Cerebrospinal Fluid Neuropeptide Y-like Immunoreactivity Correlates with Impulsive Aggression in Human Subjects

Emil F. Coccaro, Royce Lee, Tianmin Liu, and Aleksander A. Mathé

Background: Neurochemical studies have pointed to a modulatory role in human aggression for a number of central neurotransmitters; some (e.g., serotonin) appear to play an inhibitory role, while others (e.g., vasopressin) appear to play a facilitator role in the modulation of aggression. While recent animal studies of neuropeptide Y (NPY) have suggested a facilitator role for central NPY in the modulation of aggression, no human studies of central NPY have yet been reported regarding aggression.

Methods: Basal lumbar cerebrospinal fluid (CSF) was obtained from 60 physically healthy subjects with personality disorder (PD) ($n = 40$) and from healthy volunteers ($n = 20$). These samples were then assessed for CSF NPY-like immunoreactivity (NPY-LI) and other neurotransmitter-related species in CSF and correlated with measures of aggression and impulsivity.

Results: Cerebrospinal fluid NPY-LI was higher in PD subjects compared with healthy volunteers and in subjects with intermittent explosive disorder compared with those without intermittent explosive disorder. In PD subjects, CSF NPY-LI was directly correlated with composite measures of aggression and impulsivity and a composite measure of impulsive aggression. Group differences in CSF NPY-LI concentration were accounted for by measures of impulsive aggression.

Conclusions: These data suggest a direct relationship between CSF NPY-immunoreactivity concentration and measures of impulsive aggression in human subjects. This adds to the complex picture of the central neuromodulatory role of impulsive aggression in human subjects.

Key Words: Aggression, CSF, impulsivity, NPY-LI, personality, suicidal behavior

Neuropeptide Y (NPY) is a 36-amino-acid peptide that is both widely distributed throughout the central nervous system and one of the most conserved peptides in evolution (1). Activation of NPY receptors causes secondary messengers to trigger inhibitory class G-proteins that inhibit certain ion channels while activating others (2,3). There are five mammalian subtypes, four of which are known to exist in humans. While primarily implicated in food regulation and intake (4), obesity (5), anorexia nervosa (6), sleep (7), and nociception (8), clinical studies examining cerebrospinal fluid levels of NPY-like immunoreactivity (CSF NPY-LI) suggest involvement of NPY in neuropsychiatric conditions such as dementia of the Alzheimer's type (9), bipolar disorder (10), depression (11), anxiety (12), and schizophrenia (13), among others.

A role for modulating aggressive behavior in mammals is suggested by the fact that high immunoreactivity of NPY can be found in brain regions relevant to mammalian aggression (14). Along with the hypothalamus, these areas include olfactory bulb, amygdala (15), the prefrontal cortex, and periaqueductal gray (16). Rodent animal models suggest that NPY may be associated with aggressive and impulsive behavior. For example, olfactory bulbectomized rats, who exhibit increased mouse killing behavior, have high concentrations of NPY-LI in medial amygdala (17). In the apomorphine-induced mouse aggression model, neuropeptide Y1 (NPY1) antagonists reduce aggression in mice, though this may be due to an interaction with dopamine (18). Reduced territorial aggression is also seen in NPY1 receptor knockout mice, though this could be due to modulation by serotonin 1A receptors in the raphe nucleus (19). Increased impulsivity is also seen in neuropeptide Y2 (NPY2) receptor knockout mice (20). In contrast, male neuropeptide Y4 (NPY4) receptor knockout mice show elevated aggressive behavior in their home cage (21). The reasons for the differences in these results are not known but may include differences in animal models of aggression/impulsivity and in the role of different NPY receptor subtypes.

Given the results of these various animal model studies, we sought to explore if CSF NPY-LI would be associated with aggression and/or impulsivity in personality disordered and healthy volunteer subjects. We hypothesized that CSF NPY-LI would correlate directly with measures of aggression and/or impulsivity.

Methods and Materials

Subjects

Sixty physically healthy subjects participated in this study. 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 impulsive, aggressive, and other personality-related behaviors. Subjects were recruited through public service announcements seeking out 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

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Received Apr 10, 2012; revised Jul 24, 2012; accepted Jul 25, 2012.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.07.029

and signed the informed consent document approved by our Committee for the Protection of Human Subjects (Institutional Review Board).

Diagnostic Assessment

Axis I and Axis II personality disorder (PD) diagnoses were made according to DSM-IV criteria (22). The diagnosis of intermittent explosive disorder was made by research criteria as previously described (23). All diagnoses were made using information from: 1) semistructured interviews conducted by trained masters or doctoral level clinicians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (24) and the Structured Interview for the DSM-IV Personality (25); 2) clinical interview by a research psychiatrist; and 3) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures (26,27) involving at least two research psychiatrists and two clinical psychologists. This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (28). Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation were excluded from this study. 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 drug screen for illicit drugs of abuse (no one testing positive for any substance entered the study).

Forty subjects met DSM-IV criteria for a personality disorder and 20 subjects had no evidence of any DSM-IV Axis I or II psychopathology (healthy volunteers [HV]). Twenty-four of the PD subjects met DSM-IV criteria for a specific personality disorder as follows: 1) cluster A ($n = 10$), i.e., paranoid ($n = 8$), schizoid ($n = 3$), schizotypal ($n = 1$); 2) cluster B ($n = 14$), i.e., borderline ($n = 7$), antisocial ($n = 5$), narcissistic ($n = 3$), histrionic ($n = 3$); and 3) cluster C ($n = 9$), i.e., obsessive-compulsive ($n = 6$), avoidant ($n = 2$), dependent ($n = 1$). The remaining 16 subjects were diagnosed as personality disorder-not otherwise specified. These subjects met DSM-IV general criteria for personality disorder, had pathological personality traits from a variety of personality disorder categories, and had clear evidence of impaired psychosocial functioning (mean Global Assessment of Functioning [GAF] score = 62.6 ± 7.7). Most PD subjects had a life history of at least one Axis I disorder (32 of 40) and half had a current history of at least one Axis I disorder (22 of 40). Current Axis I disorders were as follows: any mood disorder ($n = 8$): major depression ($n = 2$), dysthymia ($n = 3$), depressive disorder-NOS ($n = 3$); any anxiety disorder ($n = 3$), i.e., all phobic ($n = 3$); intermittent explosive disorder (IED): IED by research criteria ($n = 11$); somatoform disorder ($n = 2$); adjustment disorder ($n = 1$); eating disorder ($n = 1$). Lifetime Axis I disorders were as follows: any mood disorder ($n = 18$): major depression ($n = 12$), dysthymia ($n = 4$), depressive disorder-NOS ($n = 5$); any anxiety disorder ($n = 4$), i.e., phobic ($n = 3$) and nonphobic ($n = 2$) anxiety disorder; alcoholism ($n = 11$), drug dependence ($n = 7$); intermittent explosive disorder: ($n = 13$); adjustment disorder ($n = 4$); eating disorder ($n = 2$); somatoform disorder ($n = 2$). By study exclusion criteria, none of the PD subjects had a life history of mania/hypomania, schizophrenia, or delusional disorder or current alcohol or other drug dependence. In addition to meeting criteria for Axis I and/or Axis II disorders, most (78%) PD subjects reported: 1) history of psychiatric treatment (60%) or 2) history of behavioral disturbance during which the subject, or others, thought they should have sought mental health services but did not (18%); HV subjects did not report this history.

Assessment of Aggression and Impulsivity

Aggression measures included the aggression score from the Life History of Aggression assessment (29) and the aggression factor score from the Buss-Durkee Hostility Inventory (BDHI) (30). Life History of Aggression assessment aggression reflects a subject's history of actual aggressive behavior, whereas BDHI aggression reflects a subject's self-assessment of his or her tendency to be aggressive in given situations. Impulsivity measures included the impulsiveness scale from the Eysenck Personality Questionnaire II (EPQ-II) (31) and the Barratt Impulsiveness Scale-Version 11 (32). These measures reflect a subject's self-assessment of how impulsive he or she is. History of suicidal behavior was assessed during the diagnostic workup as previously described (33). Other assessments used in this study include the Eysenck Personality Questionnaire Inventory scales neuroticism, psychoticism, and extraversion (34) and the remaining two scales from the EPQ-II (venturesomeness and empathy) as control dimensions of personality. Global function of subjects was assessed by the GAF scale (22).

General Preparation for Study

No subject was taking any medical or psychotropic agent for at least 4 weeks at time of study and only 6 of the 60 subjects (all PD subjects) had any lifetime exposure to psychotropic agents. Of the latter group, three PD subjects had lifetime exposure to three agents (antidepressant/benzodiazepine/stimulant [$n = 1$], antidepressant/benzodiazepine/sedative-hypnotic [$n = 1$], antidepressant/benzodiazepine/antipsychotic [$n = 1$]); one had lifetime exposure to two agents (antidepressant/benzodiazepine); and two had lifetime exposure to only one agent (benzodiazepine [$n = 1$], sedative-hypnotic [$n = 1$]). Subjects were instructed to follow a low monoamine diet for at least 3 days before the study. Subjects were also informed that initial and follow-up urine toxicology would be performed randomly just before the study; illicit drug use was not detected in any subject reported herein. Female subjects were all studied within the first 10 day of the follicular phase of the menstrual cycle.

Lumbar Puncture

Subjects reported to the Clinical Procedures Lab at approximately 8:00 PM the evening before the lumbar puncture procedure. At approximately 11:00 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 under sterile technique with the subject in the lateral decubitus position. A total of 20 cc of cerebrospinal fluid (CSF) was drawn 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, subsequently subdivided into 15 1-cc subaliquots for later analysis. One of these 15 subaliquots was used for assay of CSF NPY-LI. All CSF samples were placed in polypropylene tubes and were frozen immediately at -70°C until radioimmunoassay, in duplicate, at a later time in the laboratory of one of the authors (A.A.M.) as previously described (35). In review, NPY-LI was assessed using an NPY antibody (gift from M. Heilig, M.D., Ph.D., Clinical Director, Laboratory of Clinical and Translational Studies, NIAAA, Bethesda, Maryland, and R. Ekman, M.D., Ph.D, Senior Researcher, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg,

Sweden) that cross-reacts 100% with NPY, neuropeptide Y2–36, 5% with neuropeptide Y5–36, and .5% or less with shorter C-terminal NPY fragments. The antibody does not cross-react with pancreatic polypeptide or peptide YY. Samples or standards were preincubated with antibody for 48 hours at 41°C. After addition of Bolton-Hunter labeled 125I-NPY (Amersham, Bucks, United Kingdom), all samples were incubated for additional 24 hours. Free and antibody-bound radioligands were separated by addition of sheep anti-rabbit antibody-coated Sepharose suspension (Pharmacia-Upjohn, Uppsala, Sweden). After 30 minutes incubation at room temperature and centrifugation for 30 minutes at 1600*g* at 41°C, the supernatants were aspirated and discarded. The radioactivity in the pellets was measured in a gamma counter. The lower detection limit was .45 pmol/L and the intra-assay coefficient of variation was 5%.

Statistical Analysis and Data Reduction

Comparisons of between-group variables were performed by *t* test, with correction for unequal variances where necessary, analysis of covariance (ANCOVA), and by χ^2 tests. Correlational analyses included Pearson correlation, partial correlation, and multiple regression. A two-tailed alpha value of .05 was used to denote statistical significance for all analyses. Basal lumbar CSF NPY-LI values were normally distributed; did not correlate significantly with age, height, weight, or basal metabolic index; and did not differ as a function of gender, race, or socioeconomic status. Accordingly, raw values for CSF NPY-LI were used in all analyses. In addition, CSF NPY-LI levels did not correlate significantly with CSF levels of other neurotransmitters associated with measures of aggression, as we have previously reported (i.e., CSF 5-hydroxyindoleacetic acid or homovanillic acid (36), vasopressin (37), or oxytocin (38)). Finally, rather than use each of the aggression and impulsivity variables separately, composite variables for aggression, impulsivity, and impulsive aggression were created in a data-reduction step, as described previously (39). Composite variables were created because intercorrelations among the behavioral variables within domains were substantial (Life History of Aggression assessment aggression with BDHI aggression: $r = .57$; EPQ-II impulsivity with BIS-II impulsivity: $r = .79$; 32.5% shared variance for the aggression variables and 62.4% for the impulsivity variables). Composite variables were constructed by taking the average of each subject's *Z* scores for the primary behavioral measures. The correlation between the composite variables for aggression and impulsivity was very large ($r = .91$; 82.8% of shared variance) indicating that this impulsivity-aggression variable more fully reflected the larger construct of impulsive aggression than either component alone.

Results

Demographic and behavioral data for the HV and PD subjects are displayed in Table 1. These groups did not differ in age, height, weight, or in the distribution of gender, race, or socioeconomic class. Despite these similarities, the groups did differ, as expected, in GAF score and in aggression and in impulsivity scores. The results reported below were not altered after these demographic variables were considered in the analyses.

CSF NPY-LI in PD and HV Subjects

Personality disorder and HV subjects differed significantly in CSF NPY-LI, with PD subjects displaying moderately higher levels ($Z = .58$ SD) of CSF NPY-LI compared with HV subjects (Figure 1, left).

Table 1. Demographic and Behavioral Data for the Sample

	Healthy Volunteers ($n = 20$)	Personality Disorders ($n = 40$)	*p* Value[a]
Age (Years)	31.6 ± 8.7	33.0 ± 8.0	ns
Height (cm)	174.9 ± 10.6	174.4 ± 13.9	ns
Weight (kg)	73.9 ± 10.6	73.9 ± 13.9	ns
Gender (M/F)	16/4	31/9	ns
Race (White/Non-White)	10/10	28/12	ns
SES Class (I/II/III/IV/V)	0/6/8/5/1	1/4/13/11/11	ns
GAF Score	84.9 ± 4.1	58.4 ± 10.3	.001
LHA Aggression Score	3.9 ± 4.2	9.6 ± 6.3	.001
BDHI Aggression Score	13.6 ± 7.0	23.0 ± 10.0	.001
EPQ Impulsivity Score	4.4 ± 4.0	7.3 ± 5.2	.043
BIS-11 Impulsivity Score	55.0 ± 7.3	66.3 ± 13.5	.002

BDHI, Buss-Durkee Hostility Inventory; BIS-11, Barratt Impulsiveness Scale-Version 11; EPQ, Eysenck Personality Questionnaire; F, female; GAF, Global Assessment of Functioning; LHA, Life History of Aggression; M, male; ns, not significant; SES, socioeconomic status.

[a]Significance level after *t* test or χ^2 test.

CSF NPY-LI and Aggression and Impulsivity

Cerebrospinal fluid NPY-LI levels were significantly, and directly, correlated with composite aggression ($r = .35$, $n = 60$, $p < .01$), composite impulsivity ($r = .35$, $n = 60$, $p < .01$), and composite impulsive aggression ($r = .39$, $n = 60$, $p = .002$) in all subjects. These correlations were due to the positive correlations in the PD subjects examined separately: composite aggression ($r = .42$, $n = 40$, $p = .008$), composite impulsivity ($r = .43$, $n = 40$, $p = .006$), and composite impulsive aggression ($r = .48$, $n = 40$, $p = .002$) (Figure 2A). Cerebrospinal fluid NPY-LI levels did not correlate significantly with these variables in HV subjects, examined separately. For example, a nonsignificant, inverse, correlation was seen between CSF NPY-LI and composite impulsive aggression in HV subjects ($r = -.26$, $n = 20$, $p = .27$) (Figure 2B). This was due to the presence of three HV subjects with CSF NPY-LI levels greater then two standard deviations over the mean (i.e., outliers), without whose data the correlation coefficient was nearly zero ($r = -.06$, $n = 17$, $p = .81$) (Figure 2B).

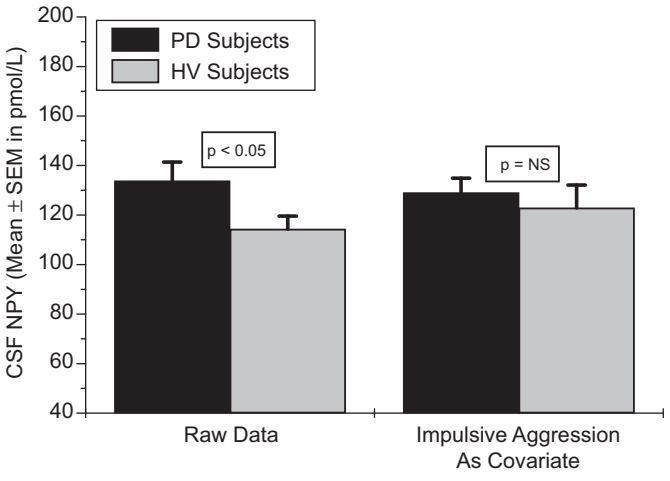

Figure 1. Mean (± SEM) group differences in cerebrospinal fluid (CSF) neuropeptide Y (NPY)-like immunoreactivity between personality disorder (PD) and healthy volunteer (HV) subjects before and after accounting for individual differences in composite impulsive aggression. NS, not significant.

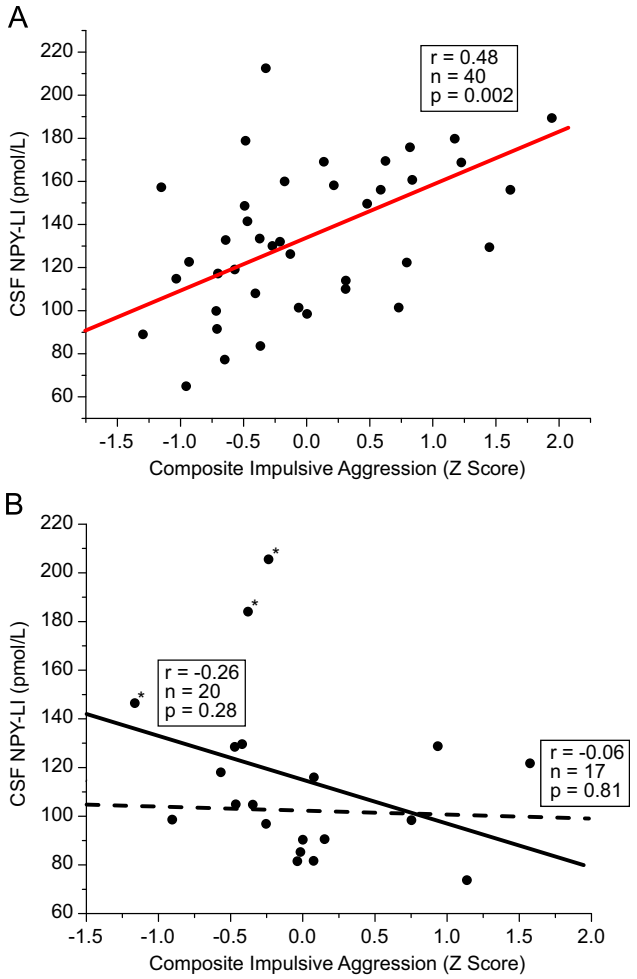

Figure 2. (A) Correlation between composite impulsive aggression and cerebrospinal fluid levels of neuropeptide Y-like immunoreactivity (CSF NPY-LI) in personality disorder subjects. **(B)** Correlation between composite impulsive aggression and CSF NPY-LI in healthy volunteer subjects (solid line: regression for all healthy volunteer subjects; dashed line: regression without three outliers*).

Given the significantly higher scores of aggression and impulsivity in the PD subjects, we added composite impulsive aggression to an ANCOVA model and noted an elimination of the group difference in CSF NPY-LI levels between PD and HV subjects (Figure 1, right).

CSF NPY-LI and Disorders of Aggression in the PD Group

A significant difference in CSF NPY-LI levels ($Z = .91$ SD) was noted as a function of current integrated research criteria for IED (IED-IR) in the PD group [$t(38) = 2.79$, $p = .008$] (Figure 3, left). A similar sized difference ($Z = .82$ SD), approaching statistical significance, was also seen as a function of lifetime IED-IR [$t(38) = 1.87$, $p = .07$]. Group differences for current and lifetime IED-IR became smaller, by at least half, and nonsignificant, when composite impulsive aggression was added to the ANCOVA model for current IED-IR (Figure 3, right). Despite impulsivity and aggression being one of the diagnostic features of borderline personality disorder (BPD) and/or antisocial personality disorder (AsPD), CSF NPY-LI did not differ as a function of BPD/AsPD

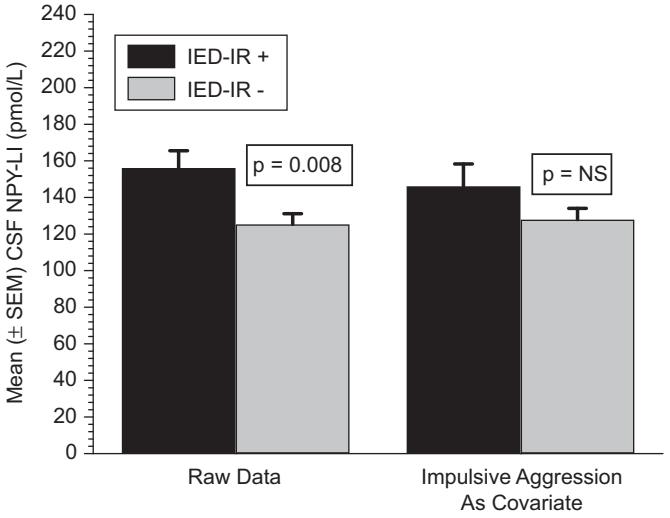

Figure 3. Mean (± SEM) group differences in cerebrospinal fluid levels of neuropeptide Y-like immunoreactivity (CSF NPY-LI) between current integrated research criteria for intermittent explosive disorder (IED-IR)+ and IED-IR− subjects before and after accounting for individual differences in composite impulsive aggression. NS, not significant.

($Z = .24$ SD; BPD/AsPD+ [$n = 9$]: 139.6 ± 30.3 pmol/L versus BPD/AsPD− [$n = 31$]: 131.8 ± 35.2 pmol/L) [$t(38) = .62$, $p = .54$].

CSF NPY-LI and History of Suicide Attempt in the PD Group

Cerebrospinal fluid NPY-LI concentrations in PD subjects with a life history of suicide attempt (SA) were not higher than in those without this history (SA+ [$n = 9$]: 145 ± 32.2 pmol/L versus SA− [$n = 31$]: 130.4 + 34.0 pmol/L) [$t(38) = 1.16$, $p = .25$].

CSF NPY-LI and Nonaggressive Diagnostic Variables in the PD Group

There was no difference in CSF NPY-LI concentration as a function of current history of mood disorder or anxiety disorder ($p > .10$ for each) in the PD group. In addition, there was no difference in CSF NPY-LI as a function of life history of mood, anxiety, or alcohol or substance use dependent disorders ($p > .30$ for each) and no difference as a function of Axis II personality disorder cluster ($p > .50$ for each).

CSF NPY-LI and Nonaggressive Behavioral Variables

Multiple regression analysis of the control personality variables (Eysenck Personality Questionnaire Inventory neuroticism, psychoticism, and extraversion, and EPQ-II venturesomeness and empathy) showed no significant relationship to CSF NPY-LI levels in all subjects [$F(5,49) = 1.74$, $p = .143$] or in PD subjects [$F(5,32) = 1.52$, $p = .210$].

Discussion

This is the first study to investigate the role of central NPY-LI levels and aggression and/or impulsivity in human subjects. The direct correlation between measures of impulsivity and aggression and CSF NPY-LI suggests a role for central NPY in the modulation of impulsive aggressive behavior, particularly in those with personality disorder. While the correlation between CSF NPY-LI and these variables in healthy volunteer subjects were inverse in nature, these correlations were not statistically

significant. In addition, the correlation coefficient was nearly zero when the three subjects with outlier values for CSF NPY-LI were removed from analysis.

Higher levels of CSF NPY-LI in subjects with personality disorder, compared with healthy control subjects, is consistent with a higher degree of impulsive aggression in these subjects and is supported by the observation that statistical control of impulsive aggression eliminated the difference in CSF NPY-LI between the groups. Also notable is the moderately large difference in CSF NPY-LI in personality disorder subjects with IED-IR compared with those without IED-IR. While the magnitudes of this difference as a function of current or lifetime IED-IR were similar, the difference for current IED-IR was statistically significant, while that for lifetime IED-IR approached statistical significance. This is likely due to the relatively small group ($n = 11$ and 13, respectively) of IED-IR subjects in the sample. Notably, these differences were substantially reduced, and nonsignificant, after statistical control of impulsive aggression, confirming that these behaviors are at the core of the differences in CSF NPY-LI levels. The modest, nonsignificant difference between personality disorder subjects with or without BPD/AsPD is notable because it does not support the hypothesis that BPD/AsPD should be similarly, or more, robustly associated with biological variables relevant to aggression than IED-IR. In this dataset, the difference in CSF NPY-LI levels is at least three times larger in IED-IR versus non-IED-IR subjects than it is among BPD/AsPD versus non-BPD/AsPD subjects, suggesting a more specific association with a disorder of impulsive aggression (i.e., IED-IR) than disorders in which impulsive aggression is one of several features. Cerebrospinal fluid NPY-LI levels in PD subjects with a history of suicide attempt, a variable highly associated with impulsive aggression in personality disordered subjects, was not significantly different than those without this history. While this may be due to the small number of personality disorder subjects with a history of suicide attempt in this sample, a similar negative finding for suicidal behavior has been reported in a study of depressed patients (40).

Our findings were not due to any confounding physical (e.g., age, height, weight) or demographic (e.g., gender, race, socioeconomic status factors. In addition, no correlations were seen between CSF NPY-LI levels and CSF levels of other neurotransmitters associated with aggression (36–38). Finally, these findings were not due to the presence of any Axis I disorder other than IED-IR, a disorder of impulsive aggression, or to other dimensions of personality apart from impulsivity and aggression. As such, these data support the idea of restructuring PD diagnoses into relevant behavioral dimensions, at least with regard to impulsive aggression.

High CSF NPY-LI levels, compared with control subjects, has been reported in patients with schizophrenia (13), anorexic nervosa (41), migraines (42), head injury (43), and Prader-Willi syndrome (44). In addition, patients with each of these conditions have been reported as having higher impulsivity and aggression scores than comparable control subjects (45–49). While this does not mean that increased central NPY expression accounts for the greater degree of impulsivity and aggression in these cases, these data are consistent with what we have observed in our subjects.

In fact, CSF NPY-LI may be lower, or not different, compared with control subjects, depending on the patient diagnosis. For example, several studies report lower CSF NPY-LI in patients with depression and a significant increase following successful antidepressant treatment (11,50–52). Lower CSF NPY-LI levels have also been reported in patients with dementia of the Alzheimer's type (53–56). In addition, several studies report no difference in CSF NPY-LI in patients with obsessive-compulsive disorder (57), alcoholism (58), multiple sclerosis (59), or obesity (60).

Neuropeptide Y-like immunoreactivity is found both in behaviorally relevant cortico-limbic areas of the brain and is secreted by cells in the paraventricular nucleus where NPY-ergic terminals are found in the hypothalamus (61). Neuropeptide Y cell bodies, and terminal fields, are also located in brain stem and spinal cord (62,63), where they can contribute to levels of CSF NPY-LI. Cerebrospinal fluid NPY-LI demonstrates no rostral-caudal gradient and this is likely due to the resistance of NPY to degradation in the CSF compartment and to contributions from brain stem and spinal cord (64). Neuropeptide Y can also flow back and forth across the blood-brain barrier, although CSF NPY-LI levels are fourfold higher than those assayed in plasma (65). Neuropeptide Y is taken up into the brain and CSF by a nonsaturable transport mechanism and diffuses back out at a slower rate (66). In animals, brain levels of NPY decay slowly and the half-life of NPY in whole brain is about 5 day (67). Neuropeptide Y is also extensively involved in peripheral sympathetic nervous system function (68), and peripheral levels reflect the activity of this pool. In humans, plasma NPY-LI concentrations correlate poorly with those in central nervous system (69), and based on large CSF-plasma differences in concentration (65), CSF NPY-LI is likely largely of central origin. Of note, CSF NPY-LI is highly reproducible across serial assessments at least 3 weeks apart ($r_s = .65$, $p < .01$] (64) and appears to be under substantial genetic influence ($h^2 = .66$] (64).

Neuropeptide Y is found in notable quantities in brain regions relevant to mammalian aggression, such as the amygdala (15) and prefrontal cortex (16), among other limbic structures. Animal studies suggest a role for NPY in aggression through its action in the medial amygdala (17), and these data are consistent with the findings reported here. Reduced aggression with NPY1 antagonists, and in NPY1 knockout mice, are also consistent with these data, though dopamine (18) and serotonin (19) may also play a role in these findings. On the other hand, increased impulsivity in NPY2 (20), and increased aggression in NPY4 (21), knockout mice suggest the possibility that stimulation of NPY2 and/or NPY4 receptors acts to inhibit impulsivity and aggression. An important next step would be an experimental study in which NPY is administered to human subjects to explore the net behavioral effects of stimulating the various central NPY receptors.

The strengths of this study include a well characterized sample, multiple validated measures of aggression and impulsivity, and a standardized approach to drug-free status, subject activity, and dietary intake to minimize the effect of extraneous factors on lumbar CSF NPY-LI levels. Limitations include, first, the fact that this is a cross-sectional study and no causal conclusions can be made from associative and correlational analyses. Second, these findings may be smaller, or nonexistent, in a larger sample. Third, the ascertainment of subjects may limit the generalizability of these findings in that these involved subjects volunteered for research study, rather than for clinical treatment. However, nearly four-fifths of the PD subjects reported a past history of psychiatric treatment or of having episodes of behavioral disturbance for which they, or others, thought they should have sought mental health services but did not. Accordingly, most of the PD subjects in this report may be similar to subjects who would have been recruited from a clinical setting.

In summary, we report a direct relationship between CSF NPY-LI concentration and aggression and impulsivity in human subjects, specifically in those with a personality disorder.

This relationship was not accounted for by any factors studied, such as other psychiatric disorder or general personality factors, other than aggression and/or impulsivity. These data are in line with the hypothesized central role NPY plays in regulation of emotionality and affect and warrant further study into the role of central NPY in impulsive aggression. Given that intermittent explosive disorder, a disorder of impulsive aggression, displays a 2% to 3% 1-year prevalence rate in the United States (70) and that currently available psychotropic treatments bring less than 50% of those treated into remission (71), additional strategies for examination and intervention of impulsive aggression in human subjects are needed.

This work was supported in part by grants from the National Institute of Mental Health, RO-1 MH46848 and KO-2 MH00095 (EFC), and in part by The Swedish Medical Research Council, Grant 10414 (AAM).

Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals, Inc.; Dr. Lee reports being the recipient of a research grant from Azevan Pharmaceuticals, Inc.; and Drs. Liu and Mathé report no biomedical financial interests or potential conflicts of interest.

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