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Regional brain metabolism in schizophrenia: The influence of antipsychotics

Seethalakshmi R, Parkar SR, Nair N*, Batra SA, Pandit AG*, Adarkar SA, Baghel NS*, Moghe SH*

ABSTRACT

Background: Schizophrenia has been associated with a plethora of metabolic changes in the brain that vary with duration and type of psychoses. Additionally, it has been observed that antipsychotics can further alter cerebral glucose metabolism. These changes resulting from antipsychotics have been postulated to be reflective of the duration and mechanism of action of the medication.

Aims: We aimed to examine the influence of antipsychotics on brain metabolism in individuals with schizophrenia in a naturalistic setting.

Settings and Design: A cross-sectional study was carried out by the psychiatry department of a tertiary care hospital in collaboration with the Radiation Medicine Centre.

Materials and Methods: Eighteen male patients with schizophrenia in different phases of treatment underwent an 18F-deoxyglucose positron emission tomography scan in a resting state 12 hours after the last dose of antipsychotic.

Statistical Analysis: The types and duration of treatment were then compared with the regional glucose uptake in 14 predetermined regions of interest. The relative Uptake Values were further compared using SPSS 11.0.

Results: An immediate increase followed by a decrease in cortical uptake was noted while the basal ganglia uptake remained high, albeit with a decreasing trend. Typical antipsychotics were associated with lower frontal cortical and higher basal ganglia and cerebellar uptake as compared to atypical antipsychotics.

Conclusion: The differential influence of the type and duration of antipsychotic on glucose uptake suggests a possible trend towards long-term side effects with typical medications that were not noted on clinical examination. This however needs to be confirmed with larger, controlled studies.

KEY WORDS: Positron emission tomography, antipsychotics, schizophrenia

There is extensive literature on the structural and functional brain abnormalities of schizophrenia. Functional modalities such as single photon emission computed tomography (SPECT) and positron emission tomography (PET - O15 and FDG) examine blood flow and metabolism respectively. Receptor-ligand studies evaluate the role of various neurotransmitters such as dopamine and the actions of different antipsychotics on these receptors. Glucose provides the energy for pumping ions involved in the propagation of action potentials and in the maintenance of membrane potential. Glucose use and thus, neuronal activity may be reflected in the differences in regional rates of glucose metabolism—the principle of FDG PET.

One of the most consistent PET abnormalities described in schizophrenia is hypofrontality associated with the deficit syndrome.[1] Positive symptoms such as delusions have been correlated with increased blood flow in the left mesiotemporal structures.[2] Hallucinations, another common symptom in schizophrenia, have been hypothesized as a dysfunction of the ‘sensory gating apparatus’—the thalamus.[3] Similar changes in cerebral glucose metabolism associated with positive and negative types of schizophrenia have been reported from India.[4] Among the dysfunctional areas is the anterior cingulate cortex that plays an important role in the regulation of emotions.[5] The cerebellum is involved in working memory, language processing and motor coordination and is associated with ‘cognitive dysmetria’ in schizophrenia.[6] The failure to identify a single primary site has led to investigation into various disconnection syndromes (e.g., dysfunctional fronto-thalamo-striatal circuit) associated with behavioral disturbances. This picture gets further complicated by the presence of psychotropic medications, particularly antipsychotics.

Antipsychotics form the mainstay of schizophrenia treatment.
Antipsychotics are broadly categorized into two groups: conventional/typical and atypical antipsychotics. Atypical antipsychotics have been credited with superior physical and cognitive side-effect profiles over conventional (typical) antipsychotic medications. Contrary to early presumptions, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE)\(^\text{[7]}\) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS)\(^\text{[8]}\) studies established that atypical and conventional medications have comparable efficacy and result in similar quality of life. Antipsychotics act by altering neurotransmitter balance in different brain regions. While typical antipsychotics primarily block dopaminergic D\(_2\) receptors, atypical antipsychotics act on both dopaminergic and serotonergic receptors. This action on neurotransmitters is translated into differential glucose metabolism in different brain regions. Studies have established that cerebral glucose uptake is influenced by both duration\(^\text{[9,11]}\) and type\(^\text{[12,13]}\) of antipsychotic. In this pilot study, we attempted to understand the effect of antipsychotic on brain glucose metabolism in individuals with schizophrenia.

**Materials and Methods**

This cross-sectional study was carried out by the psychiatry department of a tertiary care hospital in collaboration with the Radiation Medicine Centre following approval from the Institutional Ethics Committee. Eighteen males with an ICD-10\(^\text{[14]}\) diagnosis of schizophrenia and active psychotic symptoms, i.e., Positive and Negative Symptom Scale\(^\text{[15]}\) (PANSS) scores above 70 participated in the study. Patients with other comorbid Axis I diagnoses, substance abuse or dependence except nicotine dependence, mental retardation on clinical evaluation, past or current history of neurological illness or other medical illness and with blood sugar > 120 mg/dl were excluded. None of the patients had any extrapyramidal symptoms or any abnormal movements on physical examination. All patients were administered an Informed Consent Form in the language they understood (Hindi/Marathi). Consenting patients underwent FDG PET scan of the brain within 24 hours of psychiatric assessment.

Participants were advised to undergo overnight fasting and their blood sugar levels were checked prior to the scan. It was ensured that the last dose of antipsychotic in all medicated patients was administered 12 hours prior to the scan. An average dose of 200 MBq (160-230) of \(^{18}\)F-2-fluoro-2-deoxyglucose \(^{18}\)F-FDG was injected. Participants subsequently rested in a quiet, well-lit room and were asked to refrain from talking. Acquisition was carried out 30 minutes after the injection.

Cerebral metabolism of glucose was examined using a GE Advance PET System scanner NXI. The scanner has a transaxial resolution of 4.8 to 6.2 mm FWHM (Full Width Half Maximum) depending upon the distance from the center and an axial resolution of 4.0 to 6.6 mm FWHM. Emission scans of 70 slices were obtained parallel to the cantho-meatal line from the vertex to the neck. Transmission scans were obtained for the same region using Germanium-68 rod sources to carry out measured attenuation correction. The images were reconstructed using the ordered subsets expectation maximization (OSEM) algorithm. These images were reformatted and converted into 17 trans-axial slices of 8.3 mm thickness that were used for analysis.

Regional glucose metabolism was examined in 14 predetermined Regions of Interest (ROI)—elliptical ROIs for cortical (frontal, medial temporal, lateral temporal, parietal and occipital) and subcortical structures (basal ganglia, thalamus) and circular ROIs for cerebellar hemispheres. The size of the ROI for cortical and subcortical areas was kept at 6.31 sq. cm, the pixels varying from 46 to 52. The ROI for cerebellum was 14.03 sq. cm and pixels ranged from 96 to 104. Blinding was achieved by predetermining the location, shape and sizes for the ROIs. The maximum uptake values in these ROIs were further converted into relative uptake values (rUVs), the normalizing factor being the average uptake in the occipital lobes. These rUVs were used for all analyses.

On the basis of their treatment profiles, the patients were categorized into four groups: Group 1 (n=6) included patients who had not received any treatment for one year prior to assessment, Group 2 (n=5) included patients who had received treatment for less than one month, Group 3 (n=4) included treatment for 1-6 months and Group 4 (n=3) comprised of patients who had received treatment for more than six months. The maximum duration of treatment was 11 months and the minimum was one week. Four patients had received treatment with atypical antipsychotics (Group III), two each with olanzapine and risperidone. All the rest (eight out of 12) had received typical antipsychotic drugs (haloperidol and trifluoperazine, Group II)\([\text{Table 1}]\). Finally, in order to compare the influence of the amount of antipsychotic, the doses of antipsychotics were converted into chlorpromazine units (2 mg Haloperidol—5 mg Trifluoperazine—2 mg Risperidone—5 mg Olanzapine—100 mg Chlorpromazine (CPZ)).\[^{[16]}\]

**Results**

The analysis was carried out using Statistical Package for Social Sciences 11.0. (SPSS, Chicago, IL, USA). Table 1 describes individual patient profiles. All the groups considered under both variables, duration and type of antipsychotic were comparable in terms of age, chronicity of illness and severity of psychosis as assessed on the Positive and Negative Syndrome Scale (PANSS) \((P > 0.05)\). Relative glucose metabolism in most cortical ROIs showed an immediate increase with treatment (Group 2)\([\text{Figure 1}]\). However, with increasing duration of treatment (Groups 3 and 4), uptake values decreased to being lower than those of the unmedicated group. In the basal ganglia, uptake values were higher in all treatment groups (Groups 2, 3 and 4) as compared to the never-medicated group (Group 1). Uptake in the basal ganglia also showed a trend towards reduction with increasing duration of medication, being highest in individuals with less than six months’ medications and lowest in Group 4 \((P < 0.05)\), ANOVA—df 3,26,29). Amount of antipsychotic correlated negatively with most cortical ROIs, significantly with left lateral temporal rUV \((P < 0.05)\) (exceptions were
Table 1: Description of participant age, duration of illness, PANSS scores, and medications

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>DOI</th>
<th>PANSS</th>
<th>Medication</th>
<th>CPZ</th>
<th>Type</th>
<th>DOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>5y</td>
<td>31</td>
<td>16 89 No Treatment for 2 years. Past treatment with haloperidol.</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>3y</td>
<td>28</td>
<td>23 91 No Treatment for 3 years. Past treatment with trifluperazine.</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>10y</td>
<td>13</td>
<td>37 106 Olanzapine for 8 mths. Past treatment with Trifluperazine</td>
<td>100</td>
<td>III</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>2y</td>
<td>21</td>
<td>27 97 Trifluperazine for two months. No past treatment.</td>
<td>300</td>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>26</td>
<td>4y</td>
<td>18</td>
<td>23 87 Trifluperazine and chlorpromazine for 11 months. No past treatment</td>
<td>213</td>
<td>II</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>2y</td>
<td>15</td>
<td>35 114 Trifluperazine for 6 months. No past treatment</td>
<td>300</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>1y</td>
<td>31</td>
<td>31 119 Haloperidol for 22 days. No past treatment</td>
<td>875</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>45</td>
<td>19y</td>
<td>24</td>
<td>32 108 No Treatment for 3 years. Past treatment with trifluperazine</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>34</td>
<td>7y</td>
<td>29</td>
<td>22 104 Trifluperazine for 4 days. Past treatment 4 years ago</td>
<td>300</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>25</td>
<td>12y</td>
<td>23</td>
<td>12 89 Trifluperazine for 4.5 months. Past treatment with trifluperazine</td>
<td>366</td>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>34</td>
<td>15y</td>
<td>31</td>
<td>14 90 Risperidone for 1.5 months. No past treatment</td>
<td>40</td>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>5y</td>
<td>9</td>
<td>34 87 Risperidone for 6 months. No past treatment</td>
<td>60</td>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td>33</td>
<td>1y</td>
<td>26</td>
<td>16 80 Trifluperazine for 10 days. No past treatment</td>
<td>435</td>
<td>II</td>
<td>2</td>
</tr>
<tr>
<td>29</td>
<td>7y</td>
<td>23</td>
<td>13 80 No Treatment for 5 years. Treated for 5 months with Trifluperazine</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>3m</td>
<td>27</td>
<td>24 101 Olanzapine for 10 days. No past treatment</td>
<td>100</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>7m</td>
<td>28</td>
<td>23 91 Never-medicated</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>8y</td>
<td>26</td>
<td>20 99 Never-medicated</td>
<td>NA</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>6y</td>
<td>12</td>
<td>23 106 Trifluperazine and chlorpromazine for 8m. Past treatment</td>
<td>600</td>
<td>II</td>
<td>4</td>
</tr>
</tbody>
</table>

DO I - Duration of illness; DOM - Duration of medication; CPZ - Amount of medication (doses), +: Positive symptoms; -: Negative symptoms, NA - Not Applicable

rUVs in the frontal ROIs were lower in individuals on typical antipsychotics (II) than those that had not received any treatment (I) [Figure 2]. In contrast, individuals on atypical antipsychotics (III) had increased cerebral glucose uptakes in all cortical ROIs as compared to the other two groups, i.e., never-medicated participants (III) and participants on typical antipsychotics (II). The uptake in the basal ganglia and left cerebellum was highest in individuals on typical antipsychotics (II). Thalamic uptake was lower in medicated individuals (II and III) than in unmedicated individuals (I). None of these differences attained statistical significance (ANOVA, df—2,14,16). Figure 3 illustrates the difference in cortical and
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basal ganglia uptake in the three types of medicated groups: a: unmedicated (I), b: typical antipsychotics (II) and c: atypical antipsychotics (III).

Discussion

‘Hypofrontality’ has been one of the most consistently reported effects of antipsychotics. In our study, glucose metabolism showed a varying trend with increasing duration of treatment in the cortex as well as in the basal ganglia. Metabolism in the cortical regions showed an initial rise from the never-medicated state followed by a decrease. Basal ganglia metabolism, on the other hand, decreased with increasing duration but continued to remain higher than the never-medicated individuals. Contrary to our observation, Szechtman et al. did not note any cortical alterations. Instead, they observed that one year of antipsychotic alters metabolic activity in the corpus striatum. Antipsychotics acutely increased metabolism in the temporal lobes, basal ganglia and putamen while chronic haloperidol use decreased absolute cerebral glucose metabolism. Desco et al. reported that chronic administration of haloperidol was associated with increase in cerebellar, basal ganglia and motor cortex.

Figure 2: Variations in Mean relative uptake values (rUVs) in the Regions of Interest (ROI) between the different types of antipsychotic to the unmedicated group

Figure 3: (A) Cortical and basal ganglia glucose uptake in resting FDG PET scans in unmedicated schizophrenics, (B) Typical antipsychotic showing increased basal ganglia uptake, (C) Atypical antipsychotic showing increased cortical uptake
and inferior temporal metabolism. This differential uptake according to duration may explain the temporal relationship of development of side effects—acute dystonic reactions as a result of an immediate increase in basal ganglia uptake followed by extrapyramidal symptoms, (also suggested by Desco et al.[10]) and finally, Neuroleptic-Induced Deficit syndrome with long-term administration.

Conventional antipsychotics differ from atypical antipsychotics in their mechanism of action and hence, their influence on brain metabolism.[17,21] Individuals on typical antipsychotics as compared to the other two groups, showed the highest cerebral glucose uptake in the basal ganglia and the left cerebellum. In contrast, these individuals had the lowest glucose uptake in the frontal ROIs. These changes in the cortical and subcortical regions are similar to the cross-sectional findings of Miller et al.[21] In a longitudinal study comparing the metabolic effects of long-term haloperidol, Molina et al.[23] confirmed increased subcortical effect of typical antipsychotics as compared to risperidone. They also noted that the difference in cortical metabolism between the haloperidol and risperidone groups was minimal. Cohen et al.[24] and Potkin et al.[20] reported that clozapine was associated with greater prefrontal hypoactivation as compared to typical antipsychotics. This was not observed by us or Molina and co-workers[21] Both these studies studied atypicals other than clozapine, which acts on many more neurotransmitters in addition to serotonin and dopamine, probably accounting for the difference in the findings. The greater incidence of deficit and extrapyramidal symptoms among patients on typical as compared to atypical antipsychotics may be explained by these differential uptakes of the frontal cortex and the basal ganglia. The study also confirmed Miller et al.’s[21] finding of a greater decrease in cerebellar metabolism, albeit only unilaterally, in the atypical group as compared to individuals on typical medications. The increase in cerebellar metabolism resulting from typical antipsychotics has been postulated as contributory to the motor side effects of typical antipsychotics. The higher cortical uptake in individuals on atypical antipsychotics as compared to the unmedicated schizophrenic may indicate a trend towards normalization as glucose metabolism in schizophrenia is generally lower than in normal individuals.

Our study was limited in its cross-sectional nature, random sampling, small sample size and multiple statistical analyses. The amount of antipsychotic could also have acted as a potential confounding factor. Plasma drug level forms the most accurate description; we quantified drug doses in terms of chlorpromazine units—a clinical efficacy measure. Four unmedicated participants in our study had received medications in the past. Total lifetime dose of antipsychotic could have confounded the observations in this group; however it is generally accepted that the effect of antipsychotics on cerebral metabolism is washed off in a few months. Earlier studies that have studied the influence of antipsychotics following a switch from typical to atypical have indicated similar washout periods.[22,23] The cognitive state of the individual at the time of the scan is known to influence glucose uptake and could mask the influence of medication.[11] Participants in our study were not administered any activation procedures. The scans were performed in a subjective resting state, thereby assessing ‘cerebral metabolic tone’.

Participants in our study were in different phases of their illness; most individuals with less than seven days of medication were in acute exacerbation that merited higher doses of medications for therapeutic effects. The participants in later phases received comparatively lower doses as their clinical condition had stabilized. Individuals also differed in symptomatology—positive symptoms warrant higher doses than negative symptoms. The differing severity and type of symptoms, although statistically comparable among the different groups, may have influenced glucose uptake.

The complex nature of the schizophrenic illness has constrained most functional imaging studies on antipsychotics. Future studies could longitudinally examine large cohorts of schizophrenics, preferably medication-naive, at various stages of their treatment (including exacerbations). Some of the adverse effects of antipsychotics such as tardive dyskinesia, have been known to develop after many years of treatment. This, in turn, suggests that in order to definitively establish any long-term differences, this cohort may have to be followed for probably as long as twenty years.

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