Changes of some oxidative stress markers in schizophrenia: comparison between typical and atypical antipsychotics effects

M. Padurariu[1], A. Ciobica[2] , I. Dobrin[1], C. Stefanescu[1]

[1]Socola Hospital-Gr.T. Popa University of Medicine and Pharmacy, Dept. of Psychiatry, Iasi, Romania

[2]Al. I. Cuza University, Dept. of Biology, Iasi, Romania

Socola Hospital
Iasi, Romania

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Introduction

Studies performed in schizophrenia patients have generally suggested a compromised antioxidant system, but this is not always consistent with specific observed parameters, which on the whole, show evidences of dysregulation. Reduced levels of the antioxidant enzymes are generally reported in patients with schizophrenia compared with controls [1]. However, some studies have advocated a strengthening of antioxidant status in schizophrenia [2].

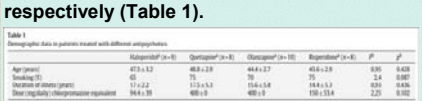
There are also controversies regarding the oxidative stress status in patients treated with typical vs. atypical antipsychotics [3,4].

The aim of the present work was to evaluate the specific activity of some peripheral antioxidant defences (SOD and GPX) and the level of MDA (lipid peroxidation maker), in schizophrenic patients treated with typical (haloperidol) or atypical (olanzapine, quetiapine and risperidone) antipsychotics, compared with age-matched healthy subjects.

Material and methods

The subjects of this study (n = 45), consisted of 35 patients (26 males and 9 females; age 46.1±2.9 years) who met DSM-IV criteria for schizophrenia [3], recruited from the Psychiatry University Hospital, Iasi, Romania and 10 healthy control age and gender-matched subjects (7 males and 3 females; age 43.25±5.2 years).

Patients were of paranoid subtype, with duration of illness for at least 5 years. They all had been receiving stable doses of oral neuroleptic medications for at least two years prior this study. Nine patients were under haloperidol (1–2mg daily dose) treatment and 26 (8/10/8) patients were under atypical treatment: quetiapine (300mg daily dose), olanzapine (20mg daily dose) or risperidone (2–4mg daily dose), respectively (Table 1).



Blood samples were collected in the morning, before breakfast, allowed to clot and centrifuged immediately. Serum was aliquoted into Eppendorf tubes and stored at −80 ◦C until measurement (figure 1).

Superoxide dismutase (SOD) activity was measured by the percentage reaction inhibition rate of enzyme with WST-1 substrate (a water soluble tetrazolium dye) and xanthine oxidase using a SOD Assay Kit (Fluka, 19160), while glutathione peroxidase (GPX) activity was measured using the GPX cellular activity assay kit CGP-1 (Sigma Chemicals). MDA levels were determined by thiobarbituric acid reactive substances (TBARs) assay (figure 1).

Figure 1. Biochemical determinations.

Results

Initial analysis of our results included all schizophrenic patients, regardless of their treatment. In this way, biochemical data showed a significant increase of SOD specific activity ($F(1,43) = 11$, $p = 0.001$) in all subjects with schizophrenia, compared to control group.On the contrary, the specific activity of GPX, the other enzymatic antioxidant defence, was significantly decreased ($F(1,43) = 5$, $p = 0.02$) in schizophrenics group, in comparison with control subjects. In addition, we found that the levels of lipid peroxidation marker MDA were significantly increased ($F(1,43) = 46$, $p = 0.0002$) in the serum of the schizophrenic patients, compared to control group.

When we analyzed separately the effects of haloperidol, quetiapine, olanzapine and risperidone on oxidative stress markers vs. control group, we observed an increased level of SOD specific activity in patients treated with haloperidol ($F(1,17) = 6$, $p = 0.01$) and quetiapine ($F(1,16) = 49$, $p = 0.0002$) treated patients. However, no significant changes were reported in the olanzapine ($F(1,18) = 3$, $p = 0.07$) and risperidone ($F(1,16) = 4$, $p = 0.06$) groups (Fig. 1).

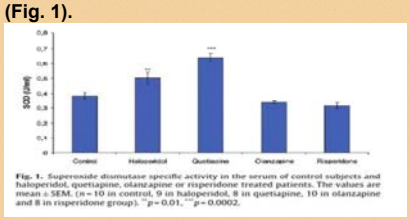


Fig. 1. Superoxide dismutase specific activity in the serum of control subjects and haloperidol, quetiapine, olanzapine or risperidone treated patients. The values are mean ± SEM. ($n = 10$ in control, 9 in haloperidol, 8 in quetiapine, 10 in olanzapine and 8 in risperidone group). $^{**}p = 0.01$, $^{***}p = 0.0002$.

Also our results showed no significant modifications of GPX specific activity in quetiapine ($F(1,16) = 3$, $p = 0.08$) and olanzapine ($F(1,18) = 3$, $p = 0.08$) group, compared to the control group. In addition, haloperidol ($F(1,17) = 7$, $p = 0.01$) and risperidone ($F(1,16) = 24$, $p = 0.0001$) treatment resulted in a significant decrease of GPX activity (Fig. 2).

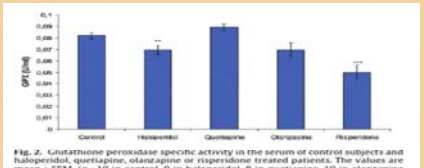


Fig. 2. Glutathione peroxidase specific activity in the serum of control subjects and haloperidol, quetiapine, olanzapine or risperidone treated patients. The values are mean ± SEM. ($n = 10$ in control, 9 in haloperidol, 8 in quetiapine, 10 in olanzapine and 8 in risperidone group). $^{**}p = 0.01$, $^{***}p = 0.0001$.

In the case of MDA concentration we observed a very significant increase in all four treated groups–haloperidol ($F(1,17) = 30$, $p = 0.0008$), quetiapine ($F(1,16) = 44$, $p = 0.0005$), olanzapine ($F(1,18) = 29$, $p = 0.0003$) and risperidone ($F(1,16) = 105$, $p = 0.0001$), compared to control subjects (Fig. 3).

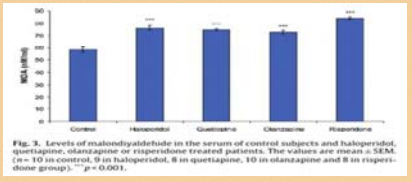


Fig. 3. Levels of malondiyaldehide in the serum of control subjects and haloperidol, quetiapine, olanzapine or risperidone treated patients. The values are mean ± SEM. ($n = 10$ in control, 9 in haloperidol, 8 in quetiapine, 10 in olanzapine and 8 in risperidone group). $^{***}p < 0.001$.

Results

The relationship between the antipsychotic dose (chlorpromazine equivalent) and oxidative stress parameters was also determined. Doses equivalent to 100 mg/day of chlorpromazine and 2mg/day of haloperidol were 75 mg/day for quetiapine, 5mg/day for olanzapine and 2mg/day for risperidone [36]. No significant correlations were found between antipsychotic dose vs. SOD activity ($n = 35$, $r = 0.187$, $p = 0.281$) or antipsychotic dose vs. GPX activity ($n = 35$, $r = 0.383$, $p = 0.063$). However, in the case of antipsychotic dose vs. MDA level, a relatively low strength of correlation was associated with a statistically significant p value ($n = 35$, $r = -0.424$, $p = 0.011$).

Discussion and Conclusions

Our results provide additional evidence of increased oxidative stress in schizophrenia, expressed by altered antioxidant enzyme activity and increased levels of lipid peroxidation. In our study, we found a significant decrease in GPX specific activity and also a significant increase of MDA levels in schizophrenic patients, regardless of their type of treatment. In addition, we observed an increase in SOD activity, that could serve as a compensatory mechanism. Further research is necessary for elucidating the effect of different antipsychotic agents on antioxidant enzymes and lipid peroxidation or the possible use of antioxidant supplementation as a therapeutic strategy.

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Disclosure

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