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Clozapine may partially compensate for task-related brain perfusion abnormalities in risperidone-resistant schizophrenia patients ☆

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Abstract

Background: Previous reports show different cerebral activity patterns during treatment with clozapine and typical neuroleptics. However, to date no study has directly compared the brain activity patterns while subjects are undergoing treatment with clozapine and other atypical antipsychotics. This comparison is of interest, given the probably different mechanism of action of clozapine in comparison with other atypicals.
Objective: To assess the effect of clozapine on perfusion deviations still evident during treatment with risperidone.
Methods: Here we used hexamethylene-propylenaminoxime single photon emission computed tomography to compare the perfusion patterns observed during the performance of a Stroop test in 10 patients sequentially treated with risperidone and clozapine, owing to a lack of response to the former, and in 10 healthy controls.
Results: Patients on risperidone showed decreased perfusion as compared to controls in the medial prefrontal, middle cingulate and insular regions, as well as increased activities in brain stem and the posterior hippocampus. After receiving clozapine, the same patients showed an even wider prefrontal perfusion deficit and the brain stem was still hyperactive, but the abnormalities in the cingulate cortex, insula and hippocampus had disappeared. Clinical improvement was directly related to an increase in thalamic perfusion.
Conclusion: Clozapine may alleviate hyperactivity in the limbic system in schizophrenia and may facilitate activation of the regions involved in cognitive tasks to a greater degree than risperidone, as well as eliciting greater inhibition of the PF region.

Keywords: Brain perfusion; Clozapine; Risperidone; Schizophrenia

1. Introduction

Previous reports have shown that clozapine decreases the activity of the frontal region more than haloperidol and fluphenazine (Cohen et al., 1997; Lahti et al., 2003b; Molina et al., 2005; Potkin et al., 2003) and, at the same time, that clozapine may increase the activation of certain areas involved in cognitive tasks, such as the cingulate region (Lahti et al., 2003a). Clozapine may also augment activity in the primary visual region in resting conditions (Molina et al., 2005).

Abbreviations: CPZ, chlorpromazine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; fMRI, functional magnetic resonance imaging; FWHM, full width half maximum; HMPAO-SPECT, hexamethylene-propylenaminoxime single photon emission computed tomography; keV, kilo-electron volts; MBq, Mega-Becquerels; MRI, magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale; SCID, Structured Clinical Interview for Diagnostic and Statistical Manual; SPM, Statistical Parametric Mapping; SD, standard deviation.

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The effects of other atypical antipsychotics on brain activity may also differ from those of typical drugs, but in a different way. Risperidone has been reported to produce a lower increase in putamen and cerebellum metabolism and a lower decrease in frontal metabolism than haloperidol (Miller et al., 2001). Moreover, risperidone has been described to increase activity in the insular and visual cortices, from a baseline of minimal treatment with haloperidol, with no difference in the prefrontal or limbic regions (Molina et al., 2003).

To our knowledge, no study has directly compared the activity patterns of clozapine and other atypical antipsychotics in schizophrenia. Only one study, in a single patient, compared brain activity between olanzapine and clozapine, reporting a clearly different pattern between these drugs (Conley et al., 2004). A direct comparison between the effects of clozapine and other atypicals on brain activity could contribute to a better understanding of their respective mechanisms of action. In this context, it would be of interest to evaluate whether the functional abnormalities described for schizophrenia may be alleviated by clozapine, as previous data may suggest (Lahti et al., 2003b).

To this end, here we compared the perfusion patterns of a group of schizophrenia patients who were switched from risperidone to clozapine due to a lack of efficacy of the former. Their activity patterns were compared to those of a healthy control group evaluated in the same conditions. Regional perfusion was studied using single photon emission tomography (SPECT) with hexamethylene-propylenaminoxime (HMPAO) during the performance of a Stroop test and the Statistical Parametric Mapping (SPM) software. From the previous literature, we hypothesized that clozapine would decrease prefrontal perfusion and normalize the activation of areas related to attention task and relevant to schizophrenia, such as the anterior cingulate and insula (Alvarez and Emory 2006). With the present design, this could be reflected in a lower perfusion in these regions in the risperidone but not in the clozapine conditions as compared to healthy controls.

2. Materials and methods

2.1. Subjects

Our sample included 10 schizophrenia patients (6 males; 8 of the paranoid and 2 of the undifferentiated subtypes, according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria). Diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual (SCID, patients version) and data obtained from clinical interviews and information from families and clinical staff. All patients were in a short-term psychiatric unit for psychotic symptoms. The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) was used to evaluate symptoms immediately prior to initiating treatment with clozapine and 1 month later (Table 1).

Ten healthy controls (6 males) with no personal or familial psychiatric antecedents were also included. To match them with the patient group, it was ensured that none of the subjects had a college-level education, and efforts were also made to match the parental school years. No differences in age or parental socioeconomic level, according to the Hollingshead and Frederick scale (Hollingshead and Frederick 1953), were observed between the patient and control groups. There were no significant differences in parental educational level between patients and controls.

Table 1
Clinical and demographic characteristics of the patients

	Risperidone	Clozapine	Controls
Age	40.6(10.6)		37.2(9.7)
School years	11.0 (4.5)		13.7(5.2)*
Parental SES	1.6 (0.9)		1.9(0.8)
PANSS Positive	29.8(3.2)	16.0(2.7)**	
PANSS Negative	26.2(6.8)	21.8(6.8)*	
PANSS General	47.2(5.9)	36.6(3.6)*	
Stroop performance (color-incongruent condition)	19.8(9,7)	24.6(8.1)**	31.4(7.6)#
Stroop (word-reading condition)	75.6(14.8)	80.3(12.7)	88.2(10.2)

Stroop performance was defined as the number of correct responses in 45 s in the word–color incongruent condition.
In the second column *$p<.05$;**$p<.01$ (Wilcoxon test); in the third column *$p<.05$ #$p<.005$ (Mann–Whitney test in comparison with patients in both treatment conditions).

Exclusion criteria were: any other axis I diagnosis, any neurological illness, a history of cranial trauma with loss of consciousness, past substance dependence, excluding nicotine or caffeine, drug abuse during the last 3 months (current consumption being ruled out by urinalysis), and any current treatment with known actions on the central nervous system. None of the patients or controls had received mood-stabilizers, antidepressants, or depot neuroleptics over the 6 months preceding the study. All patients and controls underwent a cautionary MRI scan to exclude any abnormality of neurological relevance as judged by an expert radiologist. After full information about the study had been given to the subjects, written informed consent was obtained from each patient and from a first-degree relative. The research and ethics boards of the participating institutions endorsed the study.

2.2. Medication status

All the patients had shown during the previous year a poor response to risperidone and haloperidol. Each of these treatments had been administered for more than 1 month, at doses above 800 mg/d in CPZ equivalents for treatment with the typical drug and 6 mg/d of risperidone. The inclusion was followed in all 10 patients by a period of treatment with risperidone at 6 mg/d during 4 weeks, and thus, at the time of the basal scan, all 10 patients had been receiving risperidone for at least the 4 weeks.

Among the 10 patients included, four had quit their medication prior inclusion and had been hospitalized during a psychotic episode; they received risperidone over 4 weeks to corroborate resistance to treatment. The 6 remaining patients had been continuously treated during the previous year with trials of risperidone and haloperidol, also receiving it for the four-week period at the same dose before the basal scan. Individual treatment history during the preceding year is shown in Table 2.