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CEREBROSPINAL FLUID AND PLASMA C-REACTIVE PROTEIN AND AGGRESSION IN PERSONALITY DISORDERED SUBJECTS: A PILOT STUDY

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Abstract

C-Reactive Protein (CRP), in the plasma, serves as a marker of systemic inflammation and has been shown to correlate with history of actual aggressive behavior, and as a personality trait of aggressive tendency, in human subjects. This study pilot study was conducted to determine if plasma CRP levels are correlated with cerebrospinal fluid levels (CSF CRP) and if CSF CRP also correlates with aggression. If so, this would suggest a role for central inflammatory processes in human aggression. Both plasma and basal lumbar CSF samples were obtained from seventeen subjects with DSM-5 personality disorder and assayed for CRP. Plasma and CSF CRP levels were correlated ($r = .65$, $p = .005$) and each correlated with aggression (Plasma: $r = .53$, $p = .029$; CSF: $r = .84$, $p < .001$). When considered simultaneously, CSF CRP, but not plasma CSP, uniquely correlated with aggression. No relationship was seen with other measures of psychopathology. These data suggest a positive relationship between central nervous system CRP and aggression in humans.

Keywords

CSF; CRP; Aggression; Impulsivity; Personality

INTRODUCTION

A significant positive correlation between aggression and plasma levels of C-Reactive Protein (CRP), an acute phase reactant released during the process of inflammation (Pepys & Hirschfield 2003), has been reported in generally healthy human subjects (Brummett et al., 2010; Marsland et al., 2008; Suarez 2004), in personality disordered subjects (Coccaro 2006), and in intermittent explosive disordered subjects (Coccaro et al., 2013). While

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CONFLICT OF INTEREST

Dr. Coccaro reports that he is on the Scientific Advisory Board of Azevan Pharmaceuticals, Inc. and that he has stock options in Azivan Pharmaceuticals, Inc., through this role. Dr. Lee reports that he has received a research grant from Azivan Pharmaceuticals, Inc. Dr. Coussons-Read reports no real or apparent conflicts of interest.

circulating inflammatory markers in plasma can cross into the central nervous system through a variety of mechanisms (Dantzer et al., 2008; Quan and Banks 2007), it is an open question if inflammatory markers assessed in cerebrospinal fluid (CSF) also display this relationship with aggression. This is important because CRP can also be generated in the central nervous system (Yasojima et al., 2000) and CRP is involved in the production of cellular damage through its effects on enhancing phagocytosis, complement, and on the release of inflammatory cytokines (Marnell et al., 2005). In this pilot study, we hypothesized that CSF CRP would correlate both with plasma levels of CRP and with measures of aggression in human subjects.

METHODS

Subjects

Seventeen physically healthy adult subjects, between 21 and 48 years of age, participated in this study. All subjects were afebrile, 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 aggressive and non-aggressive 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 (IRB). Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation were excluded from this study.

Diagnostic Assessment

Syndromal and personality disorder diagnoses were made according to DSM-5 criteria (American Psychiatric Association 2013). Research diagnostic assessments were performed by individuals with masters/doctoral degrees in clinical psychology with inter-rater (kappa) reliability ranging from .79-.93 (mean $\pm$ sd: $84 \pm .05$) across mood, anxiety, substance use, impulse control, and personality disorders. Final diagnoses were assigned by previously described best-estimate consensus procedures (Bunce et al., 2005) utilizing information from: (a) Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997), (b) Structured Interview for the Diagnosis of DSM-IV Personality Disorder (SIDP-IV; Phohl et al., 1997), (c) clinical interview by a research psychiatrist; and, (d) review of all available clinical data. Subjects given a diagnosis of Personality Disorder-Not Otherwise Specified (PD-NOS) met DSM-5 criteria for presence of a personality disorder but did not meet full criteria for any single personality disorder, despite meeting criteria for many personality disorder traits [mean traits ($\pm$ sd): 14.3 ± 9.6]. Medical health of all subjects was documented by medical history, physical examination, electrocardiogram, and blood hematology, chemistry (including hepatic profile), thyroid function tests, urinalysis, and drug screen (subjects screening positive for illicit drugs were not entered into study).

Psychometric Measures

The Aggression Scale from Life History of Aggression (LHA; Coccaro et al., 1997) and the Aggression Factor from the Buss-Durkee Hostility Inventory (BDHI; Buss and Durkee

1957) was used to assess aggression. The Barratt Impulsivity Scale (BIS-11; Patton et al., 2005) and Impulsiveness Scale from Eysenck Personality Questionnaire-2 (EPQ-2; Eysenck and Eysenck 1977) were used to assess impulsivity. The Hamilton Depression Rating Scale (Hamilton 1961) was used to assess state depression and the Life Experiences Survey (LES; Sarason et al., 1978), for both positive and negative stressful psychosocial life events over the previous six months, was used to assess psychological stress. Neuroticism, psychoticism, and extraversion scales from Eysenck Personality Questionnaire-1 (EPQ-1; Eysenck and Eysenck 1975) were used as measures of general personality.

Subject Preparation / Lumbar Puncture for CRP

Subjects were afebrile, medically healthy, and medication-free for at least four weeks. Subjects arrived at the Clinical Procedures Lab at approximately 8:00 pm the evening before the procedure. At 11 pm subjects were given a snack and placed at bed rest. Lumbar punctures were performed under sterile technique, with the subject in the lateral decubitus position, after at least eight hours of fasting and rest, by a research neurologist. CSF samples were placed in polypropylene tubes and frozen immediately at -70°C until assay. One sample from a pooled aliquot (3rd to 18th cc) was used for assay of CRP. Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to quantify CRP (R&D Systems). Samples were run together and tested in duplicate and according to the directions provided by the manufacturer ($\text{CV} < 6\%$). Another pooled aliquot was used for assay of CSF 5-hydroxyindolacetic acid (5-HIAA) and CSF homovanillic acid (HVA) by GC-MS (Fri, Wiesel, & Sedvall, 1974) in the Analytic Psychopharmacology Laboratory, at Nathan Kline Institute, directed by Thomas Cooper. The intra- and inter-assay coefficient of variations for these assays were both less than 8%.

Statistical Analysis

Data analysis involved Pearson correlation and multiple regression analysis with an alpha level of 0.05. Plasma and CSF CRP levels were normally distributed. The primary behavioral outcome variable was a composite of the LHA and BDHI Aggression scores created by taking the z-score for each, and dividing by two, in a data-reduction step as previously described (Coccaro et al., 2010). Impulsivity was a secondary behavioral variable and was studied as a composite of the BIS-11 and EPQ-II Impulsivity scores.

RESULTS

DSM-5 Diagnoses, Demographic, Behavioral, and CRP Data

Data regarding diagnostic, demographic, behavioral, and covariate variables, as well as Plasma and CSF CRP levels, are listed in Table I.

Plasma CRP, CSF CRP, Aggression, and Impulsivity

Plasma CRP and CSF CRP correlated to a high degree ($r = .65$, $r^2 = .42$, $p = .005$; figure 1. In turn, both Plasma CRP ($r = .48$, $r^2 = .23$, $p = .05$), and CSF CRP ($r = .84$, $r^2 = .71$, $p < .001$), levels correlated significantly with Composite Aggression scores with the difference in the magnitude of these correlations being statistically significant ($t_{14} = 2.86$, $p = .013$). Linear regression analysis ($F[2,14] = 16.38$, $p < .001$) revealed a significant relationship for

Composite Aggression and CSF CRP ($B = 0.397 \pm 0.065$, $\beta = .87$, partial $r = .78$, $r^2 = .61$, $p < .001$) but not for Plasma CRP ($B = -0.017 \pm 0.053$, $\beta = -.06$, partial $r = -.09$, $r^2 = .01$, $p = .755$). Adding the five relevant covariates (body mass index, current depression scores, recent psychosocial stress score, and current alcohol/smoking status) to the model involving CSF CRP did not meaningfully change this result ($B = 0.282 \pm 0.093$, $\beta = .62$, partial $r = .69$, $r^2 = .48$, $p = .012$); figure 2. Linear regression analysis revealed similar contributions for LHA ($B = 0.136 \pm 0.056$, $\beta = .40$, partial $r = .54$, $r^2 = .29$, $p = .03$), and BDHI ($B = 0.121 \pm 0.035$, $\beta = .58$, partial $r = .58$, $r^2 = .34$, $p = .003$), aggression score to CSF CRP level. Composite Impulsivity, which correlated significantly with Composite Aggression ($r = .58$, $r^2 = .34$, $p = .014$), also correlated significantly with CSF CRP ($r = .64$, $r^2 = .41$, $p = .006$), but not with Plasma CRP level ($r = .40$, $r^2 = .16$, $p = .112$). Linear regression analysis ($F[2,14] = 19.24$, $p < .001$) revealed a significant relationship for Composite Aggression and CSF CRP ($B = 1.541 \pm 0.373$, $\beta = .70$, partial $r = .74$, $r^2 = .55$, $p = .001$) but not for Composite Impulsivity and CSF CRP ($B = 0.448 \pm 0.332$, $\beta = .23$, partial $r = .34$, $r^2 = .12$, $p = .198$).

Relationship Between CSF CRP, CSF 5-HIAA, CSF HVA Levels, and Aggression

While relationships between aggression and CSF 5-HIAA, CSF HVA have been documented (e.g., Coccaro and Lee 2010), linear regression analyses revealed CSF CRP to be significantly related to Composite Aggression ($B = 3.118 \pm 0.635$, $\beta = .80$, partial $r = .81$, $r^2 = .66$, $p < .001$) above and beyond any association with CSF 5-HIAA ($B = 0.042 \pm 0.027$, $\beta = .36$, partial $r = .39$, $r^2 = .15$, $p = .150$) or CSF HVA ($B = -0.017 \pm 0.010$, $\beta = -.42$, partial $r = -.43$, $r^2 = .23$, $p = .113$). Adding the five relevant covariates did not meaningfully change this result ($B = 2.688 \pm .906$, $\beta = .69$, partial $r = .70$, $r^2 = .49$, $p = .017$).

CSF CRP and Other Behavioral, Diagnostic, or Demographic Variables

Linear regression analysis revealed that Composite Aggression scores continued to significantly relate to CSF CRP even when general personality variables from the EPQ (i.e., neuroticism, extraversion, and psychoticism) were included in the statistical model ($B = 1.183 \pm 0.615$; $\beta = .83$; partial $r = .66$, $r^2 = .44$, $p = .013$); none of which correlated with CSF CRP in the model. CSF CRP levels did not differ as a function of current, or lifetime, history of depressive disorder, anxiety disorder, intermittent explosive disorder, or substance use disorders. Finally, CSF CRP levels did not correlate significantly with age ($r = .26$, $r^2 = .07$, $p = .315$), SES scores ($r = .06$, $r^2 = .00$, $p = .827$) or differ as a function of gender or race.

DISCUSSION

The positive correlation between these aggression measures and CSF CRP suggests a role for inflammatory activity in the modulation of aggressive behavior. This is also consistent with animal data demonstrating that inflammatory processes are involved in the modulation of aggression (Bhatt et al., 2008; Hassanain et al., 2003, 2005; Zalcman & Siegel 2006).

These results were not due to variability in other relevant factors. First, subjects were all physically healthy, medication free, and not dependent on alcohol or other drugs. Second,

even after accounting for body mass index and other variables that might affect levels of inflammatory markers (e.g., current depressive symptoms, recent psychosocial stress, and current alcohol/smoking status; Dowlati et al., 2010; Howren et al., 2009) the results remained the same. Third, these results were not due to the presence of other psychiatric diagnostic conditions, impulsivity, or to dimensions of general personality, other than that of aggression. In this way, these data tend to support the recently proposed RDoc approach to the study of dimensions of behavior and neurobiology, rather than simply examining diagnostic entities (Insel et al., 2010). Finally, despite the known relationship between CSF 5-HIAA and HVA levels and aggression (e.g., Coccaro and Lee 2010), CSF CRP levels were positively related to aggression above and beyond the influence of CSF 5-HIAA and CSF HVA.

Inflammatory proteins are found in human CSF due to inflammatory processes in the CNS and due to transfer of these proteins from the circulation (Dantzer et al., 2008; Quan and Banks 2007). Notably, *invitro* studies of post-mortem human tissue show that CRP, and CRP mRNA, is generated in the brain (Yasojima et al., 2000). This is important because CRP can cause cellular damage, in the brain and elsewhere, by increasing phagocytosis, activating complement, and by inducing the release of pro-inflammatory cytokines which, in turn, perpetuate the inflammatory process (Marnell et al., 2005).

Limitations to this pilot study include the fact that this is a cross-sectional study of modest sample size, that no causal conclusions can be made from associative and correlational analyses, and that the magnitude of these findings may be smaller, or non-existent, in a larger sample. In addition, the ascertainment of subjects may limit the generalizability of these findings in that these involved subjects who volunteered for research study, rather than for clinical treatment. Finally, there was no healthy volunteer control group in this study. Accordingly, this study cannot speak to whether the CSF CRP levels in these subjects are elevated in the types of patients studied compared to a control group. That said, these data demonstrate a correlation between plasma and CSF CRP, and plasma levels of CRP are reported as elevated in impulsively aggressive subjects, compared with controls (Coccaro et al, 2013), and higher plasma CRP levels correlate with aggression in similar subject samples (Coccaro 2005; Coccaro et al., 2013) and in healthy volunteers (Brummett et al., 2010; Marsland et al., 2008; Suarez 2003),

In conclusion, we report a positive relationship between CSF CRP levels and aggression in human personality disordered subjects. This relationship was not accounted for by any factors studied (e.g., body mass index, current depressive symptoms, recent psychosocial stress, current alcohol/smoking status) or by any specific psychiatric disorder. That said, only, experimental studies examining aggressive responding in the laboratory, with and without pre-treatment with anti-inflammatory agents, can shed light on whether inflammatory proteins are related to aggressive behavior in any meaningful causal fashion.

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APPENDIX

APPENDIX TABLE

ABBREVIATIONS USED

BDHI = Buss-Durkee Hostility Inventory
BIS-11 = Barratt Impulsiveness Scale – 11 th version
BMI = Body Mass Index
CRP = C-Reactive Protein
CSF = Cerebrospinal Fluid
EPQ = Eysenck Personality Questionnaire
GAF = Global Assessment of Function
5-HIAA = 5-Hydroxyindolacetic Acid
HVA = Homovanillic Acid
LES = Life Experiences Survey
LHA = Life History of Aggression
PD-NOS = Personality Disorder – Not Otherwise Specified
SES = Socioeconomic Status

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Figure 1.
Correlation between Plasma and CSF CRP in Subjects.

Figure 2.

Partial regression plot for CSF C-Reactive Protein (mg/dL) and Composite Aggression score in personality disordered subjects (includes the following covariates in the model: BMI, State Depression Score, Recent Psychosocial Stress, Current Smoking Status, and Current Drinking Status).

TABLE I

DSM-5 Disorders, Demographic, Behavioral, CRP, and Covariate Data for The Sample

Variable	Frequency (%)
Current Syndromal Disorders:	3 (18%)
Any Depressive Mood Disorder	1 (6%)
Intermittent Explosive Disorder	2 (12%)
Lifetime Syndromal Disorders:	9 (53%)
Any Depressive Mood Disorder	4 (24%)
Any Anxiety Disorder	1 (6%)
Substance Use Disorder	6 (35%)
Intermittent Explosive Disorder	3 (18%)
Personality Disorders:	17 (100%)
Cluster A (Odd)	4 (24%)
Cluster B (Dramatic)	4 (24%)
Cluster C (Anxious)	3 (18%)
PD-NOS	8 (47%)

Demographic Variables	Frequency / Mean ($\pm$ SD)
Age (years)	34.0 $\pm$ 7.47
Gender (Male)	14 (82%)
Race (White)	10 (59%)
SES Score	30.2 $\pm$ 10.7
GAF Score	63.5 $\pm$ 5.7
Behavioral Variables	
LHA Aggression Score	7.3 $\pm$ 5.4
BDHI Aggression Score	20.2 $\pm$ 8.7
BIS-11 Impulsivity Score	62.4 $\pm$ 9.4
EPQ-2 Impulsivity	6.3 $\pm$ 4.3
EPQ-1 Neuroticism	8.7 $\pm$ 6.4
EPQ-1 Psychoticism	4.2 $\pm$ 3.1
EPQ-1 Extraversion	14.6 $\pm$ 4.2
Inflammatory Marker Variables	
CSF CRP (mg/dL)	1.65 $\pm$ 1.88
Plasma CRP (mg/dL)	1.58 $\pm$ 3.02

Covariate Variables	Frequency / Mean ($\pm$ SD)
Body Mass Index	25.5 $\pm$ 4.3
State Depression Score	4.1 $\pm$ 3.3
Life Experiences Survey	5.4 $\pm$ 14.6
Current Alcohol Use (Yes/No)	13 (76%)
Current Smoking (Yes/No)	4 (24%)