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INCREASED CALCIUM-INDEPENDENT LIPOPROTEIN PHOSPHOLIPASE A2 BUT NOT PROTEIN S100 IN PATIENTS WITH SCHIZOPHRENIA

Maristela Šakić[1], Dalibor Karlović[1,2], Branka Vidrih[1,2], Vjekoslav Peitl[1], Danijel Crnković[1] & Nada Vrkić[3]

[1]Department of Psychiatry, University Hospital Center "Sestre Milosrdnice", Zagreb, Croatia
[2]Croatian Catholic University, Zagreb, Croatia
[3]Department of Clinical Chemistry, University Hospital Center "Sestre Milosrdnice", Zagreb, Croatia

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SUMMARY

Background: *The aim of this paper was to investigate serum concentrations of calcium-independent lipoprotein phospholipase A2 (PLA2) and protein S100 in schizophrenia patients in comparison to healthy controls and correlate them with the clinical severity, duration, and number of schizophrenia relapses.*

Subjects and methods: *This study included 65 schizophrenia patients and 70 controls. Schizophrenia was diagnosed according to DSM-IV-TR criteria. Clinical severity was determined by PANSS. PLA2 and protein S100 concentration were assessed by the enzyme-linked immunosorbent assay (ELISA).*

Results: *PLA2 concentrations were higher in patients with schizophrenia, whereas protein S100 concentrations were not. Higher concentrations of PLA2 were positively correlated with the duration of illness and number of episodes, as determined by multivariate analysis.*

Conclusion: *PLA2 might be considered a possible biochemical trait marker for schizophrenia. Further research with larger and more homogeneous clinical samples is required.*

Key words: *schizophrenia - calcium-independent phospholipase A2 - protein S100*

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INTRODUCTION

Calcium-independent phospholipases A2 (PLA2) are key factors in phospholipid metabolism. Their activity defines the content and functionality of cell membranes in the brain; they are included in brain's maturation and synaptic remodeling (St-Gelais et al. 2004, Schaeffer & Gattaz 2005). In the process of dopamine, serotonin and glutamate neurotransmission, PLA2 leads to the increase of the second messenger level, most often arachidonic acid (Garcia & Kim 1997). According to some hypotheses, a genetically conditioned abnormal function of PLA2 may underlie the basis of schizophrenia and it interferes with the normal brain maturation, which results in dysfunctional monoamine transmission (Law et al. 2006).

The majority of published papers reported an increased activity of PLA2 in serum in case of schizophrenic patients (Gattaz et al. 1987, Gattaz et al. 1990, Lasch et al. 2003, Ross et al. 1997, Ross et al. 1999, Tavares et al. 2003), with only one exception (Katila et al. 1997) and one reported that the increased PLA2 activity was characteristic of first episode, but not of chronic patients (Smesny et al. 2005). Such findings suggest accelerated phospholipid degradation in cell membranes of schizophrenic patients, especially in drug naïve patients (Horrobin et al. 1991, Pettegrew et al. 1991). One study showed that the eight-week therapy with antipsychotics led to a decrease of PLA2 activity (Gattaz et al. 1987), i.e. the increased PLA2 activity was connected with the severity of clinical feature and the progress of the disease (Ross et al. 1997).

On the other hand, protein S100 is primarily produced in astrocytes and is included in energy metabolism in brain cells, modulation of proliferation, and differentiation of neurons and glia cells. Several studies support an association of S100 concentrations and schizophrenia. Most studies report increases in serum and CSF S100 levels in acute and chronic stages of schizophrenia (Lara et al. 2001, Ling et al. 2007, Rothermundt et al. 2001, Rothermundt et al. 2004a,b, Schroeter et al. 2003, Wiesmann et al. 1999). Some studies have also reported correlations between S100B levels and clinical features of schizophrenia, mostly with negative symptoms (Ling et al. 2007, Rothermundt et al. 2004a, Schmitt et al. 2005, Schroeter et al. 2003, Wiesmann et al. 1999). Antipsychotic treatment may affect S100B levels in schizophrenia, however there are inconsistent findings. Increased (Schroeter et al. 2003), decreased S100B concentrations (Ling et al. 2007, Rothermundt et al. 2001, Sarandol et al. 2007, Steiner et al. 2009) and no effects (Schroeter et al. 2009) have been reported in medicated patients compared to unmedicated patients.

The number of papers which bring into connection phospholipase A2 and protein S100 is limited, however

one in vitro study showed that protein S100 directly inhibited the activity of PLA2 (Wu et al. 1997). The aim of our study was to determine the level of PLA2 and protein S100 in schizophrenia patients in comparison to healthy controls and to investigate correlation of PLA2 and protein S100 with the severity and duration of clinical feature.

SUBJECTS AND METHODS

Subjects

The schizophrenia study group consisted of 65 patients (55 males and 10 females), aged between 26 and 67 years. The duration of disorder ranged from 1 to 15 years. All the investigated patients did not have any other psychiatric comorbid disorder. They had negative history of alcohol or other drugs abuse. All subjects were free of past and chronic physical illnesses or any other medical problems and medications. Twenty one subjects in the schizophrenia group were patients with a first episode of the disease; 12 of them were drug naïve and 5 had been without drugs 30 to 45 days prior to the inclusion in the study. 44 subjects in the schizophrenia group had a second episode, 26 of them having been without any medication 30 to 45 days prior to the inclusion in the study. The subjects with schizophrenia who had been on pharmacotherapy at the time of the study, 4 in the group of first psychosis and 18 in the group of relapsed disease were treated with quetiapine (N=7), risperidone (N=5), olanzapine (N=4), clozapine (N=3), ziprasidone (N=2) and haloperidol (N=1).

The control group consisted of 70 healthy subjects, 52 males and 18 females, volunteer blood donors from the Institute for Transfusion Medicine, aged between 27 and 61 years. They had no psychiatric or medical disorders, and alcohol or drug abuse on the basis of unstructured interviews. The informed consent was obtained from patients and controls after complete and extensive description of the study profile. The study was approved by the Hospital Ethics Committee. Socio-demographic and clinical parameters of all the included subjects are shown in Table 1.

Medical examination and study design

From the total pool of all patients (N=228) who were hospitalized and receiving treatment at the Department of Psychiatry in University Hospital from August 2010 to January 2011, we elected our study group which consisted of patients with schizophrenia (N=65). Patients with other psychiatric disorders (N=92), and comorbid psychiatric disorders (N=38) with, or somatic conditions (N=32) with schizophrenia were excluded from the study. Moreover, the patients who did not give the informed consent were excluded from further study (1 patient in the schizophrenia group). Diagnosis of schizophrenia was based on DSM-IV-TR classification (APA 2000).

Table 1. Sociodemographic and clinical characteristics of patients with schizophrenia (N=65), and healthy control group (N=70)

	Schizophrenia	Control group	Statistics
Sex: N(%)			χ^2=2.188; df=1; p=0.139
Male	55 (84.6.5)	52 (74.3)	
Female	10 (15.4)	18 (25.7)	
Education: N(%)			χ^2=3,721; df=2; p=0.156
Elementary	6(9.2)	6 (10.0)	
High school	43 (66.2)	30 (50.0)	
University	16 (24.6)	24 (40.0)	
Marital status: N(%)			χ^2=14.844; df=1; p=0.001
Single	43 (66.2)	19 (31.7)	
Married	22 (33.8)	41 (68.3)	
Working status: N(%)			χ^2=30.524; df=2; p=0.001
Unemployed	17 (26.2)	5(8.3)	
Employed	20(30.8)	48 (80.0)	
Retired	28(43.1)	7(11.7)	
Place of residence: N(%)			χ^2=0.450; df=1; p=0.503
Urban	53 (81.5)	46 (76.7)	
Rural	12 (18.5)	14 (23.3)	
Age in years (mean ± SD)	41.96±13.2	43.2±12.4	t=-0.550; df=133; p=0.584
No. of hospitalizations (mean ± SD)	5.26±4.27	N.A.	
Duration of disorder in years (mean ± SD)	1.7±0.65	N.A.	
PANSS-P	17.6±7.18	N.A.	
PANSS-N	23.9±6.6	N.A.	
PANSS-G	47.86±14.56	N.A.	
PANSS-T	89.35±25.46	N.A.	

Diagnoses were made for each patient by two independent experienced psychiatrists and confirmed by the structured clinical interview for DSM-IV (SCID IV) (First et al. 1995). Psychiatric symptoms were evaluated by the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987) at the time of hospital admission, during the illness acute state which required hospitalization. They were all of paranoid subtype.

Blood sample collection and PLA2 and protein S100 determination

Blood samples from antecubital vein (8 ml) were collected in a plastic syringe without anticoagulant at 08.00 AM, after overnight fast and 30-minute resting immediately before the blood collection. Blood was allowed to clot for 30 minutes at room temperature. Serum was obtained after a 10-minute blood centrifugation at 1500 g. Serum PLA2 concentration was determined by turbidimetric immunoassay using commercial kits (DiaDexus, San Francisco, USA) with analytical sensitivity for the assay at 4 ng/mL. Serum protein S100 concentration was determined by EIA method using the commercial kits (DRG Diagnostics, Germany) with analytical sensitivity for the assay at 9 ng/L. All the analyses were duplicated the same day when blood was collected. The interassay coefficient of variation for PLA2 and protein S100 concentrations in our laboratory was 2.1% and 2.4% respectively.

Statistical Analysis

Normal distribution for all measures and for each group was assessed by the Kolmogorov-Smirnov test. Sociodemographic and clinical characteristics of patients and healthy control subjects were compared by Chi-square and by Independent Samples T-Test. Serum concentrations of PLA2 and protein S100 were compared between patients and control group by the Independent Samples T-Test. The correlation between the serum concentrations of PLA2 or protein S100 was analyzed using the parametric Pearson correlation. Type of correlation between PLA2 and protein S100 with number of schizophrenia relapses, duration of schizophrenia in years, and intensity of schizophrenia symptoms based on PANSS with age in years and antipsychotic therapy as co-variants was determined by multivariant regression analysis.

Alpha values were considered significant at 0.05 level. Our sample had a post-hoc sufficient power (0.80) to detect medium effect sizes (d=0.431). When it comes to the correlation analysis, our sample had a post-hoc sufficient power (0.80) to detect large effect sizes (q=0.438). For multiple regression analysis our sample had a post-hoc sufficient power (0.80) to detect medium to large effect sizes (f2=0.264). Statistical analysis was done using SPSS software (SPSS for Windows 17.0, SPSS, Chicago, IL, USA), a power analysis was performed with the use of G·Power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/).

RESULTS

There were no differences in age, education, place of residence and gender between subjects with schizophrenia and the healthy control group, but there were differences between the two study groups in marital status and working status because subjects with schizophrenia were mostly single and unemployed (Table 1).

Table 2. Multiple linear regression analysis of correlation between serum concentration of PLA2 or S100 protein with clinical traits of schizophrenic patients

Dependent variable	Independent variable	B	Standard error	β	t-value	Significance (p)	95.0% Confidence Interval for B	
							Lower Bound	Upper Bound
Phospholipase A2	Number of relapses	7.061	2.814	0.342	2.509	0.015	1.423	12.698
	Duration of disorder	29.576	13.133	0.284	2.252	0.028	3.268	55.884
	PANSS positive	-0.077	2.027	-0.006	-0.038	0.970	-4.138	3.984
	PANSS negative	0.363	1.955	0.026	0.186	0.853	-3.552	4.278
	PANSS general	-1.375	0.962	-0.176	-1.428	0.159	-3.303	0.553
	Antipsychotic drugs	-29.432	20.082	-0.164	-1.466	0.148	-69.661	10.798
	Ages	0.284	0.809	0.045	0.352	0.726	-1.336	1.905
	Sex	-11.671	28.413	-0.049	-0.411	0.683	-68.588	45.247
Protein S100	Number of relapses	-1.555	1.092	-0.225	-1.424	0.161	-3.747	0.638
	Duration of disorder	1.305	5.170	0.038	0.252	0.802	-9.073	11.683
	PANSS positive	0.743	0.830	0.155	0.896	0.374	-0.922	2.409
	PANSS negative	-1.139	0.795	-0.233	-1.433	0.158	-2.734	0.456
	PANSS general	0.647	0.383	0.241	1.689	0.097	-0.122	1.415
	Antipsychotic drugs	-9.560	8.167	-0.159	-1.171	0.247	-25.956	6.835
	Ages	-0.023	0.328	-0.011	-0.070	0.944	-0.681	0.635
	Sex	15.645	11.168	0.200	1.401	0.167	-6.777	38.066

Subjects with schizophrenia showed differences in serum PLA2 concentrations (ng/mL) in comparison to the healthy control group (mean ± SD; 223.81±83.43 vs. 172.4±61.95; t=3.886; df=133; p=0.001). Moreover, subjects with schizophrenia showed no differences in serum protein S100 concentrations (ng/L) in comparison to the healthy control group (mean ± SD; 64.36±28.15 vs. 64.52±24.0; t=-0.27; df=133; p=0.979).

We also found a negative correlation, but statistically insignificant, between PLA2 and protein S100 concentrations in patients with schizophrenia (Pearson r=-0.308; p=0.07), while we did not find any correlation between PLA2 and protein S100 concentrations in the sample of healthy control subjects (Pearson r=257; p=0.18).

By multiple regression analysis of correlation between PLA2 concentration, duration of illness, number of episodes, PANSS score on positive, negative and general subscales (with antipsychotic therapy, age and gender as co-variants), we obtained statistically significant model (F=3.56; p=0.007). Duration of illness and number of relapses were correlated with PLA2 concentrations with statistical significance, while PANSS scores on positive, negative and general subscales with antipsychotic therapy, age and gender as co-variants did not show statistically significant correlation.

By multiple regression analysis of correlation between protein S100 concentration, duration of illness, number of episodes, PANSS score on positive, negative and general subscales (with antipsychotic therapy, age and gender as co-variants), we did not obtain statistically significant model (F=0.891; p=0.493). Duration of illness and number of relapses, PANSS scores on positive, negative and general subscales with antipsychotic therapy, age and gender as co-variants did not show statistically significant correlation with protein S100 concentrations (Table 2).

DISCUSSION

In the present study we conducted for the first time a simultaneous investigation of serum concentrations of PLA2 and protein S100 in patients with schizophrenia, their mutual relations and correlation with characteristics of schizophrenia clinical features.

According to our results, the level of serum concentration of PLA2 was higher in patients with schizophrenia when compared to the healthy control group. However, we did not find a significant difference in the concentration of protein S100. These results are in contrast with most of the studies published so far which found an elevated level of protein S100 in patients with schizophrenia (Wiesmann et al. 1999, Lara et al 2001). Some of the papers published so far have shown that the level of S100B protein lowered as the disease progressed suggesting that the protein was a marker of the early psychotic phase of the disease (Lara et al 2001). One of the possible reasons for the unchanged level of protein S100 in our patients, when compared to the healthy population, could be the fact that our patients were a mixed population of those with a first episode and those with long duration of the disease. Nevertheless, we did not find a correlation between the duration of the disease or number of relapses and the concentrations of S100. Some authors also found the association between protein S100 and the predominantly negative symptoms in the clinical feature (Rothermundt et al. 2004a). In our study we did not show the existence of correlation between protein S100 and the severity of clinical feature determined by PANSS score. However, our results are in consistence with the results of the study which did not confirm the existence of correlation between S100 proteins and the total PANSS and both subscale PANNS scores (Lara et al. 2001). The non-existence of correlation between a number of psychotic relapses and the duration of the disease, as well as the mentioned findings, could be explained by the limited influence of this growth factor on the pathophysiological mechanism of the disease itself.

As for PLA2, we observed that serum concentrations of this enzyme were significantly higher in the group of patients with schizophrenia compared to the control group. Such results are in accordance with the already published papers (Gattaz et al. 1987, Lasch et al. 2003). However, according to Smesny et al. (2005), PLA2 serum values are significantly increased only in schizophrenic patients with the first psychotic episode, while there was no difference in patients with multiple episodes when compared to the control group. These results are in direct opposition to our results which clearly illustrated connection of PLA2 concentrations with duration of disorder and number of relapses. In addition, no correlation was confirmed between the increased PLA2 concentrations and sex, ages, severity of positive, negative or general symptoms on PANSS scale or medication influence.

One of the aims of the study was also the analysis of the PLA2 and protein S100 association in the context of pathophysiology of schizophrenia and the defintion of their relation. Gattaz et al. 2000 made a hypothesis in their paper suggesting that the lowered level of protein S100B could lead to the increase of PLA2 activity. Although the mentioned studies stated only hypothetically a possible negative correlation of PLA2 and protein S100 in schizophrenia, we proved it for the first time. Negative correlation between S100 protein concentration and PLA2 concentration in schizophrenia can be explained by lack of influence of S100 protein on carboxyl region of PLA2 resulting in uninhibited growth of PLA2 concentration (Wu et al. 1997). In our study we found negative correlation between PLA2 and protein S100 but that negative correlation is not statisticaly significant.

So far there have been several attempts to connect changes in PLA2 with the psychopathology of schizophrenia. A positive correlation of BPRS summary

scores and positive symptoms with the increased PLA2 activity was found (Ross et al. 1997, Gattaz et al. 1990). However, our results show that there is no association between PLA2 activity and psychopathology determined by PANSS, which is in opposition to the mentioned studies.

We think the importance of PLA2 as a biological marker for schizophrenia should be further investigated mainly because new studies suggest that serum PLA2 is connected with the metabolism of cholesterol and the process of atherosclerosis (Caslake & Packard 2005, Brilakis et al. 2005). Since in schizophrenia the disorders of lipid metabolism are especially expressed, mainly as a consequence of atypical antipsychotics (Shen et al. 2014, Šagud 2015), we think that our results, as well as previous studies' results, which reported the increase of PLA2 in schizophrenia, could be an artifact which is not connected with the psychopathology of schizophrenia but with the change of lipid metabolism in schizophrenia as a direct consequence of antipsychotics. Having metabolic effects of antipsychotic therapy in mind we added antipsychotic therapy as co-variant in multiple regression analysis which did not show statistically significant impact of antipsychotic therapy on PLA2 concentrations. Nevertheless, the interrelation between PLA2 and change of lipids under the influence of antipsychotics should be further investigated.

This study has several limitations. Firstly, the included group of patients with schizophrenia is heterogeneous regarding the duration of the disease in comparison to subjects with first psychosis or patients with long lasting disease. The examined group is also heterogeneous regarding pharmacotherapy since we had a major number of subjects who were drug free or without pharmacotherapy for weeks, and a smaller number of subjects had been already receiving some pharmacotherapy, and according to studies conducted so far, antipsychotics can change the concentrations of PLA2 and protein S100 (Gattaz et al. 1987, Steiner et al. 2009). However, when controlling for those factors in a multivariate analysis, results did not confirm the influence of antipsychotic medication on PLA2 or protein S100 concentrations. We did not investigate serum lipids concentrations and their possible correlations with PLA2 in schizophrenic patients. In conclusion, we here reported that serum values of protein S100 do not differ in the group of patients with schizophrenia when compared to the control group, and that the concentrations of the protein S100 are not connected with the clinical feature of schizophrenia. Also, PLA2 values in patients with schizophrenia are increased, negatively correlated with protein S100 concentration, and positively connected with duration and schizophrenia relapses. PLA2 concentrations could be schizophrenia trait marker. Further studies should determine the significance of determination of PLA2 as a biological marker for schizophrenia.

CONCLUSION

To summarize, we found increased concentrations of PLA2 in schizophrenic patients. Furthermore, PLA2 concentrations were related to duration of illness and number of episodes, while we did not find a correlation with illness severity according to PANSS. In other words, PLA2 could be more of a trait than state marker of schizophrenia.

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Correspondence:
Professor Dalibor Karlović, MD, PhD
Department of Psychiatry, University Hospital Center "Sestre Milosrdnice"
Vinogradska cesta 29, 10 000 Zagreb, Croatia
E-mail: dalibor.karlovic@gmail.com