Prolactin response to d-fenfluramine in combat-related post-traumatic stress disorder

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Abstract

Central serotonergic function can be investigated by measuring the prolactin response to the serotonin releasing/uptake agent, d-fenfluramine. This study investigated the effect of diagnosis, depressive symptoms and history of alcohol or tobacco abuse or dependence on the d-fenfluramine test in combat-related post-traumatic stress disorder (PTSD). Male, non-hospitalized combat-exposed veterans diagnosed with PTSD (DSM-III-R) and a similarly aged combat-exposed control group were assessed for both PTSD and depressive symptoms and prolactin responses to a 30-mg d-fenfluramine challenge test. Ninety-five subjects were studied; 23 were controls, 46 subjects met the criteria for current PTSD and 26 for past PTSD. There were no significant differences between the three groups for baseline prolactin, peak prolactin, and time to reach peak, delta prolactin or area under the curve of the prolactin vs. time curve. Depressive symptoms and history of alcohol or tobacco abuse or dependence did not have a confounding effect on the prolactin responses to d-fenfluramine. This study suggests that a blunted prolactin response to d-fenfluramine may be a consequence of combat exposure rather than PTSD. To confirm this, further studies involving both healthy and combat-exposed control groups in addition to subjects with PTSD of similar ages are required.

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Key words: Combat-related post-traumatic stress disorder, depression, d-fenfluramine, prolactin.

Introduction

Recent studies have investigated the role of serotonin (5-HT) in the pathophysiology of post-traumatic stress disorder (PTSD). Indirect evidence for serotonergic involvement in PTSD comes from clinical studies of serotonergic agents. In particular, the selective serotonin reuptake inhibitors have been shown to be effective in short-term trials (Marshall et al., 2001; Martenyi et al., 2002b) and in prevention of relapse in PTSD (Davidson et al., 2001; Martenyi et al., 2002a). In addition, a number of studies have addressed aspects of serotonergic function in PTSD, focussing on either peripheral markers of 5-HT function or neuroendocrine challenge studies.

Platelet 5-HT transporter function has been examined by direct measurement of 5-HT uptake into platelets (Cicin-Sain et al., 2000; Mellman and Kumar, 1994) or by the measurement of \[^{3}H\]paroxetine (Arora et al., 1993; Maes et al., 1999; Maguire et al., 1998) or \[^{3}H\]imipramine (Weizman et al., 1996) binding to platelet membranes in subjects with PTSD. Platelet concentrations of 5-HT (Cicin-Sain et al., 2000; Mellman and Kumar, 1994; Muck-Seler et al., 2003; Pivac et al., 2002) and platelet-poor plasma concentrations of 5-HT (Spivak et al., 1999) have also been measured in subjects with PTSD. Findings are conflicting, with most studies consistent with no alteration of peripheral 5-HT function in PTSD when compared to either healthy or combat-exposed control groups (Cicin-Sain et al., 2000; Maguire et al., 1998; Mellman and Kumar, 1994; Muck-Seler et al., 2003; Pivac et al., 2002; Weizman et al., 1996). Diminished 5-HT activity was found by Arora et al. (1993), Maes et al. (1999) and Spivak et al. (1999) compared to healthy controls.

These studies generally involved a small number of combat-exposed males with PTSD, the largest [Maguire et al., 1998 (n = 45); Muck-Seler et al., 2003 (n = 48); Cicin-Sain et al., 2000 (n = 63)] notably not...
supportive of a peripheral 5-HT dysfunction. Although the platelet is widely accepted as a model for central serotonergic neurones (Lesch et al., 1993) it does not reflect functioning of 5-HT systems. Neuroendocrine challenge studies provide an assessment of 5-HT function, albeit indirectly.

Dinan et al. (1990) assessed eight female patients with PTSD following sexual assault, using several neuroendocrine tests including the prolactin response to buspirone, a 5-HT-1A agonist. There was no difference in the prolactin responses between the patients and healthy subjects. Prolactin and cortisol responses to dexamethasone were investigated in 30 males with combat exposure and 18 healthy controls by Grossman et al. (1996). Both combat-exposed veterans with and without PTSD showed greater suppression of prolactin compared to the control group, whereas only the PTSD group showed greater suppression of cortisol. These findings suggest that the prolactin response, a possible dopaminergic and/or serotonergic functional marker, is related to combat exposure per se rather than PTSD.

Meta-chlorophenylpiperazine (m-CPP) was used as a probe of 5-HT activity in 24 males with combat-related PTSD and 14 healthy males (Southwick et al., 1997). Panic attacks and flashbacks were induced in approximately one third of the PTSD patients following m-CPP, suggesting hyper-responsiveness of the serotonergic system in a subgroup of patients with PTSD. On the other hand Davis et al. (1999) assessed the prolactin response to d-fenfluramine in eight subjects with combat-related PTSD and eight healthy controls. The PTSD group had a significantly lower prolactin response compared to the controls suggesting hypo-responsive 5-HT function in patients with PTSD. The difference between studies may be related to the specificity of the agonists employed: mCPP specific for 5-HT2B/5-HT2C and fenfluramine a non-specific agonist. Confounding factors such as the inclusion of subjects with comorbid major depression, alcohol or substance abuse or concurrent psychotropic medication may also have influenced the findings.

To further investigate the serotonergic function in PTSD, we have studied the prolactin response to 30 mg d-fenfluramine in combat-exposed veterans with a diagnosis of either current, past or no PTSD with simultaneous assessment of depressive symptoms. Subjects were free of alcohol, tobacco or substance abuse or dependence for more than 6 months, and were psychotropic drug-free for more than 2 wk. The effect of primary diagnosis, and potential confounder variables on the prolactin response to d-fenfluramine was investigated in these subjects.

Methods

Patients

Patients were Australian Vietnam war veterans recruited from the Austin and Repatriation Medical Centre Veterans’ Psychiatry Unit, the Vietnam Veterans’ Association and the Returned Servicemen’s League. Male combat-exposed Vietnam veterans diagnosed with PTSD (DSM-III-R; APA, 1987) were recruited for the study. Patients were eligible if they had a diagnosis of either current or past PTSD subsequent to war service. Patients were excluded if they had: (i) other current major psychiatric disorders other than major depression (e.g. schizophrenia, bipolar disorder, substance abuse or dependence, organic brain syndrome), although past psychiatric illness was not an exclusion; (ii) acute or serious medical illness (e.g. endocrine, cardiac, hepatic, renal or neurological disease); (iii) recent substantial changes in weight (i.e. >3 kg); (iv) taken psychotropic or other medications likely to affect the d-fenfluramine test in the 2 wk prior to testing or (v) significant cognitive impairment.

Control subjects

A control group of male combat veterans with no PTSD, depression symptomatology or other psychiatric disorder was recruited. Control subjects were recruited predominantly from the Vietnam Veterans’ Association and the Returned Servicemen’s League.

Approval for the study was obtained from the Austin and Repatriation Medical Centre Human Ethics Committee and all patients and controls provided written informed consent.

Clinical evaluation

Details of demographic, marital, employment and military history were recorded. All subjects underwent a structured interview with a modified version of the Comprehensive International Diagnostic Interview (CIDI; WHO, 1987). Absence of serious medical illnesses was determined by medical history, clinical examination and screening laboratory tests.

Diagnosis of PTSD was made on the basis of DSM-III-R criteria for PTSD as identified by Davidson’s Interview for PTSD (Davidson et al., 1989) by two psychiatrists (M.H. and P.M.). This interview delineates patients into those who have met the diagnostic criteria within the last 4 wk, those who have had a diagnosis of PTSD during their lifetime, and those who have never had a diagnosis of PTSD. Self-reported PTSD symptoms were assessed using the Impact of Events Scale (IES; Horowitz et al., 1979). As
the IES version used did not contain a specific score of arousal symptoms, we also assessed anxiety symptoms using the Hamilton Rating Scale for Anxiety (HARS; Hamilton, 1959).

Depressive symptoms were assessed using the 21-item Hamilton Depression Scale (HDRS; Hamilton, 1960). We elected to use a score of ≥18 on this scale as indicative of significant depressive symptoms to subdivide the PTSD groups into ‘not depressed’ and ‘depressed’. Subjects were administered the Combat Exposure Scale (CES; Keane et al., 1989) as a measure of the level of wartime stressors experienced by combatants. Cognitive function was assessed with the Mini Mental State Examination (MMSE; Folstein et al., 1975).

**Neuroendocrine test**

On the day of the d-fenfluramine challenge test, patients fasted from midnight and began bed rest 1 h prior to the test. Half an hour prior to the 09:00 hours fenfluramine administration, an intravenous line was inserted into a forearm vein. Two baseline blood samples were drawn prior to oral administration of 30 mg d-fenfluramine and further samples were collected every 30 min for 6 h. A light snack was permitted 4 h after tablet ingestion. Blood samples were centrifuged at 4 °C and stored at −20 °C until assayed for plasma prolactin and fenfluramine/norfenfluramine concentrations. The prolactin was measured using a routine radioimmunoassay (Amerlite, Amersham International, Amersham, UK) with intra-assay and inter-assay coefficients of variation of 5.5–6.0% and a sensitivity of 1.0 ng/ml. Plasma fenfluramine and norfenfluramine concentrations were measured by HPLC using UV absorption at 214 nm. Inter-assay coefficients of variation ranged from 5.1% at 45 ng/ml to 8.0% at 12.5 ng/ml for d-fenfluramine and from 5.1% at 45 ng/ml to 11.9% at 12.5 ng/ml for norfenfluramine. The assay sensitivity was 1 ng/ml for d-fenfluramine and 2 ng/ml for norfenfluramine.

**Data analysis**

Neuroendocrine parameters calculated were the change in prolactin (delta prolactin) defined as the maximal response following d-fenfluramine minus the mean of the two samples taken prior to administration of d-fenfluramine (baseline). Area under the prolactin vs. time curve (AUC) was calculated using the trapezoidal rule for each subject from the time-point where the prolactin concentration came back up to the baseline concentration to the end of the study. This takes into account the initial fall in prolactin, which varied in individuals from 30 to 150 min post-dose, and was due to normal diurnal rhythms and response to stress of venepuncture. As these variables were not normally distributed and could not be normalized using commonly used transformations, the Kruskal–Wallis non-parametric statistical test was used. Clinical and demographic variables and fenfluramine/norfenfluramine concentrations were normally distributed and were analysed using one-way ANOVA with post-hoc Tukey analysis.

**Results**

Of the 95 combat-exposed subjects included in the study, 23 were controls without a diagnosis of PTSD or any other psychiatric disorder and 72 had a diagnosis of lifetime PTSD. Of the latter group, 46 subjects met the criteria for current PTSD and 26 for past PTSD only. The subjects served in Vietnam between 1968 and 1971, and the neuroendocrine testing was carried out during 1994–1996.

Table 1 contains the means (±S.D.) for age, BMI, MMSE, CES, IES, HARS and HDRS for the control, current PTSD and past PTSD groups. There were significant differences in a predictable direction (current>past>controls) between groups in the CES scores (F = 3.48, d.f. = 2, p = 0.035), IES scores (F = 57.33, d.f. = 2, p = 0.000), HARS scores (F = 35.48, d.f. = 2, p = 0.000) and HDRS scores (F = 43.97, d.f. = 2, p = 0.000). The post-hoc Tukey analysis for individual pairs is presented in Table 1.

No significant differences were found for baseline prolactin (H = 2.84, d.f. = 2, p = 0.242), peak prolactin (H = 1.84, d.f. = 2, p = 0.399), time to reach peak prolactin (H = 0.52, d.f. = 2, p = 0.766), delta prolactin (H = 1.03, d.f. = 2, p = 0.599) or AUC (H = 4.76, d.f. = 2, p = 0.092) between controls, past and current PTSD groups (Table 2). There were no significant differences in baseline prolactin (H = 0.12, d.f. = 1, p = 0.731), peak prolactin (H = 0.03, d.f. = 1, p = 0.869), time to reach peak prolactin (H = 0.11, d.f. = 1, p = 0.741), delta prolactin (H = 0.35, d.f. = 1, p = 0.555) or AUC (H = 0.03, d.f. = 1, p = 0.859) between the controls and all PTSD subjects (Table 2). Similarly, there were no significant differences in baseline prolactin (H = 2.46, d.f. = 1, p = 0.117), peak prolactin (H = 1.07, d.f. = 1, p = 0.301), time to reach peak prolactin (H = 0.51, d.f. = 1, p = 0.468), delta prolactin (H = 0.13, d.f. = 1, p = 0.715) or AUC (H = 3.68, d.f. = 1, p = 0.055) when a two-way comparison was performed between the group with a current diagnosis of PTSD and a combined group of control subjects and those with past PTSD.
Since there were no differences between the current and past PTSD subjects for any of the prolactin variables, these two groups were pooled for the following analyses. In the PTSD sample, 34 subjects had a HDRS of $\geq 18$ and hence were classed as ‘depressed’ while 38 did not and were classed as ‘non-depressed’. The mean and median values for the prolactin variables for these groups and the 23 controls are shown in Table 3. There were no significant differences between the three groups for baseline prolactin ($H = 3.26$, d.f. = 2, $p = 0.196$), peak prolactin ($H = 0.73$, d.f. = 2, $p = 0.694$), time to reach peak prolactin ($H = 0.63$, d.f. = 2, $p = 0.731$), delta prolactin ($H = 0.44$, d.f. = 2, $p = 0.802$) or AUC ($H = 1.08$, d.f. = 2, $p = 0.583$).

### Table 1. The mean (±s.d.) values for the clinical ratings for the control, current PTSD and past PTSD groups

<table>
<thead>
<tr>
<th></th>
<th>Combat-exposed controls (A)</th>
<th>Current PTSD (B)</th>
<th>Past PTSD (C)</th>
<th>Post-hoc Tukey p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>46</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>48.6 ± 3.0</td>
<td>49.2 ± 4.0</td>
<td>49.2 ± 4.2</td>
<td>All pairs, $p &gt; 0.05$</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 4.2</td>
<td>24.7 ± 3.8</td>
<td>25.0 ± 4.0</td>
<td>All pairs, $p &gt; 0.05$</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.0 ± 1.0</td>
<td>28.6 ± 1.3</td>
<td>28.6 ± 1.3</td>
<td>All pairs, $p &gt; 0.05$</td>
</tr>
<tr>
<td>CES total</td>
<td>14.5 ± 10.4</td>
<td>20.9 ± 9.1</td>
<td>18.2 ± 9.5</td>
<td>A vs. B, $p &lt; 0.05$</td>
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<tr>
<td>IES total</td>
<td>9.0 ± 10.7</td>
<td>45.7 ± 12.2</td>
<td>28.6 ± 17.4</td>
<td>All pairs, $p &lt; 0.001$</td>
</tr>
<tr>
<td>HARS</td>
<td>4.8 ± 3.2</td>
<td>20.8 ± 8.2</td>
<td>17.8 ± 8.9</td>
<td>A vs. B</td>
</tr>
<tr>
<td>HDRS</td>
<td>4.9 ± 4.2</td>
<td>20.4 ± 7.3</td>
<td>15.2 ± 6.7</td>
<td>A vs. C, $p &lt; 0.001$</td>
</tr>
</tbody>
</table>

* Combined combat-exposed controls and past PTSD.
All comparisons non-significant: controls vs. current PTSD vs. past PTSD; controls vs. all PTSD; current PTSD vs. no current PTSD (Kruskal-Wallis; see Results section for statistics).

### Table 2. The mean ±s.d. and (median) values for the prolactin variables for various groups

<table>
<thead>
<tr>
<th>n</th>
<th>Baseline prolactin (ng/ml)</th>
<th>Peak prolactin (ng/ml)</th>
<th>Time to peak (h)</th>
<th>Delta prolactin (ng/ml)</th>
<th>AUC (ng/ml·min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>4.2 ± 3.2</td>
<td>9.9 ± 6.5</td>
<td>4.7 ± 1.1</td>
<td>5.8 ± 6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.3)</td>
<td>(9.3)</td>
<td>(5.0)</td>
<td>(5.9)</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>4.5 ± 2.9</td>
<td>9.9 ± 5.3</td>
<td>4.8 ± 1.2</td>
<td>5.4 ± 4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.0)</td>
<td>(8.4)</td>
<td>(5.0)</td>
<td>(4.4)</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>3.5 ± 2.7</td>
<td>8.7 ± 6.1</td>
<td>4.5 ± 1.4</td>
<td>5.2 ± 6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.3)</td>
<td>(7.1)</td>
<td>(5.0)</td>
<td>(3.4)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>4.2 ± 2.8</td>
<td>9.5 ± 5.5</td>
<td>4.7 ± 1.3</td>
<td>5.3 ± 5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.8)</td>
<td>(7.7)</td>
<td>(5.0)</td>
<td>(4.0)</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>3.8 ± 3.0</td>
<td>9.3 ± 6.2</td>
<td>4.6 ± 1.3</td>
<td>5.5 ± 6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.3)</td>
<td>(7.4)</td>
<td>(5.0)</td>
<td>(4.3)</td>
</tr>
</tbody>
</table>

* Combined combat-exposed controls and past PTSD.
All comparisons non-significant: controls vs. current PTSD vs. past PTSD; controls vs. all PTSD; current PTSD vs. no current PTSD (Kruskal-Wallis; see Results section for statistics).
Table 3. The mean ± s.d. and (median) values for the prolactin variables for various subgroups

<table>
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<tr>
<th></th>
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<th>Peak prolactin (ng/ml)</th>
<th>Time to peak (h)</th>
<th>Delta prolactin (ng/ml)</th>
<th>AUC (ng/ml . min)</th>
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</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23</td>
<td>4.2 ± 3.3 (3.3)</td>
<td>9.9 ± 6.5 (9.3)</td>
<td>4.7 ± 1.1</td>
<td>5.8 ± 6.9 (5.9)</td>
<td>857 ± 706</td>
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<tr>
<td>PTSD subjects with depressive symptoms (HDRS ≥ 18)</td>
<td>34</td>
<td>4.1 ± 3.0 (3.8)</td>
<td>10.7 ± 6.4 (8.8)</td>
<td>4.8 ± 1.2</td>
<td>6.6 ± 5.6 (4.7)</td>
<td>968 ± 663</td>
</tr>
<tr>
<td>PTSD subjects without depressive symptoms (HDRS &lt; 18)</td>
<td>38</td>
<td>4.2 ± 2.7 (3.9)</td>
<td>8.3 ± 4.4 (7.4)</td>
<td>4.6 ± 1.3</td>
<td>4.2 ± 4.6 (3.4)</td>
<td>745 ± 514</td>
</tr>
<tr>
<td>PTSD subjects with past alcohol abuse and/or dependence</td>
<td>41</td>
<td>4.6 ± 3.0 (4.0)</td>
<td>10.3 ± 6.5 (7.7)</td>
<td>4.7 ± 1.2</td>
<td>5.6 ± 6.1 (3.8)</td>
<td>942 ± 682</td>
</tr>
<tr>
<td>PTSD subjects without past alcohol abuse and/or dependence</td>
<td>30</td>
<td>3.5 ± 2.5 (3.1)</td>
<td>8.3 ± 3.9 (7.6)</td>
<td>4.8 ± 1.3</td>
<td>4.8 ± 3.9 (4.0)</td>
<td>722 ± 443</td>
</tr>
<tr>
<td>PTSD subjects with past tobacco abuse and/or dependence</td>
<td>30</td>
<td>4.8 ± 3.5 (3.9)</td>
<td>9.5 ± 5.3 (8.1)</td>
<td>4.4 ± 1.4</td>
<td>4.8 ± 5.3 (4.2)</td>
<td>866 ± 637</td>
</tr>
<tr>
<td>PTSD subjects without past tobacco abuse and/or dependence</td>
<td>41</td>
<td>3.7 ± 2.2 (3.8)</td>
<td>9.4 ± 5.8 (7.6)</td>
<td>5.0 ± 1.1</td>
<td>5.7 ± 5.3 (3.8)</td>
<td>837 ± 578</td>
</tr>
</tbody>
</table>

* Data for alcohol and tobacco abuse/dependence missing for one subject.

All comparisons non-significant between controls/depressed/not depressed; controls/alcohol abuse/not, and controls/tobacco abuse/not (Kruskal–Wallis, see Results section for statistics).

Finally, 30 subjects had a past history of tobacco abuse or dependence and 41 did not (as determined using the CIDI). The mean and median values for the prolactin variables for these groups are also shown in Table 3. There were no significant differences between the three groups for baseline prolactin ($H = 0.67$, d.f. = 2, $p = 0.715$), peak prolactin ($H = 0.16$, d.f. = 2, $p = 0.924$), time to reach peak prolactin ($H = 3.87$, d.f. = 2, $p = 0.144$), delta prolactin ($H = 0.58$, d.f. = 2, $p = 0.750$) or AUC ($H = 0.03$, d.f. = 2, $p = 0.988$). There were only six subjects with a past history of other substance abuse or dependence.

The d-fenfluramine and norfenfluramine plasma concentrations at each time-point were measured in a subset of the patients, seven with current PTSD and seven controls with no history of PTSD. The mean ($±$ s.d.) peak d-fenfluramine concentrations were 19 ± 8 and 20 ± 5 ng/ml respectively, and the mean ($±$ s.d.) peak norfenfluramine concentrations were 9 ± 4 and 7 ± 3 ng/ml respectively. There were no significant differences between the groups for peak d-fenfluramine ($F = 0.06$, d.f. = 1,12, $p = 0.810$), time to reach peak d-fenfluramine ($F = 2.02$, d.f. = 1,12, $p = 0.181$), AUC d-fenfluramine ($F = 1.22$, d.f. = 1,12, $p = 0.291$), peak norfenfluramine ($F = 0.68$, d.f. = 1,12, $p = 0.425$), time to reach peak norfenfluramine ($F = 0.00$, d.f. = 1,12, $p = 1.000$) and AUC norfenfluramine ($F = 0.59$, d.f. = 1,12, $p = 0.459$). This subset was not significantly different to the total group for any of the clinical and demographic (one-way ANOVA) or prolactin variables (Kruskal–Wallis).

There were no significant correlations between the prolactin variables and age, and no significant differences in prolactin variables between those subjects aged above and below the median age for any of the subject groups. There were no significant correlations between CES total scores and the prolactin variables and no significant differences in prolactin variables between those subjects above and below the median CES score for any of the subject groupings.

Discussion

Central serotonergic dysfunction can be examined using the neuroendocrine response to a challenge agent. The prolactin response to d-fenfluramine, a
5-HTT releasing agent/uptake inhibitor, has been widely used since there is a clear dose–response curve and specificity of action is known (Quattrone et al., 1983). In this study, we found a similar prolactin response to d-fenfluramine in combat-exposed subjects with a current diagnosis of PTSD, a past diagnosis of PTSD and a control group with no diagnosis of PTSD. In addition, the prolactin response to d-fenfluramine was similar in the group with a lifetime diagnosis of PTSD compared to the non-PTSD controls.

A number of confounding variables were investigated for their effect on the results. The presence or absence of depressive symptoms, a past history of alcohol abuse and/or dependence and a past history of tobacco abuse and/or dependence did not alter the findings with respect to the prolactin response to d-fenfluramine.

Only one other study has investigated the d-fenfluramine challenge in PTSD (Davis et al., 1999). That study reported a blunted prolactin response to d-fenfluramine in eight subjects with combat-related PTSD compared to a healthy control group. Five of the eight subjects with PTSD were also diagnosed with major depressive disorder. Although major depression has been associated with a blunted prolactin response to d-fenfluramine (Cleare et al., 1996; O'Keane and Dinan, 1991), we do not believe this is the reason for the differences in findings. In our larger sample, depressive symptoms did not influence the prolactin responses, when the lifetime PTSD group was subdivided into those with and without significant depressive symptomatology. Our finding is in agreement with other studies in depressive illness by Park et al. (1996) and Kavoussi et al. (1998).

Another confounding variable that may have influenced the findings of Davis et al. (1999) was age. Their control group was significantly younger than their control group. The findings of Davis et al. (1999) was age. Their control group was significantly younger than their control group. However, though the age difference is significant in the Davis et al. study, it is also small (42 vs. 48 yr) and may not be of sufficient magnitude to account for the differences in prolactin response between the control and PTSD groups.

Davis et al.’s study involved a 45-mg dose of d-fenfluramine compared to our 30-mg dose and a different control group; healthy controls vs. combat-exposed controls. Otherwise, the studies were similar in methodology; all subjects were male, the PTSD subjects were Vietnam veterans, of similar mean ages. Both studies excluded alcohol or drug abuse/dependence for either 6 months (our study) or 1 yr, and psychotropic drug use for 2 wk (our study) or 3 wk.

The apparently contradictory findings of the two studies may be clarified by examining the nature of the control groups. Our controls, though healthy and non-symptomatic, had nonetheless been combat exposed. The prolactin response in the Davis et al. control group is more robust than that of our combat-exposed control group even when dose is taken into account. Although direct comparison of prolactin values across studies is problematic due to differences in assay techniques, it is reasonable to speculate that a blunted or diminished response may result from combat exposure, irrespective of diagnosis of either current, past or no PTSD when compared to non-PTSD healthy controls. Support for this suggestion comes from the study of Grossman et al. (1996). They found greater prolactin suppression following dexamethasone in combat-exposed subjects with and without a diagnosis of PTSD compared to a healthy control group. However, we looked at combat exposure as assessed by the CES scores and its relationship to the prolactin variables and found no significant correlations between CES and any of the prolactin measures. In addition, prolactin responses were not different in subjects below and above the median CES score for any subject groups.

On the basis of our study, we find that serotonergic dysfunction (as measured by the d-fenfluramine prolactin test) is not a feature of longstanding PTSD but may be associated with combat exposure in general. This concurs with our study of platelet [H]paroxetine binding which was carried out on a subset of the same subjects (Maguire et al., 1998). Interestingly, the other studies of [H]paroxetine binding found differences in binding parameters in platelets from combat-exposed PTSD subjects when compared with healthy subjects (Arora et al., 1993; Maes et al., 1999). We cannot rule out that between-group differences in 5-HT function...
may have existed early after trauma exposure, which may have then been washed out over time due to decline in receptor responsiveness or other factors associated with ageing. However, this does not seem likely as other studies involving Vietnam veterans examined some 20 yr after combat exposure still have evidence of serotonergic dysfunction (Grossman et al., 1996; Southwick et al., 1997).

This study found that certain confounding variables, such as the presence of depression, alcohol abuse disorder and nicotine dependence, may not be as influential as previously thought. Further d-fenfluramine studies involving both healthy and combat-exposed control groups in addition to subjects with PTSD of similar ages are required to elucidate the relationship between the prolactin response to d-fenfluramine, combat exposure and PTSD.

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Statement of Interest

None.

References


