Central Serotonin Activity and Aggression: Inverse Relationship With Prolactin Response to *d*-Fenfluramine, But Not CSF 5-HIAA Concentration, in Human Subjects

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Objective: *This study compared the nature and magnitude of the relationship between aggression and CSF 5-hydroxyindoleacetic acid (5-HIAA) concentration with that between aggression and the prolactin response to* d-*fenfluramine challenge in human subjects.* *Method:* *The Life History of Aggression assessment scores of 24 subjects with personality disorders were compared with their lumbar CSF 5-HIAA concentrations and with their prolactin responses to* d-*fenfluramine challenge.* *Results:* *Aggression was significantly and inversely correlated with prolactin responses to* d-*fenfluramine challenge but not with lumbar CSF 5-HIAA concentrations in these subjects.* *Conclusions:* *Prolactin response to d-fenfluramine may be more sensitive than lumbar CSF 5-HIAA concentration in detecting a relationship between aggression and central serotonin activity in noncriminally violent human subjects.*

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Inverse relationships between indexes of central serotonin (5-HT) function and aggression (particularly physical aggression against other individuals) in human and nonhuman primates have been reported for nearly two decades (1). The primary 5-HT measures used in these studies have been basal lumbar CSF concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) and hormonal responses to acute pharmacological challenge with 5-HT agents. In general, most studies involving CSF 5-HIAA concentration or hormonal responses to 5-HT agents have reported either an inverse relationship with a measure of aggression (2–12) or a reduction in these variables in impulsive aggressive subjects compared with nonimpulsive aggressive subjects (13–19).

More recently, there have been studies reporting findings at variance with these earlier reports. At present there are at least eight studies that have not reported an inverse correlation between a measure of aggression and CSF 5-HIAA levels (20–23) or between a measure of aggression and hormonal response to a 5-HT agent (24–27); four (20, 21, 25, 26) reported no correlation, and four (22–24, 27) reported a positive correlation. It is possible that these differences are due to differences in the subjects studied. It is also possible that if both types of central 5-HT measures had been assessed in the same study group, either an inverse relationship of aggression with one of them would have emerged or a more definitive assessment of the relationship between central 5-HT function and aggression would have been made. For example, would the hormonal response to a 5-HT agent correlate inversely, while the CSF 5-HIAA index correlated positively (or not at all), with a measure of aggression in the same subjects?

Despite the number of studies in this area, only two (21, 28) reported on data from subjects in whom both types of 5-HT assessments were performed. One study (28) compared the interrelationships between CSF 5-HIAA and prolactin response to *d,l*-fenfluramine challenge in suicidal subjects with mood disorders; that study did not, however, report data involving other-directed aggression. The other study (21) compared the relative magnitudes of the correlations with a measure of aggression in the same subjects. In that study of male subjects with personality disorders, prolactin responses to *d,l*-fenfluramine challenge were inversely correlated with self-reported assaultiveness and irritability, whereas

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basal lumbar CSF 5-HIAA concentrations were not. Despite this finding, the correlations of prolactin response to *d,l*-fenfluramine and of CSF 5-HIAA concentration with aggression were not significantly different from each other.

This report represents a new study in which the relationship between aggression and basal lumbar CSF 5-HIAA concentration was directly compared to the relationship between aggression and prolactin response to the more specific 5-HT probe *d*-fenfluramine in a well-characterized study group of male and female subjects with personality disorders.

METHOD

The data are from a consecutive series of 24 adult subjects meeting the DSM-III-R criteria for personality disorders who underwent both a lumbar puncture for the measurement of CSF 5-HIAA concentration and a *d*-fenfluramine challenge study to assess prolactin response to central 5-HT stimulation. All subjects were systematically evaluated with regard to aggressive and other behaviors as part of a larger ongoing program designed to study the central serotonergic correlates of impulsive aggressive behavior in subjects with personality disorders. Study subjects were recruited by newspaper and public service announcements seeking persons with and without self-reported problems with aggressive behavior. A document approved by our institutional review board was used to obtain written informed consent from all subjects after all procedures had been fully explained.

Only subjects with personality disorders were eligible for the study. Persons with a life history of mania/hypomania, schizophrenia, or delusional disorder and those with current alcoholism or drug dependence were excluded. Axis I diagnoses and axis II personality disorder diagnoses were made according to DSM-III-R criteria. The diagnosis of alcoholism was made according to modified Research Diagnostic Criteria, as in our previous reports (4). Final diagnoses were assigned through a best-estimate process (29, 30), involving two psychiatrists (E.F.C. and R.J.K.) and three psychologists (acknowledged in the author footnote), on the basis of information obtained through 1) interviews by trained clinicians using the Schedule for Affective Disorders and Schizophrenia (31) and the Structured Interview for the DSM-III-R Personality Disorders (32), 2) clinical interviews by a research psychiatrist (R.J.K.), and 3) review of all other available clinical data. The psychologists reviewed all available information about subjects and summarized this information in written narrative reports with suggested diagnoses. Each written report was then reviewed, and final consensus best-estimate diagnoses (all axis I and axis II diagnoses, both current ones and past ones in adulthood) were assigned by the best-estimate board. The physical health of all subjects was documented by medical history, physical examination, ECG, hematology, chemistry (including hepatic profile), thyroid function tests, and urinalysis (including a drug screen).

Nineteen of the 24 subjects met the DSM-III-R criteria for one or more specific personality disorders as follows: 1) dramatic cluster (N=13), i.e., histrionic (N=10), borderline (N=7), antisocial (N=3), or narcissistic (N=2); 2) anxious cluster (N=7), i.e., dependent (N=2), obsessive-compulsive (N=2), passive-aggressive (N=2), or avoidant (N=2); and 3) odd cluster (N=6), i.e., paranoid (N=6), schizoid (N=2), or schizotypal (N=1). The remaining five subjects met the criteria for personality disorder not otherwise specified. These five subjects met criteria for multiple personality disorder traits and had evidence of diminished psychosocial functioning (mean Global Assessment of Functioning Scale score=56.0, SD=9.9). Only eight subjects had a current axis I disorder. These were as follows: mood disorder of any type (N=5), i.e., major depression (N=1), dysthymia (N=1), or depressive disorder not otherwise specified (N=3); social phobia (N=2); adjustment disorder (N=1); hypochondriasis (N=1); eating disorder not otherwise specified (N=1); and substance abuse not otherwise specified (N=1). Thirteen subjects had a past history of an axis I disorder: mood disorder of any type (N=7), i.e., major depression (N=6), depressive disorder not otherwise specified (N=1), or adjustment disorder with depressed mood (N=1); alcoholism (N=8); drug use disorder (N=6); adjustment disorder (N=1); panic disorder (N=1); and anorexia nervosa (N=1). Nine subjects had neither a current nor a past history of an axis I disorder.

Only five of the 24 subjects had a documented history of treatment with psychotropic agents. These subjects had last received psychotropic medication no less than 6 weeks (N=3), 2 years (N=1), or 3 years (N=1) before the study. Regardless of medication history, all subjects were instructed to remain drug free for 2 weeks before the study and to follow a low monoamine diet for at least 3 days before the study. One subject had taken a drug overdose as part of a suicide attempt but had been otherwise drug free for at least 6 days before the study. Removal of this subject's data did not affect the results of any of the data analyses; therefore, all reported analyses include the data from this subject. Female subjects were studied within the first 10 days of the follicular phase of the menstrual cycle for both procedures.

Subjects reported to the Clinical Procedures Laboratory at approximately 9:00 p.m. the evening before the lumbar puncture procedure. At approximately 11:00 p.m. subjects had a snack and were placed at rest in the supine position in a hospital bed. Lumbar punctures were performed under sterile conditions by a research neurologist the next morning after the subjects had had at least 8 hours of fasting and rest. A total of 20 cc of CSF was drawn off in six aliquots. Aliquots 1, 2, 4, 5, and 6 each consisted of 1 cc of CSF and were set aside for future analyses. Aliquot 3 was composed of one pooled 15-cc sample of CSF that was subsequently subdivided into 15 1-cc subaliquots for later analysis; one of these subaliquots was used for assay of CSF 5-HIAA. All CSF samples were placed in polypropylene tubes and were frozen immediately at –70°C until assay by gas chromatography/mass spectrometry (33); intra-assay and interassay coefficients of variation were both less than 8%.

On a different day, subjects reported to the Clinical Procedures Laboratory at approximately 8:00 a.m. after an overnight fast. At approximately 8:30 a.m., an intravenous line was inserted in a forearm vein and kept open by normal saline at a slow drip. Basal blood samples for prolactin assessment were obtained at 9:45 a.m. and at 9:55 a.m. At 10:00 a.m. *d*-fenfluramine (0.5 mg/kg of body weight) was given orally. Post-fenfluramine blood samples for ascertaining plasma prolactin levels were obtained every 30 minutes up to 5 hours (3:00 p.m.). Samples for ascertaining plasma levels of *d*-fenfluramine and its metabolite *d*-norfenfluramine were collected in a tube coated with potassium oxalate 1 hour, 3 hours, and 5 hours after *d*-fenfluramine administration. The sampling times for plasma *d*-fenfluramine/*d*-norfenfluramine levels were chosen because of the known acute pharmacokinetics of *d*-fenfluramine/*d*-norfenfluramine. All samples were spun down immediately. Plasma was separated and then frozen at –20°C until radioimmunoassay; intra-assay and interassay coefficients of variation were 5% and 9%, respectively. The primary outcome variable was the peak delta prolactin value (i.e., the peak post-fenfluramine prolactin value minus the average baseline prolactin value). Peak prolactin values were highly correlated with "area under the curve" peak prolactin values ($r=0.89$, $df=22$, $p<0.001$); area under the curve peak prolactin values yielded results highly similar to those with peak prolactin values.

The primary measure of aggression was the aggression subscale score from the Life History of Aggression assessment. The Life History of Aggression is a revision of the Brown-Goodwin assessment for life history of aggression (34). The aggression subscale of the Life History of Aggression includes five items assessing history of 1) temper tantrums, 2) verbal assault, 3) property assault, 4) general physical fighting, and 5) direct physical assault against persons. These items are rated on an scale from 0 to 5 (0=none; 1=one event; 2=two to four events; 3=five to 10 events; 4=more than 10 events; 5=too many events to count). We have found that this subscale has good internal consistency (Chronbach's alpha=0.87), good interrater reliability (intraclass correlation coefficient=0.94), and good test-retest stability ($r=0.80$) in subjects of the type reported here (manuscript by Coccaro et al. in preparation). The 21-item Hamilton Depression Rating Scale (35) was used to assess state depression. The Global Assessment of Functioning Scale (DSM-III-R) was used to assess average psychosocial functioning over the previous year.

TABLE 1. Demographic, Biological, and Behavioral Characteristics of 24 Subjects With Personality Disorders

Variable	N	Mean	SD
Gender			
Male	16		
Female	8		
Race			
Caucasian	16		
African American	8		
Socioeconomic class			
I	3		
II–IV	16		
V	5		
Age (years)		31.9	7.3
Weight (kg)		71.4	16.4
Height (cm)		176.0	6.0
Body mass index (weight/height^2)		24.2	4.1
CSF 5-HIAA concentration (ng/ml)		22.0	6.9
Basal prolactin level (ng/ml)		4.7	2.5
Peak total *d*-fenfluramine plus *d*-norfenfluramine level (ng/ml)		36.2	8.1
Peak prolactin response to *d*-fenfluramine (ng/ml)		6.4	2.9
Life History of Aggression aggression subscale score		9.8	7.4
Life History of Aggression fighting plus assault score		3.5	3.3
Global Assessment of Functioning Scale score		55.4	10.3
21-item Hamilton Depression Rating Scale score		6.1	5.1

The primary method of data analysis relied on Pearson product-moment correlations and partial correlations. Partial correlations used gender and body mass index as covariates for prolactin response to *d*-fenfluramine and age as a covariate for CSF 5-HIAA concentration. Differences between correlations were evaluated with the t statistic, where two correlations are not independent, as devised by Williams (36) and endorsed later by Steiger (37). The mean interval between studies was 3.0 weeks (SD=3.4) for all but four subjects, whose mean interval was 6.6 months (SD=1.4); since exclusion of the data of the latter four subjects did not affect the results, data from all of the subjects are reported. All probability values are reported at the two-tailed level.

RESULTS

Basic demographic, biological, and behavioral characteristics of the study group are shown in table 1.

Gender differences were noted for body weight, height, and body mass index (i.e., weight in kilograms divided by height in meters squared; for males, mean=25.9 kg/m^2, SD=3.6, and for females, mean=20.8 kg/m^2, SD=2.7; t=3.58, df=22, p=0.002). Body mass index was inversely correlated with prolactin response to *d*-fenfluramine (r=–0.43, df=22, p<0.05) but not with basal lumbar CSF 5-HIAA concentration (r=–0.02, df=22, p=0.92). In the context of these relationships, female subjects had greater prolactin responses than male subjects (for female subjects, mean peak delta prolactin level=8.3 ng/ml, SD=2.8; for male subjects, mean peak delta prolactin level=5.4 ng/ml, SD=2.6; t=2.46, df=22, p=0.02), even in the setting of nonsignificantly lower total peak *d*-fenfluramine plasma levels (for female subjects, mean=32.4 ng/ml, SD=8.4; for male subjects, mean=38.1 ng/ml, SD=7.4; t=1.71, df=22, p=0.10). Other variables (i.e., race, age, socioeconomic status, Global Assessment of Functioning Scale score, Hamilton depression scale score, history of major depressive disorder, basal prolactin level, peak total *d*-fenfluramine level) were not correlated with prolactin response to *d*-fenfluramine in this study group. Accordingly, data on prolactin response to *d*-fenfluramine challenge were analyzed by using partial correlation procedures with body mass index and gender as covariates.

Only age was found to correlate significantly with basal CSF 5-HIAA concentration (r=–0.54, df=22, p=0.006). Other variables (i.e., gender, race, weight, height, socioeconomic status, Global Assessment of Functioning Scale score, Hamilton depression scale score, history of major depressive disorder) were not correlated with basal lumbar CSF 5-HIAA concentration in this study group. Accordingly, basal lumbar CSF 5-HIAA concentration data were analyzed by using partial correlation procedures with age as the covariate.

Among all subjects, the partial correlation between Life History of Aggression aggression subscale score and basal lumbar CSF 5-HIAA concentration was nearly 0 (r=–0.03, df=21, p=0.90). This finding was in contrast to the partial correlation between the aggression subscale score and prolactin response to *d*-fenfluramine (r=–0.45, df=20, p=0.03). Results of a multiple regression analysis including all five separate Life History of Aggression aggression subscale items were also significant (F=5.10, df=7, 16, p=0.003) and confirmed that this inverse correlation was due specifically to inverse relationships between prolactin response to *d*-fenfluramine and life history of the more severe manifestations of aggression, namely, direct physical assault against persons (beta=–0.83, t=3.03, df=16, p=0.008) and general physical fighting (beta=–0.83, t=2.38, df=16, p=0.03). The sum of scores on these two items (i.e., Life History of Aggression fighting plus assault) yielded a highly significant partial correlation with prolactin response to *d*-fenfluramine (r=–0.59, df=20, p=0.004). As with the Life History of Aggression aggression subscale score, the partial correlation between the Life History of Aggression fighting plus assault score and basal CSF 5-HIAA concentration was not significant (r=–0.02, df=21, p=0.95). Figure 1 shows the zero-order correlations between Life History of Aggression fighting plus assault score and 1) prolactin response to *d*-fenfluramine and 2) basal lumbar CSF 5-HIAA concentration. The difference between the two correlations was statistically significant regardless of whether zero-order correlation coefficients were used (t=2.45, df=21, p<0.05) or partial correlation coefficients were used (t=2.17, df=21, p<0.05). There was no significant relationship between basal lumbar CSF 5-HIAA concentration and the prolactin response to *d*-fenfluramine whether expressed as a zero-order correlation (r=0.05, df=22, p=0.81) or a partial correlation (r=0.01, df=19, p=0.96). Finally, there were no significant correlations between prolactin response to *d*-fenfluramine, or CSF 5-HIAA

concentration, and the presence of either a dramatic cluster personality disorder or a borderline/antisocial personality disorder.

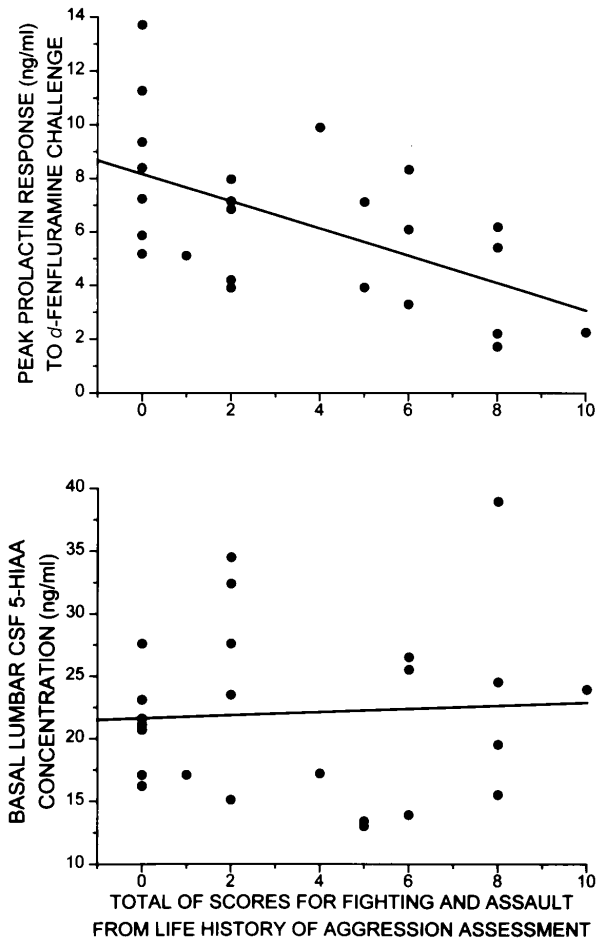
DISCUSSION

In this study group of well-characterized subjects with personality disorders, a life history of aggression—specifically, of physical fighting and physical assault against persons—was significantly and inversely correlated only with the prolactin response to *d*-fenfluramine challenge. The correlation with CSF 5-HIAA concentration was not significant and essentially neither inverse nor positive in nature.

The inverse relationship between prolactin response to *d*-fenfluramine and a history of aggression in this study group is consistent with several, though not all, studies in which an inverse relationship between prolactin responses to fenfluramine challenge in adult humans and nonhuman primates has been reported. This includes five previous studies in which *d,l*-fenfluramine or *d*-fenfluramine was used: in male veterans with personality disorders in the United States (4), in nondepressed adults with and without histories of a suicide attempt in Spain (15), in violent offenders with antisocial personality disorder in Ireland (16), and in cynomolgus macaques (17, 19). The one study with negative results in adult subjects (24) involved adult drug-dependent subjects in whom prolactin responses to *d,l*-fenfluramine were positively correlated with impulsivity. This may have been accounted for by the use of stimulant-type drugs in this group, since positive relationships between prolactin response to 5-HT agonist probes and measures of aggression have been reported in cocaine-dependent subjects (38). Similar studies in children are inconclusive; one study (27) reported elevated prolactin responses to *d,l*-fenfluramine in aggressive compared with nonaggressive children with attention deficit hyperactivity disorder, whereas an earlier study (26) reported no relationship between aggression and prolactin responses to *d,l*-fenfluramine in a group of children with disruptive behavioral disorders.

In contrast, the absence of a significant inverse correlation between aggression and CSF 5-HIAA concentration is inconsistent with several reports of studies in human subjects (2, 3, 7, 9, 13, 14, 18) and nonhuman primate subjects (8, 10), though not all reports (20–23). Most reports in the literature on humans have focused on either impulsively violent offenders or impulsive arsonists in Finland (13, 14, 18) or on behaviorally unfit military recruits in the United States (2, 3). In recent years, however, data obtained from other types of subjects have shown either no correlation (20, 21) or a positive correlation (22, 23) between CSF 5-HIAA concentration and measures of aggression. Gardner et al. (20) reported no significant correlation between CSF 5-HIAA and life history of aggression in adult female subjects with borderline personality disorder. Coccaro et al. (21) reported no significant correlation between

FIGURE 1. Zero-Order Correlation of Combined Scores on Fighting and Assault With Peak Prolactin Response to *d*-Fenfluramine Challenge[a] (top) and With Basal Lumbar CSF 5-HIAA Concentration[b] (bottom) in 24 Subjects With Personality Disorders



[a]r=–0.57, df=22, p=0.003.
[b]r=0.06, df=22, p=0.78.

CSF 5-HIAA and life history and self-reported aggression measures in adult male veterans with personality disorders. Significantly positive correlations between CSF 5-HIAA and measures of aggression have been reported both in normal adult subjects (23) and in children with disruptive behavioral disorders (22).

There are a number of reasons for these differences across studies. One possibility is that the assessment of CSF 5-HIAA concentration differed markedly among the studies. However, while the analytic methods that were used varied somewhat, a strong correlation between CSF 5-HIAA and CSF homovanillic acid (HVA) concentrations was present in studies that did not report an inverse relationship between CSF 5-HIAA concentration and aggression (mean r=0.75, SD=0.03) (21–23); the Pearson correlation coefficient for the CSF 5-HIAA/HVA relationship in the present study was r=0.76 (df=22, p<0.001). The CSF 5-HIAA/HVA relationship, widely reported as a consistent and a strong

correlation, is considered by many to represent an "internal standard" for CSF 5-HIAA and HVA (39). Accordingly, the presence of this relationship in the studies with "negative" results argues against the possibility that the absence of an inverse relationship between CSF 5-HIAA and aggression is due to some deviation in the measurement of CSF 5-HIAA. More likely, the differences in the CSF 5-HIAA/aggression relationship across studies are due to differences in the nature of impulsive aggressive behavior across study groups. Specifically, impulsive aggressive behavior severe enough to constitute criminal acts was characteristic of impulsively violent offenders (or arsonists) in whom inverse CSF 5-HIAA/aggression relationships were noted (13, 14, 18) but not of subjects in the reports of no correlations (20, 21) or positive correlations (22, 23) between CSF 5-HIAA concentrations and aggression. While it is not known whether the military recruits of Brown et al. (2, 3) committed criminal civilian acts, many of them committed impulsive aggressive acts that resulted in severe penalties from the military judicial system.

It is possible that lumbar CSF 5-HIAA concentration is not a sufficiently sensitive measure to reflect subtle differences in central 5-HT activity across subjects so that relationships with less severe, though certainly clinically meaningful, aggressive behavior can be detected. An analogous finding is the observation that only serious suicide attempts by subjects with major depression (40) or subjects with borderline personality disorder (20) are associated with reduced CSF 5-HIAA concentration.

Finally, the absence of a correlation between prolactin response to *d*-fenfluramine and lumbar CSF 5-HIAA concentration is in contrast to data from two previous studies (21, 28). While both of these studies reported a significant correlation between lumbar CSF 5-HIAA concentration and prolactin response to *d,l*-fenfluramine, one (28) reported the correlation as positive and the other (21) as inverse in direction. The subjects in the former study had mood disorders with suicidal ideation and/or behavior. The subjects in the latter study had mood and personality disorders, and most of them were not suicidal. Given the data from the present study, it appears that the relationship between prolactin response to fenfluramine and lumbar CSF 5-HIAA concentration may vary with the nature of the study group. Accordingly, no definitive statement can yet be made about the way in which these two central measures of 5-HT activity relate to each other. It is notable, however, that even where a significant correlation has been reported, the shared variance has been less than 25% in each case (21, 28). Accordingly, it should not be surprising if one, but not both, of the 5-HT indexes correlates with a measure of aggression.

In conclusion, these data suggest that hormonal responses to 5-HT challenge probes may be more sensitive than CSF 5-HIAA measures in detecting relationships between indexes of central 5-HT function and aggression in a nonforensic study group of human subjects with personality disorders.

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