Relationships between Hormonal Profile and Novelty Seeking in Combat-Related Posttraumatic Stress Disorder

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This study examines relationships between hormonal levels and novelty seeking in a group of 27 Vietnam veterans with combat-related posttraumatic stress disorder (PTSD). Novelty seeking in the veteran sample, measured by the Cloninger Tridimensional Personality Questionnaire (TPQ), was almost twice as high as previously published norms. A distinctive pattern of significant positive correlations was found between novelty seeking scores and serum total triiodothyronine (T3), free T3, the T3/free thyroxine (FT4) ratio, urinary norepinephrine and the norepinephrine/cortisol ratio, while a negative correlation was found between novelty seeking scores and urinary cortisol levels. The findings were confirmed by t test analyses of high vs low novelty seeking subgroups and do not appear to be related simply to the severity of PTSD. These preliminary findings indicate the need to include measures of characterological traits in psychoendocrine studies of PTSD and to investigate their possible usefulness in subtyping this disorder. © 1997 Society of Biological Psychiatry

Key Words: PTSD, thyroid, novelty seeking, triiodothyronine (T3)

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Introduction

Psychoendocrine studies of posttraumatic stress disorder (PTSD) in male Vietnam combat veterans have revealed preliminary evidence of an unusual hormonal profile (Mason et al 1990a), with the balance shifted towards low cortisol levels (Mason et al 1986, Yehuda et al 1990), high norepinephrine and epinephrine levels (Kosten et al 1987, Yehuda et al 1992), high testosterone levels (Mason et al 1990b), and high free and total triiodothyronine (T3), and total thyroxine (T4) levels (Mason et al 1994). The unusual combination of low cortisol and high norepinephrine levels was found, in a pilot study of very ill PTSD patients, to be associated with an elevated norepinephrine/cortisol ratio, which discriminated PTSD patients from other psychiatric diagnostic subgroups better than either hormonal measure alone (Mason et al 1988). An increase

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in the total T3/free T4 ratio has also been reported, which may indicate that there is an unusual increase in the peripheral conversion of T4 to T3 in PTSD (Mason et al 1994). All these findings raise the question of the clinical significance of such hormonal alterations and the possibility of their relationship to symptoms or psychological characteristics of PTSD patients.

It has long been recognized that hormone systems can be related to both affective and cognitive psychological mechanisms (Mason 1968, Whybrow and Ferrell 1974, Mason 1975), so that it is important to include characterological as well as state or symptom measures in the assessment of PTSD patients for psychoendocrine studies. One of the characteristics which has been especially impressive in our clinical experience with PTSD patients, in looking for possible criteria for subtyping this disorder, has been the prevalence of novelty seeking or risk taking behavior. Combat veterans and other individuals who had experienced life threatening events were reported to yield higher scores on both the Zuckerman Sensation Seeking Scale (Zuckerman et al 1978) and the Vietnam Era Stress Inventory Sensation seeking subscale (Wilson and Krause 1989) than non-traumatized controls (Wilson et al 1985). Sensation or novelty seeking behavior may be related to a characteristic tendency in many traumatized people to voluntarily expose themselves to emergency life and death situations (van der Kolk et al 1985). Accordingly, we recently began to include the Cloninger Tridimensional Personality Questionnaire (TPQ), which provides a novelty seeking (NS) subscore (Cloninger 1987b), in our ongoing psychoendocrine assessment of PTSD patients.

We have, therefore, noted with interest a recent report (Balada et al 1992) describing significant correlations between thyroid hormone levels and sensation seeking, as measured by the Zuckerman Scale (Zuckerman et al 1978). Both the Cloninger and Zuckerman measures appear to be based upon a trait description defined as "the need for varied novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experience" (McCourt et al 1993). In a study of 37 normal women studied between the first and fourth day of menstruation, a significant negative correlation was found between the Zuckerman total sensation seeking score, the experience seeking subscore, and both T4 and thyroid-stimulating hormone (TSH) levels. At the same time, a significant positive correlation was found between T3 levels and the boredom susceptibility subscore (Balada et al 1992). In a prior study involving both men and women, a significant positive relationship between T4 and the thrill and adventure subscale score was observed. In this study, the women were not controlled for their menstrual cycle and both sexes were combined in the data analysis (Arque et al 1987), so that further investigation is needed for clarification of this interesting pilot work.

The purpose of the present study is to evaluate the relationships between NS, as measured by the Cloninger instrument, and the hormones not only of the thyroid system, but also of the cortisol, norepinephrine, epinephrine, and testosterone systems, in a group of male Vietnam combat veterans with PTSD.

Methods

The sample was composed of 27 male Vietnam combat veterans with PTSD who were inpatients in the Menlo Park Division of the National Center for PTSD. The diagnosis of PTSD was established using the Structured Clinical Interview for DSM-III-R (Spitzer et al 1990). Exclusion criteria included major medical illnesses, hormonal medication, psychotic disorders, organic brain syndrome, and current drug or alcohol abuse less than 3 months prior to the study. After obtaining informed consent, hormonal and psychometric assessments were made during the same two-day period on all patients.

Two 24-hour urine samples, for which collection bottles were kept in a −20°C freezer, and a single blood sample at the point between the two urine samples were collected on all 27 patients concurrently. In addition to the TPQ (Cloninger 1987b), psychometric assessment included the Mississippi Scale for Combat-related PTSD (Keane et al 1988), the Combat Exposure Scale (CES) (Keane et al 1989), the Clinician-Administered PTSD Scale (CAPS-2) (Blake et al 1990), the Impact of Events Scale (IES) (Horowitz et al 1979), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), and the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967). Mean values ± SEM which characterize the sample from a demographic and clinical standpoint were as follows: age = 42.4 ± 1.0 years, weight = 193 ± 6 lbs., height = 70.6 ± 0.5 inches, CES = 26.3 ± 1.7, Mississippi = 126.1 ± 3.2, the CAPS-2 Frequency Sum = 32.6 ± 2.3, the IES Sum = 53.7 ± 2.3, the BPRS Sum = 15.6 ± 1.3, and the HDS Sum = 16.1 ± 1.4. The sample was 46% white, 42% Hispanic, and 8% black, but no significant differences were observed in any of the hormones measured in this study between the racial subgroups. With regard to comorbidity, diagnostic criteria were met by 59% for prior alcohol abuse, 70% for recurrent major depressive disorder (all but one patient met diagnostic criteria for current major depressive disorder) and 19% for panic disorder.

Blood samples (10 mL) were collected between 8–9 AM and the serum was divided into three 1.5 mL aliquots and frozen at −70°C until analyzed. Serum total T3 (TT3), total T4 (TT4), and free T4 (FT4) levels were measured by radioimmunoassay (RIA) procedures, using kits from the

Incstar Corporation, Stillwater, MI. The interassay coefficients of variation in our lab were 6.0% for TT3, 3.7% for TT4, and 4.2% for FT4. Serum free T3 (FT3) levels were measured using an RIA kit prepared by the Diagnostic Products Corporation, Los Angeles, CA. The interassay coefficient of variation for FT3 was 2.7% in our lab.

The 24-hour urine samples were kept frozen during the collection period in order to preserve the stability of both catecholamine and steroid hormones. After thawing the samples, untreated urine aliquots were saved for cortisol and testosterone assays, while other aliquots, following acidification to pH 2.0 and the addition of 20 μl of EGTA-glutathione reducing solution per mL of urine, were saved for catecholamine analyses, all aliquots being then stored at −70°C. Free cortisol excretion rate was measured using an RIA kit prepared by the Incstar Corporation and the interassay coefficient of variation was 4.0% in our lab. Total testosterone excretion rate was measured using an RIA kit prepared by the Diagnostic Products Corporation and the coefficient of variation in our lab was 7.1%. Norepinephrine and epinephrine excretion rates were measured by an automated Waters HPLC system, with a sample preparation kit and a cation-exchange silica column prepared by the Bio-Rad Corporation, Hercules, CA. The interassay coefficient of variation was 4.0% for norepinephrine and 6.0% for epinephrine in our lab. In all data analyses the mean values for the two 24-hour urine samples were used.

Three patients with extremely deviant hormonal values were excluded from an original sample of 30 patients on whom all serum, urine and psychometric measurements were available. One patient had a norepinephrine level of 169 μg/day (next highest was 88 μg/day) and two patients had cortisol levels of 157 and 122 μg/day (next highest was 95 μg/day).

The relationship between hormonal values and TPQ scores was assessed by calculation of Pearson product-moment correlation coefficients. In addition, to further confirm the relationship between the clinical and hormonal variables, independent *t* tests were used to compare hormonal values between two groups, a "high novelty seeking" group and a "low novelty seeking" group using a median split of novelty seeking scores as the criterion for group membership. Because the hormonal variables have such widely different units of measure, hormonal values for the two groups are presented as standardized mean scores in the graphic representation.

Results

There are three major categories in the TPQ which represent the higher-order personality dimensions of NS, harm avoidance (HA) and reward dependence (RD). The total scores for each of these represents the sum of four subscale scores. The mean ± SD of the total scores for the three dimensions reported in a sample of 326 normal men with a mean age closely similar to our PTSD sample are NS = 13.7 ± 5.2, HA = 10.6 ± 6.0, and RD = 18.5 ± 4.3 (Cloninger et al 1991). By comparison, the values for our PTSD patient group were NS = 23.1 ± 1.7, HA = 20.3 ± 6.0, and RD = 15.3 ± 3.1, i.e., almost twice as high as normals for the NS and HA scores and moderately lower for the RD scores. This TPQ profile of high novelty seeking, high harm avoidance and low reward dependence is similar to the TPQ profile associated with borderline personality disorder described by Svrakic et al (1993).

Table 1. Correlations between Hormonal and Cloninger Tridimensional Personality Questionnaire Measures in Combat-Related Posttraumatic Stress Disorder (PTSD) (n = 27)

	NS	HA	RD
TT3	.379[a]	.090	.158
FT3	.445[a]	.153	.039
TT4	.265	.350	−.080
FT4	−.244	.118	−.085
R 3/4	.462[b]	.017	.178
CORT	−.428[a]	−.242	.127
NOREP	.405[a]	−.129	.334
R N/C	.453[a]	.054	.203
EPIN	−.042	−.290	.105
TEST	.360	.206	−.261

NS = novelty seeking, HA = harm avoidance, RD = reward dependence; TT3 = total triiodothyronine, FT3 = free triiodothyronine, TT4 = total thyroxine, FT4 = free thyroxine, R3/4 = TT3/FT4, CORT = urinary cortisol, NOREP = urinary norepinephrine, R N/C = NOREP/CORT, EPIN = urinary epinephrine, TEST = urinary testosterone.
[a] = $p < 0.05$
[b] = $p < 0.01$.

Table 1 presents a summary of the Pearson "r" values for the correlations between the hormonal and TPQ measures in this PTSD sample. The primary finding of interest is the pattern of significant correlations between the novelty seeking total score (NS) and six hormonal measures. There are positive correlations between the NS scores and TT3, FT3, and norepinephrine levels, but a negative correlation with cortisol levels. There is also a strong positive correlation between NS levels and the TT3/FT4 ratio (R 3/4), which is elevated in PTSD, apparently because of an increased rate of peripheral conversion of T4 to T3 in this disorder (Mason et al 1994). The NS values also correlate positively with the ratio between norepinephrine and cortisol (R N/C) which was reported to be uniquely elevated in an early pilot study of PTSD inpatients (Mason et al 1988). The "r" values are not close to significance for any of the other hormonal measures except for a positive relationship ($p < 0.07$) between NS scores and the levels of testosterone, which a pilot study indicated may be elevated in PTSD inpatients (Mason et al 1990b).

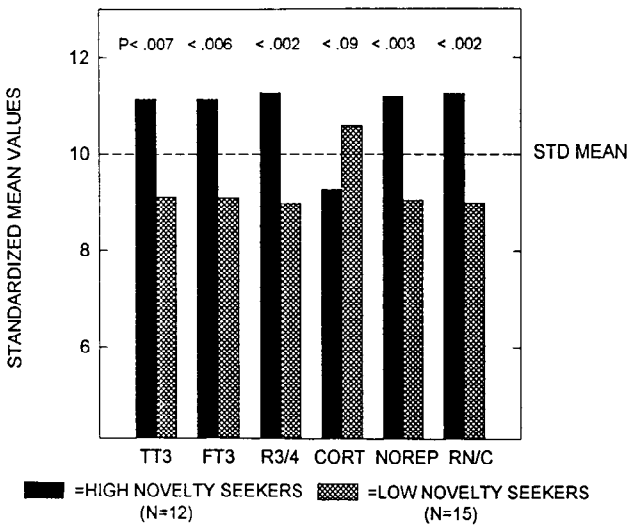

Figure 1. Hormonal profile in novelty seeking PTSD subgroups. By an unpaired T-test, the high novelty seeking subgroup shows significantly higher levels than the low novelty seeking subgroup for TT3 ($t = 2.95$, $p < 0.007$), FT3 ($t = 2.98$, $p < 0.006$), the TT3/FT4 ratio ($t = 3.53$, $p < 0.002$), urinary norepinephrine ($t = 3.23$, $p < 0.003$), and the norepinephrine/cortisol ratio ($t = 3.47$, $p < 0.002$). There is also a trend for a lower level of urinary cortisol ($t = -1.74$, $p < 0.09$) in the high novelty seeking subgroup than in the low novelty seeking subgroup.

The lack of any significant correlations between any of the hormonal measures and the HA total score or the RD total score indicates a relatively specific relationship between the novelty seeking dimension and the specific profile of hormones detailed above. Subscale analyses are not included in Table 1 because they do not add much other than to indicate that impulsiveness and extravagance are the elements of the NS scale which are largely responsible for the significant correlations with the hormone levels.

These correlational findings were put to a further confirming test by dividing the total patient sample into a "high novelty seeking" subgroup and a "low novelty seeking" subgroup, using a median split of the NS scores. Figure 1 presents the results of *t* test analyses which confirm the same pattern of hormonal relationships with the NS scores, at probability levels generally greater than the correlational analyses, except for cortisol. Note that the graph presents standardized mean scores so that the bars convey relative rather than absolute differences in hormonal levels between the two subgroups in relation to an arbitrary mean of ten for all hormones.

The question arises as to whether the hormonal differences in the two subgroups shown in Figure 1 might be due to differences in other clinical factors than the NST scores. There are, however, no significant differences between the two subgroups in age, weight, or height, nor in any of the clinical measures of severity of trauma or of PTSD symptoms, as assessed by the Combat Exposure Scale, the Mississippi PTSD Scale, the CAPS-2 sum score, or the CAPS-2 three subscores for reexperiencing, avoidance, and hyperarousal.

Discussion

The finding of substantially elevated novelty seeking and harm avoidance scores as well as moderately lower reward dependence scores in the PTSD sample compared to national norms fits the clinical presentation of many PTSD patients. The higher novelty seeking scores in our PTSD sample supports the finding by Wilson et al (1985) that combat veterans and other individuals who had experienced life threatening events scored significantly higher than a non-traumatized control group on both the Zuckerman (1978) and the Vietnam Era Stress Inventory (Wilson and Krause 1989) sensation seeking scales, and provides support for the observation that many traumatized people tend to seek out high risk situations (van der Kolk et al 1985). It is not clear to us whether novelty seeking was elevated prior to traumatization or whether it became elevated as a consequence of traumatization. Kendler et al (1993) reporting on recent stressful events in twins, suggest that early family environment and genetics could play a significant role in increasing vulnerability to psychiatric illness "by predisposing individuals to create for themselves high-risk environments." The influence of familial and genetic factors on the development of risk-taking behavior in PTSD clearly remains to be determined in future studies.

Elevated harm avoidance scale scores are associated with anticipatory worry, fear of uncertainty, sensitivity to conditioned signals of punishment, shyness and fatigability (Pfohl et al 1990). These characteristics are reflected in our clinical observations of PTSD patients, which include significant avoidance behavior, reactivity, anxiety, panic attacks and agoraphobic episodes.

At first glance, the finding of elevated novelty seeking and elevated harm avoidance may appear contradictory, yet, PTSD patients do report both sensation seeking, impulsivity, extravagance and significant avoidance, fear of uncertainty, anticipatory worry, sensitivity to conditioned signals of punishment and fatigability. By contrast, obsessive compulsive patients show elevated scores on the harm avoidance scale, but have lower than normal scores on the novelty seeking scale (Pfohl et al 1990).

High Reward Dependence scores are related to sentimentality, sensitivity to social cues, and ease of forming attachments to others. High scores on this dimension are hypothesized to correlate with low basal noradrenergic activity (Cloninger 1987a). It is not surprising then that

PTSD patients score moderately lower than normal subjects on this scale considering they often have difficulty forming attachments (Lindy 1986) and show elevated basal urinary norepinephrine levels (Kosten et al 1987; Yehuda et al 1992).

This study also provides some preliminary evidence of a significant relationship between novelty seeking, particularly the elements of impulsiveness and extravagance, and a specific profile of hormones (primarily featuring high total T3, free T3 and norepinephrine levels with low cortisol levels) associated with combat-related PTSD. A preliminary understanding of the significance of the hormonal profile characteristically altered in PTSD inpatients has previously been described elsewhere (Mason et al 1990a, Mason et al 1994). While the preliminary nature of our findings should be emphasized, the fact that the pattern of relationships between novelty seeking and hormonal levels involves rather selectively a specific hormonal profile which has been previously implicated in PTSD may add some support to warrant further more conclusive studies along these lines.

There is a need not only for replication studies in larger PTSD patient samples, but also a consideration of the extent to which patient recruitment and selection factors or different conditions of study might affect these relationships. Subsequent experience with a subsample of our West Haven PTSD patients (n = 72) did not demonstrate the same relationships described above in the Menlo Park sample and these unpublished observations have drawn our attention to some clinical differences between the two patient samples and the conditions of study. For example, the psychometric and hormonal measures were obtained at the same point in time in the Menlo Park study, while there was considerable variability, sometimes several weeks, between the time of hormonal vs psychometric measurements in the West Haven study. If, as we suspect, there are state fluctuations as well as trait factors involved in novelty seeking tendencies, then this variable of sample timing may be a critical consideration in demonstrating hormonal relationships to novelty seeking, and longitudinal studies of these relationships are needed to evaluate the importance of this issue more fully. Also, mean levels of both PTSD and general psychiatric symptoms were significantly lower in the Menlo Park sample compared to the West Haven sample as measured by the Mississippi Scale (mean ± S.E.M: 126.1 ± 3.2 vs 133.1 ± 1.8, t = 2.04, $p < 0.04$), the CAPS-2 (mean frequency scores ± S.E.M: CAPS Sum: 32.6 ± 2.3 vs 44.8 ± 1.3, t = 4.91 $p < 0.00001$; CAPS-B: 5.4 ± 0.6 vs 10.0 ± 0.4, t = 5.92, $p < 0.0001$; CAPS-C: 14.1 ± 1.3 vs 17.8 ± 0.7, t = 2.37 $p < 0.02$; CAPS-D: 12.8 ± 1.0 vs 17.0 ± 0.4, t = 4.43 $p < 0.00001$), and the Brief Psychiatric Rating Scale (mean sum ± S.E.M.: 15.6 ± 1.3, 21.0 ± 1.1, t = 2.71, $p <$ 0.008), probably because of selection factors, ward milieu factors, and the length of hospitalization at the time of sampling. If novelty seeking represents primarily a trait or characterological factor, it appears logical that its relationship to hormones might be most clearly demonstrated under conditions in which there is minimal hyperarousal or symptomatic distress superimposed upon chronic baseline conditions.

These and other issues have increasingly indicated to us the need for follow-up studies with careful attention to the details of patient sample selection, study and milieu conditions, and methodological factors including the timing of hormonal and psychometric measures (Mason et al 1995). It appears especially likely that intensive longitudinal studies of individual patients during phases of acute state change or decompensation episodes, contrasted with periods of maximal clinical improvement, may shed light upon the conditions under which a relationship between hormones and enduring factors like novelty seeking may be most evident.

Another issue raised by the findings which may have both research and clinical implications concerns the possibility that high novelty seeking levels and the altered hormonal profile associated with it may characterize a subtype of PTSD patients. The fact that the Mississippi and CAPS-2 scores are not significantly different in the high vs low novelty seeking subgroups indicates that novelty seeking and the specific hormonal pattern associated with it are not simply related to the severity of PTSD symptoms. There is a need for much larger patient samples to determine whether or not the low novelty seeking subgroup may comprise one or more PTSD subgroups, as determined by hormonal pattern or clinical measures beyond PTSD symptomatology. Meaningful subtyping is important because evidence for effective clinical treatment of PTSD, whether pharmacological or behavioral, has been elusive (Solomon et al 1992). Subtyping may identify a group or groups of patients for which a certain treatment may be particularly effective as well as expand our basic understanding of this puzzling disorder. More broadly along these lines there is, of course, an obvious need to consider in large patient samples the possible role of comorbidity in relation to these findings.

Comparison of our thyroid hormone results with those of the group (Balada et al 1992) who found a negative correlation in women between the Zuckerman Sensation Seeking score and TT4 levels which appears contrary to our findings, is complicated by the differences in the psychometric instrument used and the gender of the subjects. In the same study, however, a positive correlation was found between TT3 levels and the boredom susceptibility subscore and, in an earlier study by the same group of both men and women, a significant positive correlation

was found between TT4 and the Thrill and Adventure subscore (Arque et al 1987). These latter observations appear to reflect some compatibility with our findings. In view of questions raised about whether novelty seeking and sensation seeking are closely similar or not (McCourt et al 1993), it would appear to be valuable to include both the Cloninger and Zuckerman measures along with a full battery of thyroid measures in future studies in this area of psychoendocrine research. The observation that sensation seeking is positively associated with novelty seeking and negatively associated with harm avoidance (McCourt et al 1993) also indicates that relatively large patient samples need to be studied in order to be able to analyze subgroups based upon score or subscore combinations. The need to study possible gender differences is also evident.

Finally, the present study supports the importance of the systematic investigation of relationships between hormone levels and personality factors in PTSD, in addition to the more conventional study of hormones in relation to symptomatology, state changes or diagnosis. From a clinical standpoint, the relative prominence of character disorder features in the comorbidity of PTSD adds to the sense of the importance of the need for fuller exploration of relationships between characterological factors and hormonal balance in future psychoendocrine studies of PTSD.

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