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Platelet imipramine binding in patients with posttraumatic stress disorder before and after phenelzine treatment

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Abstract

Posttraumatic stress disorder (PTSD) is frequently associated with major depressive disorder, and antidepressants have been reported to ameliorate PTSD symptoms in some patients. The present study assessed the number and affinity of platelet imipramine binding sites, as a marker of the serotonin transporter complex, in PTSD male patients ($n = 10$) before and after phenelzine treatment (30–60 mg/day, for 4 weeks) as well as in comparison to healthy controls ($n = 10$). In our sample, there was no evidence of a significant *difference in the characteristics* (B_{max} and K_d) of platelet [^{3}H]imipramine binding between the PTSD patients and the controls and within PTSD patients before and after phenelzine treatment. Moreover, no beneficial effect of phenelzine was detected in the patients (as assessed by PTSD, anxiety, and depression scales).

Keywords: Affective disorder; Anxiety; Monoamine oxidase inhibitor; Serotonin transporter

1. Introduction

Posttraumatic stress disorder (PTSD) is defined as a psychiatric disorder that occurs after a distressing event that is outside the range of the usual human experience. Affected patients tend to reexperience the painful event, avoid stimuli evocative of the trauma, and manifest increased arousal. Several psychopharmacological studies have suggested that tricyclic antidepressants (TCAs) (Frank et al., 1988; Davidson et al., 1990, 1993) and the monoamine oxidase inhibitor (MAOI) phenelzine (Hogben and Cornfield, 1981; Frank et al., 1988) have various beneficial effects in PTSD patients, although other studies only partially supported these positive reports (Lerer et al., 1987; Shestatzky et al., 1988). Lately, the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine, and sertraline were reported to ameliorate symptoms of PTSD (Davidson et al., 1991; De Boer et al., 1992; Nagy et al., 1992; Shay,

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1992; van der Kolk et al., 1994; Brady et al., 1995). Unfortunately, there have been only a few published randomized clinical trials, and except for phenelzine, most of the drugs have been tested only once (Demartino et al., 1995). It is still an open question whether these drugs directly affect PTSD biopathology or exert their effect on the depressive symptoms that often occur concurrently with PTSD (Silver et al., 1990; Davidson, 1992; Southwick et al., 1992). Indeed, PTSD shares many symptoms with major depressive disorder (MDD): depressed mood, guilt feelings, grief, anhedonia, irritability, social withdrawal, and insomnia. And, to repeat, both PTSD and MDD benefit from antidepressants. On the other hand, PTSD has symptoms in common with panic disorder (PD), which also responds to treatment with TCAs and MAOIs. It was therefore suggested that PTSD, like PD, is a consequence of dysregulation of the locus ceruleus (Friedman, 1988). Likewise, chronic PTSD may reflect a state of hyperarousal associated with excessive sympathetic nervous activity (Friedman, 1988).

The role of the serotonergic system in the pathophysiology of PTSD is as yet unclear. The clinical similarity of PTSD and MDD and the relative efficacy of selective serotonin reuptake inhibitors in both disorders point to a possible involvement of the serotonergic system in PTSD.

One approach to studying the involvement of the serotonergic system in PTSD is to assess platelet [^{3}H]imipramine binding sites as a peripheral marker for this system. [^{3}H]imipramine labels the serotonin transporter in both brain and platelets (Langer et al., 1980; Paul et al., 1981). The high-affinity [^{3}H]imipramine binding sites identified in human brain and platelets (Paul et al., 1984; Rehavi et al., 1984a) show a biochemical and pharmacological resemblance (Paul et al., 1981). Decreased density of platelet imipramine binding sites has been reported in major depressed patients (Briley et al., 1980; Paul et al., 1984), although other investigators found unaltered [^{3}H]imipramine binding in depression (Rehavi et al., 1984b; Whitaker et al., 1984). Acute stress of war has been shown to be associated with increased imipramine binding (Weizman et al., 1992).

A recent study has demonstrated diminished platelet [^{3}H]paroxetine binding and affinity in PTSD patients (Arora et al., 1993). Furthermore, the affinity of the transporter to paroxetine appeared to be a predictor of responsiveness to fluoxetine treatment in PTSD patients (Fichtner et al., 1994). Phenelzine, another antidepressant used in the treatment of PTSD, acts through inhibition of the enzyme MAO, which is located on the outer membrane of the mitochondria, and in contrast to SSRIs, does not interact directly with the platelet imipramine binding. Thus, we designed the present study to detect possible reduction in platelet imipramine binding in untreated combat-related PTSD patients, and to assess the impact of 4 weeks of phenelzine treatment on the platelet serotonin transporter. We hypothesized that phenelzine would induce improvement in PTSD symptoms accompanied by restoration of [^{3}H]imipramine binding to the normal range.

2. Methods

2.1. Subjects

Ten men suffering from combat-related PTSD (mean age = 42.5 years, SD = 6.1, range = 33–53) and 10 healthy male volunteers (mean age = 41.1 years, SD = 6.1, range = 29–50) participated in the study. All the patients were recruited from the PTSD day-hospital unit of the Tel Aviv-Brull Mental Health Center. Diagnosis of PTSD was established by two senior psychiatrists (N.L. and A.S.) according to the *DSM-III-R* criteria (American Psychiatric Association, 1987). Full agreement between the two independent raters was required for a patient to be included in the study. Control subjects were personnel from the same center. All subjects were fully informed about the nature of the study and gave their written consent. All participants were drug free for at least 4 weeks before the study (the patients were previously treated with TCAs) and had no history of alcohol or substance abuse/dependence. Each participant was interviewed with the Structured Clinical Interview for *DSM-III-R* — Patient Version (SCID; Spitzer et al., 1989). On the basis of the SCID, the control subjects were determined to be free of mental disorder. Of the 10 PTSD patients, seven also met the

criteria for MDD, five for generalized anxiety disorder, two for PD without agoraphobia, two for PD with agoraphobia, and one for agoraphobia without PD. Symptoms of anxiety and depression started at different time points. Severity of symptoms was assessed once before initiation of drug treatment and once again after 4 weeks on phenelzine treatment (30–60 mg/day). Psychometric assessment included the following measures: Revised PTSD Inventory (Solomon et al., 1993); Impact of Event Scale (Horowitz et al., 1979); Beck Depression Inventory (BDI; Beck et al., 1961); and State-Trait Anxiety Inventory (STAI; Spielberger et al., 1977).

2.2. [^{3}H]imipramine binding

Blood samples for determination of platelet imipramine binding were obtained at 09:00–10:00 h. before and after drug treatment. Preparation of platelet membranes and [^{3}H]imipramine (specific activity 55.4 Ci/mmol, New England Nuclear, Boston, MA) binding assay were performed as previously described (Weizman et al., 1986). Eight concentrations of [^{3}H]imipramine (0.2–8 nM) were used to examine the binding to platelets of each subject; and nonspecific binding was measured in the presence of 1 μM clomipramine. Scatchard plots were constructed, and both the maximal binding (B_{max}) of [^{3}H]imipramine and its binding-site affinity (K_d) were determined by linear regression analysis. The reliability of the binding assay is 95%. We selected [^{3}H]imipramine to label the serotonin transporter because this ligand had been used extensively in our previous clinical studies, and a reliable database was available concerning its binding parameters in humans.

2.3. Statistical evaluation

Group differences (PTSD vs. control) before treatment were assessed by multivariate analysis of variance (MANOVA), with group as a between-subject factor. Pretreatment vs. posttreatment changes for the PTSD group were measured with MANOVA with repeated measures. Given the small sample size, differences between PTSD subgroups (by comorbid diagnoses) were analyzed with the Mann-Whitney nonparametric test. All analyses were performed separately for the psychological and biochemical measures.

Table 1
Comorbid diagnoses of patients with posttraumatic stress disorder (n = 10) according to the Structured Clinical Interview for *DSM-III-R* criteria

Patient No.	Past MDD	Current MDD	GAD	PD	Agoraphobia
1	–	+	–	–	+
2	–	–	–	–	–
3	–	+	+	–	–
4	–	+	+	+	+
5	–	–	+	–	–
6	–	+	+	–	–
7	–	–	–	–	–
8	–	+	–	+	–
9	–	+	–	+	–
10	–	+	+	+	+

Note. MDD, major depressive disorder; GAD, generalized anxiety disorder; PD, panic disorder.

3. Results

As shown in Table 1, most patients in our study population had multiple diagnoses. Table 2 summarizes the distribution of the diagnoses of the patient population.

Table 2
Distribution of diagnoses within the group of patients (n = 10)

Diagnosis	%
PTSD alone	20
Additional diagnoses	
1. MDD (total)	70
Past MDD	0
Present MDD	70
2. GAD	50
3. PD (total)	40
PD plus agoraphobia	20
PD without agoraphobia	20
4. Agoraphobia (total)	30
Agoraphobia plus PD	20
Agoraphobia without PD	10

Note. MDD, major depressive disorder; GAD, generalized anxiety disorder; PD, panic disorder.

Table 3
Psychological and biochemical variables in PTSD patients and controls before and after treatment with phenelzine

	Control		PTSD pre-treatment		PTSD post-treatment		PTSD pre-treatment vs. controls F (df = 1,18)	PTSD pretreatment vs. post-treatment F (df = 1,9)
	Mean	SD	Mean	SD	Mean	SD		
Psychological measures								
STAI-S	24.8	4.4	69.5	5.5	63.9	14.7	406.76***	1.83 (NS)
STAI-T	23.1	2.6	35.6	15.1	40.7	13.7	6.63*	0.84 (NS)
BDI	2.8	1.9	29.7	12.3	27.9	12.2	525.43**	0.17 (NS)
IES: intrusion	9.2	1.4	25.8	1.8	23.7	3.6	62.78***	2.78 (NS)
IES: avoidance	8.7	0.9	19.0	4.0	19.0	4.4	11.85**	0.00 (NS)
PTSD Inventory	18.2	1.0	32.8	13.4	38.7	13.0	46.73***	3.16 (NS)
Biochemical measures								
B_{max} (fmol/mg protein)	519.0	140.5	424.9	236.9	404.4	108.4	1.01 (NS)	0.05 (NS)
K_d (nM)	1.46	0.7	1.20	0.4	1.19	0.5	1.17 (NS)	0.00 (NS)

Note. PTSD, posttraumatic stress disorder; STAI-S, State portion of the State-Trait Anxiety Inventory; STAI-T, Trait portion of the State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; IES, Impact of Event Scale; B_{max}, maximal binding capacity; K_d, dissociation constant; *$P < 0.05$; **$P < 0.005$; ***$P < 0.001$.

3.1. Group differences at baseline condition

The MANOVA comparing PTSD patients before treatment with control subjects resulted in significant differences for the psychological measures (F = 111.18, df = 6,13, $P < 0.001$). All the univariate analyses yielded statistically significant results as well; that is, as expected, PTSD subjects reported more anxiety, depressive, and posttraumatic symptoms than did control subjects. For the biochemical measures (B_{max} and K_d), no significant differences were noted on either the multivariate (F = 1.09, df = 2,17, $P > 0.05$) or the univariate analyses (Table 3).

3.2. Pretreatment vs. posttreatment differences

When pretreatment and posttreatment measures were compared, no significant difference was found within the PTSD group for psychological (F = 0.07, df = 1,9, $P > 0.05$) or biochemical (F = 0.05, df = 1,9, $P > 0.05$) measures (Table 3).

3.3. Differences between PTSD subjects with and without comorbid disorders

In the pretreatment condition, subjects with MDD reported more depressive symptoms than did those without MDD as reflected by the BDI ($z = -2.39$, $P < 0.05$). Imipramine-binding characteristics did not differ between PTSD patients with or without MDD (*before*: B_{max}, $z = -0.80$, $P > 0.05$; K_d, $z = -0.23$, $P > 0.05$; *after*: B_{max}, $z = -0.57$, $P > 0.05$; K_d, $z = -1.03$, $P > 0.05$). At the posttreatment time point, PTSD subjects with MDD reported more state anxiety (STAI-S) ($z = -2.17$, $P < 0.05$) and intrusive symptoms ($z = -2.08$, $P < 0.05$) compared with those without MDD. PTSD subjects with and without PD comorbidity differed in their mean pretreatment PTSD Inventory score ($z = -2.57$, $P < 0.01$) and in their mean posttreatment state anxiety score ($z = -2.03$, $P < 0.05$).

Significant interactions between time (pretreatment vs. posttreatment) and the presence of MDD (with vs. without) were found on the state anxiety (F = 9.71, df = 1,8, $P < 0.05$) and intrusion (F = 13.36, df = 1,8, $P < 0.01$) variables. These interactions reflect a posttreatment decrease in both state anxiety and intrusive symptoms in PTSD patients without MDD as compared with unaltered symptomatology among PTSD patients with MDD (Table 4). No significant interactions between patients with and without MDD were found

Table 4
Psychological and biochemical measures (mean ± SD) in the PTSD patients ($n = 10$), divided according to the presence or absence of specific additional diagnoses, before and after phenelzine treatment

Diagnosis	STAI-S	STAI-T	IES (Intrusion)	IES (Avoidance)	PTSD Inventory	BDI	B_{max} (fmol/mg protein)	K_d (nM)
Major depressive disorder								
Pretreatment								
With ($n = 7$)	70.9 ± 3.2	38.3 ± 17.5	25.6 ± 1.8	19.7 ± 3.7	33.3 ± 16.2	35.9 ± 8.4	466 ± 255	1.2 ± 0.4
Without ($n = 3$)	66.3 ± 9.1	29.3 ± 5.1	26.3 ± 2.1	17.3 ± 4.9	31.7 ± 4.0	15.3 ± 5.0	329 ± 194	1.2 ± 0.6
Posttreatmet								
With	71.3 ± 5.5	40.0 ± 15.1	25.4 ± 1.6	19.9 ± 4.2	40.6 ± 13.3	31.3 ± 10.5	419 ± 99	1.3 ± 0.5
Without	46.7 ± 15.8	42.3 ± 12.5	19.7 ± 3.8	17.0 ± 5.2	34.3 ± 13.7	20.0 ± 14.2	371 ± 145	0.9 ± 0.4
Generalized anxiety disorder								
Pretreatment								
With ($n = 5$)	67.6 ± 6.7	35.0 ± 15.9	25.2 ± 1.8	20.2 ± 3.4	33.6 ± 15.0	34.0 ± 15.4	346 ± 260	1.3 ± 0.4
Without ($n = 5$)	71.4 ± 3.7	36.2 ± 16.1	26.4 ± 1.8	17.8 ± 4.5	32.0 ± 13.2	25.4 ± 7.4	504 ± 207	1.1 ± 0.4
Posttreatment								
With	65.6 ± 13.1	39.4 ± 15.9	24.0 ± 4.3	18.8 ± 4.6	43.8 ± 11.6	24.0 ± 16.3	435 ± 128	1.0 ± 0.5
Without	62.2 ± 17.6	42.0 ± 12.8	23.4 ± 3.1	19.2 ± 4.8	33.6 ± 13.4	31.8 ± 5.4	374 ± 38	1.4 ± 0.5
Panic disorder								
Pretreatment								
With ($n = 4$)	72.0 ± 2.8	42.5 ± 21.9	25.5 ± 2.4	20.0 ± 4.8	23.0 ± 2.4	34.0 ± 7.7	450 ± 240	1.3 ± 0.3
Without ($n = 6$)	67.8 ± 6.4	31.0 ± 7.7	26.0 ± 1.5	18.3 ± 3.7	39.3 ± 13.8	26.8 ± 14.6	408 ± 256	1.2 ± 0.5
Posttreatment								
With	74.0 ± 2.9	46.0 ± 16.8	25.7 ± 1.7	20.8 ± 5.6	33.5 ± 10.7	29.3 ± 19.7	387 ± 113	1.0 ± 0.5
Without	57.2 ± 15.8	37.2 ± 11.4	22.3 ± 3.9	17.8 ± 3.5	42.1 ± 14.1	27.0 ± 12.3	416 ± 114	1.3 ± 0.5
Agoraphobia								
Pretreatment								
With ($n = 3$)	68.7 ± 2.3	43.3 ± 19.0	25.0 ± 2.0	20.7 ± 3.5	34.0 ± 16.5	38.3 ± 4.9	475 ± 320	1.2 ± 0.5
Without ($n = 7$)	69.8 ± 6.5	32.3 ± 13.4	26.1 ± 1.8	18.3 ± 4.2	32.3 ± 13.3	26.0 ± 12.9	403 ± 220	1.2 ± 0.4
Posttreatment								
With	68.7 ± 6.1	44.7 ± 15.2	26.7 ± 1.2	20.3 ± 3.1	44.3 ± 15.5	24.0 ± 13.2	437 ± 93	1.2 ± 0.8
Without	61.9 ± 17.2	39.0 ± 13.9	22.4 ± 3.5	18.4 ± 5.0	36.3 ± 12.2	29.6 ± 12.4	390 ± 118	1.2 ± 0.4

Note. PTSD, posttraumatic stress disorder; STAI-S, State portion of the State-Trait Anxiety Inventory; STAI-T, Trait portion of the State-Trait Anxiety Inventory; IES, Impact of Event Scale; BDI, Beck Depression Inventory; B_{max}, maximal binding capacity; K_d, dissociation constant.

for the biochemical measures: (B_{max}: $F = 0.17$, $df = 1,8$, $P > 0.05$; K_d: $F = 0.43$, $df = 1,8$, $P > 0.05$).

4. Discussion

The present study indicates that platelet [^{3}H]-imipramine-binding values (B_{max}) are decreased by 18% in male PTSD patients compared with age-matched control subjects, yet this reduction does not reach a statistically significant level. Moreover, in our sample, imipramine binding did not differ in PTSD patients with or without MDD, and phenelzine treatment did not modulate the imipramine-binding capacity and did not restore the value to control levels. Moreover, the 18% difference between pretreatment PTSD values and control values became a 23% difference after treatment. Recently, a lower ($P < 0.025$) number of platelet serotonin tranporters, measured by [^{3}H]paroxetine binding, was detected in PTSD patients compared with normal controls (Arora et al., 1993). This decrease was accompanied by a significant decrease in K_d ($P < 0.01$). In a subsequent study (Fichtner et al., 1994), platelet [^{3}H]paroxetine affinity to its ligand was shown to be a possible predictor of clinical response to fluoxetine treatment in PTSD patients. The magnitude of the decrease in the present study (−18%) is similar to that observed by Arora et al. (1993) (−17%), yet the reduction in our study did not reach a significant level. The discrepancy in the results may be related to the difference in sample size ($n = 20$ in Arora et al. [1993]; $n = 10$ in the present study) or the high frequency (40%) of substance-dependence disorders among the PTSD patients in the study by Arora et al. (1993), in contrast to the absence of substance dependency in our patient population. Another possibility is that the difference in ligands, [^{3}H]imipramine vs. [^{3}H]paroxetine, used to label the platelet serotonin transporter is responsible for the inconsistency between the studies. Comorbidity of MDD in the PTSD patients did not affect platelet serotonin transporter findings, as was also demonstrated by Arora et al. (1993). [^{3}H]imipramine is not as selective a ligand for the serotonergic transport system as [^{3}H]paroxetine (Sette et al., 1983; Hrdina et al., 1990). Furthermore, [^{3}H]imipramine also appears to label a low affinity site that is not related to the serotonin-uptake site (Hrdina, 1984).

On the clinical level, the present study did not reveal any beneficial effect of phenelzine treatment in PTSD patients. Moreover, even the patients who suffered from MDD in addition to PTSD did not benefit from the drug treatment. These results agree with those of several previous studies (Lerer et al., 1987; Shestatzsky et al., 1988) but conflict with others that reported a beneficial clinical response to phenelzine (Hogben and Cornfield, 1981; Frank et al., 1988). Although the present study did not provide empirical support for a significant overall beneficial effect of phenelzine in these patients, significant decreases were observed in specific scale scores within a subgroup (PTSD without MDD), but the number of subjects was too small ($n = 3$) to warrant conclusions at this time. The small size of the sample and our study design (only a 4-week open trial without a placebo control) limit conclusions about the efficacy of the drug treatment. Ideally, the trial of phenelzine should have continued for a longer time, as clinical responsiveness to antidepressant treatment can be slow, and studies have shown that significant changes in binding parameters lag behind measurable clinical change (Suranyi-Cadotte et al., 1982). Yet, the lack of even a restricted effect of antidepressants in the treatment of PTSD, as observed in the present study and reported previously, possibly supports the hypothesis that the depression observed in PTSD is phenomenologically similar to that observed in MDD, but has a different biological underpinning as also demonstrated by different hypothalamic-pituitary-adrenal (HPA) axis abnormalities.

Dexamethasone suppression test (DST) studies of PTSD patients have shown normal suppression of cortisol in nondepressed PTSD patients (Kudler et al., 1987; Kosten et al., 1990). Furthermore, it was found that even PTSD patients with comorbid major depression did not have abnormal DST results, in contrast to non-PTSD patients with MDD (Halbreich et al., 1988, 1989; Kosten et al., 1990). Moreover, enhanced negative feedback sensitivity of the HPA axis was demonstrated in

PTSD patients with and without MDD through the use of a low dose of dexamethasone (Yehuda et al., 1993).

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