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Effects of antipsychotic treatment on membrane phospholipid metabolism in schizophrenia

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Summary. Several studies have shown an increased membrane phospholipid turnover in brain and blood cells of schizophrenic patients. However the specificity of these findings for schizophrenia and the effects of longterm antipsychotic treatment had yet to be demonstrated. In the present study we measured the concentrations of phospholipids in platelet membranes from 67 neuroleptic-free schizophrenic patients compared to both healthy and psychiatric controls, followed by repeated measurements during a 6 months antipsychotic treatment period.

At baseline, levels of the main phospholipid components phosphatidylcholine (PC) and phosphatidylethanolamine (PE) were decreased and lysophosphatidylcholine (LPC), a major breakdown product of phospholipid metabolism, was increased in schizophrenic patients compared to healthy and to psychiatric controls, suggesting a specificity of the findings for schizophrenia. During the first 3-weeks on antipsychotic drug treatment LPC levels decreased to control values, but increased again during the following 6 months, reaching significantly higher levels than controls at the end of this period. Thus, at least in peripheral cells an increased breakdown of phospholipids in schizophrenia appears to be present during the acute episode, being influenced only by initial antipsychotic treatment, but without evidence of a long lasting treatment effect on membrane metabolism.

Keywords: Schizophrenia, phospholipids, lysophosphatidylcholine, platelets, antipsychotic treatment.

Introduction

In the frontal lobe of drug-naive schizophrenic patients, an accelerated breakdown of membrane phospholipids has been demonstrated by ^{31}P-magnetic

resonance spectroscopy (P-MRS). Phosphomonoesters (PME), the precursors for membrane phospholipids were decreased and phophodiesters (PDE), breakdown products of various phospholipase enzymes, were increased (Pettegrew et al., 1991, 1993; Williamson et al., 1991; Deicken et al., 1993; Keshavan et al., 2000).

Although the in vivo determination of metabolic processes in the brain by MRS is a powerful method, single phospholipid membrane components cannot be measured using present technology. Therefore peripheral blood cells have been used as neuronal models to study metabolic processes on the cellular level in more detail. Platelets have frequently been used as models for neurons as they share similar membrane and some receptor characteristics (Rotman, 1983).

A number of studies have demonstrated altered membrane phospholipid components in platelets and erythrocytes of schizophrenic patients (reviewed by Rotrosen and Wolkin, 1987; Brody et al., 1987). Whereas the results were not consistent, probably due to different methods and tissues, one of the most replicated findings was decreased phosphatidylcholine (PC) and phosphatidylethanolamine (PE), which can be interpreted as an accelerated membrane phospholipid turnover in schizophrenia.

In a preliminary study, we found an increased concentration of lysophosphatidylcholine (LPC) in platelets of schizophrenic patients (Pangerl et al., 1991). LPC is the first breakdown-product of membrane components such as PC and PE. PE and PC are cleaved mainly by the enzyme phospholipase A_2 (PLA_2) into LPC and free arachidonic acid. Both metabolites serve as precursors for the synthesis of lipid messengers such as prostaglandins, leukotrienes and platelet-activating factor (Chang et al., 1987).

Several studies reported an increase in the activity of phospholipase A_2 in serum and platelets of neuroleptic free schizophrenic patients compared to healthy controls and non-schizophrenic psychiatric patients (Gattaz et al., 1990a,b, 1995; Ross et al., 1997). In contrast, Noponen et al. (1993) showed an elevated serum PLA_2 activity in other psychiatric patients as well, assessing the results as nonspecific for schizophrenia.

An effect of antipsychotic treatment on the phospholipase A_2 activity has been demonstrated in schizophrenic patients as elevated PLA_2 activity decreased after three weeks of antipsychotic drug treatment (Gattaz et al., 1987, 1994). It is known that the more classic antipsychotics such as haloperidol, fluphenazine and chlorpromazine inhibit PLA_2 activity by their amphiphilic character, affecting the substrate-enzyme interface (Chang et al., 1987).

It was the aim of the present study to clarify the specificity of altered phospholipid metabolism for schizophrenia by determining phospholipid membrane components in platelets of schizophrenic and nonschizophrenic psychiatric patients. Moreover, we investigated the effects of antipsychotics drugs on phospholipid metabolism during a six months treatment period.

Methods and materials

Subjects

The sample comprised 67 paranoid schizophrenic patients (30 men, 37 women, mean age 31.7 ± 9.2 years, mean duration of the disease 45 ± 57.2 months, mean ± SEM), 67 age- and gender-matched healthy controls and 66 age- and gender-matched nonschizophrenic psychiatric controls. The DSM-III-R diagnoses of the nonschizophrenic patients were major depression (31), adjustment disorder (10) personality disorder (14), bipolar affective disorder depressed (3) and generalized anxiety disorder (8).

Schizophrenic patients were diagnosed according to DSM-III-R checklist criteria. Thirty-seven Schizophrenic patients (16 men, 21 women, mean age 30.2 ± 9.9 years) were antipsychotic-naive, in the first episode of the disease. The remaining patients were drug-free for at least one week [12 ± 4.6 days (mean ± SD)]. Subjects were excluded, if they had any clinical or laboratory evidence of any significant somatic illness, drug and alcohol abuse or were taking some additional medication known to influence PLA_2 activity such as aspirine, glucocorticoids, anti-inflammatory agents, chloramphenicol or estrogens.

Fifty-three schizophrenic patients participated in our follow-up investigation at the end of the first week, 48 patients were followed-up after two and three weeks on standardized antipsychotic medication (haloperidol 10 mg/day) and 19 patients were re-examined after six months of treatment. After 3 weeks on standardized antipsychotic medication, patients received different antipsychotic drugs, including zotepine, clozapine, flupentixol and haloperidol, in sufficient clinical dosages.

At baseline examination the psychopathological state was assessed by the Brief Psychiatric Rating Scale (BPRS) (Mombour et al., 1975), the Psychological Impairment Rating Scale (PIRS) (Biehl et al., 1989) and the Present State Examination (PSE 9) (Wing et al., 1973). After one, two and three weeks, BPRS assessments were repeated. During the 6 months follow-up period, BPRS and PSE 9 were also re-examined.

In schizophrenic patients, phospholipid membrane components were determined during the follow-up period. In psychiatric inpatients, platelet phospholipids were investigated only at baseline during their acute state of the disorder.

Laboratory determinations

Platelets were obtained between 9 and 10 am from 20 ml venous citrated blood, separated by a washing and centrifugation procedure according to Patscheke (1984). Platelet morphology has been explored in earlier studies by microscopic investigation. These failed to reveal different findings in both structure and size between platelets from schizophrenic patients and controls. Screening in single cases of the three actually investigated patient and proband groups again revealed no evidence for morphological differences.

After isolation of platelets from whole blood, the samples were frozen immediately in Tris-saccharose buffer (pH 7,4) at −80° celsius.

After phospholipid extraction (Bligh and Dyer, 1959), total phosphorus content was assessed according to the method by Bartlett (1959). Phospholipid subfractions were determined by High Performance Thin Layer Chromatography (HPTLC) with 2,5-bis-[5-tert.-butylbenzoxazol(2′)]-thiophene (BBOT) as fluorescent detection agent (modified to Kraus et al., 1987). BBOT was incorporated into the methanol component of the chloroform-methylacetate-isopropanol-methanol-43 mmol KCl solvent system (25:25:25:10:9) (Touchstone et al., 1980). Fluorescence was measured at 366 nm UV light in a TLC scanner with a scan velocity of 0.5 mm/sec. Pairwise analyses were performed for each patient, healthy proband and psychiatric control. Internal phospholipid standards were evaluated on each HPTLC-plate. Phospholipid standards and BBOT were purchased from Sigma chemicals (Munich, Germany), HPTLC-Silica-Gel-60 plates were obtained from Merck (Darmstadt, Germany). Phospholipids were diluted in chloroform/methanol,

which is highly volatile at room temperature. This may be one reason, why total phospholipid concentrations exhibited high standard deviations. To offset this, we calculated single phospholipid concentrations in percent phospholipid subfraction from total phospholipid content.

Data were analyzed by non-parametric Wilcoxon Signed-Rank Test and Spearman correlation coefficients. Statistical analysis of the follow-up was performed by the non-parametric Friedman-Test. Because of nonnormal distributions of the variables to be analyzed only non-parametric tests were performed.

Results

At baseline the breakdown product LPC was significantly higher in schizophrenic patients as compared to healthy ($p < 0.01$) and to psychiatric controls ($p < 0.01$). PC levels were significantly decreased in schizophrenics compared to psychiatric controls ($p < 0.05$) and showed a trend to decrease compared to healthy controls ($p < 0.10$). In schizophrenic patients PE levels was non-significantly decreased in comparison to healthy controls ($p < 0.10$) (Table 1). The examination of phospholipid subfractions sphingomyelin, phosphatidylinositol and phosphatidylserine showed similar levels for all groups. Total platelet phospholipid content did not differ between schizophrenic patients and controls. The LPC level was correlated to PSE total score ($p < 0.05$) and to PSE subscores behavior and delusions ($p < 0.1$). BPRS and PIRS subscores did not correlate to biochemical variables (Table 3).

When the 37 first-episode schizophrenic patients and the schizophrenics with recurrent episodes were compared separately to their matched healthy controls, the significance for LPC differences was stronger in the neuroleptic-naive, first-episode patients. Compared to the whole subset of schizophrenics, there were no statistical group differences (Table 2). LPC levels in schizophrenics clustered into one subgroup with very low levels (near zero)

Table 1. Phospholipid component baseline levels in schizophrenic patients and controls

Phospholipid-subfraction	Schizophrenic patients Total sample	Healthy controls	Psychiatric controls
LPC %	11.7 ± 14.2	5.4 ± 6.3**	4.1 ± 5.9**
(concentration)	(63.27 ± 81.03)	(24.34 ± 45.22)	(23.32 ± 72.81)
PC %	25.8 ± 8.2	26.4 ± 9.1^{t}	28.6 ± 7.5*
(concentration)	(122.70 ± 59.19)	(143.04 ± 66.2)	(157.8 ± 78.54)
PE %	27.2 ± 9.4	30.3 ± 9.6^{t}	25.4 ± 8.9
(concentration)	(139.43 ± 63.76)	(162.9 ± 86.06)	(157.42 ± 64.14)

*$p < 0.05$; **$p < 0.01$; $^{t}p < 0.1$. The presentated p-values refer to Wilcoxon-Tests comparing schizophrenic patients (total sample) with (a) healthy controls and (b) psychiatric controls. Concentration of phospholipids is expressed as μg phospholipid/10^9 platelets. A significant group difference is found for the baseline LPC levels in schizophrenic patients compared to control groups. PC and PE levels showed a tendency to be decreased in schizophrenics compared to their matched healthy controls. PC levels were also decreased compared to nonschizophrenic patients. Between psychiatric controls and schizophrenic patients no group difference was found regarding PE levels

Table 2. Phospholipidlevels in first-episode, neuroleptic-naive schizophrenic patients and schizophrenics with recurrent episodes withdrawing from antipsychotics

Phospholipid-subfraction	First-episode schizophrenic patients n = 37	Schizophrenic patients with recurrent episodes n = 30
LPC %	12.17 ± 15.32**	10.47 ± 12.06*
(concentration)	(66.23 ± 90.85)	(59.56 ± 86.38)
PC %	27.1 ± 8.22	24.11 ± 7.89^{t}
(concentration)	(127.56 ± 65.41)	(116.73 ± 52.12)
PE %	26.29 ± 9.78^{t}	28.26 ± 9.39
(concentration)	(126.56 ± 72.56)	(155.29 ± 71.47)

*$p < 0.05$; **$p < 0.01$; $^{t}p < 0.1$. In neuroleptic-naive first-episode schizophrenic patients and schizophrenics with recurrent episodes, p-values relate to their appropriate age- and gender matched healthy controls. First-episode schizophrenic patients showed stronger significance in LPC levels compared to their controls. Both groups did not differ significantly from the total sample of schizophrenic patients. Concentrations are expressed as μg phospholipid/10^{9} platelets

and a subgroup of patients with higher levels. Thus, we compared high and low LPC levels with biochemical measurements, demographic variables and psychopathological scores. In the high-LPC subgroup LPC levels were negatively correlated to low PC ($p < 0.01$) and PE levels ($p < 0.01$) (Figs. 1 and 2). Sociodemographic and clinical variables such as age, duration of the disease, treatment duration and number of previous psychiatric inpatient stays were not related to high or low LPC levels.

Patients with low PC levels had significantly more positive symptoms measured by PIRS compared to patients with high PC levels (14.25 ± 5.6 vs. 9.0 ± 5.1 $p < 0.05$). Patients with high LPC levels showed a trend towards higher delusion-scores in the PSE compared to low LPC levels (15.17 ± 8.1 vs. 9.36 ± 7.5 $p < 0.1$).

Total BPRS baseline score was at 58.1 ± 11.0 and declined to 38.6 ± 10.5 in the third week of haloperidol medication ($p < 0.01$). After 6 months treatment, BPRS scores remained low (35.3 ± 9.8).

After the first week of haloperidol medication LPC levels declined ($p < 0.05$), remaining lower during the second week before increasing slightly

Table 3. Correlation between phospholipid levels and psychopathological subscores

PL	PIRS positiv	PIRS negat	PSE del	PSE beh	PSE sum	BPRS anxiet	BPRS anerg	BPRS thoug	BPRS activit	BPRS hostil	BPRS sum
LPC	0.198	0.134	0.246^{t}	0.251^{t}	0.27*	0.17	0.077	−0.159	−0.035	0.036	0.023
PC	−0.232	0.04	−0.082	0.228^{t}	0.149	−0.064	0.107	−0.037	0.017	−0.042	−0.034
PE	−0.09	0.007	−0.116	−0.24^{t}	−0.24^{t}	−0.154	0.027	0.206^{t}	0.01	0.112	0.089

*$p < 0.05$; $^{t}p < 0.1$. Spearman rank correlation coefficients: correlation between LPC and PSE sum and, to a lesser degree between LPC and PSE delusions and PSE behavior subscores

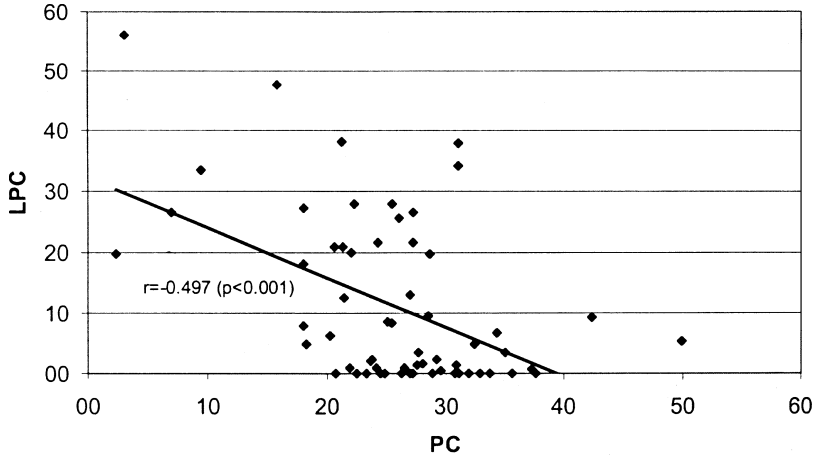

Fig. 1. Distribution of LPC compared to PC levels in schizophrenic patients

during the third week ($p < 0.1$). After 6 months, LPC levels no longer differed from baseline values. The PC level showed a trend to increase after the first week on treatment ($p < 0.1$). After 6 months, PC levels increased significantly ($p < 0.05$). During follow-up, PE values remained within the same range as baseline level before displaying a decrease in the sixth month ($p < 0.01$) (Fig. 3).

Discussion

In this study we detected differences in membrane phospholipid components between schizophrenic patients and controls. The finding of increased platelet LPC levels in schizophrenia is in line with the results from our previous study in a smaller sample (Pangerl et al., 1991). In the present sample, we found in platelets of schizophrenic patients a slight reduction of the main phospholipid components PC and PE. In subjects with high LPC, PC and PE levels were

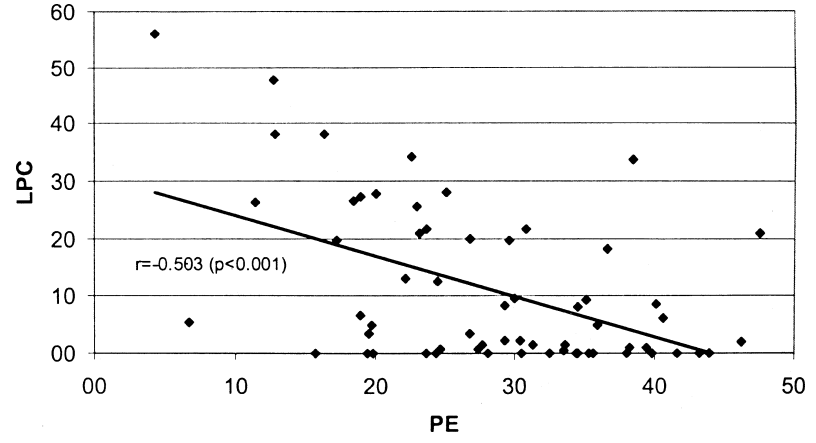

Fig. 2. Distribution of LPC compared to PE levels in schizophrenic patients

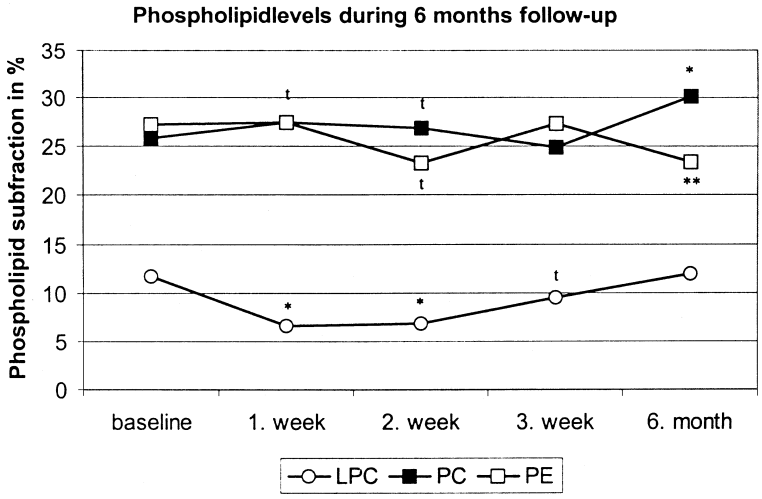

Fig. 3. These curves show phosholipid subfraction levels in schizophrenic patients at baseline and during antipsychotic treatment. After one and two weeks, LPC levels show a decline during week one and two and returned to baseline levels after week three. PC levels increased after 6 months of treatment. PE level decreased during the second week, returned to baseline during week three and were again decreased at six-months follow-up. p-values refer to pairwise comparisons between baseline and one of the follow-up measurements (Wilcoxon-Test). During entire follow-up, the Friedman-Test was performed (LPC $p = 0.06$, PC $p = 0.04$, PE $= 0.07$)

significantly decreased and negatively correlated to their breakdown product LPC, indicating an accelerated phospholipid turnover in at least a subgroup of schizophrenic patients. A more pronounced decrease in PC and PE levels has previously been described in blood cells of schizophrenic patients (Hudson, 1996; Rotrosen and Wolkin, 1987). However, in contrast to these studies we failed to find increased phosphatidylserine in platelet membranes of schizophrenics.

Our results in drug-free patients are in accordance with increased PLA_2-activity in platelets of schizophrenic patients, as previously reported (Gattaz et al., 1995). In the present study an increased phospholipid turnover was not found in psychiatric controls, suggesting that accelerated membrane metabolism in schizophrenia is not a result of unspecific stressors linked to mental disorders in general. The lack of association in our sample between biological variables and psychopathological subscores for stress, anxiety and agitation suggests further that unspecific psychiatric symptoms are unlikely to induce the observed alterations in membrane phospholipid metabolism.

Our data suggest a transient reduction of phospholipid turnover by haloperidol treatment lasting up to three weeks. However, during the 6 months on antipsychotic treatment the phospholipid metabolite LPC returned to initial values, suggesting that long-term antipsychotic drug treatment do not normalize an ongoing process with accelerated phospholipid turnover in schizophrenia. In plasma and platelets, PLA_2 activity has been shown to decrease during short-term haloperidol treatment (Gattaz et al., 1987, 1994). In an animal

experiment, investigating the effects of several neuroleptics on rat brain-PLA_2, differential effects on PLA_2 activity were observed after a four week-treatment: haloperidol and sulpiride decreased PLA_2 activity, whereas fluphenazine and thioridazine increased the enzyme activity (Trzeciak, 1995). In a recent study, two-week haloperidol treatment reduced significantly calcium-independent PLA_2 activity in the rat striatum but did not affect calcium-dependent PLA_2 (Ross et al., 1999).

PLA_2 cleaves phospholipids into lysophospholipids such as LPC and the liberated unsaturated fatty acid arachidonic acid. It has been shown that schizophrenia is associated with a deficiency of arachidonic acid in cell membranes, which in turn could be explained by an enhanced turnover of membrane phospholipids (Horrobin, 1998). Even in chronic, neuroleptic-treated patients, substantial depletions of polyunsaturated fatty acids with a bimodal distribution have been demonstrated, suggesting an increased turnover of phospholipids by PLA_2 which does not appear to be influenced by continuous antipsychotic treatment (Peet et al., 1995).

In accordance with our results in platelets during antipsychotic therapy, one study with ^{31}P-MRS reported increased phosphodiester (PDE) levels in the frontal lobe of medicated chronic schizophrenic patients (Deicken et al., 1994). PDEs are the breakdown products of phospholipid precursors by PLA_2 activity. In first-episode, antipsychotic-naive patients, who demonstrated decreased phosphomonoesters (PME) and increased PDE levels, alterations continued after 4 weeks of antipsychotic treatment (Keshavan et al., 1989). In contrast, Stanley et al. (1995) reported decreased PME, but no increase in PDE levels in medicated schizophrenic patients. These authors suggested that PDE levels are more dependent on the length of illness than on medication status, as they found no correlations with medication dosage or length of therapy. In our study, the findings in first-onset patients and the lack of correlation between phospholipid components and the duration of the disease suggest that membrane disturbances are present before the beginning of the first psychotic episode. In a ^{31}P-MRS study comprising eight schizophrenic patients, PDE levels were increased after antipsychotic medication (Volz et al., 1999). In the temporal lobe, PDE levels were increased in chronic, medicated schizophrenic patients (Fujimoto et al., 1992; Fukuzako et al., 1996). In drug-naive schizophrenic patients haloperidol treatment reduced the excess of PDE in the left temporal lobe, although PDE concentration remained higher than in controls (Fukuzako et al., 1999), suggesting only a limited influence of haloperidol on brain membrane metabolism. These results are in line with our results of increased LPC after long-term antipsychotic treatment.

In a postmortem study calcium independent PLA_2 was increased by 45% in the temporal cortex of schizophrenic patients, but calcium-stimulated PLA_2 was decreased in the temporal and prefrontal cortices and putamen from patients medicated with haloperidol, fluphenazine or thioridazine prior to their death (Ross et al., 1999). In the caudate region of autopsied, medicated schizophrenic patients, the phospholipids PE and PC were significantly reduced (Yao et al., 2000), which is also in agreement with our findings in platelets.

Taking together, our findings in platelets are in line with the hypothesis of an accelerated breakdown of membrane phospholipids in schizophrenia, suggesting further that long-term antypsychotic treatment has not a lasting effect in normalizing the differences between patients and controls. To investigate whether our results in platelets are related to changes in the brain, we are presently investigating in schizophrenia the phospholipid metabolism simultaneously in the brain through ^{31}P-MRS and in peripheral blood cells.

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