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Platelet serotonin and serum lipids in psychotic mania

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Short title: Platelet serotonin in mania

Abstract

Background. The role of serotonergic system and lipid status in the etiology of mania and its subtypes is not clear. The aims of the study were to determine platelet serotonin (5-HT) concentration, platelet monoamine oxidase (MAO) activity, and serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG) in patients with psychotic and nonpsychotic subtypes of mania and in healthy control subjects. **Methods:** The serum lipids, platelet 5-HT and MAO were determined in 40 (17 psychotic, 23 nonpsychotic) drug free male inpatients with type I bipolar affective disorder, current episode mania (DSM-IV criteria), and in 32 healthy male subjects. **Results:** Platelet 5-HT levels in manic patients were similar to the values in healthy controls. Serum cholesterol and LDL values were significantly lower in manic patients than in healthy controls. Patients with psychotic features had increased platelet 5-HT concentrations and decrease levels of cholesterol and LDL as compared to the nonpsychotic manic patients and healthy controls. There was no significant difference in age, body mass index, platelet MAO activity, serum levels of TG and HDL between psychotic and nonpsychotic manic patients and healthy subjects. **Limitation:** Data on physical activity, dietary habits and alcohol consumption before hospitalization were not collected. **Conclusion:** The results of the present study suggest that biological differences between subtypes of mania might depend upon the presence of the psychotic symptoms. Our data confirm our previous results showing the increased platelet 5-HT concentration in psychotic disorders across the different diagnoses.

Key words: Bipolar I disorder, mania, psychotic features; platelet monoamine oxidase, platelet serotonin, serum lipids

1. Introduction

Serotonergic system might be involved in the pathophysiology of bipolar disorder (Shiah and Yatham, 2000; Mahmood and Silverstone, 2001; Shastry, 2005). A few studies investigated serotonin (5-hydroxytryptamine, 5-HT) levels (Takahashi, 1976; Saxena et al., 1999), monoamine oxidase (MAO) activity (Takahashi, 1977) and 5-HT_{2A} receptors (Pandey et al., 2003) in manic patients using blood platelets as a peripheral model for the central serotonergic neurons (Plain and Berk, 2001). Manic patients had lower cholesterol levels than healthy controls (Ghaemi et al., 2000; Cassidy and Carroll, 2002; Atmaca et al., 2002), but no data are available either regarding the low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides (TG) levels in mania, or platelet 5-HT, platelet MAO activity and lipid levels, especially in psychotic subtype of mania. The aim of the present study was to determine platelet 5-HT concentration, platelet MAO activity, serum cholesterol, LDL, HDL, TG and their relationship in male patients with psychotic and nonpsychotic bipolar I disorder - mania, and in healthy men.

2. Methods

The study included 40 male inpatients, with bipolar I disorder, current episode mania (DSM-IV criteria; APA, 1994), with Young Mania Rating Scale (YMRS) (Young et al., 1978) ≥ 18 scores, and 17-item Hamilton Rating Scale for Depression (HAM-D) ≤ 7 scores (Hamilton, 1960). YMRS and HAM-D total scores were 31.0 ± 7.1 and 1.7 ± 1.9 , respectively. The duration of bipolar I disorder was 9.24 ± 8.85 years. The current manic phase lasted 38.8 ± 40.6 days. The number of lifetime manic and depressive episodes was

4.92 ± 5.83 and 4.73 ± 5.14, respectively. Patients with alcohol dependence, serious medical disease, recent change of the body weight, history of elevated cholesterol levels and on cholesterol-lowering drugs were excluded. Drug free period lasted 2 weeks. Six patients had a first episode of mania. Two patients had a history of previous suicide attempt. Benzodiazepines were allowed for nighttime sedation. The patients were subclassified according to the score on item 8 (content) of YMRS into psychotic (score ≥ 5) and nonpsychotic (score < 5) subgroups.

Control group included 32 drug-free healthy men with no personal or familiar history of psychiatric disorders. Thirty patients and 8 healthy persons were smokers. Body mass index (BMI) was calculated by dividing weight (in kilograms) by squared height (in meters). All subjects signed an informed consent. Local Ethics Committee approved the study.

For the determination of platelet 5-HT concentration (Muck-Seler et al., 1996) and MAO activity (Krajl, 1965), blood (4 ml) was taken after an overnight fasting in a plastic syringe with 1 ml of ACD anticoagulant, and determined spectrofluorimetrically, while platelet protein concentration was determined by the method of Lowry et al. (1951). Serum lipid levels were determined using standard laboratory methods.

All results were expressed as mean ± SD. Student t-test, one-way analysis of variance (ANOVA) followed by Tukey's test, analysis of covariance (ANCOVA) and Pearson's coefficient of correlation were used for the statistical evaluation of the results.

3. Results

Serum cholesterol and LDL values were significantly lower in manic patients than in healthy controls, while age, BMI, and other biochemical parameters were similar between groups (Table 1). The number of recurrent episodes significantly correlated with age ($r=0.52$; $P<0.000$), but did not correlate significantly ($P>0.05$) with other biochemical parameters. There was no significant ($P>0.05$) correlation between platelet 5-HT concentration or platelet MAO activity and serum lipid levels in healthy controls or patients.

Total YMRS scores were significantly ($t=4.54$; $df=38$; $p<0.001$, Student's t-test) higher in psychotic (35.8 ± 7.6) than in nonpsychotic (27.0 ± 4.6) manic patients. Platelet 5-HT differed significantly ($F=3.81$; $df=2,69$; $P= 0.027$, ANOVA) among groups (Fig. 1). Platelet 5-HT concentration was significantly ($P<0.05$, Tukey's test) higher in psychotic patients than in nonpsychotic patients and healthy controls (Fig. 1). Serum cholesterol ($F=4.56$; $df=2,69$; $P= 0.014$) and LDL ($F=8.21$; $df=2,69$; $P= 0.001$) values significantly differed among groups (Fig 2), with significantly lower ($P<0.05$, Tukey's test) serum cholesterol and LDL values in psychotic manic patients than in nonpsychotic patients and healthy controls. The significant difference in cholesterol and LDL levels among groups persisted when data were adjusted (ANCOVA) for age ($F=5.78$; $P=0.001$, $F=5.99$; $P=0.001$), and BMI ($F=4.07$; $P=0.01$, $F=6.12$; $P=0.001$) as covariates, respectively. There was no significant ($P>0.05$) correlation between platelet 5-HT and cholesterol or LDL values in psychotic and nonpsychotic patients.

No significant difference in platelet MAO activity, serum TG and HDL values between psychotic and nonpsychotic manic patients and healthy subjects were found (data not shown).

4. Discussion

To our knowledge, this is the first study that simultaneously compares platelet 5-HT content, platelet MAO activity and serum lipid levels in drug free patients with bipolar I disorder in a manic phase and psychotic and nonpsychotic subtypes.

The similar platelet 5-HT values in manic patients and healthy controls (present data) contrasts the increased (Saxena et al., 1999) or decreased (Takahashi, 1976) platelet 5-HT concentrations found in mania. The disagreement between studies might be due to the different number of patients, different gender and the presence of psychotic features. In contrast to a small number of patients with mild or moderate symptoms of mania in the above-mentioned studies, our study includes a considerable number of patients in a severe manic state. Since sex differences in platelet 5-HT values were observed in healthy persons (Oxenkrug, 1979; Muck-Seler et al., 1996; Muck-Seler et al., 1999; Pivac et al., 2004) and psychiatric patients (Muck-Seler et al., 1996; Muck-Seler et al., 1999; Pivac et al., 2001; Pivac et al., 2004), only male subjects participated in our study, while both male and female patients were included in the other studies (Takahashi, 1976; Saxena et al., 1999).

In agreement with the increased platelet 5-HT concentration in other psychiatric disorders with psychotic features (Stahl et al., 1983; Muck-Seler et al., 1988; Muck-Seler et al., 1991; Muck-Seler et al., 1996; Meszaros et al., 1998; Pivac et al., 2006a), the major

finding of our study is a different platelet 5-HT concentration between psychotic and nonpsychotic subtypes of mania. Platelet 5-HT concentration is the result of a dynamic balance between its synthesis and uptake by platelets and breakdown by MAO. Increased platelet 5-HT concentration in psychotic mania might result from the altered platelet 5-HT uptake. Decreased (Marazziti et al., 1991), increased (Meagher et al., 1990), or unchanged (Modai et al., 1984) platelet 5-HT uptake was found in mania. Although both platelet 5-HT concentration and platelet 5-HT uptake were higher in manic patients than in healthy controls, correlation between these two parameters was not reported (Saxena et al., 1999).

Although low platelet MAO activity has been associated with high impulsivity, disinhibition and excessive risk-taking behavior (Verkes et al., 1998), which are frequently present in mania, unchanged platelet MAO activity (present study; Takahashi, 1977) was found in mania. Platelet MAO activity is reduced in healthy male smokers compared to nonsmokers (Berlin and Anthenelli, 2001; Pivac et al., 2006b). Since a high proportion of our patients were smokers, our data might indicate that the effect of smoking was abolished by the diagnosis.

The present study showed that patients with mania, unrelated to the presence of psychotic symptoms, have low levels of serum cholesterol and LDL, but unaltered TG and HDL levels, compared to healthy persons. This finding agrees with aberration of cholesterol in a single manic (Pae et al., 2004), mixed (Cassidy and Carroll, 2002), or pure manic (Ghaemi et al., 2000; Cassidy and Carroll, 2002; Atmaca et al., 2002) episode.

The underlying mechanism for the altered lipid status in manic patients is unclear. Possible explanation might be sought in the nutritional status, gender, weight loss and physical activity. Similar BMI among groups suggests that hypocholesterolaemia, observed in our patients, is not related to different body weight. To eliminate the gender difference found in lipid levels (Sudhop et al., 1999), our study included only male subjects. The hypocholesterolaemia occurring among our manic patients is not related to suicidality (Atmaca et al., 2003; Kim and Myint, 2004), since only two patients had history of suicide attempts.

Since no correlation was found between high platelet 5-HT and low cholesterol and LDL in mania (present study), or low platelet 5-HT and low cholesterol levels in suicide attempters (Alvarez et al., 1999), it is possible that platelet 5-HT and cholesterol levels are negatively correlated only in the presence of hypercholesterolaemia (Smith and Betteridge, 1997).

Limitation of the study is a lack of particular data (physical activity, dietary habits), which might influence cholesterol levels. Since manic patients have decreased insight, the anamnestic data on alcohol abuse prior to the hospitalization might be unreliable.

In conclusion, our results support the hypothesis that platelet 5-HT concentration might be used as a peripheral biomarker for the psychotic states. Increased platelet 5-HT, across different diagnoses, suggests that psychotic subtypes of the different diagnostic entities might share similar biochemical abnormalities.

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Table 1

Age, BMI, platelet 5-HT levels, platelet MAO activity and lipids values (mean \pm SD) in manic patients and healthy control subjects.

	Healthy controls	Manic patients	Student's t-test	
	(32)	(40)	df= 70	
			t	p
Age (years)	36.8 \pm 10.3	42.2 \pm 14.1	1.78	0.07
BMI (kg/m ²)	25.6 \pm 2.6	25.3 \pm 2.7	1.13	0.26
Platelet 5-HT (nmol/mg protein)	1.29 \pm 0.31	1.42 \pm 0.37	1.61	0.112
Platelet MAO (nmol 4-HOQ/mg protein/h)	21.2 \pm 9,1	26.5 \pm 17.0	1.59	0.116
Cholesterol (mmol/l)	5.7 \pm 1.2	4.9 \pm 1.0	2.84	0.006*
TG (mmol/l)	1.81 \pm 1.2	2.05 \pm 1.2	0.82	0.418
HDL (mmol/l)	1.13 \pm 0.2	1.05 \pm 0.1	1.70	0.094
LDL (mmol/l)	3.67 \pm 0.8	2.94 \pm 0.8	3.73	0.001*

Legends

Fig 1.

Platelet 5-HT concentration in healthy controls and in psychotic and nonpsychotic manic patients. Bars represent mean \pm S.D. with number of subjects in parentheses. * $P < 0.05$ vs. healthy controls and nonpsychotic patients with mania (ANOVA and Tukey's test).

Fig 2.

Serum cholesterol and LDL values in healthy controls and in psychotic and nonpsychotic patients with mania. Bars represent mean \pm S.D. with number of subjects in parentheses. * $P < 0.05$ vs. corresponding values in healthy controls and in nonpsychotic patients with mania (ANOVA and Tukey's test).