Cerebrospinal Fluid Substance P-Like Immunoreactivity Correlates with Aggression in Personality Disordered Subjects

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Background: Neurochemical studies have pointed to a modulatory role in human aggression for a variety of central neurotransmitters; some seem to play an inhibitory role, whereas others seem to play a facilitory role in the modulation of aggression. Laboratory animal studies of substance P suggest a facilitory role for this undecapeptide in the modulation of aggression, but no studies of substance P have yet been reported with regard to human aggression.

Methods: Basal lumbar cerebrospinal fluid samples were obtained from 38 physically healthy subjects with personality disorder (PD) and substance P-like immunoreactivity was measured and correlated with measures of aggression and impulsivity.

Results: The cerebrospinal fluid substance P-like immunoreactivity levels were directly correlated with a composite measure of aggression and, more specifically, with Buss-Durkee Aggression. No correlation was seen with any measure of impulsivity or of general dimensions of personality.

Conclusions: These data suggest a direct relationship between central nervous system substance P containing neural circuits and aggression in human subjects. This finding adds to the complex picture of the central neuromodulatory role of impulsive aggression in human subjects.

Key Words: Aggression, CSF, impulsivity, neurokinin-1, personality, substance P

Substance P is an eleven amino acid neuropeptide that functions as both a classical neurotransmitter and neurotransmitter (1,2). Although first discovered in an extract from tissues that induces intestinal contraction (3), substance P is released from the terminals of specific sensory nerves and is also found in neurons in the central nervous system (CNS). The endogenous receptor for substance P is neurokinin-1 (NK_1) receptor, a member of the tachykinin receptor subfamily of G-protein coupled receptors (4). Substance P and the NK_1 receptor are both widely distributed in the CNS and are specifically found in the limbic regions, including the hypothalamus, amygdala, and the periaqueductal gray (PAG) (5). They are also found in close association with serotonin (5-HT)- and norepinephrine (NE)-containing neurons (6). Substance P has been associated with—in addition to the regulation of pain (7)—the regulation of emotion including depression, anxiety, and stress (8); reinforcement (9); and neurogenesis (10).

A modulating role of substance P in aggressive behavior in mammals is suggested by high concentrations of substance P in brain regions relevant to mammalian aggression. These areas include the hypothalamus, amygdala, and the PAG (11). Studies in lower mammals have provided evidence that substance P promotes aggressive behavior activating hypothalamic NK_1 receptors and inducing rage and aggressive behavior (12–15). In addition, PAG injections of NK_1 agonists in the cat result in spontaneous hissing (16). Furthermore, intrathecal injections of substance P in the rat results in agonistic behavior (17) as well as in behavioral excitation (18,19). Finally, NK_1 receptor antagonists have been shown to reduce defensive aggression in cats (15).

We sought to explore, given the results of these laboratory animal studies, whether cerebrospinal fluid NPY-like Immunoreactivity (CSF NPY-LI) is associated with aggression and/or impulsivity in personality disordered subjects. We hypothesized that CSF NPY-LI would correlate directly with measures of aggression and/or impulsivity.

Methods and Materials

Subjects

Thirty-eight 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 in human subjects. Subjects were recruited from clinical settings and through newspaper advertisements seeking out individuals who considered themselves as having difficulty managing their aggressive behaviors and nonaggressive individuals interested and willing to participate in biological studies of personality traits. All subjects met DSM-IV criteria for a personality disorder (PD), and all gave informed consent 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 PD diagnoses were made according to DSM-IV criteria (20). The diagnosis of intermittent explosive disorder was made by research criteria as previously described (21). Diagnoses were assessed and assigned through a best-estimate process as described in previous reports (22). Medical health of all subjects was documented by medical history; physical examination; electrocardiogram; and

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blood hematology, chemistry (including hepatic profile), and thyroid function tests; and urinalysis, including drug screen.

All subjects met DSM-IV criteria for a PD. Of these PD subjects, 23 met DSM-IV criteria for a specific PD as follows: 1) Cluster A ($n = 9$): paranoid ($n = 7$), schizoid ($n = 3$), schizotypal ($n = 1$); 2) Cluster B ($n = 13$): borderline ($n = 7$), antisocial ($n = 4$), narcissistic ($n = 3$), histrionic ($n = 3$); and 3) Cluster C ($n = 9$): obsessive-compulsive ($n = 6$), avoidant ($n = 2$), dependent ($n = 1$). The remaining 15 subjects were diagnosed as personality disorder-not otherwise specified (PD-NOS). These subjects met DSM-IV general criteria for PD, had pathological personality traits from a variety of PD categories, and had clear evidence of impaired psychosocial functioning (mean Global Assessment of Function scale score = 62.1 ± 7.8). Most PD subjects had a life history of at least one Axis I disorder (30 of 38), and one-half had a current history of at least one Axis I disorder (21 of 38). 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 ($n = 3$): all phobic ($n = 3$); intermittent explosive disorder: IED by research criteria ($n = 10$); somatoform disorder ($n = 2$); adjustment disorder ($n = 1$); eating disorder ($n = 1$). Lifetime Axis I disorders were as follows: any mood disorder ($n = 16$): major depression ($n = 11$), dythymia ($n = 3$), depressive disorder-NOS ($n = 4$); any anxiety disorder ($n = 4$): phobic ($n = 3$), and nonphobic ($n = 2$) anxiety disorder; alcohol dependence ($n = 9$), other drug dependence ($n = 7$); intermittent explosive disorder: ($n = 11$); 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, delusional disorder, or current alcohol or other drug dependence.

Assessment of Aggression and Impulsivity

Aggression measures included the Aggression score from the Life History of Aggression assessment (LHA) (23) and the aggression factor score from the Buss-Durkee Hostility Inventory (BDHI) (24). The LHA aggression reflects the history of actual aggressive behavior of a subject, whereas BDHI Aggression reflects a subject's self-assessment of his or her tendency to be aggressive in given situations. The BDHI Aggression reflects four subscales related to direct physical aggression, indirect physical aggression, verbal aggression, and irritability. Impulsivity measures included the Impulsiveness Scale from the Eysenck Personality Questionnaire-2 (EPQ-2) (25) and the Barratt Impulsiveness Scale-Version 11 (BIS-11) (26). These measures reflect a subject's self-assessment of how impulsive he or she is. History of suicidal behavior was assessed during the diagnostic assessment as previously described (27). Other assessments used in this study include the EPQ-1 scales neuroticism, psychoticism, and extraversion (28) and the remaining two scales from the EPQ-2 (venturesomeness and empathy) as control dimensions of personality. Global function of subjects was assessed by the Global Assessment of Function scale (20).

Lumbar Puncture

All subjects were instructed to remain drug-free for 2 weeks before study and to follow a low monoamine diet for at least 3 days before study. Female subjects (all pre-menopausal) were studied within the first 10 days of the follicular phase of the menstrual cycle. The evening before the lumbar puncture, subjects reported to the Clinical Procedures Lab at approximately 8:00 PM. 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. The procedure was performed under sterile technique with the subject in the lateral decubitus position. A total of 20 cc of CSF was obtained 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 1 pooled 15-cc sample of CSF, subsequently subdivided into 15 1-cc subaliquots for later analysis. One pooled aliquot was used for assay of substance P-like immunoreactivity (SP-LI). All CSF samples were placed in polypropylene tubes and were frozen immediately at −70° C until assay at a later time.

Assay of CSF SP-LI

The CSF SP-LI was determined in blinded CSF samples by a solid phase radioimmunoassay with a highly specific substance P antibody. Briefly, Nunc immunomodule plates (Fisher Scientific, Roskilde, Denmark) were incubated for 1 hour at room temperature with protein G (250 ng/well) in .1 mol/L sodium (Na) bicarbonate, pH 9.0. The plates were rinsed three times in wash buffer (150 mmol/L potassium hydrogen phosphate, 20 mmol/L sodium dihydrogenorthophosphate, 200 mmol/L ascorbic acid, .2 % Tween 20, .1% Na Azide, pH 7.6). Substance P antibody (100 μL; Peninsula Laboratories, San Carlos, California; #T-4105, 500 rxn lyophilized, reconstituted in 50 mL wash buffer containing .1% gelatin) was added to each well and incubated at room temperature for 2 hours. The antibody solution was aspirated, and the samples and standards were added to the wells in a volume of 100 μL. Labeled [^{125}I]-Substance P (Peninsula Laboratories; #H-5104) was diluted to approximately 18,000 cpm/25 μL wash buffer, and 25 μL was added to each well. Nonspecific binding was determined in wells containing only protein G (no antibody). Plates were incubated at 4°C for 24 hours. After this period, wells were aspirated, separated, placed in 12 × 75 borosilicate glass tubes, and counted on a two-channel ã counter. The sensitivity of the assay was 6 fmol/mL. Intra-assay variability was 6.5%, and inter-assay variability was 9.4%.

Statistical Analysis and Data Reduction

In this initial CSF SP-LI study of impulsive aggressive behavioral correlates, rank-ordered, nonparametric statistics were used, to be conservative. Comparisons of between-group variables were performed by Mann-Whitney *U* test and χ^2 tests. Correlational analyses were performed by Spearman correlation (r_s). A two-tailed α value of .05 was used to denote statistical significance for all analyses. Basal lumbar CSF SP-LI concentration 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 SP-LI concentration were used in all analyses. Finally, composite variables for aggression, impulsivity, and impulsive aggression were created in a data-reduction step—rather than use each of the aggression and impulsivity variables separately—as described previously (27). Composite variables were created, because intercorrelations among the behavioral variables within domains were substantial (LHA aggression with BDHI aggression: $r_s = .52$, $p = .001$; BIS-11 with EPQ-2 Impulsivity: $r_s = .84$, $p < .001$). 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 similar in magnitude ($r_s = .57$; $p < .001$), 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 subjects in this study are displayed in Table 1.

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