Short-term effects of typical and atypical antipsychotic medication on caudate nucleus volume in drug-naïve first-episode schizophrenia patients

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Introduction

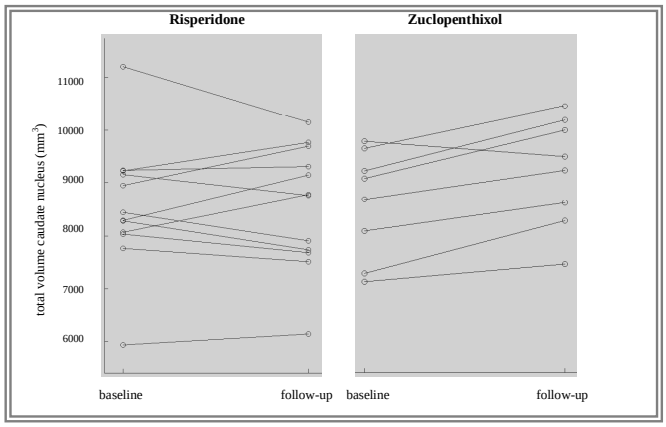
Findings of longitudinal structural MR studies investigating the caudate nucleus in first-episode schizophrenia patients indicate that increased caudate volumes observed in chronic schizophrenic patients are most likely due to typical antipsychotic medication use. Atypical compounds do not seem to induce caudate nucleus enlargement and, particularly clozapine, may reverse caudate nucleus enlargement in patients previously treated with a typical compound. It has been hypothesized that differences between typical and atypical compounds in their respectively high and (generally) low affinity for D_2 receptors (abundantly present in the basal ganglia) may underlie their differential effects on caudate nucleus volume. Atypical antipsychotic compounds differ, however, from one another with regard to their pharmacological mechanisms including their affinity for D2-receptors. There is a need for longitudinal clinical studies of randomized drug-naïve schizophrenic patients to further elucidate the effect of different antipsychotic compounds on caudate volume.

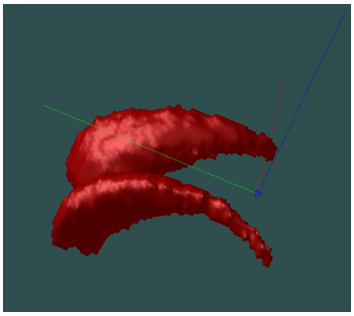
Hypothesis

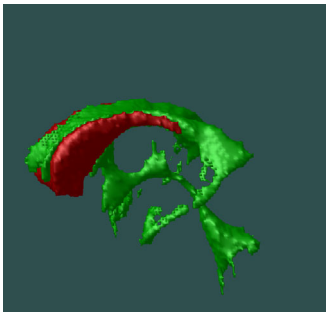
Three months exposure to typical, but not atypical, antipsychotic compounds lead to increased caudate volume in drug-naive first-episode schizophrenia patients

Methods

Twenty drug-naive patients (mean age = 26.2 years; SD = 5.1) with first-episode schizophrenia (ICD-10) were randomly allocated to treatment with the typical compound zyclopenthixol (N = 8, 6 males) or the atypical compound risperidone (N = 12, 9 males). Clinical symptom severity was measured with the Positive and Negative Syndrome Scale. Extrapyramidal symptoms were rated using the Extrapyramidal Symptom Rating Subscale. The caudate nucleus was manually traced on high resolution MRI-scans (whole head 3D T1-weighted MPRAGE; 1mm isotropic voxels) that were acquired before and after 12 weeks exposure to antipsychotic medication by a single rater, blind to subject identification, time of scan and brain hemisphere (Intra-rater reliability: ICC = 0.91). Images were reoriented to fit the Talairach coordinate system (no scaling).







Results

Patients in the two medication groups did not differ significantly with respect to gender, handedness, socio-economic status, education, duration of untreated psychosis and intracranial volume. Mean daily dose of zuclopenthixol and risperidone were respectively 10.3 (SD = 6.5) and 3.3 mg (SD = 1.4). A significant main effect for Time ($F_{1,18}$ = 5.1; $p < 0.04$) and Time x Group interaction ($F_{1,18}$ = 5.0; $p < 0.04$) was found. Significant larger caudate volumes at follow-up were explained by a significant caudate volume increase in the zuclopenthixol ($t = -3,9$; $df = 7$; $p < 0.01$) group while no volume change was observed in the risperidone group ($t = -0.0$; $df = 11$; $p < 0.99$). Patients receiving zuclopenthixol developed significant more EPS than patients treated with risperidone. Zuclopenthixol and risperidone blood plasma levels were both positively correlated to EPS severity. No significant correlations were observed between caudate volume changes and changes in PANSS or EPS scores.

Discussion

In drug-naive patients with first-episode schizophrenia, caudate volume increase is already observable after brief exposure to a typical, but not atypical antipsychotic compound. It has been hypothesized that differences in (striatal) D_2-receptor affinity between typical and atypical compounds might underlie this differential effect. However, because the doses of risperidone administered in the present study are supposed to give approximately 65% to 80% D_2 receptor occupancy, equivalent to that of typical compounds, D_2 receptor blockade alone is not sufficient to explain caudate nucleus enlargement.