

# 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.

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**T**HE 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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3-7</sup> opiate,<sup>8,9</sup> andro-

gen,<sup>10,11</sup> and adrenocorticotropin<sup>11,12</sup> 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,<sup>13-18</sup> in rats,<sup>19-21</sup> and in prairie voles.<sup>22</sup> In the case of hamsters, injections of AVP into either the anterior<sup>15,16,18</sup> or ventrolateral<sup>17</sup> hypothalamus turns on aggressive display behavior and attacks on intruder hamsters, while treatment with an AVP receptor antagonist<sup>13,14</sup> 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<sup>18</sup> and behavioral pharmacologic<sup>15-18</sup> 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<sup>23</sup> and are listed in **Table 1**. A diagnosis of alcoholism was made using modified Research Diagnostic Criteria, as in our previous reports.<sup>24-26</sup> Diagnoses were assessed and assigned through a best estimate<sup>27,28</sup> process, as described in previous reports.<sup>25,26</sup> The medical health of all subjects was documented by medical history, physical examination, electrocardiogram, and blood hematology tests, blood chemistry tests (including a hepatic profile), thyroid function tests, and urinalysis, including a drug screen.

### GENERAL PREPARATION FOR STUDY

Only 5 of the 26 subjects had a documented history of treatment with psychotropic agents. Three subjects had last received psychotropic medication approximately 6 weeks prior to study (fluoxetine,  $n = 2$ ; clonazepam,  $n = 1$ ); 1 had last received imipramine, lithium, and fluoxetine 2 years prior to study, and 2 had last received imipramine 3 years prior to study. All subjects were instructed to remain drug-free for 2 weeks prior to study and to follow a low-monoamine diet for at least 3 days prior to study. One subject had taken a drug overdose as part of a suicide attempt but otherwise had been drug-free for at least 6 days prior to study. Removal of this subject's data did not affect the results; accordingly, all reported analyses include this subject's data. Females were studied within the first 10 days of the follicular phase of the menstrual cycle for both procedures.

### ASSESSMENT OF AGGRESSION AND IMPULSIVITY

Interview (historical) and self-report measures of aggression and impulsivity were used in this study. The aggression score from the LHA assessment<sup>26</sup> was used as the historical variable of aggression. As in previous studies,<sup>25,26</sup> the LHA assessment was completed by a research clinician after a semistructured interview with the subject and after consideration of other available clinical data. The LHA aggression assessment includes 5 items, assessing the history of (1) temper tantrums, (2) verbal assault, (3) property assault, (4) general physical fighting, and (5) specific assault against persons, rated on a scale from 0 to 5. The LHA aggression assessment has good to excellent psychometric characteristics in subjects of the type described in the present report.<sup>26</sup> The primary assessment of impulsivity was the self-rated Barratt Impulsiveness Scale,<sup>29</sup> version 11 (BIS-11); BIS-11 data were available for all but 4 subjects. The 21-item Hamilton Depression Rating Scale<sup>30</sup> (HDRS) depressed

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cerebrospinal fluid (CSF) concentrations of AVP, (2) CSF 5-hydroxyindoleacetic acid (5-HIAA), (3) prolactin (PRL) responses to challenge with the 5-HT releaser/uptake inhibitor *d*-fenfluramine (*d*-FEN), and (4) life history of aggression (LHA). We hypothesized that CSF AVP concentrations would correlate directly and that the measures of central 5-HT system function would correlate inversely with aggression. Finally, we hypothesized that CSF AVP concentrations would correlate inversely with the measures of 5-HT system function.

## 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 sub-

jects categorized as generally aggressive ( $n = 10$ :  $7.5 \pm 3.1$  ng/mL;  $t_{24} = 2.36$ ,  $P = .03$ ) or as aggressive against persons ( $n = 12$ :  $7.3 \pm 3.0$  ng/mL;  $t_{24} = 2.54$ ,  $P = .02$ ) compared with subjects categorized as nonaggressive by the LHA aggression score ( $n = 16$ :  $5.0 \pm 2.4$  ng/mL) and the LHA aggression against persons score ( $n = 14$ :  $4.7 \pm 2.2$  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  $R^2$  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 aggres-

mood item and total scores were used to assess the severity of current depressed mood and associated "depressive" symptoms, respectively; HDRS data were available for all but 3 subjects. The Spielberger State Anxiety Inventory<sup>31</sup> was used to assess the severity of current levels of anxiety. Global function of subjects was assessed by the Global Assessment of Function<sup>23</sup> scale.

#### 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 sterile technique with the subject in the lateral decubitus position. A total of 20 mL of CSF was drawn off in 6 aliquots: Aliquots 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 subaliquots 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  $-70^{\circ}\text{C}$  until the assay could be run at a later time. Using procedures described previously,<sup>32</sup> 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<sup>33</sup>; 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.<sup>34</sup>

#### *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 (0.5 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  $-20^{\circ}\text{C}$  until assay. Prolactin was assayed by radioimmunoassay.<sup>25</sup> 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<sup>35</sup>; 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.<sup>34</sup>

#### 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 assessment 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  $\pm$  SD:  $3.8 \pm 3.7$  and  $1.0 \pm 1.4$ , respectively).<sup>26</sup> A 2-tailed  $\alpha$  value less than .05 was used to denote statistical significance.

sion score, CSF AVP concentration, and PRL[*d*-FEN] response, the CSF 5-HIAA concentration was not correlated significantly with either LHA variable ( $r = 0.15$  for general aggression,  $r = 0.06$  for aggression against persons), CSF AVP concentration ( $r = -0.17$ ), or PRL[*d*-FEN] response ( $r = 0.02$ ).

Neither the CSF AVP concentration ( $t_{24} = 0.42$ ,  $P = .68$ ) nor the PRL[*d*-FEN] response ( $t_{24} = 0.47$ ,  $P = .64$ ) differed as a function of a life history of suicide attempt, possibly due to the small number of suicide attempters ( $n = 6$ ). Finally, no significant correlations were observed between the BIS-11 measure of impulsivity and the CSF AVP/5-HIAA concentration or the PRL[*d*-FEN] response.

The relationship between LHA aggression measures and CSF AVP concentrations was not due to potentially intercorrelated variables, such as age, race, socioeconomic class, body weight, height, HDRS total or depressed mood score, Spielberger State Anxiety Inventory score, or Global Assessment of Function score. In addition, no significant relationships were noted between CSF AVP concentration and history of an Axis I or specific Axis II personality disorder. While sex was not correlated with the CSF vasopressin concen-

tration, the positive correlation between CSF vasopressin concentration and aggression was notably stronger among male subjects ( $r = 0.65$ ,  $n = 18$ ,  $P = .004$ ) than among female subjects ( $r = 0.27$ ,  $n = 8$ ,  $P > .50$ ).

Relationships between LHA aggression measures and PRL[*d*-FEN] responses were also not due to potentially intercorrelated factors (age, race, socioeconomic class, basal PRL level, peak *d*-FEN and *d*-norfenfluramine plasma levels, etc). While PRL[*d*-FEN] responses were inversely correlated with body weight ( $r = -0.56$ ,  $n = 26$ ,  $P = .004$ ) and male sex ( $r = -0.43$ ,  $n = 26$ ,  $P = .03$ ), relationships between PRL[*d*-FEN] response and other key variables were similar after the effects of body weight and sex were controlled for statistically.

#### 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-

**Table 1. Axis I and II Diagnoses for the Sample**

	No. of Patients	
	Current	In Remission
<b>Axis I Disorders</b>		
Mood disorder		
Major depression	2	6
Dysthymia	1	0
Depressive disorder, not otherwise specified	4	1
Anxiety disorder		
Panic disorder	0	1
Social phobia	2	0
Substance abuse/dependence		
Alcoholism*	0	9
Drug (nonalcohol)	1†	7
Other disorders		
Intermittent explosive disorder	3	0
Adjustment disorder	0	2
Eating disorder	1‡	1
Somatization disorder	1‡	0
<b>Axis II Disorders</b>		
Dramatic cluster (n = 14)		
Antisocial	4	
Borderline	7	
Histrionic	11	
Narcissistic	2	
Anxious cluster (n = 6)		
Avoidant	2	
Dependent	2	
Obsessive-compulsive	2	
Eccentric cluster (n = 6)		
Paranoid	4	
Schizoid	2	
Schizotypal	1	

\*Diagnosis of alcoholism was made by modified Research Diagnostic Criteria.

†Drug abuse, not otherwise specified.

‡The "not otherwise specified" subtype of this disorder.

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.<sup>36</sup> Accordingly, our findings may reflect a real sex difference in the relationship between central AVP and aggression in humans.

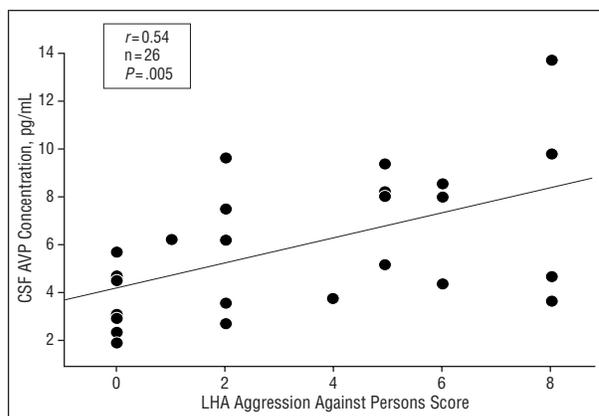
A positive relationship between aggressive behavior and CSF AVP in human subjects has not previously

**Table 2. Demographic, Biological, and Behavioral Data for the Sample\***

Age, y†	32.4 ± 7.7
Weight, kg†	72.3 ± 15.4
Height, m†	1.7 ± 0.1
Male/female, No.	18/8
White/African American, No.	18/8
Socioeconomic class I/class II-IV/class V, No.	3/18/5
CSF vasopressin, pg/mL†	5.9 ± 2.9
CSF 5-HIAA, ng/mL†	22.0 ± 6.8
PRL[d-FEN] response, ng/mL†	6.4 ± 3.0
GAF score†	56.1 ± 10.2
LHA assessment	
General aggression score	9.4 ± 7.1
Aggression against persons score	3.3 ± 3.0
History of suicide attempt, yes/no	6/20
BIS-11 impulsivity score	52.0 ± 22.8
HDRS	
Total score	4.9 ± 5.0
Depressed mood item score	0.4 ± 0.8
SSAI score†	47.4 ± 16.1

\*CSF indicates cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid; PRL[d-FEN], prolactin response to d-fenfluramine challenge; GAF, Global Assessment of Function; LHA, Life History of Aggression; BIS-11, Barratt Impulsiveness Scale, Version 11; HDRS, Hamilton Depression Rating Scale; and SSAI, Spielberger State Anxiety Inventory.

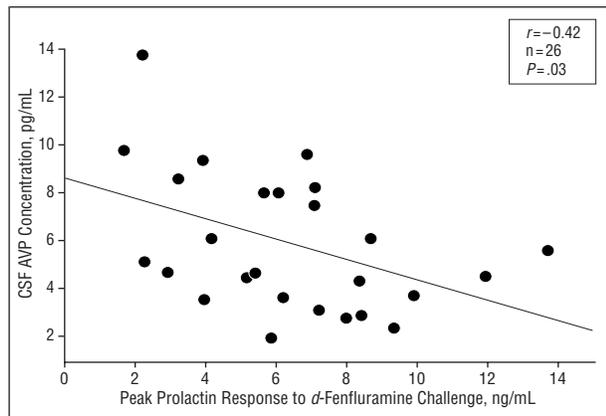
†Values are mean ± SD.



**Figure 1.** Correlation between Aggression Against Persons (the fighting and assault items) scores on the Life History of Aggression (LHA) assessment and cerebrospinal fluid (CSF) arginine vasopressin (AVP) concentrations in 26 individuals who met the DSM-IV criteria for personality disorder.

been reported. Cerebrospinal fluid AVP concentrations have been reported to be similar among violent offenders, impulsive arsonists, and normal controls.<sup>11</sup> 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,<sup>13-18</sup> rats,<sup>19,21</sup> and prairie voles.<sup>22</sup> In golden hamsters, microinjection of AVP into the anterior<sup>15,16,18</sup> or ventrolateral<sup>17</sup> hypothalamus significantly increases the number of biting at-



**Figure 2.** Correlation between cerebrospinal fluid (CSF) arginine vasopressin (AVP) concentration and peak prolactin response to d-fenfluramine challenge in 26 individuals who met the DSM-IV criteria for personality disorders.

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 model<sup>13</sup> and in a model in which animals are paired in a neutral arena.<sup>14</sup> 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,<sup>19,20</sup> as well as surgically induced elevation of the CSF AVP concentration,<sup>21</sup> 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.<sup>22</sup>

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 state<sup>37,38</sup> and elevated during the manic state.<sup>39</sup> While this suggests a role for central vasopressin in mood regulation, studies of nondepressed subjects<sup>40,41</sup> 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.<sup>42,43</sup> 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.<sup>44</sup> In obsessive-compulsive disorder, the CSF AVP concentration has been variously reported as elevated<sup>40</sup> or normal<sup>41</sup> in adults or as correlated inversely with obsessive-compulsive symptoms in children and adolescents.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> Vasopressin is synthesized at a number of central sites, including the hypothalamus, bed nucleus of the stria terminalis, and locus ceruleus.<sup>48</sup> From the hypothalamus, vasopressinergic cells project both to structures proximal to the ventricular system and to structures in the forebrain, limbic system, and brainstem.<sup>48,49</sup> 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 supra-chiasmatic nucleus (in the hypothalamus) leads to an almost complete reduction in CSF AVP levels.<sup>50</sup> 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 humans<sup>51</sup> 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.<sup>19</sup> 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.<sup>16,17</sup> Similar experimental data with respect to aggression are not available for higher mammals, however, although treatment with 5-HT uptake inhibitors (ie, fluoxetine, clomipramine) has been reported to reduce CSF AVP concentrations in humans.<sup>52,53</sup>

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. In

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 aggression<sup>54</sup> and CSF AVP concentrations,<sup>52,53</sup> 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.<sup>25,55-57</sup> 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.<sup>40,41,45</sup> 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,<sup>58</sup> the central site accounting for much of the AVP in the CSF,<sup>50</sup> 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.<sup>59,60</sup>

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.

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## REFERENCES

- Coccaro EF, Kavoussi RJ. Neurotransmitter correlates of aggression. In: Stoff DM, Cairns RB, eds. *The Neurobiology of Clinical Aggression*. Mahwah, NJ: Lawrence J. Erlbaum Associates, Inc; 1996:67-85.
- Depue RA, Spoont MR. Conceptualizing a serotonin trait: a behavioral dimension of constraint. *Ann N Y Acad Sci*. 1986;487:47-62.
- Eichelman B, Barchus J. Facilitated shock-induced aggression following antidepressant medication in the rat. *Pharmacol Biochem Behav*. 1975;3:601-604.
- Stolk JM, Conner RL, Levine S, Barchas JD. Brain norepinephrine metabolism and shock-induced fighting behavior in rats: differential effects of shock and fighting on the neurochemical response to a common footshock stimulus. *J Pharmacol Exp Ther*. 1984;190:193-209.
- Coccaro EF, Lawrence T, Trestman R, Gabriel S, Klar HM, Siever LJ. Growth hormone responses to intravenous clonidine challenge correlates with behavioral irritability in psychiatric patients and in healthy volunteers. *Psychiatry Res*. 1991; 39:129-139.
- Datla KP, Sen AP, Bhattacharya SK. Dopaminergic modulation of footshock induced aggression in paired rats. *Indian J Exp Biol*. 1992;30:587-591.
- Ordway GA, Widdowson PS, Smith KS, Halaris A. Agonist binding to alpha-2-adrenoceptors is elevated in the locus coeruleus from victims of suicide. *J Neurochem*. 1994;63:617-624.
- Post RM, Pickar, D, Ballenger JC, Naber D, Rubinow DR. Endogenous opiates in cerebrospinal fluid: relationship to mood and anxiety. In: Post RM, Ballenger JC, eds. *Neurobiology of Mood Disorders*. Baltimore, Md: Williams & Wilkins, 1984: 356-368.
- Coid J, Allolio B, Rees LH. Raised plasma met-enkephalin in patients who habitually mutilate themselves. *Lancet*. 1983;2:545-546.
- Archer J. The influence of testosterone on human aggression. *Br J Psychol*. 1991; 82:1-28.
- Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, Nemeroff C, Bissette G, Kalogeris K, Karonen SL, Linnoila M. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. *Arch Gen Psychiatry*. 1994;51:20-27.
- Higley JD, Mehlman PT, Taub DM, Higley SB, Suomi SJ, Vickers JH, Linnoila M. Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. *Arch Gen Psychiatry*. 1992;49:436-441.
- Ferris CF, Potegal M. Vasopressin receptor blockade in the anterior hypothalamus suppresses aggression in hamsters. *Physiol Behav*. 1988;44:235-239.
- Potegal M, Ferris CF. Intraspecific aggression in male hamsters is inhibited by intrahypothalamic vasopressin-receptor antagonist. *Aggressive Behav*. 1989; 15:311-320.
- Ferris CF, Delville Y. Vasopressin and serotonin interactions in the control of agonistic behavior. *Psychoneuroendocrinology*. 1994;19:593-601.
- Ferris CF. Serotonin diminishes aggression by suppressing the activity of the vasopressin system. *Ann N Y Acad Sci*. 1996;794:98-103.
- Delville Y, Mansour KM, Ferris CF. Serotonin blocks vasopressin-facilitated offensive aggression: interactions within the ventrolateral hypothalamus of golden hamsters. *Physiol Behav*. 1996;59:813-816.
- Ferris CF, Meloni RH, Koppel G, Perry KW, Fuller RW, Delville Y. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. *J Neurosci*. 1997;17:4331-4340.
- Koolhaus JM, Van den Brink THC, Roozendaal B, Boersma F. Medial amygdala and aggressive behavior: interaction between testosterone and vasopressin. *Aggressive Behav*. 1990;16:223-229.
- Koolhaus JM, Moor E, Hiemstra Y, Bohus B. The testosterone-dependent vasopressinergic neurons in the medial amygdala and lateral septum: involvement in social behavior of male rats. In: Jard S, Jamison R, eds. *Vasopressin*. Paris, France: INSERM/John Libbey Eurotext Ltd; 1991:213-219.
- Haller J, Makara GB, Barna I, Kovacs K, Nagy J. Compression of the pituitary stalk elicits chronic increases in CSF vasopressin, oxytocin as well as in social investigation and aggressiveness. *J Neuroendocrinol*. 1996;8:361-365.
- Winslow JT, Hastings N, Carter CS, Haraugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature*. 1993;365: 545-548.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
- Coccaro EF, Siever LJ, Klar H, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry*. 1989;46:587-599.
- Coccaro EF, Kavoussi RJ, Berman ME, Hauger RL. Relationship of prolactin response to d-fenfluramine to behavioral and questionnaire assessments of aggression in personality disordered males. *Biol Psychiatry*. 1996;40:157-164.
- Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. *Psychiatry Res*. 1997;73:147-157.
- Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM. Best estimate of lifetime psychiatric diagnosis: a methodologic study. *Arch Gen Psychiatry*. 1982;39:879-883.

28. Klein DN, Quimette PC, Kelly HS, Ferro T, Riso LP. Test-retest reliability of a team consensus best-estimate diagnoses of Axis I and II disorders in a family study. *Am J Psychiatry*. 1994;151:1043-1047.
29. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol*. 1995;51:768-774.
30. Guy W. *ECDEU Manual for Psychopharmacology*. Washington, DC: US Dept of Health, Education, and Welfare; 1976. Publication ADM 76-338.
31. Spielberger CD. *Manual for the State-Trait Anxiety Inventory: STAI (Form Y)*. Palo Alto, Calif: Consulting Psychologists Press; 1983.
32. Ferris CF, Pilapil G, Hayden-Hixson D, Wiley RG, Koh ET. Functionally and anatomically distinct populations of vasopressinergic magnocellular neurons in the female golden hamster. *J Neuroendocrinol*. 1992;4:193-205.
33. Fri C-G, Wiesel F-A, Sedvall G. Simultaneous quantification of homovanillic acid and 5-hydroxyindolacetic acid in cerebrospinal fluid by mass fragmentography. *Life Sci*. 1974;14:2469-2480.
34. Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Central serotonin and aggression: inverse relationship with prolactin response to *d*-fenfluramine, but not with CSF 5-HIAA concentration in human subjects. *Am J Psychiatry*. 1997;154:1430-1435.
35. Krebs HA, Chens LK, Wright GJ. Determination of fenfluramine and norfenfluramine in plasma using a nitrogen-sensitive detector. *J Chromatogr*. 1984;310:412-417.
36. Delville Y, Mansour KM, Ferris CF. Testosterone facilitates aggression by modulating vasopressin receptors in the hypothalamus. *Physiol Behav*. 1996;60:25-29.
37. Gold PW, Robertson GL, Ballenger JC, Rubinow DR, Kellner CR, Post RM, Goodwin FK. Neurohypophyseal function in affective illness. *Psychopharmacol Bull*. 1983;19:426-431.
38. Gjerris A, Hammer M, Vendsborg P, Christensen NJ, Raffelson OJ. Cerebrospinal fluid vasopressin changes in depression. *Br J Psychiatry*. 1985;145:696-701.
39. Sorensen PS, Gjerris A, Hammer M. Cerebrospinal fluid vasopressin in neurological and psychiatric disorders. *J Neurol Neurosurg Psychiatry*. 1985;48:50-57.
40. Altemus M, Pigott T, Kalogeras KT, Demitrack M, Dubbert B, Murphy DL, Gold PW. Abnormalities on the regulation of vasopressin and corticotropin releasing factor secretion in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:9-20.
41. Leckman JF, Goodman WK, North WG, Chappell PB, Price LH, Pauls D, Anderson GM, Riddle MA, McSwiggan-Hardin M, McDougle CJ, Barr LC, Cohen DJ. Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder: comparison with Tourette's syndrome and healthy controls. *Arch Gen Psychiatry*. 1994;51:782-792.
42. Mazurek MF, Growdon JH, Beal MF, Martin JB. CSF vasopressin concentration is reduced in Alzheimer's disease. *Neurology*. 1986;36:1133-1137.
43. Raskind MA, Peskind ER, Lampe TH, Risse SC, Taborsky GJ, Dorsa D. Cerebrospinal fluid vasopressin, oxytocin, somatostatin, and beta-endorphin in Alzheimer's disease. *Arch Gen Psychiatry*. 1986;43:382-388.
44. Gold PW, Kaye W, Robertson GL, Ebert M. Abnormalities in plasma and cerebrospinal fluid arginine vasopressin in patients with anorexia nervosa. *N Engl J Med*. 1983;308:1117-1123.
45. Swedo SE, Leonard HL, Kruesi MJP, Rettew DC, Listwak SJ, Berrettini W, Stipetic M, Hamburger S, Gold PW, Potter WZ, Rapoport JL. Cerebrospinal fluid neurochemistry in children and adolescents with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1992;49:29-36.
46. Sorensen PS, Vilhardt H, Gjerris F, Warberg J. Impermeability of the blood-cerebrospinal fluid barrier to 1-deamino-8-D-arginine-vasopressin (DDAVP) in patients with acquired, communicating hydrocephalus. *Eur J Clin Invest*. 1984;14:435-439.
47. Sorensen PS, Hammer M. Vasopressin in plasma and ventricular cerebrospinal fluid during dehydration, postural changes, and nausea. *Am J Physiol*. 1985;248:R78-R83.
48. Buijss RM. Vasopressin and oxytocin localization and putative functions in the brain. *Acta Neurochir Suppl (Wien)*. 1990;47:86-89.
49. Brownfield MS, Kozlowski GP. The hypothalamo-choroidal tract, I: immunohistochemical demonstration of neurophysin pathways to telencephalic choroid plexus and cerebrospinal fluid. *Cell Tissue Res*. 1977;178:111-127.
50. Schwartz WJ, Reppert SM. Neural regulation of the circadian vasopressin rhythm in cerebrospinal fluid: a preeminent role for the suprachiasmatic nuclei. *J Neurosci*. 1985;5:2771-2778.
51. Hammer M, Sorensen PS, Gjerris F, Larsen K. Vasopressin in the cerebrospinal fluid of patients with normal pressure hydrocephalus and benign intracranial hypertension. *Acta Endocrinol*. 1982;100:211-215.
52. DeBellis MD, Gold PW, Geraciotti TD, Listwak SJ, Kling MA. Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *Am J Psychiatry*. 1993;150:656-657.
53. Altemus M, Swedo SE, Leonard HL, Richter D, Rubinow DR, Potter WZ, Rapoport JL. Changes in cerebrospinal fluid neurochemistry during treatment of obsessive-compulsive disorder with clomipramine. *Arch Gen Psychiatry*. 1994;51:794-803.
54. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry*. 1997;54:1081-1088.
55. Moss HB, Yao JK, Panzak GL. Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. *Biol Psychiatry*. 1990;28:325-338.
56. Coccaro EF, Gabriel S, Siever LJ. Buspirone challenge: preliminary evidence for a role for 5-HT-1a receptors in impulsive aggressive behavior in humans. *Psychopharmacol Bull*. 1990;26:393-405.
57. O'Keane V, Moloney E, O'Neill H, O'Connor A, Smith C, Dinan TG. Blunted prolactin responses to *d*-fenfluramine in sociopathy: evidence for subsensitivity of central serotonergic function. *Br J Psychiatry*. 1992;160:643-646.
58. Coccaro EF, Klar HM, Siever LJ. Prolactin responsiveness to fenfluramine challenge does not correlate with prolactin responsiveness to TRH challenge in psychiatric patient. *Biol Psychiatry*. 1994;36:344-346.
59. Coccaro EF, Kavoussi RJ, Trestman RL, Gabriel SM, Cooper TB, Siever LJ. Serotonin function in human subjects: intercorrelations among central 5-HT indices and aggressiveness. *Psychiatry Res*. 1997;73:1-14.
60. Moller SE, Mortensen EL, Breum L, Alling C, Larsen OG, Boge-Rasmussen T, Jensen C, Bennicke K. Aggression and personality: association with amino acids and monoamine metabolites. *Psychol Med*. 1996;26:323-331.