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Title:

The influence of daylight exposure on platelet 5-HT levels in patients with major depression and schizophrenia

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Abstract

Platelet serotonin (5-HT) can be used as a limited, peripheral model for the central 5-HT synaptosomes. Altered platelet 5-HT concentrations have been associated with psychiatric disorders like depression and schizophrenia. The aim of the present study was to compare platelet 5-HT concentrations during long, medium and short period of natural daylight exposure in a large number of medication-free male and female schizophrenic and depressed patients and sex-matched healthy controls. Platelet 5-HT concentration was determined spectrofluorimetrically in 240 (97 female, 143 male) schizophrenic and 258 (153 female, 105 male) nonpsychotic, nonsuicidal depressed medication-free patients and 328 (149 women, 179 men) healthy subjects during periods with short (<12), long (>12) and medium (average 12) hours of the natural daylight. Platelet 5-HT concentration was significantly lower in women compared to men in all groups. Healthy male subjects had significantly higher ($p=0.011$) platelet 5-HT concentrations during long compared to medium period. There were no significant differences ($p>0.05$) in platelet 5-HT concentration between different periods in healthy women. The significant increase in platelet 5-HT values were found in female ($p=0.01$) and male ($p=0.029$) depressed patients during long compared to short period. There were no significant associations between platelet 5-HT concentrations and different periods in both male and female schizophrenic patients. The results indicate the sex-related differences in the serotonergic system. The alterations of platelet 5-HT concentrations, observed across period with different durations of daylight exposure, point to a direct or indirect effect of light on peripheral 5-HT system that could be related to different sensitivity of the pineal gland to light and/or melatonin influence on 5-HT metabolism.

Key words: periods of daylight exposure, platelet 5-HT, schizophrenia, depression

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter implicated in a variety of somatic functions that are disturbed in psychiatric disorders like depression and schizophrenia [1]. Biological factors predisposing a person to a major depression point to alterations in presynaptic and postsynaptic 5-HT activity in the brain and their relationship with the neuroendocrine system [2] . Alterations in the serotonergic system have also been related to specific symptoms and treatment of schizophrenia, since novel antipsychotic agents, which are 5-HT2A receptors antagonists, provide better treatment response than classical neuroleptics [3].

Serotonin is synthesized from the amino acid tryptophan, an essential amino acid found in the human diet which contains an indole ring. Tryptophan, due to its indole structure, is capable of absorbing the light energy [4]. Biosynthesis of 5-HT in the human body takes place in the nervous system (serotonergic neurons, spinal cord), peripheral organs (gastrointestinal tract, lungs, liver, ovaries), glands (thyroid, pancreas, pineal) [5-7] and some neoplastic tissues (carcinoid tumors and phaeocromocytoma) [8-9]. In the pineal gland, with very pronounced 5-HT synthesis rate [10], 5-HT is the precursor of the neurohormone melatonin [11-12]. Melatonin regulates biological rhythms and levels of biomolecules that exert various peripheral actions, thus affecting many critical processes [13]. Various studies have shown altered melatonin secretion in depression [14-19], seasonal affective disorder (SAD) [20-21], schizophrenia [22-26], panic disorder [27], obsessive-compulsive disorder [17,28] and Alzheimer's disease [29], suggesting an interaction of melatonin with the central neurotransmitter systems.

Goergen et al (2002) have shown that light-controlled rhythm could be the primary regulator of neuronal proliferation and that previously demonstrated hormonal and activity-driven influences over neurogenesis may be the secondary events in a complex circardian control pathway [30]. Recently, it has been shown that brain 5-HT concentration correlates positively with the hours of sun exposure per day in a healthy male volunteers [31]. Since 5-HT does not cross the blood-brain barrier, direct studies on brain 5-HT metabolism are still very limited. Blood platelets have been used in neurobiological studies as a limited, peripheral model for serotonergic nerve endings in the brain. Uptake, storage, and release of 5-HT into platelets and the kinetic and pharmacological characteristics of platelet receptors resemble the corresponding processes and receptors in the central serotonergic neurons [32-33]. Previous studies have shown unchanged [34a,b] or decreased [35] platelet 5-HT concentration in depressed patients. In schizophrenic patients platelet 5-HT concentration was increased [36-38] or unaltered [39-40]. There are several studies reporting altered platelet 5-HT uptake depending on the season in depressed [41-42] and schizophrenic [43] patients and indicating that in schizophrenic patients platelet 5-HT levels depend on the season of birth [44]. These results suggest that platelet 5-HT concentrations could depend on duration of natural daylight.

Since there are no data related to the effects of natural daylight on platelet 5-HT levels, the aim of the present study was a) to determine platelet 5-HT concentration in a large number of medication-free male and female schizophrenic and depressive patients and in sex-matched healthy controls b) to compare platelet 5-HT concentrations in all groups during long, medium and short period with different duration of natural daylight.

Materials and Methods

The population studied comprised of 97 nonsuicidal female (mean age 40.6 ± 10.8 years, range 36-59 years) and 143 male (mean age 39.2 ± 10.5 years, range 29-55 years) schizophrenic patients and 153 female nonpsychotic, nonsuicidal (mean age 43.6 ± 10.2 years, range 37-59 years) and 105 male (mean age 44.2 ± 11.8 years, range 35-60 years) depressed patients. The clinical diagnosis of schizophrenia and major depression was made by a team of psychiatrists during a comprehensive screening evaluation, using the structured clinical interview (SCID) [45] based on DSM-IV criteria [46]. In schizophrenic patients mean score on Brief Psychiatry Rating Scale was 56.5 ± 8.9. The severity of depression was evaluated using on 17-item Hamilton Depression Rating Scale (HAM-D) [47]. In depressed patients mean HAMD was 25.4 ± 3.3. Before blood sampling, patients were not treated with any neuroleptic or antidepressant drugs for at least 7 days. The study was performed during a 2 year period. Clinical ratings and biochemical measures were made blindly to each other. The control group consisted of medication free 149 healthy women (mean age 39.5 ± 7.7; years, range 25-57 years) and 179 men (mean age 35.4 ± 8.7; years, range 24-54 years) with no personal or family history of psychopathology. The study was approved by Local Ethics Committee and all participants gave their informed consent.

Blood samples were taken from patients and healthy controls in three periods of the year with different duration of natural daylight:1) long period with average 16 hours (from 21st May to 21st July), 2) short period with average 8 hours (from 21st November to 21st January) and 3) medium period with average 12 hours (from 21st February to 21st April 21st and from 23thAugust to 23th September) of natural daylight. At the time of blood collection, all female subjects were in the same day of menstrual cycle. Blood (4 ml) was drawn from cubital vein at 8:00 h in a plastic syringe with 1 ml of acid citrate dextrose (ACD) anticoagulant. Platelet-rich-plasma (PRP) was obtained by centrifugation (935 x g) for 70 s at room temperature. Platelets were sedimented by

further centrifugation of PRP at 10,000 x g for 5 min. The pellet was washed with saline and centrifuged again. Platelet 5-HT concentrations were determined by spectrofluorimetric method [36]. Briefly, platelets were destroyed by sonication (20 kHz, amplitude 8 x 10^{-3} mm for 30 sec). Specimens of standard, blank (water) and platelet sonicates were analyzed in duplicate. All samples were deproteinized with 1 ml of 10% $ZnSO_4$ 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 a Varian Cary Eclipse spectrofluorimeter. Platelet protein was determined by the method of Lowry et al., [48]. All data are presented as mean ± SD. The differences between groups were assessed by Kruskal Wallis one way analysis of variance (ANOVA) on ranks, followed by Mann Whitney t-test for comparison of the two groups. The statistical package used was SigmaStat 3.1.

Results

The sex-related difference in platelet 5-HT concentrations was observed (Table 1) in depressed and schizophrenic patients and healthy controls. Healthy men and male patients with depression or schizophrenia had significantly ($p<0.05$) higher platelet 5-HT concentrations than healthy women and female depressed or schizophrenic patients, respectively.

In male depressed patients and healthy men significant ($H=12.01$; $df=5$; $p<0.035$; Kruskal-Wallis ANOVA) differences in platelet 5-HT concentrations were found across different periods (Fig 1). Platelet 5-HT concentrations were significantly increased ($p=0.029$, Mann Whitney test) in male depressed patients during long period compared to platelet 5-HT

values in those patients during short period. Similarly, healthy male subjects had significantly higher ($p=0.011$) platelet 5-HT concentrations during long period compared to medium period.

Figure 2. shows significant differences ($H=22,8$; $df=5$; $p<0.001$; Kruskal-Wallis ANOVA) in platelet 5-HT concentrations during long, short or medium periods in female depressed patients and sex matched healthy controls. Depressed female patients had significantly ($p=0.025$ and $p<0.001$) lower platelet 5-HT concentrations during medium and short period than healthy female controls in the corresponding periods. Platelet 5-HT values in patients during long period were significantly higher than platelet 5-HT levels in patients during short ($p=0.01$) and medium ($p<0.001$) periods. There were no significant ($p>0.05$) differences in platelet 5-HT concentrations during different periods in healthy female control subjects (Fig 2).

Platelet 5-HT concentrations in male and female schizophrenic patients and male and female healthy controls during periods with different duration of natural daylight are shown in Table 2. A significant ($p<0.01$) increase in platelet 5-HT concentrations was observed in both male and female patients compared to sex-matched healthy controls, independent of the long, medium or short period.

Discussion

In the present study, we have confirmed and extended our previous results showing different platelet 5-HT concentrations in male and female depressed [34 a,b] and schizophrenic patients [44] and healthy controls [34a,b, 44]. The observed sex-related

difference in platelet 5-HT concentration is in line with the findings that brain 5-HT synthesis rate is lower in healthy women than in healthy men [49]. Further support is the sex-related difference obtained in healthy volunteers in response to m-chlorophenyl-piperazine (mCPP) challenge test, a measure of serotonergic function [50]. Taken together, these results suggest that sex-related differences in 5-HT system could be the reason for higher incidence of depression in women compared to men [51].

Our result, indicating the sex-related difference in platelet 5-HT concentration in depressed patients, is in line with the finding of the sex-dependent alteration in 5-HT uptake into platelets. Different kinetic characteristics of platelet [^{14}C]-5-HT uptake and [^{3}H]-paroxetine binding were determined in male and female depressed patients [52]. In addition, the sex-related difference in diencephalon 5-HT transporter availability was discovered in depression, explaining why women respond better to treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants compared to men [53]. These results illustrate important sex-related differences associated with human 5-HT system dysfunction present in depression and characterize the pathophysiology of the illness itself.

Furthermore, our findings support the opinion of other authors [54-60] who emphasize that different approaches to treatment of disorders heavily associated with 5-HT system (depression, schizophrenia, anorexia nervosa, panic disorder, personality disorders, posttraumatic stress disorder, irritable bowel syndrome, Alzheimer disease) should be exercised depending on the sex of the patient.

The main finding in the present study is the association between platelet 5-HT concentrations and the amount of the natural daylight in healthy male subjects and male and

female depressed patients. Our results, showing that healthy male subjects have higher platelet 5-HT values during period with highest duration of natural daylight (long period) compared to platelet 5-HT values during other periods, are in agreement with the observed increase of 5-HT levels and 5-HT turnover in the brain on bright days in medication-free healthy male volunteers [31] and with the increased platelet 5-HT uptake in healthy subjects in summer compared to autumn [61]. At present, we are unable to explain the lack of the similar finding in the case of healthy female subjects. The sex-related difference in platelet 5-HT content could be linked to sex difference in the sensitivity of the pineal gland to light and/or to difference in melatonin influence on 5-HT metabolism and subsequent neurotransmission [62-65].

The chronobiological mechanisms controlling the release of melatonin, which plays a significant role in the control of the central and the peripheral metabolism of 5-HT, could account for the observed differences in platelet 5-HT content depending on different duration of exposure to natural daylight. Our results, showing lower platelet 5-HT levels in depressed patients compared to healthy control subjects within the same period, could be a direct consequence of the altered melatonin production and/or disruption of melatonin's biological functions present in depressive disorders. Although in our study we did not measure the plasma melatonin levels, literature data shows increased secretion of melatonin in depressed patients [14-18], suggesting an interaction of melatonin with the 5-HT system.

In the present study we have not observed the association between platelet 5-HT concentration and duration of daylight exposure in medication-free schizophrenic patients. This finding is in agreement with our previous results showing no seasonal influence on platelet 5-HT concentrations in schizophrenic patients [38]. The literature data on the

circadian rhythm and melatonin secretion in schizophrenic patients is scarce and often contradictory. To our knowledge, there is no data regarding the melatonin secretion in schizophrenic patients depending on different duration of natural daylight. Several studies [22,25,26,66] indicate diminution of melatonin secretion in schizophrenia, which argues in support of the overall increase in the platelet 5-HT levels observed in patients compared to controls. The effect of decreased melatonin production, resulting in premature calcification and enlargement of the pineal gland, has been correlated with the frontal lobe atrophy observed in schizophrenic patients and consequently implicated in the pathogenesis of schizophrenia [24,67,68].

Our results, showing an increase in the platelet 5-HT content during long and a decrease during short period, point to a direct or an indirect effect of light on the central and the peripheral 5-HT system. The pineal gland has an essential role in the regulation of the circadian rhythm and responds to light by sending the information via a retinohypothalamic tract to suprachiasmatic nuclei, densely innervated by 5-HT neurons from the mid-brain raphe complex [69-71], resulting in the secretion of melatonin. Melatonin, following its synthesis from the precusor 5-HT, acts as an important biochemical mediator, controlling the neural mechanisms responsible for receiving and transmitting the light stimulus. Its synthesis and secretion is regulated by the circadian clock in the hypothalamus which is synchronized with the light/dark period [72]. It has been shown that melatonin blocks the circadian rhythm of 5-HT synthesis in the pineal gland, inhibits the pineal 5-HT uptake and alters the hypothalamic 5-HT release [73a,b,74]. Another study by Monnet (2002) provides a direct evidence that melatonin affects the circadian rhythm of 5-HT neurotransmission in the hippocampus, a major target of serotoninergic antidepressants, suggesting the involvement of at least two different mechanisms by which melatonin regulates the spontaneous efflux of 5-HT during

the dark phase and the evoked release of 5-HT during the light phase in the hippocampus [72]. The mechanism behind the pattern of melatonin secretion during the dark cycle is controlled by the rate-limiting enzyme in melatonin synthesis - serotonin N-acetyltransferase, which is low during daylight and peaks during the dark phase [76]. Additionally, it has been shown that melatonin acts as a 5-HT2c receptor antagonist [77].

Recently, melatonin has been regarded as a cytoskeletal modulator, actively participating during axogenesis and neurite formation [78]. Some neurodegenerative and psychiatric diseases such as schizophrenia, Alzheimer's and Parkinson's disease have been associated with abnormal cytoskeleton organization of neurons that loose synaptic connectivity leading to impaired neurotransmission. With respect to that, increased melatonin secretion would act in the context of cytoskelatal disorganisation and impaired neurite formation, providing for disease progression [78-79]. In addition, due to its cytoskeleton-modulating features, melatonin has been considered as a possible therapeutic agent for mental disorders [78].

The limitation of the present study is that we did not compare platelet 5-HT concentrations with the daylight hours in a particular samples. Although some authors [31] suggest that 5-HT levels are directly implicated with the hours of sun exposure per day, we did not measure the intensity of the natural daylight.

Conclusion

The results have shown that platelet 5-HT concentration is sex dependent, being constantly lower in female subjects compared to male regardless of the mental health status.

The duration of natural daylight exposure is associated with platelet 5-HT concentration in healthy male subjects and depressed male and female patients but not in healthy female subjects and schizophrenic patients. The magnitute of described effects of daylight on peripheral serotonin concentration was small but significant statistically, however taken that even the most subtle changes in the brain chemistry can have profound effects on the well being of healthy persons and psychiatric patients, these effects should not be overlooked. Overall, the results of the present study suggest that different platelet 5-HT concentrations, observed in depressed patients across different photoperiods, could be linked to differences in the sensitivity of the pineal gland to light or to diverse effects of melatonin on the 5-HT metabolism. More detailed investigations of the relationship between the light exposure, melatonin and the 5-HT system would help in understanding the pathophysiology of depression and schizophrenia.

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Figure legends

Fig 1. Platelet 5-HT concentrations in healthy men and depressed men patients during periods with different duration of natural daylight. Bars represent mean ± S.D. with number of subjects in parentheses.

*p=0.029 vs. depressed patients during short period;

** p=0.011 vs. healthy men during medium period (Kruskal-Wallis ANOVA, followed by Mann-Whitney test)

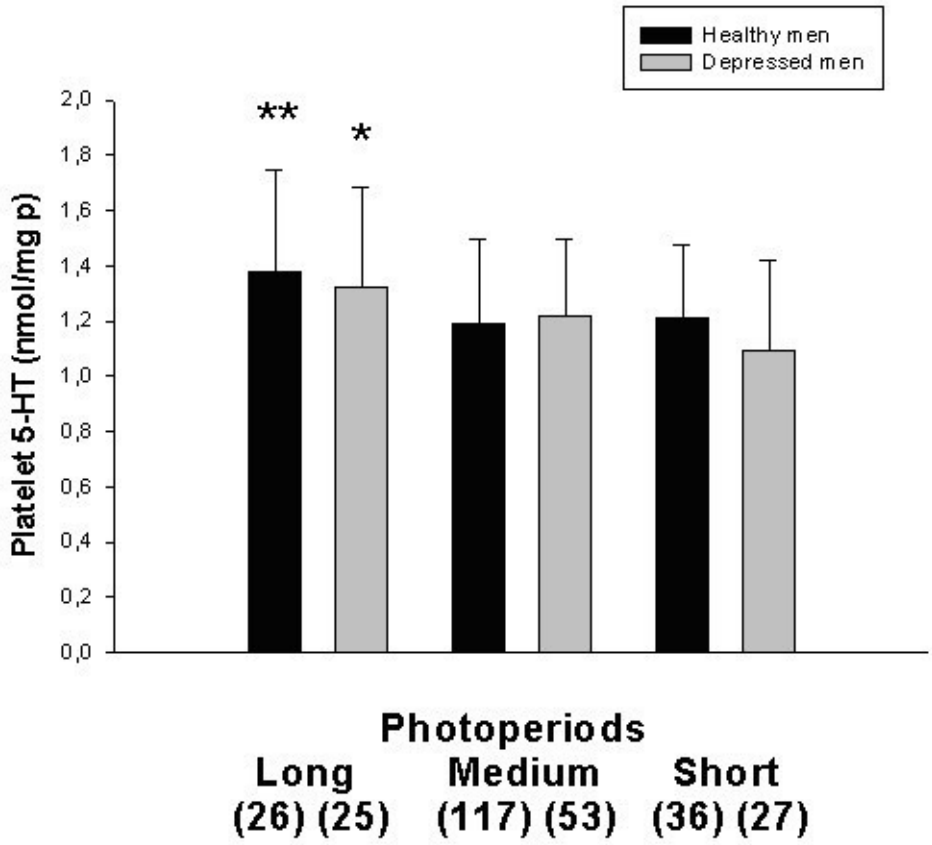

Fig 2. Platelet 5-HT concentrations in healthy women and depressed women during periods with different duration of natural daylight. Bars represent mean ± S.D. with number of subjects in parentheses.

*p=0.025 vs. healthy women during short period;

** p<0.001 vs. healthy women during medium period

p=0.01 vs. depressed patients during short period

p<0.001 vs. depressed women during medium period (Kruskal-Wallis ANOVA, followed by Mann-Whitney test)

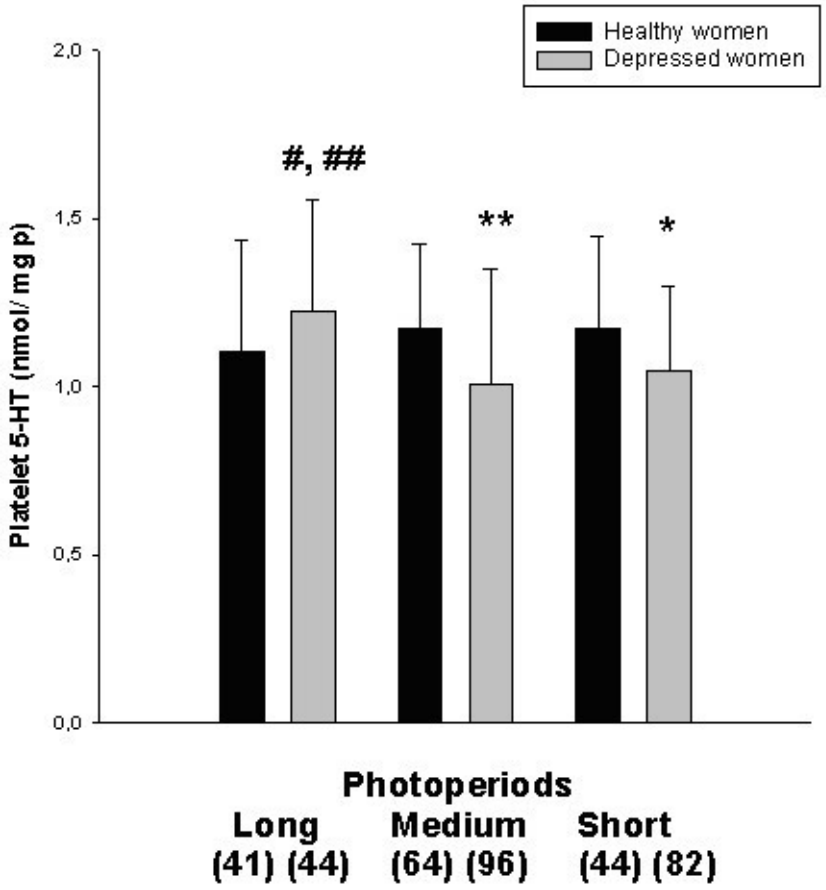

Table 1. Platelet 5-HT concentrations in male and female healthy controls, depressed and schizophrenic patients. Results are expressed as mean ± SD. Number of subjects is given in parenthesis.

	Platelet 5-HT (nmol/ mg proteins)	ANOVA F	df	P
Healthy controls: -men (179) -women (149)	 1.22 ± 0.31 1.15 ± 0.28	3.945	1,326	0.048
Depressed patients: -men (105) -women (153)	 1.21 ± 0.32 1.12 ± 0.35	4.041	1,256	0.045
Schizophrenic patients: -men (143) -women (97)	 1.54 ± 0.53 1.39 ± 0.50	4.935	1,338	0.027

Table 2. Platelet 5-HT concentrations in male and female healthy controls and schizophrenic patients during periods with different duration of natural daylight. Results are expressed as mean ± SD. Number of subjects is given in parenthesis.
*p<0.01 vs. sex matched healthy controls in corresponding photoperiod (Kruskal-Wallis ANOVA, followed by Mann-Whitney test).

	Platelet 5-HT (nmol/ mg proteins)			Kruskal-Wallis ANOVA df =5 H	p
	Period				
	Long	Medium	Short		
Men:					
Healthy controls	1.38 ± 0.37 (26)	1.19 ± 0.31 (117)	1.21 ± 0.26 (36)	42.7	<0.001
Schizophrenic patients	1.46 ± 0.38* (27)	1.51 ± 0.56* (79)	1.64 ± 0.55* (37)		
Women:					
Healthy controls	1.11 ± 0.33 (41)	1.18 ± 0.25 (64)	1.17 ± 0.28 (44)	22.6	<0.001
Schizophrenic patients	1.45 ± 0.45* (24)	1.36 ± 0.51* (57)	1.45 ± 0.44* (27)		