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ScienceDirect
Journal of Psychiatric Research 41 (2007) 488–492
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

CSF testosterone: Relationship to aggression, impulsivity, and venturesomeness in adult males with personality disorder

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Received 1 December 2005; received in revised form 11 April 2006; accepted 21 April 2006

Abstract

Objective: Studies of various species suggest that testosterone, assayed in various compartments, is correlated with aggression and possibly related behaviors. The objective of this study was to assess the relationship between cerebrospinal fluid testosterone (CSF TEST) and measures of aggression, impulsivity, and venturesomeness in male personality disordered subjects and test the hypothesis that CSF TEST would correlate directly with each measure in this group.
Methods: Lumbar CSF for morning basal levels of testosterone were obtained from 31 male subjects with personality disorder. Aggression was assessed dimensionally through the use of the life history of aggression (LHA) assessment, and categorically by the research diagnosis of intermittent explosive disorder. Impulsiveness and venturesomeness were assessed using the Eysenck personality questionnaire - II (EPQ-II).
Results: CSF TEST did not correlate with measures of aggression or impulsivity but did correlate directly with venturesomeness ($r = .42$, $p = .021$). Adjusting for age and height modestly reduced the magnitude and statistical significance of this correlation.
Conclusions: In contrast to some published studies, CSF TEST was not found to have a significant relationship with aggression. The presence of a modest correlation between CSF TEST and venturesomeness, but not impulsivity, in male personality-disordered subjects suggests a possible relationship between CSF TEST and a type of sensation-seeking that involves consideration of the consequences of action taken.
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Keywords: CSF testosterone; Aggression; Impulsivity; Venturesomeness; Personality disorder

1. Introduction

Examination of extant empiric data supports a role for testosterone in mediating aggressive behaviors in both animal and human studies. In such studies, seasonal changes in testosterone correlate with seasonal changes in aggression (Lincoln and Davidson, 1977), pubertal increases in testosterone correlate with pubertal increases in aggression (Brain, 1979), and pharmacological administration of testosterone results in an increase in aggression (Sware and Gandelman, 1975). These links are not as clear in humans, however, where relationships between basal testosterone levels and aggression are only modestly positive at best (Archer, 1991; Halpern et al., 1993; Mazur and Booth, 1998; Harris, 1999; Simpson, 2001; Book et al., 2001). With respect to the effect of exogenous testosterone on aggression, testosterone's effect on human aggression appears most likely at pharmacologically enhanced, rather than at physiological replacement, levels of the hormone. In one study, physiological replacement levels of testosterone in men had minimal effects on behavior while higher doses were associated with adverse psychological effects (Yates et al., 1999). In other studies, moderately higher doses

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doi:10.1016/j.jpsychires.2006.04.009

(200 mg/wk) of testosterone given to male volunteers have been found to increase aggressive responding in laboratory paradigms (Kouri et al., 1995) and high dose testosterone administration (600 mg/wk) to men has been reported to increase manic symptoms, as well as verbal aggression, in some vulnerable individuals (Pope et al., 2000).

The relationship between basal levels of testosterone and aggression in subjects with psychopathologic conditions is similarly equivocal. In a study of alcoholic violent and nonviolent offenders, impulsive offenders had higher CSF testosterone concentrations than healthy volunteers; in addition, CSF testosterone levels reportedly discriminated between violent and nonviolent offenders (Virkkunen et al., 1994a). In a different group of offenders, the same authors found positive correlations between CSF levels of free testosterone and aggressiveness (Virkkunen et al., 1994b). In contrast, one study of recent suicide attempters reported lower CSF levels of testosterone than those seen in other studies of aggressive violent subjects and positive correlations between CSF testosterone with irritability and verbal aggression, only, in a small group of Cluster B personality disordered patients (Gustavsson et al., 2003). In a study of domestic violence perpetrators, nonalcoholic perpetrators had similar CSF testosterone concentrations to that of healthy controls (George et al., 2001). Similarly, patients with PTSD, a disorder in which aggressive behavior is often prominent, have been shown to have lower CSF testosterone concentrations than healthy controls (Mulchahey et al., 2001).

Differences among these studies may be due to differences in subject groups and in the assessments of aggression and related behaviors. In this study, we sought to examine the relationship between CSF levels of testosterone and of aggression in a group of well-defined male personality-disordered subjects with validated assessments of aggression and other related behavioral traits. Since aggression and testosterone may also associated with impulsivity (Bjork et al., 2001) and with aspects of sensation-seeking (Aluja and Torrubia, 2004) we also sought to examine the relationship between CSF Testosterone and assessments reflective of impulsivity and sensation-seeking: impulsivity (narrowly defined) and venturesomness (Eysenck and Eysenck, 1977). Overall, we sought to test the hypothesis that CSF Testosterone would correlate positively with aggression, impulsivity, and sensation-seeking impulsivity.

2. Methods

2.1. Subjects

This article reports data from 31 physically healthy male subjects with a history of personality disorder in whom CSF was collected for testosterone measurement. All subjects were medically healthy and were systematically evaluated in regard to aggressive and other behaviors as part of a larger program designed to study the biological correlates of personality-trait behavior in individuals with personality disorder. Study subjects were recruited by newspaper and public service announcements seeking subjects for biological studies of personality in general. Written informed consent, using an institutional review board-approved consent form, was obtained from all subjects after all procedures were fully explained. Medical health of all subjects was documented by medical history, physical examination, electrocardiogram, and blood hematology, chemistry (including hepatic profile), thyroid function tests, and urinalysis, including a urine screen for drugs of abuse.

2.2. Diagnostic assessment

Axis I and Axis II personality disorder (PD) diagnoses were made according to DSM-IV criteria (1994). Diagnosis of alcoholism (Coccaro et al., 1989, 1996) and intermittent explosive disorder (Coccaro, 2003) were made as previously described. Diagnoses were made using information from: (a) semi-structured interviews conducted by trained masters, or doctoral, level clinicians using the schedule for affective disorders and schizophrenia (Spitzer and Endicott, 1987) modified to include modules for the diagnosis of DSM Axis I disorders not covered by the original SADS for Axis I disorders, and the Structured Interview for the Diagnosis of DSM personality disorder (Pfohl et al., 1989) for Axis II disorders; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures (Leckman et al., 1982; Klein et al., 1994) involving at least two research psychiatrists and three clinical psychologists as previously described (Coccaro et al., 1996). This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (Kosten and Rounsaville, 1992). Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), current alcoholism or drug dependence, were excluded from this study.

The distribution of the personality disorders were as follows: Cluster A ($n = 7$) i.e., paranoid [$n = 6$], schizoid [$n = 2$], schizotypal [$n = 1$]; Cluster B ($n = 10$) i.e., antisocial [$n = 5$], borderline [$n = 4$], narcissistic [$n = 3$], histrionic [$n = 1$]; cluster C ($n = 8$) i.e., avoidant [$n = 1$], dependent [$n = 1$], obsessive–compulsive [$n = 6$}. Fourteen subjects were diagnosed with personality disorder NOS, and 23% of subjects met criteria for more than one personality disorder. Subjects had a mean of 0.6 ± 0.7 current Axis I disorders, a mean of 1.9 ± 1.6 lifetime Axis I disorders and a mean of 1.8 ± 1.0 Axis II disorders. Lifetime Axis I disorders were as follows: (a) mood disorder of any type [$n = 11$; i.e., major depression ($n = 8$), dysthymia ($n = 2$), depression NOS ($n = 3$)]; (b) intermittent explosive disorder ($n = 10$), (c) alcohol and/or drug dependence disorder ($n = 6$) and, (d) anxiety disorder of any type ($n = 2$) (i.e., simple phobia [$n = 1$] and specific phobia [$n = 1$].

2.3. Assessment of aggression, impulsivity, and sensation-seeking

Aggression was assessed both dimensionally and categorically. The dimension of aggression was assessed using the aggression score from the life history of aggression (LHA), as described in previous studies (Coccaro et al., 1997). Categorical aggression was assessed using research criteria for intermittent explosive disorder (IED-IR; Coccaro, 2003). Impulsivity was assessed using the Impulsivity scale from the Eysenck personality questionnaire (EPQ-II; Eysenck and Eysenck, 1977). Sensation-seeking like behavior was assessed using the venturesomeness scale from the EPQ-II. General personality traits were assessed with the EPQ-I scales of neuroticism, psychoticism, and extraversion.

2.4. Subject preparation

Three of the 31 (10%) subjects had a lifetime history of exposure to psychotropic agents (i.e., anxiolytics: $n = 3$, antidepressants: $n = 2$; sedative-hypnotics: $n = 1$, stimulants: $n = 1$). Despite this prior exposure, none of the subjects were taking prescribed psychotropic medication at time of study. Moreover, all subjects were instructed to remain free of all drugs for at least two (2) weeks prior to study and to follow a low monoamine diet for at least three (3) days prior to study.

2.5. Lumbar puncture

Subjects reported to the clinical procedures lab the evening before the lumbar puncture procedure. At approximately 11 pm subjects had a snack and were placed at rest in a supine position in a hospital bed. Lumbar punctures were performed by a research neurologist in the morning hours after no less than eight hours of fasting and rest. The procedure was performed under sterile technique with the subject in the lateral decubitus position. A total of 20 cc of CSF was drawn off in six aliquots: Aliquots 1, 2 and 4, 5, 6 each consisted of one cc of CSF and were set aside for future analyses. Aliquot 3 was composed of one pooled 15 cc sample of CSF, subsequently subdivided into 15 one cc subaliquots for later analysis. One pooled aliquot was used for assay of CSF Testosterone. All CSF samples were placed in polypropylene tubes and were frozen immediately at −70 °C until assay at a later time. Testosterone was measured in duplicate in each CSF sample using a double antibody radioimmunoassay (RIA) kit from ICN Biomedicals, Inc. (Costa Mesa, CA) as previously described (Mulchahey et al., 2001). The intra- and interassay coefficients of variation for this assay, respectively, were 6.4% and 7.2%.

2.6. Statistical analysis

Relationships among biological and behavioral variables were assessed by Pearson correlation and multiple regression analysis as appropriate. Comparisons of between group variables were performed by t-test, with correction for unequal variances where necessary and by x^2 tests. A two-tailed alpha value of 0.05 was used to denote statistical significance.

3. Results

Demographic, biologic, and behavioral data for the subjects studied are displayed in Table 1.

The CSF TEST concentrations demonstrated no correlation between the primary dimensional measure of aggression (LHA: $r = .18$, $p = .34$), or between the categorical presence or absence of aggression as assessed by IED-IR criteria (IED-IR+: 83.0 + 29.2 pmol/ml vs. 78.0 + 22.2 pmol/ml; $t_{(29)} = 0.53$, $p = .601$). In addition, CSF TEST concentrations displayed no correlation with EPQ-II Impulsivity ($r = .02$, $p = .941$). In contrast, a significant positive correlation between CSF TEST was noted with EPQ-II Venturesomeness ($r = .42$, $p = .021$); Fig. 1. Partial correlation using age and height (both of which correlated inversely with CSF TEST: age: $r = -.50$, $p < .01$; height: $r = -.36$, $p < .05$) modestly reduced, but did not eliminate, the correlation between CSF TEST and venturesomeness ($r = .37$, $p = .052$). CSF TEST did not differ as a function of any Axis

Table 1
Demographic, biologic and behavioral data for the sample

Variable	Mean ± SD
Age (years)	33.3 ± 7.9
Weight (kg)	78.3 ± 16.7
Height (m)	177.3 ± 0.1
Male/female, (n =)	31 / 0
White/nonwhite, (n =)	21 / 10
Socioeconomic status: I/II–IV/V	0/22/9
CSF Testosterone (pmol/ml)	79.6 ± 24.3
LHA aggression score	10.1 ± 6.4
EPQ-II impulsivity	6.8 ± 4.6
EPQ-II venturesomeness	10.8 ± 3.2

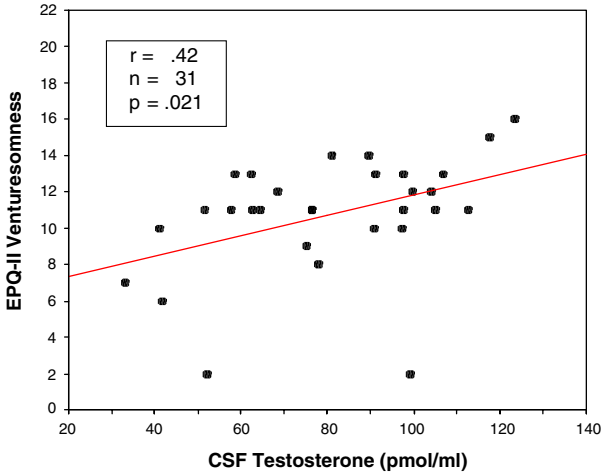

Fig. 1. Correlation between CSF testosterone and EPQ-II venturesomeness in 31 male personality disordered subjects.

I or Axis II condition, or history of suicide attempt and did not correlate with any general measures of personality (e.g., EPQ-I neuroticism, psychoticism, extraversion).

4. Discussion

The results of this study provide support for a relationship between basal levels of CSF Testosterone and a form of sensation seeking, venturesomeness, but not between CSF Testosterone and overt aggression (assessed dimensionally or categorically) or impulsiveness, in male personality disordered subjects. The magnitude of this relationship may be affected by other factors, however, and adjustment for variability in age and height in this sample, for example, did reduce the magnitude of the relationship between CSF Testosterone and venturesomeness. The observation that CSF Testosterone did not correlate meaningfully with other relevant behavioral variables, including life history of Axis I or II disorder, history of suicide attempt, or general personality traits suggests the possibility that the relationship between CSF Testosterone and venturesomeness may be relatively specific in nature.

A role for centrally active testosterone in venturesomeness has not previously been reported. Little is published regarding the biology of venturesomeness. However, individual differences in central levels of testosterone and venturesomeness may relate to individual differences in testosterone and competitiveness in sporting activities. Specifically, studies of the physiological role of testosterone suggest a relationship with competitiveness and success in sporting events, particularly those known for their physical risk. While venturesomeness is not synonymous with competitiveness in this regard, individuals high in venturesomeness are characterized as individuals who knowingly engage in risky endeavors (as opposed to impulsive individuals who engage in risky behaviors without consideration of the risks). As such, venturesome people are likely to engage in physically risky sports. Along these lines, higher levels of salivary testosterone have been reported in soccer players just prior to playing an opposing team rated as an "extreme rival" compared to that measured prior to playing an opposing team rated as only a "moderate rival" (Neave and Wolfson, 2003). In addition, young men with better outcomes in judo competitions have greater testosterone increases (Salvador et al., 2003). This effect is even noted for observers of sports where sports fans of winning teams display an increase in testosterone levels while sports fans of losing teams display a reduction in testosterone to the same degree (Bernhardt et al., 1998).

The nature of testosterone in the CSF is understood to a limited degree. The majority of testosterone in CSF is free, as opposed to protein-bound, and is thus available to impact upon neuronal systems (Schwarz and Pohl, 1992). Overall, the CSF testosterone level is thought to reflect the integrated effects of testosterone uptake from the circulation as well as its central metabolism and clearance into the plasma. CSF testosterone concentrations may also be influenced by CSF flow dynamics though we have no relevant data in these subjects that would allow us to comment on this issue.

The presence of a weak, non-significant, relationship between aggression (or impulsivity) and testosterone in this study is consistent with many of the studies in the literature. Meta-analyses of human studies demonstrate only small correlations between various measures of aggression and testosterone regardless of how the variables are measured. The existence of only small correlations between these variables maybe due to variance in study design, methodology and measurement, type of steroids measured (free vs. total vs. bioavailable), site of sample collection (e.g., serum vs. urine vs. saliva), time of specimen collection (diurnal variation), ages of subjects (pubertal vs. mature vs. elderly), types of subjects (healthy volunteers vs. clinical samples vs. criminal populations), gender, and changing variables such as stress, sexual activity, exercise and alcohol intake. In light of these difficulties in comparing studies of aggression, for example, Archer (1991) performed a meta-analysis by limiting methodological variables and discovered in a sample size of 230 subjects (complied from five studies) that while correlations between testosterone and aggression were low, there were positive overall ($r = .115$) associations for trait measures, and slightly higher when other-ratings were used ($r = .18$). In a more recent article on this topic, Book et al. (2001) found 106 articles on the testoterone and aggression, and included 45 studies (54 results) in a meta-analysis. This approach yielded a combined sample size of 9760 subjects. The aggregate unweighted mean correlation across all the included studies was 0.23; when effect size was weighted by number of participants, the mean correlation was significant but of smaller magnitude ($r = .14$). In light of these meta-analytic data, only a very large sample (e.g., 240 subjects for the LHA aggression correlation of $r = .18$) would have demonstrated a statistically significant correlation between the variables in this study. Contributing to this may have been the fact that the subjects in this study may not have been as violent as subjects in other studies that reported more substantial positive relationships between CSF testosterone and that included subjects from more violent populations (Virkkunen et al., 1994a,b).

A number of limitations regarding this study warrant comment, particularly regarding the relationship between CSF testosterone and venturesomeness. First, this is a cross-sectional study and no causal conclusions can be made from associative and correlational analyses. Second, the sample size (and magnitude of effect size) is in the moderate range and it is possible that these findings may be smaller in a larger sample. In addition, covariation with age and height reduced the statistical significance of the correlation to that of a statistical "trend" and so this finding should be considered preliminary. Third, the ascertainment of subjects may limit the generalizability of these findings in that these subjects those who volunteered for research studies and it is possible that these data may not

generalize to a population- based, or to clinic-based, sample of subjects with personality disorder. Finally, females were not included in the study so as to avoid additional confounding factors, to circumvent biochemistry differences observed in the development of the brain and because baseline information on females and testosterone is scarce. Regardless, it is noteworthy to report that there is recent evidence to suggest that administration of exogenous testosterone to female subjects causes a shift in decision-making to more risky decisions (Van Honk et al., 2004). This study found that sublingual administration of testosterone to females was associated selecting choices in a gambling task suggesting a change in the motivational balance for a lowered sensitivity for punishment and heightened sensitivity for reward, the same imbalance in the etiology and maintenance of psychopathy (Van Honk et al., 2004) and perhaps ''venturesomeness''. More work in the biology of venturesomeness may be warranted.

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