasma antipsychotic concentration. Exclusion criteria included neurological or other medical conditions and substance misuse. Anticholinergic drugs or benzodiazepines that do not interfere with D_2 dopamine receptors (Burt *et al*, 1976; Boyson *et al*, 1988) were not withdrawn. The patient groups were compared with a group of six normal control men (mean age=24 years, s.d.=4) who underwent a medical examination and a psychiatric interview in order to rule out any medical condition. The Henri Mondor ethics committee approved the protocol. After a complete description of the study to the subjects, written informed consent was obtained.

Brain imaging

Brain imaging, image analysis and determination of the D_2 dopamine blockade by

503

Table I Characteristics of the patients

Subject code	Age (years)	Gender	Positive symptom score[1]	Negative symptom score[1]	Drug	Oral drug dose (mg/day)	Plasma drug concentration (µg/l)	Binding index (%)		
								Striatum	Thalamus	Temporal cortex
H1	34	F	16	29	Haloperidol	3	6	66.6	91.2	88.3
H2	22	M	14	19	Haloperidol	8	8.3	80.6	94.9	91.8
H3	42	M	23	24	Haloperidol	15	22	84.7	96.3	89
H4	29	F	15	21	Haloperidol	60	52	94.3	94.3	97.5
R1	41	M	21	15	Risperidone	6	41	67	92.2	92.2
R2	32	M	17	25	Risperidone	8	43	57	86.1	94.6
R3	30	M	23	22	Risperidone	12	59	65.8	91.2	88.1
C1	40	M	24	28	Clozapine	200	114	34.8	58.3	71.7
C2	32	M	20	23	Clozapine	400	262	17.8	51.8	71.6
C3	37	F	10	13	Clozapine	200	434	45.9	79	90.1
A1		M	7	32	Amisulpride	200	153.88	43.6	73.6	93.5
A2	29	M	19	20	Amisulpride	400	91.1	16.1	50.7	53
A3	23	M	18	22	Amisulpride	600	298.6	43.6	82.6	82.5
A4	21	M	19	25	Amisulpride	1200	342.7	43.4	89.8	87.5
A5	26	M	12	24	Amisulpride	1000	390.8	61.5	69.9	87.8
O1	38	M	17	35	Olanzapine	5	ND	48.5	58.5	90
O2	40	M	24	28	Olanzapine	10	ND	18.7	43	83.7
O3	21	M	17	30	Olanzapine	10	ND	43.7	64.3	68.7
O4	25	M	16	23	Olanzapine	20	ND	69.6	91.9	91.8

ND, not determined.
1. Positive and Negative Syndrome Scale (PANSS): each score represents the sum of seven items; a score of 7 means an absence of symptoms; the maximum score is 49.

the computation of a binding index were performed according to a methodology described previously (Xiberas *et al*, 2001). Briefly, for each subject a 1.5 T Signa Imager (General Electric, Milwaukee, WI) provided 128 anatomical slices parallel to the orbito-meatal line. Afterwards, 63 cerebral slices parallel to the orbito-meatal line were acquired with a Siemens HR+ positron tomograph (of spatial resolution 2.5 mm; Knoxville, TX). Just before injecting the [76Br]-FLB457, venous blood was sampled for plasma concentration of the antipsychotic drug. Approximately 1 mCi of [76Br]-FLB457 was injected into each subject (mean (s.d.)=0.98 (0.20) mCi for healthy subjects and 1.03 (0.23) mCi for patients, Mann–Whitney $U=53.5$, $P=0.82$), with a high specific activity of $264\pm164\,\mu$Ci/nmol for healthy subjects and $481\pm299\,\mu$Ci/nmol for patients (Mann–Whitney $U=29$, $P=0.08$). Afterwards, a first image series was acquired: two 5-min images, two 10-min images and

two 15-min images. Then the subjects were removed from the tomograph for 60 min and afterwards placed in the same position using a thermoplastic-modelled mask as well as skin marks with respect to a laser beam system, in order to acquire a late image series: one 30-min and one 15-min image. Finally, a second transmission scan was performed for co-registration purposes.

Image analysis

For each subject, the first PET image series was co-registered on the magnetic resonance image (MRI) using the first transmission scan (Mangin *et al*, 1994). Because the radioactivity concentrated mainly in the striatum in the late image series, the cortical structures could not be used for registration. Therefore, the second transmission scan was used for PET to MRI co-registration. Regions of interest (ROIs) were drawn on the co-registered MRI slices, following the visible borders of the structures in each hemisphere. Caudate

and putamen were defined on five slices, thalamus on four slices and temporal cortices on four slices below the lowest striatum slice; finally, ROIs were defined in the cerebellar grey matter on four slices.

Regional radioactivity concentrations for each region (injected dose- and decay-corrected) were computed by pooling the corresponding ROI values and by summing the left and right regional values.

Determination of D$_2$ dopamine receptor blockade: binding index computation

Regional radioactivity was measured for each sequential scan and plotted against time. Specific binding in the ROIs was defined as the difference between radioactivities in the ROIs and the cerebellum. The activity measured (A_m) in the ROIs represents the sum of the free (and nonspecific binding) and bound radioligand concentrations:

$$A_{\mathrm{m}}(\mathrm{ROIs}) = A_{\mathrm{sb}}(\mathrm{ROIs}) + C$$

where A_{sb} is the specifically bound radioactive concentration in the ROIs and C is the activity measured in the cerebellum, which represents (under the assumption that the concentration of D_2 dopamine receptors in the cerebellum is negligible with respect to the concentration in the other regions) both free ligand and non-specific binding. This method has been validated *in vitro* (Altar *et al*, 1985) and *in vivo* using PET with previous D_2 dopamine receptor ligands (Farde *et al*, 1985), as well as for the [⁷⁶Br]-FLB457 (Xiberas *et al*, 2001). Hence, for each patient a binding index (BI) of the antipsychotic compound was derived from the patient's measured regional radioactivity concentrations in the striatum, the extrastriatal regions (thalamus, temporal cortex) and the cerebellum at the time of 165 min, taking the measures of control subjects as a baseline:

$$\mathrm{BI}\ (\%) = 100 - 100 \left[\frac{(\mathrm{regional}\ A_{\mathrm{m}} - C)_{\mathrm{patients}}}{(\mathrm{regional}\ A_{\mathrm{m}} - C)_{\mathrm{controls}}} \right]$$

Plasma drug concentration determination

Haloperidol

After extraction from alkalinised plasma by a mixture of hexane/isoamylic alcohol, haloperidol was purified from a Kromasil C8 column ($5\,\mu\mathrm{m}$, $250 \times 4.6\,\mathrm{mm}$) using a 73/23 mixture of phosphate buffer (pH 3) and acetonitrile as mobile phase. The wavelength was set at 280 nm. The detection limit was $1.0\,\mu\mathrm{g/l}$.

Risperidone

After extraction from alkalinised plasma by a mixture of hexane/ethylacetate, the risperidone was purified from a Kromasil C8 column with the same characteristics as those described for haloperidol.

Clozapine

After extraction from alkalinised plasma by a mixture of hexane/isoamylic alcohol, the clozapine was purified from a Spherisorp C8 column ($5\,\mu\mathrm{m}$, $250 \times 4.6\,\mathrm{mm}$) using a 55/40/5 mixture of phosphate buffer (pH 3), acetonitrile and methanol as mobile phase. The wavelength was set at 230 nm. The detection limit was $2.5\,\mu\mathrm{g/l}$.

Amisulpride

After extraction from alkalinised plasma by a mixture of diethyl ether and chloroform, the amisulpride was purified from a μBondapak C18 column ($5\,\mu\mathrm{m}$, $150 \times 4.6\,\mathrm{mm}$) using a 90/10 mixture of phosphate buffer (pH 3) and acetonitrile as mobile phase. Detection was performed using a fluorimetric detector set at $\lambda_{\mathrm{ex}} = 280\,\mathrm{nm}$ and $\lambda_{\mathrm{em}} = 370\,\mathrm{nm}$. The detection limit was $0.5\,\mu\mathrm{g/l}$.

Olanzapine

Owing to technical reasons, plasma drug concentration determinations were not available.

RESULTS

Individual characteristics of patients and treatments, as well as antipsychotic plasma concentrations and binding index values, are reported in Table 1. Figure 1 shows an example of time–radioactivity curves. Paired comparisons for the binding indices in striatal and extrastriatal regions across treatment groups (Table 2) showed that the striatal and thalamic binding indices graded the haloperidol and atypical antipsychotics (Fig. 2). This was not the case in the temporal cortex.

Striatal and thalamic binding indices

Striatal and thalamic binding indices clearly distinguished haloperidol-treated from atypical antipsychotic-treated patients: indices were lower with atypical antipsychotics. In the thalamus, the D_2 binding indices induced by clozapine, amisulpride and olanzapine were lower than that induced by haloperidol. Analogous trends were detected in the thalamus and striatum of risperidone-treated patients.

Temporal binding indices

Binding indices in the temporal cortex were similarly high, whatever the antipsychotic compound.

DISCUSSION

Patients treated with the usual antipsychotic dose ranges of haloperidol, risperidone, clozapine, amisulpride and olanzapine had a similarly high D_2 dopamine receptor blockade in the temporal cortex, as estimated by the binding index of [⁷⁶Br]-FLB457. In contrast, the atypical antipsychotic drugs induced a significantly lower D_2 binding index than haloperidol in basal ganglia (i.e. in the thalamus and particularly in the striatum).
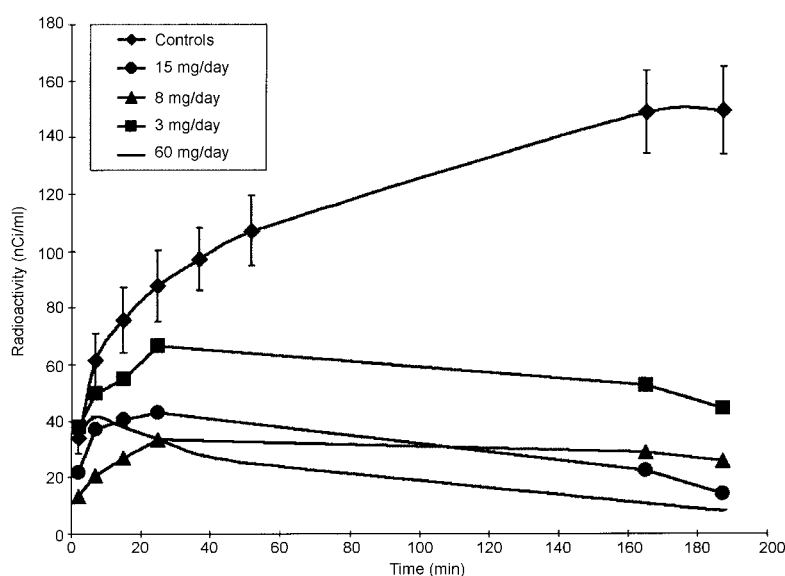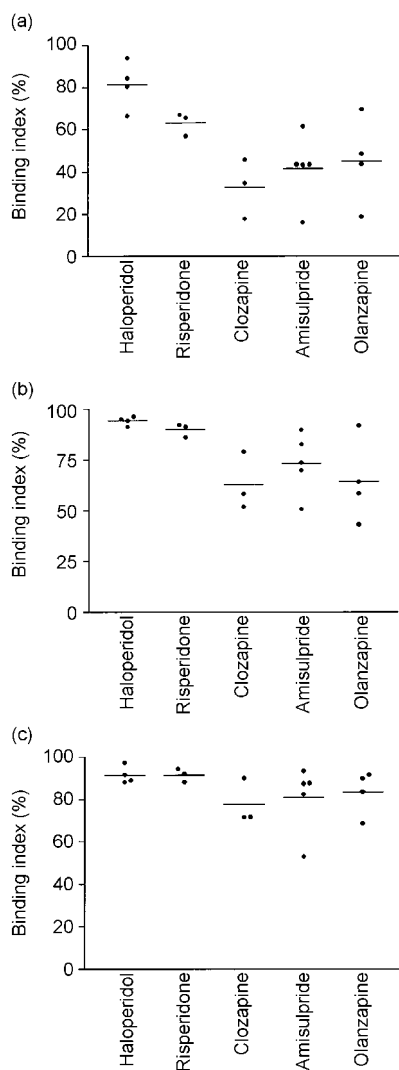

Fig. I Time–radioactivity curves in the striatum of control subject group and of patients treated with various dosages of haloperidol.

Table 2 Comparison of binding indices in striatum, thalamus and temporal cortex

	Intergroup comparisons by Kruskal–Wallis test	Paired-group comparisons (mean (s.d.)) by Mann–Whitney test			
		Haloperidol v. risperidone	Haloperidol v. clozapine	Haloperidol v. amisulpride	Haloperidol v. olanzapine
Striatum	$H=11.8$; $P=0.02$	81.5 (11.5) v. 63.3 (5.5)	81.5 (11.5) v. 32.8 (14.2)	81.5 (11.5) v. 41.6 (16.3)	81.5 (11.5) v. 45.1 (20.9)
		$U=1.0$; $P=0.11$	$U=0.0$; $P=0.05$	$U=0.0$; $P=0.01$	$U=1$; $P=0.05$
Thalamus	$H=11.3$; $P=0.02$	94.2 (2.1) v. 89.8 (3.3)	94.2 (2.1) v. 63.0 (14.2)	94.2 (2.1) v. 73.3 (14.8)	94.2 (2.1) v. 64.4 (20.4)
		$U=1.5$; $P=0.11$	$U=0.0$; $P=0.05$	$U=0.0$; $P=0.02$	$U=1$; $P=0.05$
Temporal cortex	$H=5.7$; $P=0.23$	91.7 (4.2) v. 91.6 (3.3)	91.7 (4.2) v. 77.8 (10.7)	91.7 (4.2) v. 80.9 (16.1)	91.7 (4.2) v. 83.6 (10.5)
		$U=6.0$; $P=1$	$U=2.0$; $P=0.23$	$U=3.0$; $P=0.11$	$U=4.5$; $P=0.34$

Fig. 2 Binding indices of haloperidol, risperidone, clozapine, amisulpride and olanzapine in the striatum (a), thalamus (b) and temporal cortex (c).

Methodological considerations

Long-time-frame PET imaging

For each patient, a binding index of the antipsychotic drug was derived from the patient's measured regional radioactivity concentrations in the striatum, the extra-striatal regions (thalamus, temporal cortex) and the cerebellum 165 min after injection (Fig. 1), using the measures in control subjects as a baseline. The time was chosen from modelling studies in primates, because it tallies with the duration required for the radioligand's equilibrium in the extra-striatal regions (Delforge *et al*, 1999). However, according to the same model, equilibrium is reached only at $t=300$ min after injection in striatal regions. In one control subject, we measured the concentration of the radioactivity in the striata at 165 and 315 min after injection: an increase of 10% only (139 *v*. 152 nCi/ml) was observed at 315 min. Thus, the binding in the striatum is probably slightly underestimated and values reported for striatal regions should not be considered as effective D_2 receptor occupancy figures but as approximate values. They are, nevertheless, useful to compare the striatal D_2 receptor blockade induced *in vivo* by various antipsychotic drugs.

Picomolar affinity radioligand

The picomolar affinity of [^{76}Br]-FLB457 for D_2 receptors accounts for the detection of a decrease of cerebellar radioactivity values in treated patients, which is likely to reflect some degree of occupancy of the small concentration of cerebellar D_2 receptors. This was not detected in previous studies using lower-affinity D_2 radioligands. Although the cerebellar radioactivity cannot be considered as solely reflecting non-specific binding of the [^{76}Br]-FLB457, in the conditions of the present study the use of a subtractive operator in the binding index computation (i.e. regional $A_m - C$) limits the incidence of the cerebellar specific binding for comparison of the binding index under various antipsychotic treatments. Indeed, by using the mean cerebellar value observed in the healthy subjects as a reference, under-estimation of binding index values was below 5% in the striatum but ranged from 4% (haloperidol) to 12% (clozapine) in the temporal cortex.

This underestimation, more marked in cortical than in striatal structures, strengthens the observation of a high binding index in cortical regions with all antipsychotics and the differential binding index values between haloperidol and atypical compounds in the basal ganglia. This observation is in keeping with a modelling study, correlating the affinity of a ligand with the B_{max} in the structure studied. According to that modelling, the apparent affinity of a radioligand is correlated with the B_{max} in the structure: when the B_{max} is low, the apparent affinity of the radioligand to its receptor increases (Delforge *et al*, 1999).

Consistency with previous *ex vivo* findings in animals

The high D_2 blockade induced in the temporal cortex by each of the five antipsychotic drugs is consistent with reports using different methodologies. The topographical selectivity of atypical antipsychotics on dopamine blockade has been reported previously from *ex vivo* measurements in animals. For instance, studies have demonstrated a higher affinity of amisulpride for D_2 dopamine receptors in the temporal regions than in striatum (Schoemaker *et al*, 1997). Also, chronic treatment with clozapine has been shown specifically to up-regulate cortical D_2 mRNA turnover and cortical D_2 receptor binding, at variance with haloperidol, which seems to upregulate both striatal and cortical D_2 receptors (Lidow & Goldman-Rakic, 1994). Atypical antipsychotics raise dopamine turnover

more in limbic structures than in striatum, whereas traditional antipsychotics affect the dopamine turnover in both regions to the same degree (Westerink *et al*, 1977). In addition, the *c-fos*-like immunoreactivity is increased by atypical antipsychotics in limbic areas and in cortices, whereas traditional antipsychotics also lead to an increased *c-fos* expression in the dorsolateral striatum (Fink-Jensen & Kristensen, 1994).

Consistency with previous in vivo *findings in humans*

Our results obtained with a quantitative imaging technique are in agreement with previous *in vivo* reports using a radioligand with the same picomolar affinity for D₂ receptors [^{123}I]-epidepride) and single photon emission tomography to assess the 'occupancy' of D₂ receptors by antipsychotic drugs in the striatum and temporal cortex. Indeed, the elevated occupancy figures observed with traditional compounds (haloperidol, fluphenazine, flupenthixol, pipotiazine, droperidol) in both temporal (mean 82%) and striatal (mean 73%) regions (Bigliani *et al*, 1999), and the small difference between striatal and temporal cortex blockade were analogous to those determined in the haloperidol-treated patients of the present study. Thus, although a relative temporal cortex selectivity in D₂ blockade (Pilowsky *et al*, 1997; Bigliani *et al*, 2000) appears to characterise atypical antipsychotics, a similar high D₂ blockade in both temporal and striatal regions is induced by usual antipsychotic doses of traditional antipsychotics.

On the whole, the convergence of *ex vivo* and *in vivo* data strongly suggests that cortical D₂ dopamine receptors are a common target of both traditional and atypical antipsychotics for therapeutic action.

Finally, from a clinical point of view, our results are in keeping with the association of antipsychotic efficacy (attributed to an action on meso-cortico-limbic dopamine pathways) and lower extrapyramidal side-effects (attributed to an antidopaminergic activity in the dorsolateral striatum) with atypical antipsychotics than with traditional compounds. Searching for a high *in vivo* binding to the D₂ receptors in the cortex co-occurring with a lower binding in the basal ganglia therefore could be suggested as an indicator of a favourable benefit/risk profile for a putative antipsychotic compound.

CLINICAL IMPLICATIONS

■ Cortical D₂ dopamine receptors are a common target of both traditional and atypical antipsychotics for therapeutic action.

■ In the basal ganglia, atypical antipsychotics antagonise the dopamine transmission mediated by the D₂ receptor to a lower level than traditional antipsychotics.

■ The co-occurrence of a high *in vivo* binding to the D₂ receptors in the cortex and a lower binding in the basal ganglia could be an indicator of a favourable benefit/risk profile for a putative antipsychotic compound.

LIMITATIONS

■ Owing to the small patient samples, inter-individual variability was not assessed extensively.

■ The binding indices approximate the effective D₂ receptor occupancy.

■ The study was not designed to assess therapeutic effects longitudinally.

XAVIER XIBERAS, MD, JEAN LUC MARTINOT, MD, INSERM U 334, Service Hospitalier Frédéric Joliot; LUC MALLET, MD, A. Chenevier Hôpital, Créteil, and INSERM U 334, Service Hospitalier Frédéric Joliot, Orsay; ERIC ARTIGES, MD, C. LOC'H, BSc, B. MAZIÈRE, PharmD, INSERM U 334, Service Hospitalier Frédéric Joliot, Orsay; MARIE LAURE PAILLÈRE-MARTINOT MD, Pitié-Salpêtrière Hôpital, Paris, France

Correspondence: Jean-Luc Martinot, INSERUM U 334, SHFJ, CEA, 4 Place Gl. Leclerc, 91401 Orsay, France. E-mail: martinot@shfj.cea.fr

(First received 13 February 2001, final revision 29 June 2001, accepted 6 July 2001)

ACKNOWLEDGEMENTS

REFERENCES

Altar, C. A., O'Neils, S., Walter, R. J. Jr., et al (1985) Brain dopamine and serotonin receptor sites revealed by digital subtraction autoradiography. *Science*, **228**, 597–600.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Bigliani, V., Mulligan, R. S., Acton, P. D., et al (1999) *In vivo* occupancy of striatal and temporal cortical D₂/D₃ dopamine receptors by typical antipsychotic drugs. [^{123}I]-epidepride single photon emission tomography (SPET) study. *British Journal of Psychiatry*, **175**, 231–238.

__, __, __, et al (2000) Striatal and temporal cortical D₂/D₃ receptor occupancy by olanzapine and sertindole *in vivo*: a [^{123}I]epidepride single photon emission tomography (SPET) study. *Psychopharmacology*, **150**, 132–140.

Boyson, S. J., McGonicle, P., Luthin, G. R., et al (1988) Effects of chronic administration of antipsychotic and anticholinergic agents on densities of D₂ dopamine and muscarinic cholinergic receptors in rat striatum. *Journal of Pharmacology and Experimental Therapeutics*, **244**, 987–993.

Burt, D. R., Creese, I. & Snyder, S. H. (1976) Binding interaction of lysergic acid diethylamide and related agents with dopamine receptors in the brain. *Molecular Pharmacology*, **12**, 631–638.

Chivers, J. K., Gommeren, W., Leysen, et al (1988) Comparison of the *in vitro* receptor selectivity of substituted benzamide drugs for the brain neurotransmitter receptors. *Journal of Pharmacy and Pharmacology*, **40**, 415–421.

Coukell, A. J., Spencer, C. M. & Benfield, P. (1996) Amisulpride. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of schizophrenia. *CNS Drugs*, **6**, 237–256.

Delforge, J., Bottlaender, M., Loc'h, C., et al (1999) Quantification of extrastriatal D₂ receptors using a very high affinity ligand (FLB 457) and the multi-injection approach. *Journal of Cerebral Blood Flow and Metabolism*, **19**, 533–516.

Editions du Vidal (1993) *Dictionnaire Vidal*. Paris: Editions du Vidal.

Farde, L., Ehrin, E., Eriksson, L., et al (1985) Substituted benzamides as ligand for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proceedings of the National Academy of Sciences of the USA*, **82**, 3863–3867.

__, **Nordström, A. L., Wiesel, F. A., et al (1992)** Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical antipsychotics and clozapine. Relation to extrapyramidal side effects. *Archives of General Psychiatry*, **49**, 538–544.

Fink-Jensen, A. & Kristensen, P. (1994) Effects of typical and atypical antipsychotics on Fos protein expression in the rat forebrain. *Neuroscience Letters*, **182**, 115–118.

Fitton, A. & Heel, R. (1990) Clozapine. A review of its pharmacological properties and therapeutic use in schizophrenia. *Drugs*, **40**, 722–747.

Kasper, S. (1998) Risperidone and olanzapine: optimal dosing for efficacy and tolerability in patients with schizophrenia. *International Clinical Psychopharmacology*, **13**, 253–262.

Kessler, R. M., Whetsell, W. O., Ansari, M. S., et al (1993) Identification of extrastriatal dopamine D_2 receptors in post mortem human brain with ^{123}I-epidepride. *Brain Research*, **609**, 237–243.

Lidow, M. S. & Goldman-Rakic, P. S. (1994) A common action of clozapine, haloperidol, and remoxipride on D_1- and D_2-dopaminergic receptors

in the primate cerebral cortex. *Proceedings of the National Academy of Sciences of the USA*, **91**, 4353–4356.

Loc'h, C., Halldin, C., Bottlaender, M., et al (1996) Preparation of ^{76}Br-FLB-457 and ^{76}Br-FLB-463 for examination of striatal and extrastriatal dopamine D_2 receptors with PET. *Nuclear Medicine and Biology*, **23**, 813–819.

Mangin, J. F., Frouin, V., Bloch, I., et al (1994) Fast nonsupervised 3D registration of PET and MRI images of the brain. *Journal of Cerebral Blood Flow and Metabolism*, **14**, 749–762.

Martinot, J. L., Paillère-Martinot, M. L., Loc'h, C., et al (1990) Central D_2 receptor blockade and antipsychotic effects of neuroleptics. Preliminary study with PET. *Psychiatry and Psychobiology*, **5**, 231–240.

Moller, H. J. (2000) State of the art of drug treatment of schizophrenia and the future position of novel/atypical antipsychotics. *World Journal of Biological Psychiatry*, **1**, 214.

Moore, H., West, A. R. & Grace, A. A. (1999) The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. *Biological Psychiatry*, **46**, 40–55.

Nordström, A. L., Farde, L., Wiesel, F. A., et al (1993) Central D_2 dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biological Psychiatry*, **33**, 227–235.

Nyberg, S., Erikson, B., Oxenstierna, G., et al (1999) Suggested minimal effective dose of risperidone based on PET-measured and $5HT_{2A}$ receptor occupancy in

schizophrenic patients. *American Journal of Psychiatry*, **156**, 869–875.

Pilowsky, L. S., Mulligan, R. S., Acton, P. D., et al (1997) Limbic selectivity of clozapine. *Lancet*, **350**, 490–491.

Schoemaker, H., Claustre, Y., Fage, D., et al (1997) Neurochemical characteristics of amisulpride, an atypical dopamine D_2/D_3 receptor antagonist with both presynaptic and limbic selectivity. *Journal of Pharmacology and Experimental Therapeutics*, **280**, 83–97.

Stephenson, C. M. E., Bigliani, V., Jones, H. M., et al (2000) Striatal and extra-striatal D_2/D_3 dopamine receptor occupancy by quetiapine in vivo. $[^{123}I]$-epidepride single photon emission tomography (SPET) study. *British Journal of Psychiatry*, **177**, 408–415.

Westerink, B. H., Lejeune, B., Korf, J., et al (1977) On the significance of regional dopamine metabolism in the rat brain for the classification of centrally acting drugs. *European Journal of Pharmacology*, **42**, 179–190.

Xiberas, X., Martinot, J. L., Mallet, L., et al (2001) *In vivo* extrastriatal and striatal D_2 dopamine receptor blockade by amisulpride in schizophrenia. *Journal of Clinical Psychopharmacology*, **21**, 207–214.

Zimbroff, D. L., Kane, J. M., Tamminga, C. A., et al (1997) Controlled, dose−response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. *American Journal of Psychiatry*, **154**, 782–791.