Psychoneuroendocrinology (2009) **34**, 1567—1573

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder

Royce Lee [a,*], **Craig Ferris** [b], **L.D. Van de Kar** [c,1], **Emil F. Coccaro** [a]

[a] *Clinical Neuroscience and Psychopharmacology Research Unit, Department of Psychiatry, The Pritzker School of Medicine, The University of Chicago, Chicago, IL, USA*
[b] *Department of Psychiatry, University of Massachusetts School of Medicine, Worcester, MA, USA*
[c] *Department of Pharmacology, Loyola University of Chicago, Stritch School of Medicine, USA*

Received 11 April 2008; received in revised form 1 June 2009; accepted 4 June 2009

KEYWORDS
Oxytocin;
Aggression;
Personality disorder;
Intermittent Explosive Disorder

Summary
Background: Data from animal studies have identified oxytocin as an important modulator of social aggression. We have previously reported on a relationship between cerebrospinal fluid (CSF) levels of vasopressin and life history of aggressive behavior, a finding that is consistent with animal data. We hypothesized that *CSF Oxytocin* levels would be inversely related to dimensional measures of lifetime aggression.
Methods: Lumbar CSF for morning basal levels of oxytocin was obtained from 58 consenting subjects with and without DSM-IV personality disorders. Aggression was assessed dimensionally using an interview instrument (*Life History of Aggression* (*LHA*)). The primary analysis was conducted using a linear regression model predicting variance in *CSF Oxytocin* concentration, including the predictors of *LHA* score, *Sex*, *Height*, and the presence or absence of personality disorder.
Results: The model predicting variance in *CSF Oxytocin* concentration including *LHA* score was statistically significant, after removal of a single multivariate outlier. Inclusion of the outlier resulted in a most likely spurious interaction between *Sex* and *LHA* score. Presence or absence of personality disorder was not associated with variance in *CSF Oxytocin* levels. Exploratory analyses revealed a possible inverse relationship between *CSF Oxytocin* level and history of suicidal behavior.
Conclusions: As hypothesized, *CSF Oxytocin* levels were inversely correlated with life history of aggression. This represents the first such report of a relationship between oxytocin levels and aggression. The correlational, cross-sectional study design precludes causal inferences, but the data are consistent with the known effects of oxytocin on aggressive behavior in animals.

* Corresponding author at: Department of Psychiatry, MC 3077, The University of Chicago, 5841 S Maryland Ave., Chicago, IL, 60637, USA. Tel.: +1 773 834 5673; fax: +1 773 834 4536.
E-mail address: rlee@yoda.bsd.uchicago.edu (R. Lee).
[1] *Deceased.* Previously at Department of Pharmacology, Loyola University of Chicago, Stritch School of Medicine, USA.

0306-4530/$ — see front matter
doi:10.1016/j.psyneuen.2009.06.002

1. Introduction

Non-lethal aggression against conspecifics occurring outside of predation and defense is an enduring aspect of social behavior. In vertebrate animals, within-species aggression occurs in a social context, with rules of engagement determined largely by dominance hierarchies. The close relationship between dominance-related behaviors and aggression in non-human animals may provide an important clue regarding the neurobiological mechanism of aggression in humans. A body of evidence has emerged for a prominent role of the hypothalamic neuropeptide oxytocin in animal social behavior. Along with its sister neuropeptide, vasopressin, oxytocin appears to exert its effect not by directly affecting the motoric aspects of aggression, but by altering motivational aspects of social behavior (Winslow et al., 1993; Stribley and Carter, 1999).

In humans, pathological aggression is characterized by non-defensive physical or verbal assaults directed towards another person. The magnitude of the aggressive response is disproportionate to the trigger, and consequently the aggressive acts usually have deleterious health or social effects on the perpetrator and victim. Pathological aggression is encountered in a range of clinical syndromes, including the dementias, delirium, demyelinating disorders, psychotic disorders, affective disorders, and personality disorders. Impulsive aggression that is not secondary to another Axis I disorder, but still of clinical importance, is accounted for, albeit imperfectly, in the DSM as Intermittent Explosive Disorder (IED). IED is usually comorbid with Axis II personality disorders, and is most closely associated with borderline and antisocial personality disorders. Recent epidemiological surveys found that DSM-IV IED affects up to 7% of the US population at some time in their lives (Coccaro et al., 2004; Kessler et al., 2006). It is important to note that the aggression in IED does not ''come out of the blue''. Instead, the aggression is triggered by social interaction. In the prototypical example, an interpersonal provocation elicits anger or contempt, and the aggressor responds with verbal or physical aggression.

A body of work in non-human vertebrate animals has revealed a role for oxytocin in social aggression. Preclinical studies have manipulated oxytocin by (1) exogenous peptide administration and/or (2) comparison of gene knockout mutants with their wild-type counterparts. Administration of oxytocin receptor agonists *increases* maternal aggression (Ferris et al., 1992a,b; Bosch et al., 2005) but *reduces* territorial aggression (Harmon et al., 2002). Knockout of the oxytocin gene or its receptor results in altered social behaviors, including an increase in aggression (DeVries et al., 1997; Ragnauth et al., 2004, 2005; Takayanagi et al., 2005; Winslow et al., 2000).

Humans also express oxytocin receptors in frontal and limbic brain regions (Loup et al., 1991), establishing the biological plausibility for a role of oxytocin in social and emotional behaviors. We have previously reported on a positive linear relationship between cerebrospinal fluid (CSF) levels of vasopressin and life history of aggression in males with personality disorder (Coccaro et al., 1998). No human studies have yet examined the relationship between measures of central oxytocin and aggression. The purpose of this study is to further investigate the relationship between oxytocin and aggression in individuals with and without personality disorder. We performed lumbar puncture to collect CSF samples for oxytocin assay from 58 medication-free male and female subjects with and without personality disorder. Subjects performed assessments of lifetime aggressive behavior. We hypothesized the oxytocin would be negatively correlated with life history of aggression.

2. Methods

2.1. Subjects

Data are available from 58 physically medication-free subjects with ($n = 40$) and without ($n = 18$) a DSM-IV diagnosis of personality disorder in whom cerebrospinal fluid (CSF) measures of oxytocin were collected (see Table 1). All subjects were systematically evaluated as part of a larger program designed to study the biological correlates of abnormal personality. Study subjects were recruited by newspaper and public service announcements seeking subjects with, and without, self-reported problems with aggressive behavior and personality disorder-related problems. Written informed consent, using an institutional review board-approved consent form, was obtained from all subjects after the experimental procedures were fully explained. The medical health of all subjects was ascertained by medical history, physical examination, and a panel of clinical laboratory studies, including a urine screen for drugs of abuse.

2.2. Diagnostic assessment

Axis I and Axis II personality disorder (PD) diagnoses were made according to DSM-IV criteria (1994). Diagnosis of Intermittent Explosive Disorder was made by Research Diagnostic Criteria as previously described (Coccaro, 2003). Diagnoses were made using information from: (a) semi-structured interviews conducted by trained masters or doctoral-level clinicians using the Schedule for Affective Disorders and Schizophrenia (Spitzer et al., 1978), and the Structured Interview for the Diagnosis of DSM personality disorder (Pfohl et al., 1995) for Axis II disorders; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures (Klein et al., 1994) involving at least two research psychiatrists and three clinical psychologists as previously described (Coccaro et al., 1997). Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), current alcoholism or drug dependence, were excluded from the study.

The distribution of the personality disorders were as follows: Cluster A [$n = 10$; i.e., Paranoid ($n = 8$), Schizoid ($n = 3$), Schizotypal ($n = 1$)]; Cluster B [$n = 14$; i.e., Borderline ($n = 7$), Antisocial ($n = 5$), Histrionic ($n = 3$), Narcissistic ($n = 3$)]; Cluster C [$n = 9$; i.e., Obsessive—Compulsive ($n = 6$), Avoidant ($n = 2$), Dependent ($n = 1$)]. Sixteen (40%) subjects were diagnosed with personality disorder NOS, and nine (23%) subjects met criteria for more than one personality disorder. Subjects in the personality disorder group had a mean of 0.8 ± 0.9 comorbid current Axis I disorders, and a mean of 2.2 ± 1.7 Lifetime Axis I disorders. Current Axis I