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The role of striatal dopamine D2 receptors in the occurrence of extrapyramidal side effects: Iodine-123-iodobenzamide single photon emission computed tomography study

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ABSTRACT

Levels above 75% of striatal dopamine 2 receptor occupancy (D2RO) have been associated with extrapyramidal symptoms (EPS). The aim of the present study is to investigate the relationship between D2RO and EPS in a sample of psychotic patients in current treatment with both typical and atypical antipsychotics. Brain iodine-123-iodobenzamide single photon emission computed tomography (^{123}I-IBZM SPECT) was performed in 81 patients taking stable doses of haloperidol, risperidone, olanzapine, quetiapine, clozapine or ziprasidone. First, the degree of D2RO and Positive and Negative Syndrome Scale (PANSS) scores was compared between the group of patients who presented EPS and the group free of EPS. Afterwards, these variables were compared among the different antipsychotic medications. The group with EPS presented means of D2RO significantly higher than the group free of EPS. Significant differences in D2RO were found in clozapine, quetiapine and ziprasidone groups compared with the haloperidol group. No differences were observed between either olanzapine or risperidone and haloperidol. No quetiapine- or clozapine-treated patients developed EPS. Haloperidol and risperidone demonstrated a relationship between striatal D2RO and EPS. The findings suggest that higher D2RO is related to appearance of EPS. Occupancy in the group with EPS was in agreement with previous studies that suggested a high degree of D2RO is necessary for the occurrence of EPS.

1. Introduction

The precise mechanism of action of antipsychotic drugs has not yet been determined. Although they present a varied pharmacological profile, there is no effective antipsychotic without some ability to block the dopamine-2 receptor (D2R), and drugs that do not antagonize the D2R lack antipsychotic properties, which suggests that antagonism of dopamine activity, particularly the antagonism of D2R, seems to play an essential role (Farde et al., 1988; Seeman, 2002; Agid et al., 2007).

The D2R blockade in the nigrostriatal pathway, which connects the substantia nigra to the striatum and controls motor function and movements, has been associated with motor side effects (Nguyen et al., 2004). It has been suggested that the atypical antipsychotics, also called second-generation antipsychotics (SGAs), induce fewer extrapyramidal symptoms (EPS) than the typical antipsychotics (Lambert and Castle, 2003), also called first-generation antipsychotics (FGAs). Initially, based on the profile of clozapine, the effect of SGAs on serotonin-2A (5HT2A) receptors was proposed as the factor responsible for this property. However, many FGAs, like trifluoperazine, fluphenazine or perphenazine, have strong affinities for 5HT2A receptors and some drugs with clinical characteristics in common with SGAs, like amisulpride, have no activity on 5HT2A receptors (Trichard et al., 1998; Kapur and Seeman, 2001). Moreover, various neuroimaging studies with different typical and atypical antipsychotics have associated a level around 60% of striatal D2R occupancy

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(D2RO) with antipsychotic response, and levels of occupancies higher than 70–75% with EPS (Farde et al., 1992; Kapur et al., 2000). In those studies, concomitant potent 5HT2A blockade apparently offers no protection against EPS with the mentioned degree of D2RO.

Hence the appearance of EPS seems to be mainly determined by the degree of striatal D2RO, even though the antipsychotic shows an atypical clinical profile, which suggests that the current classification of antipsychotics as typical or atypical needs to be reviewed in order to integrate the findings of neuroimaging studies.

In the present study, the degree of striatal D2RO using single photon emission computed tomography (SPECT) was investigated in a clinical sample in current treatment with antipsychotics of both generations from a psychiatric service of a general hospital. The degree of striatal D2RO was compared between patients who presented EPS and those who did not. In order to investigate the effect of treatment on the occupancy levels, patients were divided into the antipsychotic type they received, and the relationship between D2RO and EPS was investigated in each group.

2. Material and methods

2.1. Subjects

Eighty-one patients (38 with current EPS and 43 free of EPS) treated with a stable dose (S.D.) of antipsychotic, defined as at least 2 weeks of antipsychotic treatment at the same dose, were included in the present study. All patients were taking only one of the following antipsychotics: haloperidol, risperidone, olanzapine, ziprasidone, quetiapine and clozapine. No patient was taking depot antipsychotic treatment. All subjects met the diagnostic criteria for one of the disorders included in the chapter Schizophrenia and Other Psychotic Disorders of the DSM-IV (American Psychiatric Association, 2000). Subjects with psychiatric diagnosis due to a general medical condition, with diagnosis of substance-related disorder (except nicotine) abuse or dependence, and subjects taking any dopaminergic drugs different from the listed antipsychotics were excluded from the study. Those patients who were not capable of understanding the procedures and the aim of the study were also excluded. Demographic characteristics of the patients are summarized in Table 1.

The study protocol and all procedures involved were previously approved by the ethics commission of the Hospital de la Santa Creu i Sant Pau, and all subjects gave written informed consent after a description of the study and prior to inclusion in the study. This study was developed according to the principles of the Declaration of Helsinki (World Medical Association, 2000).

2.2. Clinical assessments

On the day of the SPECT scan (±24 h) patients were clinically assessed and their psychopathology was rated by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) the presence or absence of EPS was also evaluated. At least two clinicians assessed the presence of EPS symptoms. Patients with any symptom of parkinsonism and/or akathisia and/or dystonia and patients who needed an anticholinergic medication during the stable dosage period were included in EPS group.

Table 1
Subjects: demographic and clinical characteristics.

Antipsychotic	*N*	Male/female	Age	Doses
Haloperidol	19	12/7	31.5 ± 9.4	12.1 ± 6.9
Olanzapine	12	7/5	25.9 ± 6.1	17.1 ± 10.1
Risperidone	17	10/7	26.7 ± 9.0	4.0 ± 1.9
Quetiapine	9	3/6	29.4 ± 8.9	625.0 ± 436.7
Clozapine	8	5/3	28.0 ± 3.7	255.0 ± 177.1
Ziprasidone	16	10/6	28.2 ± 5.7	102.5 ± 20.5
Total	81	47/34	28.3 ± 7.9	

Values are expressed as mean ± S.D., except for *N* and male/female columns.

2.3. SPECT procedure

Brain SPECT was performed 12 h after last antipsychotic dose administration, with a double-headed gammacamera (GEMS Helix) equipped with two low-energy and high-resolution collimators. The tracer used was iodine-123-iodobenzamide (^{123}I-IBZM). The image acquisition and reconstruction procedures were performed according to the European Association of Nuclear Medicine guidelines for striatal D2R SPECT imaging (Tatsch et al., 2002) previously described elsewhere (Guardia et al., 2000; Perez et al., 2003). Image acquisition started 90 min after intravenous injection of 5 mCi (185 MBq) of 123I-IBZM (Nycomed—Amersham) flushed with 10 ml of saline. Perchlorate p.o. (8 mg/kg) was administered 20 min prior to the IBZM injection to minimise radiation exposure to the thyroid gland. Thirty-second images were obtained every 6° through a circular orbit of 360° in a 64×64 matrix, with a zoom of 1.5. Following the scanning procedure, images were processed and quantified with an Elscint Xpert computer. For reconstruction, filtered back projection with a Butterworth filter was used, and Chang's attenuation correction method was applied, with a factor of 0.12. The final pixel size was 4 mm. Two-pixel-thick oblique slices in the fronto-occipital direction, as well as coronal and sagittal slices, were obtained. For quantification, striatum/occipital cortex uptake (S/O) ratios, which reflect specific/nonspecific binding, were obtained. Standard templates of irregular regions of interest (ROIs) for the striatum (mirrored ROIs, one for each hemisphere) and for the occipital cortex (a single ROI including both hemispheres) were used. ROIs were placed on the two consecutive oblique slices that contained the maximum striatal uptake, and averaged mean counts/pixel of the two slices were used for calculations. Percentage of receptor occupancy (%RO) was calculated as a percentage of change of the uptake ratios obtained during antipsychotic treatment ([S/O]t) related to a mean baseline value ([S/O]b), according to the formulae previously reported (Klemm et al., 1996; Tauscher et al., 2002): %RO = ([S/O]b − [S/O]t)/[S/O]b.

In this case, the mean S/O ratio obtained in a previous study from nine treatment-naive schizophrenia patients (Perez et al., 2003) was used as the mean baseline value ([S/O]b), for %RO calculation.

2.4. Statistical analysis

For statistical assessment SPSS for Windows (version 18.0) was used. Student *t*-tests were conducted to compare the group of subjects who presented EPS with the group free of EPS with regard to the following variables: D2R occupancy, age, PANSS total score and PANSS subscale scores. The variables gender and use of cannabis were compared by means of chi-square test.

As a secondary analysis, the whole sample was divided in terms of antipsychotic treatment. ANOVA and post-hoc tests were conducted to compare all antipsychotic treatment groups to D2RO, age, PANSS total score and PANSS subscale scores. The treatment groups were also compared with respect to gender and the presence or absence of EPS by Fisher's exact test. For each treatment group, the correlation between antipsychotic dose and D2RO was evaluated using Spearman's correlation coefficient. Analysis of the relationship between the presence or absence of EPS and D2RO, antipsychotic dose and age was performed by means of Mann–Whitney *U* test. For all tests $p<0.05$ was considered statistically significant.

3. Results

Statistically significant differences in striatal D2RO and PANSS negative subscale scores were found between patients who presented