

Sex differences, season of birth and platelet 5-HT levels in schizophrenic patients

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Summary. Similar occurrence of schizophrenia was observed in men and women independent of their season of birth. Platelet 5-HT concentration was determined in 116 healthy control subjects (61 male and 55 female) and 152 patients with schizophrenia (96 male and 56 female). Platelet 5-HT concentration was significantly higher in male than in female healthy persons and schizophrenic patients. Male and female healthy subjects born in different seasons had similar platelet 5-HT concentrations, whereas schizophrenic patients with different birth-seasons had significantly different platelet 5-HT concentrations. The highest platelet 5-HT levels were observed in both male and female schizophrenic patients born in winter when compared to matched healthy controls. Male schizophrenic patients born in winter had higher platelet 5-HT levels than schizophrenic men born in spring and summer. Female schizophrenic patients born in winter had higher platelet 5-HT than schizophrenic women born in all other seasons. These results indicated sex differences in platelet 5-HT levels in healthy persons and schizophrenic patients. The relationship between season of the birth and platelet 5-HT concentration observed only in schizophrenic patients added further support to the presumption that schizophrenia is connected with a disturbance in the central serotonergic system.

Keywords: Platelet 5-HT, male and female subjects, season of birth, schizophrenia, healthy subjects.

Introduction

Numerous studies have reviewed the role of serotonin (5-hydroxytryptamine, 5-HT) in the pathogenesis of schizophrenia (Breier, 1995; Iqbal and van Praag, 1995; Roth and Meltzer, 1995; Kappur and Remington, 1996; Abi-Dargham et al., 1997), suggesting abnormal 5-HT metabolism and function in this mental disorder. Postmortem brain studies have found regional differences

in the concentrations of 5-HT and its main metabolite 5-hydroxyindole acetic acid (5-HIAA). A decreased 5-HT transmission in cortical regions (Winblad et al., 1979) and increased 5-HT transmission in subcortical areas like putamen (Crow et al., 1979), accumbens and pallidus (Farley et al., 1980) was observed. Schizophrenic patients had also significantly lower density of 5-HT₂ receptors (Arora and Meltzer, 1991), imipramine binding sites (Rotman et al., 1982) and number of 5-HT transporter in the frontal cortex (see the review of Abi-Dargham et al., 1997).

Since uptake, storage and release of 5-HT into platelets resemble the corresponding processes in the central nervous system (CNS), blood platelets have been widely used as an easy available, peripheral model for the central serotonergic synaptosomes (Stahl, 1985; Andres et al., 1993). Increased (Jackman et al., 1983; Mück-Šeler et al., 1988, 1991; Jakovljević et al., 1991, 1997) or unaltered (Kovalowska and Molyneux, 1987; Bräuning et al., 1989) platelet 5-HT levels have been reported in schizophrenic patients. The discrepancies between various reports could be due to the various factors like age, prior medication, sex, or nutrition.

The data of the sex differences in platelet 5-HT concentrations in schizophrenic patients remain obscure. Some studies (Jackman et al., 1983; Kolakowska and Molyneux, 1987; Mück-Šeler et al., 1988; Rao et al., 1994) failed to find sex differences in platelet 5-HT concentrations. Since we have previously shown sex related differences in platelet 5-HT concentrations in healthy matched controls and in depressed and suicidal patients (Mück-Šeler et al., 1996a), and sex differences in platelet 5-HT were detected in depressed patients and healthy controls (Oxenkrug, 1979), in the present study we wanted to elucidate whether sex differences exist also in platelet 5-HT concentration in schizophrenic patients.

There is an increasing evidence about the sex differences in the neurostructural aspects of the normal brain, specially in the regions like hippocampus and cortex that are involved in the regulation of mood and behaviour. Normal women have a greater ratio of gray matter volume to total volume in the areas involved in higher order cognitive functions like language, sustained attention, working memory (caudatus, hippocampus, dorsolateral frontal cortex and superior temporal gyrus) than men (for references see Goldstein, 1996, 1997). Therefore, sex difference in the brains of schizophrenic patients might be a consequence of the normal sexual dimorphism of the brain. The effect of gender was also observed in the manifestation of the clinical symptoms (Goldstein and Link, 1988). These sex differences were not attributed to diagnostic classification, differences in diagnostic subtypes or to possible biases arising from the chronicity of the patient's illness. It was also shown that male and female relatives of female schizophrenic probands have a higher risk for schizophrenia, schizophreniform and schizoaffective disorders than those of male schizophrenic probands (Goldstein et al., 1990).

Seasonality has been reported for the incident of schizophrenia. Some studies (Bradbury and Miller, 1985; Boyd et al., 1986; Franzek and Beckmann, 1992; Dassa et al., 1996) reported that schizophrenia occurs more frequently

in subjects born in winter or spring. Winter born schizophrenics have increased cerebral sulcal prominence (Degreef et al., 1988) and more prevalent lateral ventricular enlargement (Sacchetti et al., 1992). Seasonal variations were detected for some parameters of 5-HT system, including platelet 5-HT uptake (Marazziti et al., 1990), ^3H -imipramine binding (DeMet et al., 1989) and plasma L-tryptophan levels (Maes et al., 1995). We have previously reported similar seasonal distribution of platelet 5-HT concentrations within schizophrenic patients as well as in healthy controls (Jakovljević et al., 1997). To our knowledge, there are no data comparing platelet 5-HT concentrations and season of birth in healthy persons and schizophrenic patients of both sexes.

Therefore, the aims of the present study were a) to determine the distribution of birth-season in schizophrenic patients, b) to determine sex difference in platelet 5-HT concentrations in healthy subjects and schizophrenic patients, and c) to determine the relationship between season of birth and platelet 5-HT concentrations in both healthy persons and schizophrenic patients.

Material and methods

Subjects

The population studied comprised of 96 male (mean age 28.9 ± 7.5 ; range 16–58 years) and 56 female schizophrenic patients (mean age 31.6 ± 8.3 ; range 17–52 years) recruited in the study during a two-year period. Clinical diagnosis of schizophrenia was made by a psychiatrists team by a best estimate according to DSM-III-R criteria (American Psychiatric Association, 1987). Semistructured interviews were used. Study was approved by the Ethics committee. The illness started with 24.9 ± 6.7 years (range 15–52 years) in male patients and 25.3 ± 7.1 years (range 15–40 years) in female schizophrenic patients. The average duration of the illness was 3.9 ± 4.6 years (range 0.08–22 years) and 4.6 ± 5.6 years (range 0.16–25 years) for male and for female schizophrenic patients, respectively. On admission, 12 patients had been drug free for about 1 year and the others were medicated with different neuroleptics, except clozapine. None of the patients received depot neuroleptics. After admission the patients were not treated with any neuroleptic or antidepressant drugs for at least 7 days.

The patients were additionally subdivided according to the season of birth into 4 groups: winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November), according to the categorization published by Dassa et al. (1996).

The control group consisted of 61 healthy men (mean age 40.8 ± 10.4 ; range 20–66 years) and 55 healthy women (mean age 44.3 ± 11.5 ; range 25–65 years) with no personal or family history of psychopathology and no medical treatments.

Biochemical analysis

After a drug free interval (during which the patients received placebo), blood (4 mL) was drawn from cubital vein at 8 h in a plastic syringe with 1 mL of acid citrate dextrose (ACD) anticoagulant. Platelet-rich-plasma (PRP) was obtained by centrifugation ($935 \times g$) for 70 s at room temperature. Platelets were sedimented by further centrifugation of PRP at $10,000 \times g$ for 5 min. The platelet pellet was washed with saline and centrifuged again. Platelet 5-HT concentrations were determined by the spectrofluorimetric method (Mück-Šeler et al., 1988). Briefly, platelets were destroyed by sonication (20 KHz, amplitude 8×10^{-3} mm for 30 sec). Specimens of standard, blank (water) and platelet sonicates were analysed in duplicate. All samples were deproteinized

with 1 mL of 10% ZnSO₄ and 0.5 mL of 1 N NaOH. For the preparation of fluorophore, 0.2 mL of L-cysteine (0.1%) and 1.2 mL of orthophthalaldehyde (0.05%) were added to deproteinized samples. The measurement of the 5-HT fluorescence was performed on an Aminco-Bowman spectrofluorimeter. Platelet protein was determined by the method of Lowry et al. (1951).

Data analysis

All data are presented as mean \pm SD. The differences between groups were assessed by one-way analysis of variance (ANOVA) followed by Newman Keuls test for the pairwise comparisons. Two- and three-way ANOVAs were used to test the significance of the effects of several variables (diagnosis, sex, birth-season), and to test the interaction between them. The frequency of the occurrence of schizophrenia in patients with different seasons of birth was determined by χ^2 test. Two-tailed Student's t-test was used for comparisons between two groups only. The correlation between parameters was determined by Pearson's coefficient of correlation. The criterion for significance in all tests was $p < 0.05$.

Results

Table 1 shows significant ($F_{3,264} = 15.06$, $p < 0.001$, one-way ANOVA) differences in platelet 5-HT concentration among schizophrenic patients and healthy controls. Both male and female schizophrenic patients had higher ($p < 0.05$, Newman Keuls test) platelet 5-HT concentrations than healthy men and women, respectively. In addition, sex difference, i.e. higher ($p < 0.05$, Newman Keuls test) platelet 5-HT concentration in men than in women was observed among healthy persons as well as between schizophrenic patients (Table 1).

In the group of schizophrenics, female patients were older than male patients ($t = 2.06$, $p < 0.05$, Student's t-test), while there was no difference in age between male and female healthy persons ($t = 1.72$, $p = 0.09$). Male and female schizophrenic patients were younger than male ($t = 6.36$, $p < 0.001$) and female ($t = 6.66$, $p < 0.001$) healthy subjects, respectively. No significant correlation between the age and platelet 5-HT levels in male

Table 1. Platelet 5-HT concentrations in male and female healthy controls and schizophrenic patients

	Platelet 5-HT (nmol/mg protein)	
	Men	Women
Healthy controls	1.21 \pm 0.20* (61)	1.11 \pm 0.29 (55)
Schizophrenic patients	1.46 \pm 0.43 ^{#,+} (96)	1.31 \pm 0.42* (56)

Results are expressed as mean \pm SD. Numbers in parentheses denote number of subjects

* $p < 0.05$ vs. healthy women, # $p < 0.05$ vs. schizophrenic women, + $p < 0.05$ vs. healthy men (ANOVA followed by Newman Kuels test)

($r = 0.09$, $p = 0.49$) and female ($r = 0.03$, $p = 0.83$) healthy persons or in male ($r = 0.08$, $p = 0.78$) and female ($r = 0.06$, $p = 0.43$) schizophrenic patients was found.

Similar occurrence of schizophrenia was observed in men and women independent of their season of birth ($\chi = 3.91$, $df = 3$; $p = 0.27$, χ^2 test).

Figure 1 shows significant differences ($F_{7,144} = 3.00$, $p < 0.006$, one-way ANOVA) in platelet 5-HT concentrations in male and female schizophrenic patients born in different seasons. Platelet 5-HT concentrations in male healthy controls with different birth-seasons were not significantly different from the values in female healthy controls ($F_{7,108} = 1.00$, $p = 0.44$, one-way ANOVA).

When subjects were divided by sex, one-way ANOVAs showed significant differences in platelet 5-HT levels between male healthy subjects and male schizophrenic patients ($F_{7,149} = 4.15$, $p < 0.001$) as well as between female healthy subjects and female schizophrenic patients ($F_{7,103} = 3.76$, $p < 0.001$).

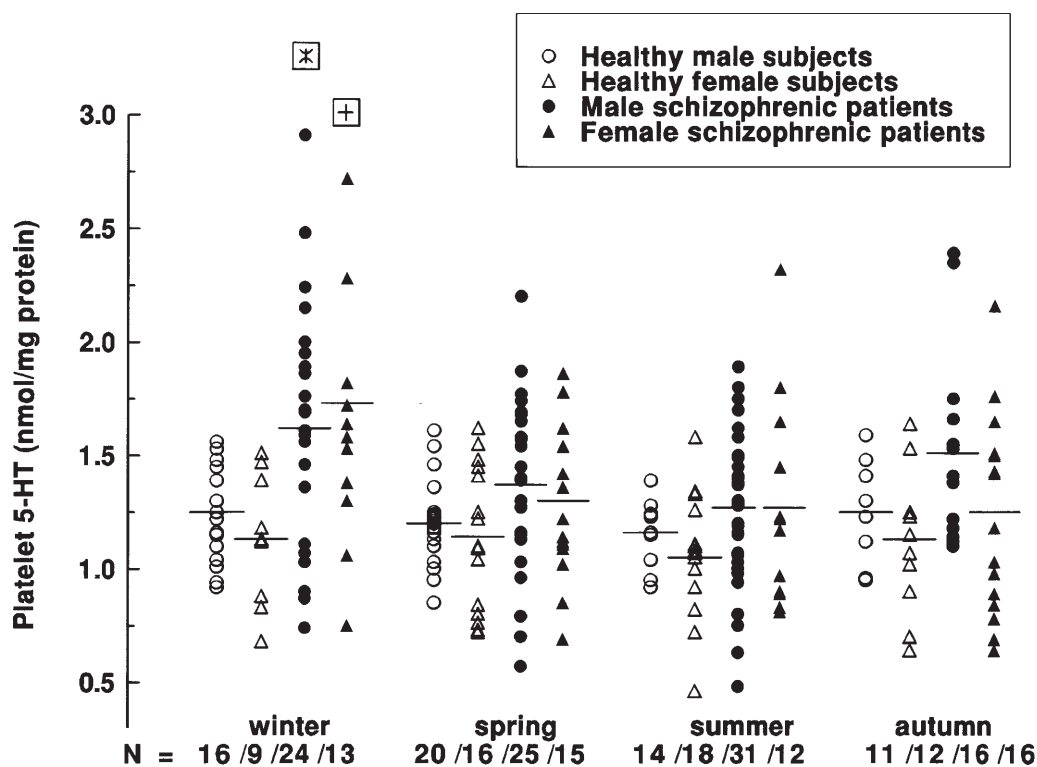


Fig. 1. Individual platelet 5-HT values in male and female healthy subjects and schizophrenic patients born in different seasons. The mean value in each group is indicated by a horizontal line drawn through the corresponding data points. N is the number of subjects in the group. \boxtimes $p < 0.05$ – 0.01 vs. healthy male persons born in winter and vs. schizophrenic patients born in spring and summer (Newman Keuls test); \boxplus $p < 0.05$ – 0.01 vs. healthy female persons born in winter and vs. female schizophrenic patients born in spring, summer and autumn (Newman Keuls test)

born in different seasons (Fig. 1). Male schizophrenic patients born in winter had higher ($p < 0.01$) platelet 5-HT concentration than healthy men born in winter, and than male schizophrenic patients born in spring ($p < 0.05$) or summer ($p < 0.01$). Among female subjects, schizophrenic patients born in winter had higher ($p < 0.05$) platelet 5-HT concentration than healthy women born in winter, or than schizophrenic female patients born in spring ($p < 0.01$), summer ($p < 0.05$) or autumn ($p < 0.01$).

To further evaluate the effects of the birth-season, diagnosis and sex on platelet 5-HT concentrations, two- and three-way ANOVAs were used, where appropriate. Three-way ANOVA revealed significant effect of the season of birth ($F_{1,3} = 6.34, p < 0.000$), and diagnosis ($F_{1,3} = 24.73, p < 0.000$), but no significant effect of sex ($F_{1,3} = 1.76, p = 0.19$) on platelet 5-HT concentration in subjects born in different seasons. The interaction between sex and diagnosis ($F_{1,3} = 0.186, p = 0.61$) and sex and birth-season ($F_{1,3} = 0.807, p = 0.49$) was not significant by two-way ANOVA.

Discussion

In the present work we have found for the first time the relationship between season of birth and platelet 5-HT concentrations in schizophrenic patients. Increased platelet 5-HT concentration was a characteristic feature of both male and female schizophrenic patients, specially those born in winter, while platelet 5-HT concentrations in healthy men and women were not correlated with their season of birth. In agreement with our previously published works (Mück-Šeler et al., 1988, 1991; Jakovljević et al., 1997) hyperserotonemia was observed only in schizophrenic patients.

Although our study showed no relationship between season of birth and incidence of schizophrenia, there are some reports that this mental disorder occurs more frequently in subjects born in winter (Dassa et al., 1996) or in first half of the spring (Franzek and Beckmann, 1992). The lack of significance between season of birth and prevalence of schizophrenia in the present study might be due to a limited sample size of the patients born in particular season. It has been suggested that schizophrenia is a developmental disorder associated with the brain abnormalities due to viral infection (like influenza) during second trimester of pregnancy (Takei et al., 1993). Since we have no data available on the prenatal exposure of our patients to viral infection the former presumption could not be confirmed.

Similar occurrence of schizophrenia in both sexes without season of birth-effects described in our study is in agreement with the finding that schizophrenia is an illness which occurs in equal rates in both sexes (Dohrenwend and Dohrenwend, 1976). Schizophrenia is expressed differentially in men and women, regarding age at onset, premorbid history, clinical symptoms, and the course of the illness (Goldstein, 1997). However, in our study schizophrenia started in both male and female patients with 25 years of age, and duration of the illness was similar for both sexes. The sex-related differences in the manifestation of the clinical symptoms of schizophrenia were reported. Paranoia, impulsivity, sexually inappropriate behaviour and depressive symptoms

predominate in schizophrenic women, while the symptoms like withdrawal/isolation, inability to function, and negative symptoms prevail in male patients (Goldstein and Link, 1988). Sex-specific cerebral lateralization i.e. more pronounced asymmetry in female schizophrenic has been also reported (Reite et al., 1997).

In the present study we confirmed our previously published data about the sex difference in platelet 5-HT concentrations in healthy persons and extended it to the schizophrenic patients. The results (Mück-Šeler et al., 1996a; and present study) of a higher platelet 5-HT concentration in male than in female healthy controls are in agreement with the data of Oxenkrug (1979), but are completely opposite to the data of Le Quan-Bui et al. (1984) and Kovalowska and Molyneux (1987). On the other hand, some studies (Jackman et al., 1983; Le Quan-Bui et al., 1984; Kovalowska and Molyneux 1987; Mück-Šeler et al., 1988) failed to find sex difference in platelet 5-HT levels between schizophrenic patients, presumably because of the relatively small groups of subjects in these studies. Sex differences in platelet 5-HT levels, observed among schizophrenic patients in the present study, disappeared when groups were divided according to their seasons of birth. Since these groups consisted of the relatively small number of patients, we might assume that we failed to detect the difference that possibly existed.

Since there are striking similarities how both CNS and platelets store and metabolize 5-HT (although platelets do not synthesize 5-HT), (Stahl, 1985; Andres et al., 1993), decreased platelet 5-HT concentrations in women, found in the present study, could indicate an alteration in central 5-HT system. In this respect, it is noteworthy that sex differences have been reported in the rate of 5-HT synthesis in the brain, showing higher synthesis rate in normal men than women (Nishizawa et al., 1997). The same group has also found higher plasma free tryptophan concentrations in male than in female subjects (Nishizawa et al., 1997). Although at present we have no direct evidence, it is possible that the rate of 5-HT synthesis in the enterochromaffine cells of the gut (main site of the synthesis of peripheral 5-HT) is sex related, too.

It is speculated that increased platelet 5-HT levels in schizophrenia might be a consequence of decreased platelet MAO activity (Marcolin and Davis, 1992). Sex difference in platelet MAO activity was detected in healthy subjects (Jackman and Meltzer, 1983; Mück-Šeler et al., 1991; Veral et al., 1997), while the data in schizophrenic patients are inconsistent. One study (Mück-Šeler et al., 1991) failed to find sex differences in platelet MAO activity, whereas the other (Pandey et al., 1992) observed higher platelet MAO activity in schizophrenic women than in men. Although these two studies investigated platelet MAO activity in the similar number of patients, the results could not be compared because of the different substrates used for the determination of MAO activity. Nevertheless, increased 5-HT concentration found in male subjects in the present study could not be related to the altered platelet MAO-B activity since 5-HT is not a specific substrate for this type of MAO.

In our study a sex difference in the age between groups were observed. Our finding that female are older than male schizophrenics is in agreement

with the earlier onset of schizophrenia and prior first admission in male patients (Lewine et al., 1997). In spite of the fact that our healthy control group was older than group of schizophrenic patients and female patients were older than male schizophrenic patients, no significant correlation between the age and platelet 5-HT concentration for male or female healthy controls (Mück-Šeler et al., 1996b and present study) or schizophrenic patients (Jackman et al., 1983; Mück-Šeler et al., 1996b and present study) was found.

Although sex differences in schizophrenia (Goldstein, 1997) and in the neurotransmitter systems (DeVries, 1990) exist, there are still some studies of the role of 5-HT in schizophrenia without separating patients by the sex. However, sex differences in platelet 5-HT concentrations in schizophrenia (present study), depression and suicide (Mück-Šeler et al., 1996a), in platelet ³H-imipramine binding (Halbreich and Lumley, 1993), and in platelet MAO activity (Pandey et al., 1992), indicate the importance of matching patients and controls according to the sex in the clinical investigations of the alterations of 5-HT system in psychiatric disorders.

Many investigators have studied the effect of neuroleptic treatment on platelet 5-HT concentrations. We have previously shown (Mück-Šeler et al., 1988) that 14 or 28 days of neuroleptic treatment did not affect platelet 5-HT concentration in schizophrenic patients. Our results are in agreement with the data from Kolakowska and Molyneux (1987), and Jackman et al. (1983). Moreover, whole blood 5-HT concentration was similar in medicated and unmedicated schizophrenic patients (DeLisi et al., 1981). Neuroleptic treatment did not change the number and the affinity of platelet 5-HT₂ receptors in schizophrenic patients (Pandey et al., 1993). No correlation between kinetic constants of ¹⁴C-5-HT uptake in blood platelets and duration of washout period in schizophrenic patients was shown (Arora and Meltzer, 1982). On the other hand, it was recently shown that long-term clozapine treatment increased serum 5-HT levels in schizophrenic patients (Schulz et al., 1997). Since our patients were not treated with clozapine, increased platelet 5-HT concentration found in the present study could not be associated with a previous neuroleptic treatment.

Although we have no direct evidence that the changes in platelet 5-HT levels correspond to the changes in the central 5-HT system, it is noteworthy that abnormal computerized tomographic brain scans correlated with high platelet 5-HT levels (DeLisi et al., 1981). In addition, prenatal disturbance in neuronal cell migration in the second trimester of pregnancy, caused genetically and/or environmentally (Franzek and Beckman, 1992), has been suggested in schizophrenia (Jakob and Beckmann, 1986). In this respect, our results of increased platelet 5-HT concentrations in schizophrenic patients born in winter add further support to the concept that schizophrenia might be neurodevelopmental disorder. However, in order to prove the role of 5-HT in the etiology of schizophrenia, some studies like simultaneous determination of the rate of 5-HT synthesis by positron emission tomography (PET) in the brain and the concentrations of 5-HIAA in CSF and/or 5-HT in blood platelets are needed.

In conclusion, our results established sex-related differences in platelet 5-HT concentration in healthy persons and schizophrenic patients. Increased platelet 5-HT was a characteristic feature of both schizophrenic male and female patients born in winter compared to the patients born in all other seasons. Contrarily to schizophrenic patients, there was no association between platelet 5-HT concentrations and season of birth in healthy controls. The relationship between season of the birth and platelet 5-HT concentration observed only in schizophrenic patients added further support to the presumption that schizophrenia is connected with a disturbance in the central serotonergic system.

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