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Brief report

# Platelet serotonin in combat related posttraumatic stress disorder with psychotic symptoms

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**Short Title:** Platelet 5-HT and psychotic PTSD

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**Key words:** combat related posttraumatic stress disorder, psychotic symptoms, platelet serotonin, war veterans

**Abstract**

*Background:* Combat-related posttraumatic stress disorder (PTSD) is severe form of PTSD, frequently associated with psychotic symptoms. Platelet serotonin (5-hydroxytryptamine, 5-HT) was used as a peripheral 5-HT marker to identify particular symptoms in PTSD.

*Methods:* Platelet 5-HT was determined fluorimetrically in 67 war veterans with combat related PTSD, 36 combat exposed veterans who did not develop PTSD, 35 veterans with PTSD complicated with psychotic features. PTSD diagnosis of current and chronic PTSD, and clinical symptoms of PTSD and psychoses were assessed according to DSM-IV criteria, using the Clinician Administrated PTSD Scale, and Positive and Negative Syndrome Scale (PANSS).

*Results*: Platelet 5-HT concentration was significantly higher in veterans with psychotic PTSD than in veterans with non-psychotic PTSD, veterans without PTSD, or in control subjects. Platelet 5-HT was significantly positively correlated with the positive symptoms in PANSS subscale, and with the symptoms of delusions within PANSS positive subscale.

*Limitations*: The results were obtained on peripheral 5-HT marker, i.e. platelet 5-HT concentration.

*Conclusions:* Since the delusions are the core psychotic symptoms occurring in our psychotic PTSD patients, the result of the increased platelet 5-HT concentration, associated with delusions, indicate that platelet 5-HT might be used as a trait marker of psychotic symptoms in PTSD, but not as a state marker for PTSD.

## 1. Introduction

Posttraumatic stress disorder (PTSD) occurs after an extreme, life threatening traumatic event. Combat-related PTSD is a severe form of PTSD, sometimes associated with psychotic symptoms (Hamner, 1997; Hamner et al., 1999). The underlying neurobiological dysfunction of PTSD includes the abnormalities in different neurotransmitter and neuroendocrine systems (Morgan III et al., 2003). Serotonin (5-hydroxytryptamine, 5-HT) is implicated in the pathophysiology of PTSD, since 5-HT alterations might contribute to the cognitive disturbances in PTSD (van Praag, 2004) and aggression (Goveas et al., 2004), 5-HT drugs (sertraline) show clinical efficacy of in the treatment of PTSD (Brady et al., 2000), and administration of the 5-$HT_2$ agonist meta-chlorophenylpiperazine provokes PTSD symptoms (Southwick et al., 1997).

Blood platelets share similarities (receptors, transporter, uptake, storage and release of 5-HT) with the central 5-HT synaptosomes (Camacho and Dimsdale, 2000; Stahl, 1985), and platelet 5-HT has been associated with depressive symptoms in PTSD (Muck-Seler et al., 2003), and aggression (Goveas et al., 2004). Since biological markers are associated to single psychological dysfunction (Mueller-Oerlinghausen et al., 2004; van Praag, 2004), we hypothesized that platelet 5-HT concentration might be related with specific PTSD or psychotic symptoms in patients with combat related PTSD. The aim of the study was to evaluate the association between particular PTSD or psychotic symptoms, and platelet 5-HT concentration, in drug-free male war veterans with combat related PTSD, combat-exposed war veterans who did not develop PTSD, war veterans who had PTSD complicated with psychotic symptoms, and in healthy male control subjects.

## 2. Materials and methods

Participants were 39.4 ± 7.1 years old (range 24-56 years) male, drug-free war veterans (N=138) with chronic and current combat related PTSD, hospitalized at the Department of Psychiatry, University Hospital Dubrava, during 2001-2004 period. Diagnosis of chronic and current combat related PTSD was established using Structured Clinical Interview (SCID) based on DSM-IV criteria (APA, 1994). Groups were divided into 67 veterans with PTSD, 35 veterans with psychotic PTSD, and 36 veterans who did not develop PTSD. PTSD and psychotic symptoms were assessed with Clinician Administrated PTSD Scale (CAPS) (Weathers et al., 2001), and Positive and Negative Syndrome Scale (PANSS)

(Kay et al., 1987). Only patients with total Hamilton Rating Scale for Depression (HAMD) scores ≤ 18 (Hamilton, 1960) were included. The onset of PTSD in psychotic PTSD patients preceded the onset of psychosis. Psychotic symptoms (hallucinations or delusions on the psychotic module of the SCID, or specific disturbance in form of thoughts by mental status examination) and exclusion/inclusion criteria were described in our previous papers (Pivac et al., 2004a; Kozaric-Kovacic et al., 2005). The procedure was fully explained and written informed consent was obtained from all patients. Human ethics committee of the University Hospital Dubrava approved this protocol.

Control group consisted of 136 male drug-free healthy controls, mainly medical stuff, with no personal or family history of psychopathology, substance abuse or dependence, and no medical treatment. Veterans and healthy controls were sampled in the same period of the year.

Blood (4 ml) was drawn from cubical vein at 8.00 a.m. in a plastic syringe with 1 ml of acid citrate dextrose (ACD) anticoagulant. Platelet 5-HT concentrations were determined by the spectrofluorimetric method, as described before (Pivac et al., 2004b). Platelet protein was determined by the method of Lowry et al. (1951).

Statistical evaluation of the results, expressed as means ± SD, was done using one-way analysis of variance (ANOVA), followed by a Tukey's multiple comparison test, and correlations were determined by a Pearson's coefficient of correlation. The significance was accepted when $p<0.05$.

## 3. Results

The demographic data are presented in Table 1. Platelet 5-HT concentration differed significantly ($F(3,266)=3.387$, $p=0.019$), with significantly (Tukey's test) higher platelet 5-HT concentration in veterans with psychotic PTSD than in veterans with PTSD ($p=0.019$), without PTSD ($p=0.040$), or in control subjects ($p=0.029$). Platelet 5-HT concentration did not differ significantly ($p>0.05$) between control subjects, veterans with PTSD or veterans who did not develop PTSD (Fig. 1).

Age of the subjects (Table 1) differed significantly ($F(3,266)=10.839$, $p=0.000$), and control subjects (33.04 ± 11.24 years) were significantly (Tukey's test) younger than veterans with PTSD ($p=0.000$), without PTSD ($p=0.037$), or with psychotic PTSD ($p=0.019$).

No significant correlation was found between platelet 5-HT concentration and age in control subjects ($r=-0.013$; $p=0.909$), veterans with PTSD ($r=0.078$; $p=0.531$), without PTSD ($r=-0.023$; $p=0.896$), or with psychotic PTSD ($r=-0.222$; $p=0.208$).

Since platelet 5-HT was significantly increased in 35 psychotic PTSD patients, to find out the association between platelet 5-HT concentration and psychotic symptoms, a correlation between platelet 5-HT and the corresponding total and subscale scores in PANSS and CAPS was evaluated in these patients (Table 2). Platelet 5-HT concentration was significantly correlated with the scores in PANSS positive subscale. Scores in other subscales in the PANSS or CAPS were not significantly related to platelet 5-HT concentration. To find out which symptoms were related with the increased platelet 5-HT concentration, platelet 5-HT was correlated with each single item listed in PANSS positive subscale. Platelet 5-HT concentration was significantly correlated with the symptoms of delusions. Other symptoms were not significantly correlated with platelet 5-HT concentration (Table 2).

## 4. Discussion

Our results showed that platelet 5-HT concentration was increased in drug-free veterans with chronic and current combat related PTSD complicated with psychotic features, when compared to veterans with or without PTSD, or to control subjects. A positive correlation was found between platelet 5-HT and positive symptoms listed in PANSS subscale, and this correlation was due to the relationship between increased platelet 5-HT and delusions.

The highest platelet 5-HT concentration was found in psychotic PTSD patients with delusions. This finding agrees with the association between platelet 5-HT content and aggression (Goveas et al., 2004), impulsivity and violence (Askenazy et al., 2000), psychotic symptoms of depression (Muck-Seler et al., 1996a; Pivac et al., 1997a), delusions in dementia (Meszaros et al., 1998), positive (Pivac et al., 1997b) or paranoid (Muck-Seler et al., 1991) symptoms of schizophrenia, supporting the hypothesis that platelet 5-HT concentration is related to trait markers (Askenazy et al., 2000; Peirson et al., 1999), such as psychotic symptoms in PTSD (present study). Our data suggest that platelet 5-HT may distinguish between PTSD subjects with and without psychotic symptoms. In line with previous data (Maguire et al., 1998; Mellman and Kumar, 1994; Muck-Seler et al., 2003; Pivac et al., 2002), our veterans with or without combat related PTSD had similar platelet 5-HT concentration as control subjects or combat exposed veterans who did not develop PTSD, indicating that platelet 5-HT is not associated with diagnosis of PTSD (van Praag, 2004). Platelet 5-HT concentration might be affected by sex, age or seasonality. The effect of sex was excluded with the inclusion of only male subjects; the possible effect of age on platelet 5-HT content was

neglected as no significant relation between age and platelet 5-HT was found in healthy (Muck-Seler et al., 1996b; Pivac et al., 2001; Pivac et al., 2004b) or PTSD (present study) subjects, and the possible seasonal influence on platelet 5-HT parameters (Jakovljevic et al., 1997) was avoided since war veterans and healthy controls were sampled in the same season.

The lack of significant relationship between platelet 5-HT and other subscales of PANSS or CAPS indicates that only delusions were associated with increased values of platelet 5-HT. In support to our data no association was found between platelet 5-HT and CAPS scores in less severely ill patients without psychotic symptoms (Pivac et al., 2002), or between platelet 5-HT content and uptake and scores measuring PTSD, depressive and anxiety symptoms (Maguire et al., 1998; Mellman and Kumar, 1994).

Although psychotic PTSD is not recognized as a separate entity, 30-40% of combat related PTSD patients develop psychotic symptoms, which add to a more severe form of PTSD (Butler et al., 1996; Hamner, 1997; Hamner et al., 1999; Mueser et al., 2002; Kozaric-Kovacic and Borovecki, 2005; Kozaric-Kovacic and Kocijan-Hercigonja, 2001; Kozaric-Kovacic et al., 2005; Pivac et al., 2004a). Psychotic features in our PTSD patients were not due to previous comorbidity, as we excluded patients with previous Axis I disorders. Increased concentration of cerebrospinal fluid corticotrophin releasing hormone (Sautter et al., 2003), decreased activity of the plasma dopamine beta hydoxylase (Hamner and Gould, 1998), and increased platelet 5-HT concentrations (present study) were found in psychotic PTSD, suggesting a biologically distinct psychotic PTSD subtype.

The limitation of the study was the use of peripheral marker, platelet 5-HT concentration. The advantage of the study was in the inclusion criteria of only drug-free war veterans with or without combat related PTSD, and/or psychotic symptoms, a large sample (N=138), and detailed clinical assessment with instrument measures such as SCID, CAPS and PANSS.

In conclusion, platelet 5-HT concentration was increased in war veterans with psychotic PTSD, and there was a significant relationship between psychotic symptoms, especially delusions, and platelet 5-HT concentration in these patients. The data suggest that platelet 5-HT concentration might be used as a trait marker for PTSD with psychotic features.

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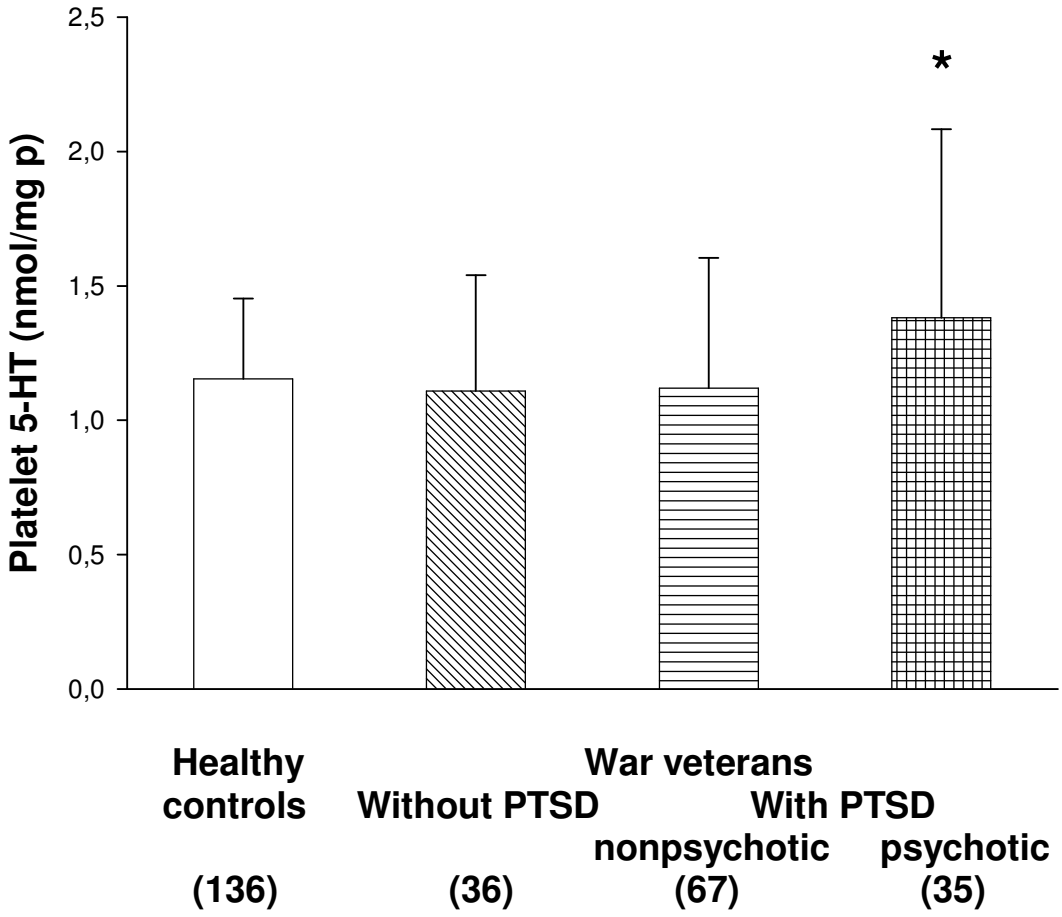


Figure 1: Platelet 5-HT concentration (mean ± SD) in war veterans with psychotic PTSD, war veterans with nonpsychotic PTSD, war veterans without PTSD, and in male healthy controls. Number of subjects is given in brackets. * $p < 0.05$ vs. platelet 5-HT concentration in war veterans with nonpsychotic PTSD, war veterans without PTSD or control subjects, Tukey's test.

Table 1. Demographic data in war veterans with nonpsychotic or psychotic PTSD, and in war veterans without PTSD. Data are expressed as mean ± SD. Number of subjects is given in brackets.

| | War veterans (138) | | |
|---|---|---|---|
| | With PTSD (102) | | Without PTSD |
| | Nonpsychotic (67) | Psychotic (35) | (36) |
| Age (years) | 40.7 ± 7.3 | 37.9 ± 8.0 | 37.7 ± 4.3 |
| PANSS total | 73.3 ± 15.5 | 101.6 ± 16.4 | 36.0 ± 1.5 |
| PANSS positive | 13.2 ± 3.8 | 23.3 ± 6.0 | 7.3 ± 0.5 |
| PANSS negative | 10.5 ± 4.2 | 15.5 ± 4.8 | 7.4 ± 0.5 |
| PANSS gen. psychopathology | 41.4 ± 8.1 | 52.6 ± 7.2 | 17.8 ± 0.8 |
| PANSS supplementary items | 8.3 ± 2.4 | 10.7 ± 1.7 | 3.4 ± 0.5 |
| CAPS total | 71.9 ± 4.3 | 98.3 ± 3.0 | 18.8 ± 11.5 |

Table 2. Pearson's coefficient of correlation (r) between platelet 5-HT and scores in clinical scales (total and subscale scores in PANSS and in CAPS) and symptoms in PANSS positive subscale in war veterans with psychotic PTSD.

| Clinical scales | correlation (r) | p |
|---|---|---|
| CAPS total | -0.061 | 0.730 |
| PANSS total | 0.068 | 0.703 |
| PANSS positive | 0.379 | 0.027* |
| PANSS negative | -0.176 | 0.319 |
| PANSS general psychopathology | -0.056 | 0.751 |
| PANSS supplementary items | -0.007 | 0.967 |
| | | |
| Symptoms in PANSS positive subscale: | | |
| -Delusion | 0.448 | 0.008* |
| -Conceptual disorganization | 0.303 | 0.081 |
| -Hallucinatory behavior | 0.312 | 0.073 |
| -Excitement | 0.076 | 0.671 |
| -Grandiosity | 0.115 | 0.519 |
| -Suspicioness/persecution | 0.180 | 0.309 |
| -Hostility | 0.161 | 0.364 |

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