Cerebral metabolism and risperidone treatment in schizophrenia

V. Molinaa, J.D. Gispertb, S. Reigb, J. Sanza, J. Pascaub, A. Santosc, T. Palomoa, M. Descoa, b, *

aDepartment of Psychiatry, Hospital Doce de Octubre, Madrid, Spain
bDepartment of Experimental Medicine, Hospital General Universitario “Gregorio Marañón”, Dr. Esquerdo, 46, E-28007, Madrid, Spain
cETS de Ingenieros de Telecomunicación, Universidad Politécnica, Madrid, Spain

Received 14 September 2001; accepted 31 January 2002

Abstract

This paper compares the metabolic changes associated with risperidone treatment in schizophrenia to those induced by haloperidol, as a representative typical neuroleptic. A group of 11 schizophrenic patients of recent onset underwent two [18F] fluoro-desoxi-glucose (FDG)-positron emission tomography (PET) scans at rest: the first one at the moment of the diagnosis, after a minimal treatment with haloperidol followed by wash-out, and the second one after 6 months on risperidone. The study also included 34 patients on chronic haloperidol for comparison. PET images were analyzed using Statistical Parametric Mapping (SPM' 99) methods. The only change after treatment with risperidone with respect to the baseline was a slight increase in activity in the primary visual area and the right insula. Patients on chronic haloperidol showed increased activity in the motor cortex and cerebellum, as compared to both minimally treated and risperidone-treated patients. The pattern of metabolic changes induced by risperidone appears to be different from that produced by typical antipsychotics.

Keywords: Cerebral metabolism; Risperidone; Haloperidol; SPM; FDG (PET)

1. Introduction

Treatments with typical and atypical antipsychotics produce different cerebral metabolic effects. The former have been reported to increase basal ganglia metabolism (Buchsbaum et al., 1987; DeLisi et al., 1985; Holcomb et al., 1996) and to decrease frontal lobe metabolism (Bartlett et al., 1994; Holcomb et al., 1996). On the other hand, the typical antipsychotic clozapine’s preferential action on the prefrontal cortex (Robertson and Fibiger, 1992) produces a greater metabolic decrease in that region than typical drugs (Cohen et al., 1997; Potkin et al., 1994).

The clinical properties of risperidone suggest that this drug situates itself in an intermediate position in the typical–atypical spectrum (Breier et al., 1999; Chouinard et al., 1998; Davies et al., 1998). Several groups have studied its effects on brain activity. Using SPECT, Berman et al. (1996) reported no significant changes with risperidone in six previously treated cases. A longitudinal study by Liddle et al. (2000) (n = 8) reported an initial decrease of subcortical metabolism, followed by a decrease in frontal activity after 6 weeks. Miller et al. (2001) compared the effects of haloperidol and risperidone after 3 weeks of treatment with those of...
a medication-free state. They found a greater increase in subcortical perfusion and decrease in prefrontal perfusion with haloperidol as opposed to risperidone, as well as a lower metabolic activity in the cerebellum with risperidone. However, this study did not offer direct comparisons between basal and risperidone scans, an important difference with respect to other studies and the paper presented here. No data are available on the effects of risperidone after longer treatment periods.

The aim of this work is to describe the long-term metabolic effects of risperidone, as compared to those of haloperidol, using longitudinal within-subject paired comparisons.

2. Patients and methods

The study includes 45 paranoid schizophrenic (DSM-IV) patients, 11 recent-onset (8 males) and 34 chronic (24 males). Diagnosis was confirmed with the SCID (patient version), clinical interviews, and information from families and clinical staff. The PANSS was used for clinical assessment. All the subjects in both groups were outpatients, hospitalized during a psychotic break. After complete description of the study, written informed consent was obtained from each patient as well as from a first-degree relative. The research and ethical boards of the participating institutions endorsed the study.

Since the recent-onset patients were in an acute psychotic state, they received a minimum dose of haloperidol (5 mg/day) for 2 days before the PET study, except for the 12 h prior to the scan. They had never previously received any other antipsychotic treatment. The PET studies were repeated after 6 months on risperidone (6 mg/day, plus biperiden or propanolol when indicated).

All the patients in the comparison group had undergone long-term administration of classical antipsychotics. A final period on haloperidol of 4 weeks

Table 1
Demographic and clinical values in the chronic and recent-onset groups, expressed as mean (S.D.)

<table>
<thead>
<tr>
<th>Region</th>
<th>Before risperidone</th>
<th>After risperidone</th>
<th>Chronic haloperidol-treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (year)</td>
<td>1.90 (2.07)</td>
<td>7.40 (8.50)</td>
<td></td>
</tr>
<tr>
<td>Age at onset (year)</td>
<td>23.46 (4.65)</td>
<td>24.03 (6.39)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>25.43 (6.48)</td>
<td>31.31 (10.22)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.86 (8.44)</td>
<td>169.59 (8.80)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.52 (12.01)</td>
<td>74.19 (11.08)</td>
<td>79.77 (14.81)</td>
</tr>
<tr>
<td>Education (year)</td>
<td>11.23 (4.16)</td>
<td>8.91 (3.37)</td>
<td></td>
</tr>
<tr>
<td>Positive subscale</td>
<td>21.73 (5.47)</td>
<td>12.73 (6.01)**</td>
<td>23.07 (5.68)</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>23.00 (10.24)</td>
<td>21.89 (9.64)</td>
<td>26.53 (6.71)</td>
</tr>
<tr>
<td>General subscale</td>
<td>41.63 (10.33)</td>
<td>33.05 (13.46)*</td>
<td>49.87 (10.71)</td>
</tr>
</tbody>
</table>

Clinical scores correspond to the PANSS; asterisks refer to the significance of changes between pre- and post-risperidone conditions.

* $p<0.05$.

** $p<0.01$.

Table 2
Areas that showed significant differences of activity in different comparisons

<table>
<thead>
<tr>
<th>Region</th>
<th>$x$, $y$, $z$</th>
<th>$z_{\text{max}}$</th>
<th>$N_{\text{vox}}$</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$BR (N=11) &lt; AR (N=11)$ (Fig. 1)</td>
<td>Primary visual (M)</td>
<td>$-8$, $-60$, $12$</td>
<td>3.49</td>
<td>46 (L3)</td>
</tr>
<tr>
<td>Insula (R)</td>
<td>$-42$, $-8$, $0$</td>
<td>3.48</td>
<td>83 (L3)</td>
<td></td>
</tr>
<tr>
<td>$HC (N=34) &gt; BR (N=11)$ (Fig. 2)</td>
<td>Motor (L and R)</td>
<td>$-12$, $-28$, $-58$</td>
<td>4.95</td>
<td>8439 (L1)</td>
</tr>
<tr>
<td>Motor (R)</td>
<td>$-16$, $-28$, $50$</td>
<td>4.15</td>
<td>1213 (L2)</td>
<td></td>
</tr>
<tr>
<td>Motor (L)</td>
<td>$16$, $44$, $60$</td>
<td>3.41</td>
<td>216 (L3)</td>
<td></td>
</tr>
</tbody>
</table>

$BR =$ before risperidone, $AR =$ after risperidone, $HC =$ chronic haloperidol.

Figures showing the corresponding SPM maps are indicated in brackets. For each area, the table shows the SPM coordinates of the maximum, its $z$-value, the number of voxels, and the level of evidence. Levels of evidence are (L1) peak-height corrected $p$-value lower than $p<0.05$; (L2) extent-corrected $p$-value lower than $p<0.05$; (L3) uncorrected $p$-value below $p<0.001$ in an area that has previously been reported as relevant in schizophrenia (see Patients and methods for details).
or more (10–15 mg/day) preceded the scan in these cases.

Exclusion criteria were: any other axis I condition or neurological illness, history of cranial trauma with loss of consciousness, substance abuse (excluding nicotine or caffeine) in the 5 years prior to the study (confirmed by urinalysis), and any current treatment with known CNS action. No patient had received mood-stabilizers, antidepressants, or depot neuroleptics during the preceding 3 months. All patients and controls underwent a cautionary MRI scan to exclude any clinically relevant abnormality as judged by an expert radiologist blind to the diagnosis.

Demographic and clinical data can be found in Table 1.

2.1. PET procedure

PET studies were obtained with a Posicam EZL PET scanner 20 min after the injection of 370 MBq of \(^{18}\)FDG. Matrix size was 256 × 256 × 61, and 2.6-mm-thick slices were used. Subjects were instructed to lie in a supine position in a dark, silent room with eyes open and ears unplugged for 10 min before FDG administration and for an additional 20 min before image acquisition. They received no other special instructions, except to try to remain as relaxed as possible. PET study was performed after a fasting period of over 6 h. Coffee or psychoactive beverages were forbidden.

2.2. Image analysis

PET images were analyzed with the SPM99 software package (Frackowiak et al., 1997) using proportional scaling, 12 × 12 × 12 mm FWHM smoothing. The grey-level threshold was set at 0.8, i.e. only voxels with an intensity level above 0.8 of the mean level for that scan were included in the statistical analysis. Studies were transformed into a Talairach stereotactic space (Talairach and Tournoux, 1988) matching each scan (in a least squares sense) to a reference template image.

Differences between groups were assessed by one-tailed \(t\)-tests, without including covariate effects such as age or sex, previously determined as nonsignifi-
significant. Comparisons before and after risperidone were performed by means of paired t-tests. A z-score and p-value were assigned to the differences.

p-Values must be corrected so as to overcome the problem of multiple comparisons. SPM provides two correction criteria: (1) peak-height corrected p-value and (2) extent-corrected p-value (Poline et al., 1997).

Setting the proper thresholds to consider an observed p-value as significant is critical in this type of study (Andreasen, 1996). For this reason, a validation procedure was carried out to determine the adequate significance threshold for our data. Assuming that no significant differences should be expected within the control group, we used a bootstrap (random sampling) technique to extract 200 random subgroups on which we performed the same tests as on the patient groups (Efron and Tibshirani, 1986). This procedure provided an empirical validation of the significance threshold used for our data (uncorrected p < 0.001).

Finally, the significance of the changes in activation was assessed and labeled according to three different decreasing levels of evidence: (L1) peak-height corrected p-value below 0.05, (L2) extent-corrected p-value below 0.05, and (L3) uncorrected p-value below 0.001, and the area has already been previously reported as relevant in schizophrenia or is known to be functionally linked to another significant area in our statistical map. Areas with an uncorrected p-value below 0.001 that did not match any of the above criteria were considered false positives and not reported in the results.

3. Results

Patients treated with risperidone presented a positive clinical response, with a decrease in positive and general subscale scores on the PANSS (Table 1). The only significant change in PET scans before and after risperidone treatments was a slight increase in activity in the primary visual area and the right insula (Table 2, Fig. 1). Activity in the motor area was significantly

Fig. 2. Regions with higher activity in the chronic-haloperidol condition (HC) as compared to before-risperidone condition (BR). Images are in radiological convention: left of the image is right of the patient. Regions are superimposed to the SPM MR template.

Fig. 3. Regions with higher activity in the chronic-haloperidol condition (HC) as compared to after-risperidone condition (AR). Images are in radiological convention: left of the image is right of the patient. Regions are superimposed to the SPM MR template.
greater in patients receiving chronic treatment with haloperidol than in both minimally treated patients and those taking risperidone (Table 2, Figs. 2 and 3).

4. Discussion

According to our results, the pattern of metabolic changes attributable to long-term risperidone is different from that ascribed to chronic haloperidol treatment.

Long-term haloperidol-treated patients showed a higher motor area metabolism than in those who had been on risperidone treatment for 6 months. Antipsychotics-related parkinsonism has been linked to increased motor area perfusion in chronically treated patients (Molina Rodriguez et al., 1997), supporting the increase in motor area activity observed in this study in patients on long-term haloperidol treatment as a correlate of motor side effects. This agrees with the lower striatal activation detected with risperidone than with haloperidol (Miller et al., 2001), given the role of basal ganglia in neuroleptic-induced parkinsonism (Tauscher et al., 1999). These different effects of risperidone in motor areas are consistent with a lower rate of motor side effects associated with this drug as compared to classical neuroleptics (Chouinard et al., 1998). Thus, the lack of hyperactivation of the motor area with risperidone administration suggests that patients respond differently to this drug than they do to typical neuroleptics, insofar as collateral motor effects are concerned. The absence of differences in the motor area in the study of Miller et al. (2001) may have to do with the relatively short treatment period (3 weeks) used in their study, given that some patients in that study had been receiving typical antipsychotics prior to risperidone. Changes in cortical activity induced by the chronic administration of typical neuroleptics may last for months, as suggested by the higher cortical perfusion in drug-free (wash-out longer than 4 weeks) than in drug-naive patients (Vita et al., 1995) and the persistence of the effects of haloperidol on adenylyl cyclase for months (Clow et al., 1980). These metabolic effects may continue to influence the second scan.

Miller et al. (2001) described a decrease in cerebellar activity with risperidone when compared to haloperidol. This finding was not replicated in our study. However, it is conceivable that the effect might not be due to the risperidone administration itself, but is the consequence of haloperidol withdrawal in the cases treated with this drug prior to risperidone. Bartlett et al. (1994) reported that haloperidol produces an increase in activity in the cerebellum, a structure closely related to motor function (Fox and Williams, 1970).

Our study also did not replicate the changes reported by Liddle et al. (2000) in untreated patients. They described an immediate reduction of ventral striatum and thalamic perfusion, followed by a reduction in prefrontal activity after 6 weeks of treatment. This discrepancy can be explained by different factors: the study by Liddle et al. was performed using O15-PET, whereas, we measured glucose metabolism. In addition, our scans of risperidone-treated patients were performed after a longer treatment period (6 months) than in the Liddle et al. study. Finally, our basal scan was obtained at a point when low doses of haloperidol might have decreased prefrontal metabolism, according to previously reported data (Holcomb et al., 1996; Bartlett et al., 1994), thus masking possible risperidone-induced changes. This implies that the prefrontal hypoactivation seen with risperidone is not significantly greater than that induced by short-term haloperidol (Bartlett et al., 1994). In fact, the comparison of changes in frontal activity produced by these two drugs suggests that there is a greater decrease with haloperidol (Miller et al., 2001), although mention must be made of the fact that they employed a lower significance threshold than we did in our study. Other studies, however, match our results when comparing risperidone with a baseline condition in which patients were being treated with classic neuroleptics (Berman et al., 1996).

Previous data show that clozapine decreases prefrontal metabolism to a greater extent than typical antipsychotics (Cohen et al., 1997; Potkin et al., 1994), indicating that atypical neuroleptics may exert a greater prefrontal hypoactivation than classical ones. That we did not observe this decrease, but did detect motor hyperactivation in our group, makes a strong case for the existence of a distinctive metabolic effects profile of risperidone when compared to both typical and atypical drugs.

Another effect observed in our study is the increase of visual cortex activity. This could be attributed to risperidone’s having less of a sedative effect than
haloperidol. However, a study performed with neuroleptic-naı¨ve patients at rest found visual area hypoactivity (Andreasen et al., 1997), thus making it conceivable that treatment with risperidone corrects a preexisting functional deficit. Moreover, abnormalities of the visual processing have been shown in schizophrenia using evoked potentials (Javitt et al., 1993) or single-photon emission tomography (Lewis et al., 1992). This deficit may be related to thalamic alterations consistently described in schizophrenia (Andreasen et al., 1994; Buchsbaum et al., 1996; Pakkenberg, 1992; Young et al., 2000). These thalamic alterations might show a greater effect on the cortex where the thalamus has divergent, excitatory projections (Steriade et al., 1997).

The deficient visual cortex activation at rest may also relate to the observed increase in activity of the right insula, since this structure also receives excitatory afferences from the thalamus (Mufson and Mesulam, 1984). As in the case of visual area, insular hypoactivity has also been reported in medication-free patients (Kim et al., 2000).

On the other hand, hypoactivation of the visual area was also evident after ketamine administration (Lahti et al., 1999), which may help to explain our findings, given the relevance that a hypofunction of the N-methyl-D-aspartate receptors may have in schizophrenia (Tamminga, 1999).

The main limitation of our study is the relatively small sample size. Nevertheless, the paired intrasubject design has higher statistical power than transversal studies. Another limitation may derive from the initial administration of low doses of haloperidol, instead of studying strictly neuroleptic-naı¨ve patients. This latter approach also presents important drawbacks, since many patients cannot undergo the imaging procedures without a minimum of treatment. Excluding these patients could produce an uncontrolled bias in the results.

In summary, our results suggest that the metabolic effects of risperidone show a different profile as compared to typical neuroleptics.

Acknowledgements

The authors thank Dr. M.A. Pozo and Dr. A. Maldonado from the Centro PET Complutense (Madrid) for their advising and collaboration performing the PET scans. This work has been partially supported by grants from: Comunidad de Madrid (III PRICIT), Fundación La Caixa (99/042-00), TIC 99-1085 and FIS (00/0036).

References


Fox, M., Williams, D., 1970. The caudate nucleus-cerebellar pathways: an electrophysiological study of their route though the midbrain. Brain Res. 20 (140), 144.


