



Cerebrospinal fluid glutamate concentration correlates with impulsive aggression in human subjects



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ABSTRACT

Neurochemical studies have pointed to a modulatory role in human aggression for various central neurotransmitters. Some (e.g., serotonin) appear to play an inhibitory role, while others appear to play a facilitator role. While recent animal studies of glutaminergic activity suggest a facilitator role for central glutamate in the modulation of aggression, no human studies of central glutaminergic indices have yet been reported regarding aggression. Basal lumbar cerebrospinal fluid (CSF) was obtained from 38 physically healthy subjects with DSM-IV Personality Disorder (PD; $n = 28$) and from Healthy Volunteers (HV; $n = 10$) and assayed for glutamate, and other neurotransmitters, in CSF and correlated with measures of aggression and impulsivity. CSF Glutamate levels did not differ between the PD and HC subjects but did directly correlate with composite measures of both aggression and impulsivity and a composite measure of impulsive aggression in both groups. These data suggest a positive relationship between CSF Glutamate levels and measures of impulsive aggression in human subjects. Thus, glutamate function may contribute to the complex central neuromodulation of impulsive aggression in human subjects.

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1. Introduction

Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system (Niciu et al., 2012). Glutamate is stored in vesicles at chemical synapses where nerve impulses trigger release of glutamate from the pre-synaptic neuron onto post-synaptic glutamate receptors such as the ionotropic NMDA and AMPA/Kainate receptors and the G-protein coupled metabotropic glutamate receptors. Glutamate plays an important role in brain synaptic plasticity and is involved in a number of cognitive functions including learning and memory in the hippocampus, neocortex, and other brain regions.

Glutamate has been implicated to play a role in a variety of neuropsychiatric disorders including schizophrenia (Lin et al., 2012), mood disorder (Machado-Vieira et al., 2012), anxiety disorders (Riaza Bermudo-Soriano et al., 2012), addictive disorders (Olive et al., 2012), and other neuropsychiatric disorders (e.g., Hu et al., 2012; Carlson, 2012). While little work has been reported

on the role of glutamate in human aggressive behavior, preclinical studies suggest that stimulation of central glutamate receptors typically increases aggressive behavior in lower mammals.

As demonstrated in a number of preclinical studies in rodents, an excitatory amino acid pathway from the medial hypothalamus (MH) to the periaqueductal gray (PAG) is associated with aggressive behavior (Beart et al., 1998, 1990; Beitz, 1989). In the rat, there is a dense and distinct group of glutamatergic neurons expressing glutamate transporter protein over the entire hypothalamic attack area, with the rostral portion predominantly containing glutamatergic, and the caudal portion having both glutaminergic and, to a lesser degree, GABAergic, neurons (Hrabovszky et al., 2005). Microinjections of glutamate into the cat PAG elicit defensive rage (Bandler, 1984), a finding consistent with the release of glutamate by MH neurons and the activation of PAG neurons in the expression of defensive rage in the cat. This was confirmed in subsequent studies demonstrating that pretreatment with the glutamate antagonist kynurenic acid blocked MH facilitation of PAG elicited defensive rage, and that NMDA injected into PAG defensive rage sites facilitated the rage response elicited from that site (Lu et al., 1992). Administration of an NMDA receptor antagonist into the PAG blocked MH facilitation of PAG-elicited defensive rage. The antagonist dose-dependently suppressed defensive rage elicited by stimulation of the MH (Schubert et al., 1996). This study also reported that a considerable number of glutamate neurons within the

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anteromedial hypothalamus project to PAG defensive rage sites (Schubert et al., 1996).

Excitatory inputs from the basal amygdala also project to the PAG and there is evidence for PAG NMDA receptor mediated defensive rage following their stimulation (Shaikh et al., 1994); basal amygdaloid neurons projecting to PAG defensive rage sites also stain immunopositive for glutamate. In addition, mice bred for reduction of function in the NMDA R1 subunit display an absence of species-typical fighting in the resident intruder model of aggression (Duncan et al., 2004).

Preclinical studies of the other ionotropic glutamate receptor, AMPA, and as well as metabotropic glutamate receptors support a glutamate hypothesis of aggressive behavior. For example, mice deficient for the AMPA receptor GluR-A1 subunit are less aggressive than their wild-type counterparts (Vekovischeva et al., 2004) and treatment with AMPA receptor antagonists also reduces aggression in aggressive mice strains (Vekovischeva et al., 2007). Knockout of the GluA3-AMPA receptor subunit in mice is associated with a reduction in aggressive behavior (Adamczyk et al., 2012). In addition, genome-wide scans to identify aggression quantitative trait loci in aggressive mice strains find that the *Gria3* gene, which encodes for a subunit of the AMPA3 receptor, accounts for the strain differences in aggressive behavior in the resident-intruder mouse model of aggression (Brodtkin et al., 2002). Finally, selective mGlu-1 (Navarro et al., 2008) and mGlu-5 (Navarro et al., 2006), receptor blockade reduce aggression in mice models of aggression (Navarro et al., 2006). In contrast, agonist stimulation of auto-inhibitory mGlu-2/3 (Ago et al., 2012) or mGlu-7 (Navarro et al., 2009) receptors reduces aggression in mice.

Given the results of these various preclinical studies, we sought to explore if cerebrospinal fluid (CSF) Glutamate would be associated with aggression and/or impulsivity in personality disordered and healthy volunteer subjects. We hypothesized that CSF Glutamate would correlate directly with measures of aggression and/or impulsivity.

2. Methods

2.1. 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. Subjects were recruited through public service announcements seeking out individuals who considered themselves to have difficulty managing their aggressive behaviors and, non-aggressive individuals interested and willing to participate in biological studies of personality traits. Subjects with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), mental retardation, or current substance dependence disorder, were excluded from this study. Medical health of all subjects was documented by a comprehensive medical history and physical examination and included a drug screen for amphetamine, barbiturates, benzodiazepines, cocaine, opiates, methadone, methamphetamine, phencyclidine, oxycodone, and marijuana (no one who tested positive for any substance was entered into the study). All subjects gave informed consent and signed the informed consent document approved by our Committee for the Protection of Human Subjects (IRB).

2.2. Diagnostic assessment

Axis I and Axis II Personality Disorder diagnoses were made according to DSM-IV criteria (APA, 1994). The diagnosis of

Intermittent Explosive Disorder was made by Integrated Research Criteria as previously described (IED-IR: Coccaro, 2011, 2012). Diagnoses were assessed and assigned through a best estimate process as described in previous reports (Bunce et al., 2005).

Twenty-eight subjects met DSM-IV criteria for a Personality Disorder (PD) and ten subjects had no evidence of any DSM-IV Axis I or II psychopathology (Healthy Volunteers: HV). Eighteen of the PD subjects met DSM-IV criteria for a specific personality disorder as follows: a) Cluster A ($n = 8$), i.e., Paranoid ($n = 6$), Schizoid ($n = 3$), Schizotypal ($n = 1$); b) Cluster B ($n = 10$), i.e., Borderline ($n = 5$), Antisocial ($n = 3$), Narcissistic ($n = 2$), Histrionic ($n = 3$); c) Cluster C ($n = 7$), i.e., Obsessive-Compulsive ($n = 5$), Avoidant ($n = 1$); Dependent ($n = 1$). The remaining ten subjects were diagnosed as Personality Disorder-Not Otherwise Specified (PD-NOS). 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 GAF score = 63.4 ± 7.5). Just over half of PD subjects had a life history of at least one Axis I disorder (15 of 28) and three-quarters had a current history of at least one Axis I disorder (21 of 28). Current Axis I disorders were as follows: Any Mood Disorder ($n = 5$): major depression ($n = 1$), dysthymia ($n = 3$), depressive disorder-NOS ($n = 1$); Any Anxiety Disorder ($n = 3$), i.e., all phobic ($n = 3$); Intermittent Explosive Disorder-IR ($n = 7$); Somatoform Disorder ($n = 2$); Eating Disorder ($n = 1$). Lifetime Axis I disorders were as follows: Any Mood Disorder ($n = 12$): major depression ($n = 8$), dysthymia ($n = 4$), depressive disorder-NOS ($n = 2$); Any Anxiety Disorder ($n = 4$), i.e., phobic ($n = 3$), and non-phobic ($n = 2$) anxiety disorder; Alcohol Dependence ($n = 6$), Drug Dependence ($n = 5$); Intermittent Explosive Disorder-IR: ($n = 7$); Adjustment Disorder ($n = 2$); Eating Disorder ($n = 2$); Somatoform Disorder ($n = 2$). In addition to meeting criteria for Axis I and/or II disorders, most (79%) PD subjects reported: a) history of psychiatric treatment (64%) or, b) history of behavioral disturbance during which the subject, or others, thought they should have sought mental health services but did not (15%).

2.3. Assessment of aggression and impulsivity

Aggression measures included the Aggression score from the Life History of Aggression assessment (LHA; Coccaro et al., 1997) and the Aggression Factor score from the Buss–Durkee Hostility Inventory (BDHI; Buss and Durkee, 1957). LHA 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; Eysenck and Eysenck, 1977) and the Barratt Impulsiveness Scale-Version 11 (BIS-11; Patton et al., 1995). These measures reflect a subject's self-assessment of how impulsive he or she is. History of suicidal behavior was assessed during the diagnostic work-up as previously described (Bunce et al., 2005). Other assessments used in this study include the EPQ-I scales Neuroticism, Psychoticism, and Extraversion (Eysenck and Eysenck, 1975) 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 Global Assessment of Function scale (GAF, APA, 1994).

2.4. General preparation for study

No subject was taking any medical or psychotropic agent for at least four weeks at time of study and only six (16%) of the thirty-eight subjects (all PD subjects) had any lifetime exposure to psychotropic agents. Of the latter group, three PD subjects had lifetime

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