



Inverse relationship between numbers of 5-HT transporter binding sites and life history of aggression and intermittent explosive disorder

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ABSTRACT

The objective of this study was to determine if platelet 5-HT transporter (5-HTT) sites vary as a function of aggression, and/or impulsiveness, and differ as a function of Intermittent Explosive Disorder (IED). Accordingly, the number of platelet 5-HTT sites was assessed in 100 personality disordered (PD) individuals with varying degrees of aggressiveness. The number of platelet 5-HTT sites was assessed by examining the Bmax of H³-Paroxetine Binding to the blood platelet. Life history of aggression was assessed by Life History of Aggression. Impulsivity was assessed by the Barratt Impulsiveness Scale. Diagnoses of IED were made by both DSM-IV and Research Criteria. Examination of the data revealed that Bmax, but not Kd, values of Platelet H³-Paroxetine Binding correlated inversely with the LHA Aggression score ($r = -.42$, $n = 87$, $p < .001$) but not with the BIS-11 Impulsivity score ($r = .03$, $n = 77$, $p = .777$). PD subjects meeting Research Criteria for IED demonstrated a significant reduction in Bmax values for Platelet H³-Paroxetine Binding. These results were similar after accounting for the effect of lifetime history of depressive mood disorder on Bmax values for Platelet H³-Paroxetine Binding. These data indicate a significant inverse relationship between platelet 5-HTT and aggression, though not impulsivity, as a dimensional variable in personality disordered individuals. Results from the examination of IED as a categorical aggression variable suggest that Research, rather than DSM-IV, criteria better identify individuals with reduced numbers of platelet 5-HTT sites.

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1. Introduction

More than two decades of research has supported the hypothesis that reductions in brain serotonin (5-HT) function is associated with aggressive behavior, particularly impulsive aggression (Coccaro and Siever, 2002). While most studies of various central measures of 5-HT support this hypothesis, studies using peripheral 5-HT receptor measures have been less consistent in their findings, specifically, in studies examining 5-HT transporter (5-HTT) binding sites on the platelet. Although the platelet constitutes a peripheral site, and does not share the same microenvironment as central 5-HT neurons (Murphy et al., 1990), platelet 5-HTT sites are structurally identical to corresponding sites on central 5-HT neurons (Lesch et al., 1993; Ramamoorthy et al., 1993) and are, thus, under the same genetic influence as those on 5-HT terminals in the brain. Note, also, that the 5-HTT promoter genotypes (e.g., ss genotype) associated with less production of transporter protein synthesized

by 5-HT neurons, are also associated with less transporter protein on platelets in human subjects (Little et al., 2006).

The finding that the number of platelet 5-HTT binding sites correlated with aggressive behavior in humans was first noted by our laboratory (Coccaro et al., 1996). In our first study, we reported a significant inverse correlation between life history of aggression and the Bmax of ³H-Paroxetine on the platelet in twenty-four subjects with personality disorder. Since that report, six other studies have been published in different clinical populations with varying results. One study of 105 cocaine-dependent subjects reported an inverse correlation between aggression and Bmax of Platelet ³H-Paroxetine Binding (Patkar et al., 2003a) while another study of eleven currently aggressive schizophrenic subjects reported greater numbers of 5-HTT binding sites (Modai et al., 2000). Another study of forty schizophrenic subjects (Maguire et al., 1997), and a study of twenty-one Obsessive–Compulsive Disorder subjects (Marazziti et al., 2001) also reported no relationship between these two variables. Finally, two studies of twenty adolescents with ADHD, (Oades et al., 2002) or forty-three subjects with Conduct Disorder (Unis et al., 1997), also report no correlation between measures of aggression and Bmax of Platelet ³H-Paroxetine Binding. Differences in these results may be due to differences in the measures that were used and to differences in the brain-behavioral substrates underlying the pathology in the groups.

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In this study we report on a sample of personality disordered subjects that includes an additional seventy-six subjects from our original report of twenty-four subjects. In addition, we explore the potential differences in 5-HTT binding in subjects classified as aggressive by the diagnosis of Intermittent Explosive Disorder (IED). IED is a disorder of impulsive aggression not better accounted for by other psychiatric/medical conditions, or the influence of pharmacologically induced behavioral states.

2. Methods and materials

2.1. Subjects

This paper reports data from 100 consecutive physically healthy personality disordered individuals in whom platelet measures of ³H-Paroxetine Binding were assessed. All subjects were systematically evaluated as part of a larger program designed to study the biological correlates of personality traits in human subjects. Study subjects (83 male, 17 female) were recruited by newspaper and public service announcements seeking subjects with, and without, histories of anger and aggression, to take part in medically related studies. Written informed consent, using an IRB-approved consent document, was obtained from all subjects after all procedures were fully explained. Medical health of all subjects was documented by medical history, physical examination, and a variety of clinical laboratory studies including a urine screen for illicit drugs.

2.2. Diagnostic assessment

Axis I and Axis II Personality Disorder (PD) diagnoses were made according to DSM-IV criteria (American Psychiatric Association, 1994). Diagnosis of Alcoholism were made by modified Research Diagnostic Criteria as described in previous reports (Coccaro et al., 1996, 1989). Diagnosis of Intermittent Explosive Disorder (IED) were made by both DSM-IV (1994) and by Research Criteria using both the initially proposed Research Criteria (IED-R; (Coccaro et al., 1998), and the most recently proposed Integrated Research Criteria (IED-IR; (Coccaro et al., 2004) for IED. Research Criteria (Coccaro et al., 1998) differ from DSM-IV criteria in that they require: (a) one-month (or more) period of aggressive outbursts (including verbal outbursts only, or outbursts in which property is not destroyed) occurring twice a week on average, (b) aggressive outbursts to be, primarily, impulsive in nature, (c) aggressive outbursts to be associated with significant subjective distress or psychosocial impairment, and that they allow for comorbid diagnoses of Borderline, or Antisocial, Personality Disorder. Integrated Research Criteria for IED (Coccaro et al., 2004) are the same except that they allow an for an IED diagnosis if there are at least three episodes of serious assaultive or destructive behavior (even when there are not recurrent aggressive outbursts within the one-month time frame as required by the initially proposed Research Criteria); accordingly, this revision “integrates” the originally proposed Research Criteria with DSM-IV Criteria.

All 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 and Endicott, 1978) modified to include modules for the diagnosis of DSM Axis I disorders not covered by the original SADS, or the Structured Clinical Interview for DSM Diagnoses (SCID-I; First MB et al., 1997) for Axis I disorders, and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP: Pfohl et al., 1989, 1997) 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; Leckman et al.,

1982) involving at least two research psychiatrists and three clinical psychologists as previously described (Coccaro et al., 1996). This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (Kosten and Rounsaville, 1992). Subjects with a life history of Bipolar disorder, Schizophrenia (or other psychotic disorder), or mental retardation were excluded from this study.

Fifty-four of the 100 PD subjects met DSM-IV criteria for a specific personality disorder as follows: (a) Cluster A ($n = 22$), i.e., Paranoid ($n = 16$), Schizoid ($n = 8$), Schizotypal ($n = 2$); (b) Cluster B ($n = 29$), i.e., Borderline ($n = 13$), Narcissistic ($n = 13$); Antisocial ($n = 12$); Histrionic ($n = 5$); (c) Cluster C ($n = 19$), i.e., Obsessive-Compulsive ($n = 16$), Avoidant ($n = 6$). The remaining 46 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 = 62.1 + 6.6). Most PD subjects had a life history of at least one Axis I disorder (79 of 100) and nearly half had a current history of at least one Axis I disorder (49 of 100). Current Axis I disorders were as follows: Any Mood Disorder ($n = 17$): major depression ($n = 2$), dysthymia ($n = 7$), depressive disorder-nos ($n = 9$); Any Anxiety Disorder ($n = 9$), i.e., phobic ($n = 6$), and non-phobic ($n = 4$) anxiety disorder; Intermittent Explosive Disorder: IED by DSM-IV ($n = 18$), IED-R ($n = 32$, IED-IR ($n = 35$); Adjustment Disorder ($n = 1$); Somatoform Disorder ($n = 1$). Lifetime Axis I disorders were as follows: follows: Any Mood Disorder ($n = 44$): major depression ($n = 22$), dysthymia ($n = 9$), depressive disorder-nos ($n = 17$); Any Anxiety Disorder ($n = 16$), i.e., phobic ($n = 8$), and non-phobic ($n = 10$) anxiety disorder; Substance Use Disorders ($n = 32$): Alcoholism ($n = 24$), Drug Dependence ($n = 18$); Intermittent Explosive Disorder: IED by DSM-IV ($n = 23$), IED-R ($n = 36$), IED-IR ($n = 44$); Non-IED Impulse Control Disorders ($n = 1$); Adjustment Disorder ($n = 8$); Eating Disorder ($n = 1$); Somatoform Disorder ($n = 1$).

2.3. General preparation for study

Only seventeen of the 100 subjects had any lifetime history of exposure to psychotropic agents. In order of frequency, these agents fell into the following classes: anxiolytics ($n = 14$), antidepressants ($n = 9$), neuroleptics ($n = 5$), stimulants ($n = 4$), and sedative-hypnotics ($n = 3$). Subjects were instructed to remain drug-free for at least two-weeks prior to study and no subject was taking any psychotropic agent for at least two-weeks at time of study. Subjects were also instructed to follow a low monoamine diet for at least three (3) days prior to study. At the time that samples for platelets were obtained, subjects had been fasting, without smoking, from midnight the night before. Subjects were informed that initial and follow-up urine toxicology would be performed randomly just prior to study; illicit drug use was not detected in any subject reported herein. Females were all studied within the first ten days of the follicular phase of the menstrual cycle.

2.4. Platelet study

All blood samples for platelet study were obtained between 9:00 and 9:30 am through a 20 gauge indwelling intravenous catheter that was in place for the purposes of other biological studies being performed in our unit. 20 cc of venous blood was collected in a plastic syringe and transferred to EDTA containing vacutainer collection tubes. Samples were processed and assayed for ³H-Paroxetine Binding parameters as previously described (Coccaro et al., 1996).

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