Progress in Neuro-Psychopharmacology & Biological Psychiatry 36 (2012) 277–281

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Inter-relationship between different platelet measures of 5-HT and their relationship to aggression in human subjects

Robert Marseille, Royce Lee, Emil F. Coccaro *

Clinical Neuroscience & Psychopharmacology Research Unit, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, United States

ARTICLE INFO

Article history:
Received 16 August 2011
Received in revised form 5 October 2011
Accepted 6 October 2011
Available online 12 October 2011

Keywords:
5-HT
Aggression
Platelets

ABSTRACT

The objective of this study was to explore the inter-relationship of three platelet measures of serotonergic function (5-HT): 5-HT Transporter Binding, 5-HT-2 Receptor Binding and 5-HT Content and to explore their inter-relationship with measures of aggression and impulsivity. 58 male subjects with personality disorder were studied. Numbers of platelet 5-HT Transporter and 5-HT-2 Receptor sites were assessed by examining the Bmax of ^{3}H-Paroxetine Binding and the Bmax of ^{125}I-LSD Binding to the blood platelet; 5-HT Content was assessed by measuring the amount of 5-HT in the platelet material. Life history of aggression was assessed by Life History of Aggression. Impulsivity was assessed by the Impulsivity Scale of the Eysenck Personality Questionnaire-II. Platelet 5-HT Transporter Binding correlated with both 5-HT-2 Receptor Binding and 5-HT Content; the latter two variables did not correlate with each other. Only Platelet 5-HT Transporter binding correlated significantly with LHA Aggression. These data suggest that while Platelet 5-HT Transporter binding correlates with both 5-HT-2 Receptor Binding and with 5-HT Content, that only 5-HT Transporter Binding represents a correlate of aggression in male personality disordered subjects.

1. Introduction

Assessment of serotonin (5-HT) function in human subjects may be done by measuring 5-HT metabolites in cerebrospinal fluid (CSF), physiologic responses to acute challenge with 5-HT agents, and 5-HT and 5-HT related receptor elements on blood platelets. The first method is quite invasive and requires a lumbar puncture under strict conditions. The second, while less invasive, requires a research unit procedure involving several hours and serial blood draws along with other physiologic and behavioral assessments. In contrast, 5-HT indices on blood platelets involves obtaining only a blood sample and, unless platelet 5-HT uptake kinetics are assessed, one only needs the capacity to process the blood sample into platelet rich plasma, from which a platelet pellet is produced which is then frozen for later assay of binding site parameters of the 5-HT transporter (5-HTT) and the 5-HT2a receptor, and the quantification of platelet 5-HT content. While platelet 5-HT uptake kinetics yield information on the speed of 5-HT uptake, this measure requires a special on-site laboratory to assay platelet-rich plasma on the same day it is obtained.

Platelets have been used as a proxy for central 5-HT neurons (DaPrada et al., 1988; Stahl, 1985) for many years. However, as blood platelets are peripheral to the brain, and do not share the same microenvironment as central 5-HT neurons, some suggest that blood platelets are inferior to other methods as an index of 5-HT (Murphy et al., 1990). In fact, platelet 5-HT transporter sites are structurally identical to corresponding sites on central 5-HT neurons (Lesch et al., 1993; Ramamoorthy et al., 1993) and platelet 5-HT2a receptors are also structurally identical to those found on central 5-HT neurons (Cook et al., 1994). In addition, the 5-HT transporter promoter genotypes associated with lower production of transporter proteins in central 5-HT neurons are also associated with lower transporter protein synthesis in platelets (Little et al., 2006). Finally, just as it has been demonstrated that there is an correlation between reduced 5-HTT binding in the midbrains of violent offenders and aggression (Tiihonen et al., 1997) and in the anterior cingulate cortex of impulsive aggressive personality disordered subjects (Frankle et al., 2005), studies have also indicated that the same inverse correlation with aggression also exists for platelet 5-HTT sites (Coccaro et al., 1996; 2010), and for platelet 5-HT Content (Goveas et al., 2004), in personality disorder subjects.

Since three 5-HT indices may be assessed from a single platelet sample, an important question relates to how these indices correlate with one another and how they compare in their potential correlation with behaviors such as aggression. In this study we examined the inter-relationship between three indices of platelet 5-HT function and measures of aggression and impulsivity. Neither the first, nor the second comparison regarding the relationship between these platelet indices and aggression and impulsivity, have been reported before. Based

Abbreviations: 5-HT, Serotonin; CSF, Cerebrospinal Fluid; 5-HTT, 5-HT Transporter (5-HTT); 5-HT2a, 5-HT2a Receptor; ^{3}H-Paroxetine, Tritiated Paroxetine; ^{125}I-LSD, Iodinated Lysergic Acid; PD, Personality Disorder; IED, Intermittent Explosive Disorder; LHA, Life History of Aggression; EPQ, Eysenck Personality Questionnaire; Bmax, Maximal binding of ligand.

* Corresponding author at: Clinical Neuroscience & Psychopharmacology Research Unit, Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, United States. Tel.: +1 773 834 4083; fax: +1 773 834 7427.

E-mail address: ecoccaro@yoda.bsd.uchicago.edu (E.F. Coccaro).

0278-5846/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2011.10.004

upon relationships between these types of platelet measures with behaviors such as aggression (2010; Coccaro et al., 1997a, 1997b; Goveas et al., 2004), we hypothesized that the number of Platelet 5-HTT binding sites and the quantity of Platelet 5-HT Content would correlate directly with each other and that each would correlate inversely with the number of Platelet 5-HT2a receptor binding sites. We further hypothesized that each platelet measure would contribute uniquely to measures of aggression.

2. Methods and materials

2.1. Subjects

This paper reports data from 58 consecutive physically healthy males (34.7 ± 9.1 years) with personality disorder in whom platelet measures of ^{3}H-Paroxetine Binding, ^{125}I-LSD Binding, and 5-HT Content 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 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 was made by modified Research Diagnostic Criteria as described in previous reports (Coccaro et al., 1989). Diagnosis of Intermittent Explosive Disorder (IED) was made by both DSM-IV (American Psychiatric Association, 1994) and by Integrated Research Criteria (IED-IR) for IED (Coccaro, 2011; Coccaro et al., 2004). 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 et al., 1997) for Axis I disorders, and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP: Pfohl et al., 1989, 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; 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.

Thirty-two of the subjects met DSM-IV criteria for a specific personality disorder as follows: a) Cluster A (n = 18), i.e., Paranoid (n = 14), Schizoid (n = 6), Schizotypal (n = 2); b) Cluster B (n = 15), i.e., Borderline (n = 8), Narcissistic (n = 8); Antisocial (n = 7); Histrionic (n = 4); c) Cluster C (n = 12), i.e., Obsessive–Compulsive (n = 11), Avoidant (n = 3). The remaining 26 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 = 61.0 ± 7.2). Most subjects had a life history of at least one Axis I disorder (45 of 58) and half had a current history of at least one Axis I disorder (29 of 58). Current Axis I disorders were as follows: Any Mood Disorder (n = 7): major depression (n = 2), dythymia (n = 4), depressive disorder-nos (n = 2); Any Anxiety Disorder (n = 6), i.e., phobic (n = 3), and non-phobic (n = 4) anxiety disorder; Intermittent Explosive Disorder: IED by DSM-IV (n = 11), IED-R (n = 18), IED-IR (n = 19); Adjustment Disorder (n = 1); Somatoform Disorder (n = 1). Lifetime Axis I disorders were as follows: Any Mood Disorder (n = 23): major depression (n = 16), dysthymia (n = 5), depressive disorder-nos (n = 5); Any Anxiety Disorder (n = 10), i.e., phobic (n = 3), and non-phobic (n = 8) anxiety disorder; Alcohol Dependence (n = 14), Drug Dependence (n = 10); Intermittent Explosive Disorder: IED by DSM-IV (n = 15), IED-R (n = 21), IED-IR (n = 26); Adjustment Disorder (n = 5); Somatoform Disorder (n = 1).

2.3. General preparation for study

Only 10 of the 58 (17%) subjects had any lifetime history of exposure to psychotropic agents. In order of frequency, these agents fell into the following classes: anxiolytics (n = 8), antidepressants (n = 6), neuroleptics (n = 4), stimulants (n = 2), 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.

2.4. Platelet study

All blood samples for platelet study were obtained between 9:00 and 9:30 am through a 20 gage indwelling intravenous catheter that was in place for the purposes of other biological studies being performed in our unit. 20 cm^{3} of venous blood was collected in a plastic syringe and transferred to EDTA containing vacutainer collection tubes. As previously described, samples were processed and assayed for ^{3}H-Paroxetine Binding (Coccaro, et al., 1996), ^{125}I-LSD (Coccaro et al., 1997a, 1997b), and Platelet 5-HT Content (Goveas, et al., 2004), parameters.

2.5. Dimensional assessment of aggression, impulsivity, and other behavioral variables

Aggression was assessed dimensionally (in most, though not all subjects) using the Aggression scale of the Life History of Aggression (n = 48; Coccaro et al., 1997a). Impulsivity was assessed using the score of the Impulsivity scale from the Eysenck Personality Questionnaire (EPQ-II; n = 44; Eysenck and Eysenck, 1977). Secondary variables included general personality variables (i.e., neuroticism, psychoticism, and extraversion) from the original EPQ-I (n = 46; Eysenck and Eysenck, 1975). Global psychosocial function was assessed using the Global Assessment of Function (GAF; American Psychiatric Association, 1994).

2.6. Statistical analysis

Comparisons between groups were performed by *t*-test, with correction for unequal variances where necessary, or univariate/multivariate ANOVA/ANCOVA as appropriate. Correlational relationships were assessed by Pearson correlation, partial correlation, and multiple regression, where appropriate. All reported p-values are two-tailed. Values for Bmax for ^{3}H-Paroxetine binding, Bmax for ^{125}I-LSD binding, and 5-HT Content followed normal distributions. Further analysis revealed a significant correlation between Bmax