Cerebrospinal Fluid Vasopressin Levels Correlates With Aggression and Serotonin Function in Personality-Disordered Subjects

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Background: Animal studies suggest that central vasopressin plays a facilitatory role in aggressive behavior. To examine this possibility in humans, the relationship between cerebrospinal fluid (CSF) arginine vasopressin (AVP) and indices of aggression and central serotonin system function was examined in personality-disordered subjects.

Methods: We used CSF (AVP), CSF 5-hydroxyindoleacetic acid, and the prolactin response to d-fenfluramine challenge (PRL[d-FEN]) as central indices of vasopressin and serotonergic system function, respectively, in 26 subjects who met the DSM-IV criteria for personality disorder. Measures of aggression and impulsivity included the Life History of Aggression assessment and the Barratt Impulsiveness Scales.

Results: The CSF AVP level was correlated directly with life history of general aggression and aggression against persons and inversely with PRL[d-FEN] responses (but not with CSF 5-hydroxyindoleacetic acid), which in turn was correlated inversely with these 2 measures of life history of aggression. The positive relationship between CSF AVP and life history of aggression remained even when the variance associated with PRL[d-FEN] responses in these subjects was accounted for.

Conclusion: Central AVP may play a role in enhancing, while serotonin plays a role in inhibiting, aggressive behavior in personality-disordered individuals. In addition to the possibility of central AVP and serotonin interacting to influence human aggression, central AVP may also influence human aggressive behavior through a mechanism independent of central serotonin in personality-disordered subjects.

Arch Gen Psychiatry. 1998;55:708-714

The role of disordered central serotonergic (5-hydroxytryptamine [5-HT]) system function has been the most prominent driving force underlying the biological study of suicidal and impulsive aggressive behavior in human subjects. Specifically, an inverse relationship between suicidal and/or impulsive aggressive behavior and a variety of 5-HT indices has been reported in human subjects. A reduction in central 5-HT system function is hypothesized to lead to a reduction in behavioral constraint, so that aggressive impulses are disinhibited in individuals with reduced 5-HT system function. Implicit in this model is a role for interacting behaviorally facilitatory mechanisms that lead to fight or flight responses to aversive stimuli.

In contrast to central 5-HT, there are limited data regarding which central neurotransmitter/modulator systems might be involved in facilitating impulsive aggressive behavior in human subjects. Central catecholaminergic, opioid, and adrenocorticotropic systems have all been suggested as possibly playing a facilitatory role. However, data implicating these systems in impulsive aggressive behavior in humans are often inconsistent with preclinical data and are generally independent of involvement with the central 5-HT system.

Centrally acting arginine vasopressin (AVP) has been reported to have a facilitatory role for aggression in the golden hamster, in rats, and in prairie voles. In the case of hamsters, injections of AVP into either the anterior or ventrolateral hypothalamus turns on aggressive display behavior and attacks on intruder hamsters, while treatment with an AVP receptor antagonist blocks the aggressive response to intruders of the same species. A relationship between central AVP and 5-HT and aggressive behavior is also suggested in anatomical and behavioral pharmacologic studies.

To examine the relationship between central vasopressin and 5-HT and aggression in human subjects, we measured (1)
SUBJECTS AND METHODS

SUBJECTS

Subjects were drawn from an ongoing study of the role of serotonin in impulsive aggressive behavior in personality-disordered individuals. The first 26 healthy male and premenopausal female subjects diagnosed with DSM-IV personality disorder for whom data was available from both central neurochemical and d-FEN challenge studies were included. Subjects were recruited from clinical settings and through newspaper advertisements seeking individuals who considered themselves to have difficulty managing their aggressive behaviors and nonaggressive individuals interested and willing to participate in biological studies of personality traits. All subjects gave informed consent and signed the informed consent document approved by our Committee for the Protection of Human Subjects.

DIAGNOSTIC ENTRY CRITERIA AND ASSESSMENT

Only personality-disordered subjects were eligible for study. Subjects with a life history of mania/hypomania, schizophrenia, or delusional disorder or current alcoholism or drug dependence were excluded. Axis I and Axis II personality disorder diagnoses were made according to DSM-IV criteria and are listed in Table 1. A diagnosis of alcoholism was made using modified Research Diagnostic Criteria, as in our previous reports. Diagnoses were assessed and assigned through a best estimate process, as described in previous reports. The medical health of all subjects was documented by medical history, physical examination, electrocardiogram, and blood hematologic tests, blood chemistry tests (including a hepatic profile), thyroid function tests, and urinalysis, including a drug screen.

RESULTS

Demographic, biological, behavioral, and diagnostic data for the personality-disordered subjects studied are displayed in Table 2.

The CSF AVP concentrations were positively correlated with a history of general aggression using LHA aggression scores (r = 0.41, n = 26, P = .04). The relationship with aggression against persons scores (ie, LHA fighting plus assault scores) was stronger (r = 0.54, P = .005) (Figure 1). This relationship was confirmed in subsequent analyses in which the CSF vasopressin concentration was higher in subjects categorized as generally aggressive (n = 10: 7.5 ± 3.1 ng/mL; t2 = 2.36, P = .03) or as aggressive against persons (n = 12: 7.3 ± 3.0 ng/mL; t2 = 2.54, P = .02) compared with subjects categorized as nonaggressive by the LHA aggression score (n = 16: 5.0 ± 2.4 ng/mL) and the LHA aggression against persons score (n = 14: 4.7 ± 2.2 ng/mL). The PRL[d-FEN] responses were inversely correlated with both the LHA general aggression and LHA aggression against persons scores (r = -0.48 for both, P = .01). In turn, the CSF AVP concentration and the PRL[d-FEN] response were inversely correlated (r = -0.42, n = 26, P = .03) (Figure 2). In order to determine if the CSF AVP concentration uniquely accounted for a proportion of the variance with aggression apart from its shared variance with the PRL[d-FEN] response, a hierarchical multiple regression analysis was conducted in which the CSF AVP concentration was entered into the model (LHA aggression against persons score as the dependent variable) after the PRL[d-FEN] response was entered. Addition of the CSF AVP concentration into the model was associated with a significant increase in the R2 value from 0.232 (PRL[d-FEN] entered on step 1) to 0.367 (F change on step 2 after the entry of CSF AVP = 4.92, P = .04). Despite the interrelationships noted between the LHA aggression...
mood score and total scores were used to assess the severity of current depressed mood and associated "depressive" symptoms, respectively; HARS data were available for all but 3 subjects. The Spielberger State Anxiety Inventory was used to assess the severity of current levels of anxiety. Global function of subjects was assessed by the Global Assessment of Function score.

LUMBAR PUNCTURE

Subjects reported to the Clinical Procedures Laboratory at approximately 8 PM 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 8 hours of fasting and rest. The procedure was performed by a research neurologist using aseptic technique with the subject in the lateral decubitus position. A total of 20 mL of CSF was drawn off in 6 aliquots: Aliquot 1, 2, 4, 5, and 6 each consisted of 1 mL of CSF and were set aside for future analyses. Aliquot 3 consisted of 1 pooled 15-mL sample of CSF, subsequently subdivided into fifteen 1-mL sub aliquots for later analysis. One pooled aliquot each was used for assay of CSF AVP and 5-HIAA. All CSF samples were placed in polypropylene tubes and were frozen immediately at −70°C until the assay could be run at a later time. Using procedures described previously, CSF AVP was extracted and analyzed by radioimmunoassay; the intra-assay coefficient of variation was less than 7%. The CSF 5-HIAA concentration was determined by gas chromatography–mass spectrometry; the intra-assay and interassay coefficients of variation were less than 8%. The CSF 5-HIAA data from all but 2 of the subjects have been previously reported.

d-FEN CHALLENGE

On another day, subjects reported to the Clinical Procedures Laboratory at approximately 8 AM after an overnight fast. At approximately 8:30 AM, an intravenous catheter was inserted in a forearm vein and kept open by normal saline at a slow drip. Basal blood samples for PRL were obtained at 9:45 AM and at 9:55 AM. d-Fenfluramine (0.1 mg per kilogram of body weight) was given orally at 10 AM. Post-d-FEN blood samples for plasma PRL were obtained every 30 minutes for up to 5 hours (3 PM). Samples for plasma levels of d-FEN and its metabolite d-norfenfluramine were collected in a potassium oxalate–coated tube 1, 3, and 5 hours after d-FEN administration. All samples were spun down immediately. Plasma was separated and then frozen at −20°C until assay. Prolactin was assayed by radioimmunoassay. Interassay and intra-assay coefficients of variations were less than 5% and less than 9%, respectively. Plasma d-FEN and d-norfenfluramine levels were determined by gas chromatography with electrochemical detection; intra-assay and interassay coefficients of variation were less than 7%. The primary outcome variable used was the peak change in PRL value (peak post–d-FEN PRL minus average baseline PRL), hereafter designated as PRL[d-FEN]. The PRL[d-FEN] values were highly correlated with the PRL[d-FEN] area under the curve (r = 0.90, n = 26, P<.001). The PRL[d-FEN] data from all but 2 of the subjects have been previously reported.

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 using the t test, with correction for unequal variances where necessary. Dimensional relationships with general aggression were assessed using the total LHA aggression score; relationships with aggression against persons were assessed using the sum of the LHA aggression fighting and assault items. Subjects were also classified as generally aggressive if their LHA aggression score was greater than 12 and as aggressive against persons if their LHA assessment fighting plus assault score was greater than 4. These cutoffs represented scores that were 2 SDs greater than the mean for corresponding LHA scores in 63 normal male and female control subjects studied in our laboratory (mean ± SD: 3.8 ± 3.7 and 1.0 ± 1.4, respectively). A 2-tailed a value less than .05 was used to denote statistical significance.

COMMENT

These data suggest that central vasopressinergic activity may be positively associated with a life history of aggressive behavior, particularly aggressive behavior against persons, in personality-disordered individuals. In addition to a posi-
tive correlation between the CSF AVP concentration and life history of aggression, subjects classified as aggressive demonstrated elevated CSF AVP concentrations compared with subjects classified as nonaggressive, who in turn had life history of aggression scores within the range of normal control subjects. Despite a significant relationship between the CSF AVP concentration and the PRL\[d-FEN\] response, the relationship between the CSF AVP concentration and aggression was present even after variance associated with central 5-HT system function, as reflected by PRL\[d-FEN\] responses, was accounted for.

The observation that the relationship between the CSF AVP concentration and a life history of aggression was much stronger among male than female subjects is potentially noteworthy. It is possible that this is an artifact of sample size, since this study included only 8 women. However, it should be noted that offensive aggression has not been observed after AVP administration in castrated male hamsters deprived of testosterone.36 Accordingly, our findings may reflect a real sex difference in the relationship between central AVP and aggression in humans.

A positive relationship between aggressive behavior and CSF AVP in human subjects has not previously been reported. Cerebrospinal fluid AVP concentrations have been reported to be similar among violent offenders, impulsive arsonists, and normal controls.11 However, since actual CSF AVP data were not displayed in the published study, it is unknown if there was a trend for the CSF AVP concentration to be higher or lower as a function of aggression. Moreover, this sample of forensic/criminally violent subjects is very different from our sample, and this may account for differences in results.

A positive relationship between the CSF AVP concentration and a life history of aggression is consistent with a direct relationship between central vasopressinergic activity and aggression, as studied in golden hamsters,13-18 rats,19-21 and prairie voles.22 In golden hamsters, microinjection of AVP into the anterior15,16,18 or ventrolateral hypothalamus significantly increases the number of biting at-
tacks by resident hamsters on intruders. Conversely, microinjection of an AVP receptor antagonist into the anterior hypothalamus leads to a dose-dependent inhibition of offensive aggression in hamsters both in a resident-intruder model13 and in a model in which animals are paired in a neutral arena.14 Reduction of offensive aggression in these latter studies was considered a specific effect, since other social behaviors, such as general activity and sexual behavior, were not affected. Similarly, infusion of AVP into the amygdala or lateral septum,19,20 as well as surgically induced elevation of the CSF AVP concentration,21 facilitates offensive aggression in rats. In studies with the pair-bonding prairie vole, central vasopressinergic activity was found to be both necessary and sufficient for aggression in male voles.22

The role of central vasopressin in psychiatry has been investigated in a variety of subjects with mood disorders, dementia of the Alzheimer type, anorexia nervosa, and obsessive-compulsive disorder. In depressed patients, the CSF AVP concentration has been reported to be low during the depressed state27,38 and elevated during the manic state.39 While this suggests a role for central vasopressin in mood regulation, studies of nondepressed subjects do not confirm this. In this study, no relationship was noted between the CSF AVP concentration and history of mood disorder or between the CSF AVP concentration and the severity of current depressive symptoms, if present. The CSF AVP concentration has also been reported to be reduced in patients with dementia of the Alzheimer type.42,43 In contrast to depression or Alzheimer dementia, the CSF AVP concentration has been reported as elevated or at least highly variable in patients with anorexia nervosa.44 In obsessive-compulsive disorder, the CSF AVP concentration has been variously reported as elevated45 or normal46 in adults or as correlated inversely with obsessive-compulsive symptoms in children and adolescents.45 Since no subject in this study met the criteria for mania, Alzheimer dementia, anorexia nervosa, or obsessive-compulsive disorder, the positive relationship between CSF AVP concentration and life history of aggression cannot be accounted for by the presence of these psychiatric conditions previously associated with alterations of the CSF AVP concentration.

The relevance of CSF measures to the central or peripheral function of a particular neurotransmitter is always an issue in human studies. This is especially important in the case of vasopressin, because one of its key roles is to function as an antidiuretic hormone outside the central nervous system. Despite this, CSF AVP appears largely to represent the central nervous system vasopressin pool rather than the peripheral vasopressin pool released from the posterior pituitary and involved in the regulation of plasma osmolarity. First, an effective blood-brain barrier keeps back-diffusion of the 2 pools to a minimum.46 Second, CSF AVP concentrations are not affected by the various stimuli that affect plasma vasopressin levels, such as changes in plasma osmolarity, postural changes, and nausea.47 Vasopressin is synthesized at a number of central sites, including the hypothalamus, bed nucleus of the stria terminalis, and locus ceruleus.48 From the hypothalamus, vasopressinergic cells project both to structures proximal to the ventricular system and to structures in the forebrain, limbic system, and brainstem.49,50 Accordingly, vasopressin can enter the CSF either by direct release into the ventricular system or by diffusion from intrasynaptic sites. In the rat, destruction of the suprachiasmatic nucleus (in the hypothalamus) leads to an almost complete reduction in CSF AVP levels.50 This suggests that most vasopressin in CSF may be of hypothalamic origin. The observation that lumbar CSF AVP concentrations are similar to those measured in ventricular CSF in humans51 suggests further that spinal neurons play little or no role in the accumulation of AVP measured in the lumbar CSF.

The inverse relationship between the CSF AVP concentration and PRL[d-FEN] responsiveness noted in this sample suggests a functional and reciprocal relationship between central AVP and 5-HT. This relationship is supported by anatomic data in which double-staining immunofluorescence studies reveal overlapping receptor binding sites as well as a dense plexus of immunoreactive fibers for both AVP and 5-HT in the anterior hypothalamus of the golden hamster.52 In this same species, a functional link between central AVP and 5-HT is supported by pharmacologic studies that demonstrate that a 3-fold increase in 5-HT (induced by an acute injection of fluoxetine) yields a dramatic fall in AVP levels in the anterior hypothalamus and in offensive aggression.16,17 Similar experimental data with respect to aggression are not available for higher mammals, however, although treatment with 5-HT uptake inhibitors (ie, fluoxetine, cimpramine) has been reported to reduce CSF AVP concentrations in humans.52,53

The influence of increasing central AVP on central 5-HT activity is not known at this time. Accordingly, the 5-HT/AVP interaction may only be unidirectional, with 5-HT inhibiting AVP. If so, it is possible that the direct relationship observed between the CSF AVP concentration and life history of aggression in this sample was due primarily to an effect of 5-HT on central AVP. However, in a hierarchical multiple regression analysis, the CSF AVP concentration accounted for a significant and unique proportion of the variance in life history of aggression scores even after the influence of 5-HT function (ie, the PRL[d-FEN] response) on these scores was accounted for.
This sample, CSF AVP uniquely accounted for 46.6% of its own variance with a life history of aggression against persons and 36.8% of all variance accounted for by both the CSF AVP concentration and the PRL[d-FEN] response. Accordingly, central AVP may play an important role in aggression on its own and thus may add to the rationale for the development of AVP antagonists for human use. Conversely, since 5-HT uptake inhibitors have been shown in separate studies to reduce human aggression49 and CSF AVP concentrations,52-53 it is possible that the antiaggressive effect of these agents in human subjects may be mediated in part by a 5-HT effect on central AVP.

The presence of an inverse relationship between the PRL[d-FEN] response and aggression is consistent with most reports of hormonal responses to 5-HT agents in personality-disordered subjects.51,53-57 The absence of a significant relationship between the CSF AVP and CSF 5-HIAA concentrations is consistent with the findings of several reports in the literature.50,41,61 It is possible that PRL[d-FEN] responses display a relationship with the CSF AVP concentration because these responses more specifically reflect 5-HT activity in the hypothalamus,50 the central site accounting for much of the AVP in the CSF,50 than do CSF 5-HIAA concentrations. Finally, while the absence of an inverse relationship between the CSF 5-HIAA concentration and aggression is in contrast with reports in criminally aggressive subjects, this finding is consistent with the results of a number of studies of non–criminally aggressive adult subjects.59,60

In conclusion, these data suggest that central AVP activity, as reflected by the CSF AVP concentration, is directly related to a life history of aggression, particularly in men, and indirectly related to central 5-HT function, as reflected by PRL[d-FEN] responses in human subjects with personality disorder. While the CSF AVP concentration is inversely related to an index of 5-HT function, a distinct relationship between central AVP and a life history of aggression appears to exist apart from its relationship with central 5-HT function.

Accepted for publication April 24, 1998.

This work was supported in part by grants RO-1 MH64848 and KO-2 MH00095 to Dr Coccaro and grant RO-1 MH52280 to Dr Ferris from the National Institute of Mental Health, Rockville, Md.

We thank Mitchell E. Berman, PhD, Jennifer D. Lish, PhD, and Lauren Y. Weinberg, MSED, for their contributions to the best estimate procedures involved in the final assignment of subject diagnosis. Also noted are the technical contributions of Michael Oakes and Michelle Stozek.

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