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Platelet serotonin content correlates inversely with life history of aggression in personality-disordered subjects

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Abstract

The objective of this study was to test the hypothesis that platelet serotonin (5-hydroxytryptamine, 5-HT) content is correlated with measures of aggression in healthy human subjects. Platelet 5-HT content (ng/mg protein) was measured in personality-disordered (PD) and normal control (NC) subjects. Aggression was assessed with the Life History of Aggression (LHA), the Buss–Durkee Hostility Inventory (BDHI), and the Motor Aggression and Research Criteria for Intermittent Explosive Disorder (IED-IR); impulsivity was assessed with the Eysenck Personality Questionnaire II (EPQII) and the Barratt Impulsiveness Scale (BIS-11). LHA Aggression, but not impulsivity, scores showed significant inverse correlations with platelet 5-HT content in all subjects or in PD subjects alone. The findings in PD subjects remained significant after co-varying for race. PD subjects with IED-IR had lower platelet 5-HT content compared with PD subjects who did not have IED-IR, although this finding only approached significance after controlling for race. This study demonstrates an association between reduced platelet 5-HT content and aggression in PD subjects. Similar to other studies of platelet 5-HT markers, these data suggest that platelet 5-HT content may also reflect central 5-HT alterations and may be used as a biological marker in appropriate patient samples.

Keywords: Personality; Impulsivity; 5-Hydroxytryptamine in platelets; Hostility

1. Introduction

Evidence of an inverse correlation between central serotonergic measures and impulsive-aggressive and/or suicidal behavior in human subjects has been reported over the past two decades (Coccaro, 1998). For example, inverse relationships between cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and measures of impulsive aggression have been demonstrated in male personality-disordered subjects (Brown et al., 1979, 1982), male violent offenders (Linnoila et al., 1983), and male alcoholics (Limson et al., 1991). Similarly, reduced CSF 5-HIAA concentrations have been reported in violent suicide attempters (Åsberg et al., 1976). These findings extend beyond the CSF compartment. Similar inverse relationships between hor-

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monal responses to acute serotonergic (5-hydroxytryptamine, 5-HT) challenge and measures of impulsive aggression have been demonstrated in personality-disordered subjects as well (e.g. Coccaro et al., 1989, 1997a,b; Moss et al., 1990; O'Keane et al., 1992).

Due to the methodological complexities associated with CSF and/or pharmacologic challenge studies, the assessment of 5-HT indices on blood platelets has been proposed as a proxy for central monoaminergic structure and function (Stahl, 1985; Da Prada et al., 1988). This proposal fell into disfavor in the late 1980s and early 1990s, largely due to the fact that platelets are not neurons and are not in the same microenvironment as neurons. However, recent data support the notion that platelet 5-HT measures have greater relevance to central 5-HT processes than previously thought. Structural identity between central and platelet serotonin transporters (Lesch et al., 1993), and 5-HT-2a receptor sites (Cook et al., 1994) has been reported. Further, relationships between platelet 5-HT indices and selected behaviors (e.g. aggression and suicide attempts) parallel those observed with central 5-HT indices. First, the observation of an inverse relationship between platelet 5-HT transporter sites and life history of aggression in personality-disordered subjects (Coccaro et al., 1996) parallels the observation of reduced 5-HT transporter binding in the midbrains of violent offenders as imaged by single photon emission computed tomography (SPECT) (Tiihonen et al., 1997). Second, the observation of increased platelet 5-HT2 receptor binding in suicide attempters (Biegon et al., 1994; Pandey et al., 1995) parallels the increased 5-HT2 receptor binding in the prefrontal cortex of violent suicide victims (Stanley and Mann, 1983; Arora and Meltzer, 1989).

Although there have been a number of studies in the area of peripheral 5-HT indices and psychiatric disorders, only a few have looked into the relationship between platelet 5-HT content and aggression, and all have been performed in children, adolescents and young adults. These studies found elevated platelet 5-HT content in impulsive adolescents (Askenazy et al., 2000), violent conduct-disordered adolescents (Unis et al., 1997) and conduct-disordered juvenile offenders (Pliszka et al., 1988) compared with healthy controls. In young adults, a recent report notes elevated platelet 5-HT content in 21-year-old violent males (Moffitt et al., 1998). While seemingly at variance with the expected inverse relationship between 5-HT and aggression (Coccaro, 1998), many studies of young subjects have demonstrated correlations between selected measures of aggression and 5-HT function that are positive rather than inverse in nature (Castellanos et al., 1994; Halperin et al., 1997; Pine et al., 1997). In contrast to studies in young subjects, most studies in adults have examined the relationship between platelet 5-HT content and suicidal behavior and report a negative correlation between these parameters. Across four studies, low platelet 5-HT content is reported as a function of suicide attempt history in depressed patients (Mann et al., 1992; Muck-Seler et al., 1996) and in a variety of patients with history of violent suicide attempt (Alvarez et al., 1999; Spreux-Varoquaux et al., 2001). In contrast, one study reported a positive relationship between platelet 5-HT content and future suicidal behavior in a mostly personality-disordered group of suicide attempters (Verkes et al., 1997) and one study reported a similarly positive relationship with aggression and comorbid borderline personality disorder in patients with major depressive disorder (Mann et al., 1992).

Despite the relevance of aggression and suicidal behavior to personality disorder, no studies have examined the relationship between platelet 5-HT content and aggression or impulsivity in a group of well-characterized personality-disordered adults. Based on previous data demonstrating inverse relationships between measures of 5-HT and aggression (Coccaro, 1998), we hypothesized that platelet 5-HT content would correlate inversely with measures of aggression in adult personality-disordered subjects.

2. Methods

2.1. Subjects

The subjects in this report were 77 physically healthy outpatient (66 male and 11 female) subjects diagnosed with one or more DSM-IV

(American Psychiatric Association, 1994) personality-disordered (PD) and 30 psychiatrically healthy (25 male and five female) controls (HC) with no documented psychopathology. All subjects were systematically evaluated for aggressive, suicidal, self-injurious, and other behaviors as part of a larger program designed to study the biological correlates of impulsive-aggressive behavior in personality-disordered and healthy volunteer subjects. Subjects with personality disorders were recruited from newspaper advertisements seeking out individuals who considered themselves to have difficulty controlling their aggressive tendencies and other individuals willing to participate in biological studies of personality. Healthy volunteers were also recruited by newspaper advertisement. Written informed consent, using an IRB-approved consent document, was obtained from all subjects after all procedures had been fully explained.

2.2. Diagnostic and medical assessment

Axis I and II diagnoses were made according to DSM-IV criteria. Alcoholism was diagnosed with modified Research Diagnostic Criteria as in our previous reports (Coccaro et al., 1996). In addition, a research diagnosis of Intermittent Explosive Disorder-Integrated Revised (IED-IR) was also made (Coccaro et al., 1998; Coccaro, 2003). These criteria differ from DSM-IV criteria in that IED-IR (a) requires a minimum of two impulsive-aggressive outbursts per week for at least 1 month or a minimum of three severe impulsive-aggressive outbursts in any given year; (b) includes verbal and non-destructive aggressive behavior if associated with subjective distress or functional impairment; and (c) does not exclude borderline or antisocial personality disorder. A recent analysis of IED-IR and non-IED-IR subjects in our program confirmed that IED-IR subjects were significantly more impulsive-aggressive and less functional than non-IED-IR subjects (Coccaro, 2003). Final diagnoses were assigned by team best-estimate consensus procedures as previously described (Coccaro et al., 1996). Diagnoses were made using information from (a) semi-structured interviews by trained clinicians using the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott, 1978) or the Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1996) and the Structured Interview for the Diagnosis of DSM Personality Disorder (Pfohl and Zimmerman, 1989, 1994); (b) clinical interview by a research psychiatrist; and (c) review of all other available clinical data. Personality-disordered subjects with a life history of bipolar disorder, schizophrenia, or other psychotic disorders were excluded from study entry. All healthy control subjects were without any lifetime DSM-IV Axis I or II disorder.

Thirty-nine of the 77 personality-disordered subjects met DSM-IV criteria for a specific personality disorder as follows: (a) Cluster A ($n=20$): paranoid ($n=15$), schizoid ($n=7$) and schizotypal personality ($n=2$); (b) Cluster B ($n=19$): antisocial ($n=9$), borderline ($n=8$), histrionic ($n=5$) and narcissistic personality ($n=9$); (c) Cluster C ($n=14$): avoidant ($n=3$) and obsessive-compulsive personality ($n=13$). The remaining 38 subjects met criteria for personality disorder not otherwise specified (NOS). These subjects met criteria for multiple personality disorder traits and had evidence of diminished psychosocial function (mean Global Assessment of Functioning score = 59.8 ± 8.6). Thirty-six personality-disordered subjects had a current Axis I disorder. These were as follows: (a) unipolar mood disorder ($n=8$): major depression ($n=2$) and dysthymia ($n=6$); (b) anxiety disorder ($n=6$): social phobia ($n=2$), simple phobia ($n=2$), and generalized anxiety disorder ($n=4$); (c) adjustment disorder ($n=1$); (d) somatoform disorder ($n=1$). In addition, 25 subjects met research criteria for current IED-IR. Finally, 56 PD subjects had a lifetime history of an Axis I disorder as follows: (a) unipolar mood disorder ($n=30$): major depression ($n=19$) and dysthymia ($n=7$); (b) anxiety disorder ($n=11$): social phobia ($n=3$), specific phobia ($n=3$), panic disorder ($n=2$) and generalized anxiety disorder ($n=5$); (c) substance use disorder ($n=35$): alcoholism ($n=20$) and other drug use disorder ($n=18$); (d) adjustment disorder ($n=7$); (f) somatoform disorder ($n=1$); and (e) IED-IR ($n=32$).

Medical health of all subjects was documented by comprehensive medical history, physical exam-

ination, electrocardiogram, and a variety of clinical laboratory studies such as complete blood picture (including platelets), serum chemistry analysis (including hepatic profile), thyroid function tests, and urinalysis (including a urine screen for drugs of abuse). Subjects were excluded from the study if they had any clinically significant medical (including hematological) condition, whether or not medication was required.

2.3. Assessment of aggression, impulsivity and other behavioral variables

Aggression was assessed dimensionally using the Life History of Aggression (LHA; Coccaro et al., 1998) Assessment and the Motor Aggression scale of the Buss–Durkee Hostility Inventory (BDHI; Buss and Durkee, 1957). Impulsivity was measured with the Impulsivity Subscale of the Eysenck Personality Questionnaire II (EPQII; Eysenck et al., 1985) and the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). General personality dimensions were assessed using the subscales of the Eysenck Personality Questionnaire I (EPQ I; Eysenck and Eysenck, 1975) and the remaining subscales of the EPQ II. History of suicide attempt was assessed during the diagnostic assessment as described above. Trait anxiety was assessed using the 20-item Spielberger Trait Anxiety Scale (STAS; Spielberger, 1983). The Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) scale was used to assess average psychosocial functioning over the previous year.

2.4. Platelet studies

All subjects were unmedicated and instructed to remain drug-free for at least 2 weeks before the study, to follow a low monoamine diet for at least 3 days before the study and to fast, without smoking, after midnight the night before the study. Female subjects were all studied within the first 10 days of the follicular phase of their menstrual cycle. After these preparatory procedures, subjects reported to the Clinical Procedures Laboratory at approximately 08.00 h after an overnight fast. At approximately 08:30 h., an intravenous (IV) line was inserted into a forearm vein and kept open by a slow saline drip. The IV catheter was placed for the purpose of repeated venipuncture during the context of a pharmacologic challenge procedure. All blood samples for the platelet 5-HT study were obtained in a plastic syringe between 09.00 and 09.30 h before the administration of any medication. Twenty milliliters of venous blood were collected and immediately transferred to a tube containing ethylenediaminetetraacetic acid (EDTA). Samples were kept at room temperature and processed to obtain platelet pellets within 3 h. Platelet harvesting was performed as previously described (Coccaro et al., 1996) with the immediate freezing of platelet pellets on dry ice and subsequent storage at -70 °C until assay in the laboratory of one of the coauthors (JGC) at Washington University School of Medicine. Samples for platelet 5-HT content were assayed by high pressure liquid chromatography with electrochemical detection (HPLC-EC), as previously described (Whiteford et al., 1993), without knowledge of the diagnostic status of the subject or any of the behavioral data. Intra- and inter-assay coefficients of variation were $<8\%$.

2.5. Statistical analysis

The primary biological variable in this study was platelet 5-HT content. Platelet 5-HT content did not deviate from normality (Kolmogorov-Smirnov $Z=0.92$, $P=0.36$), and these data were used without transformation. LHA Aggression and IED-IR were employed as primary dimensional and categorical aggression variables, respectively; BDHI Motor Aggression and History of Suicide Attempt were employed as secondary aggression variables. EPQ-II Impulsivity was employed as the primary impulsivity variable; BIS-11 Impulsivity was used as a secondary impulsivity variable. Tertiary/control variables included EPQ I Neuroticism, Psychoticism, and Extraversion; EPQ II Venturesomeness and Empathy; and Spielberger Trait Anxiety. Initial analyses employed Pearson correlations to examine the relationship between platelet 5-HT content and the primary, secondary, tertiary and GAF scores. Group differences in

Table 1
Demographic, biological, and behavioral data on subjects

Variable (*N*)	NC (*N*=30)	PD (*N*=77)	Test statistic	d.f.	*P*
Age (years):	28.8±6.9	34.2±9.4	$t=-2.85$	105	0.005
Race:			$x^2=11.41$	1	NS
% White (61)	56.7% (17)	57.1% (44)			
% Non-white (41)	43.3% (13)	42.9% (33)			
Male/Female:	25/5	66/11	$x^2=0.096$	1	0.756
GAF score:	84.2±5.3	59.8±8.6	$t=14.55$	105	0.000
Platelet 5-HT content (ng/mg protein):	1287.86±654.54	1235.30±833.61	$t=0.310$	105	0.757
Aggression:					
LHA (88)	5.00±4.0 (25)	11.05±7.04 (63)	$t=-4.03$	86	0.000
BDHI (94)	12.85±6.9 (26)	23.01±10.02 (68)	$t=-4.75$	92	0.000
Impulsivity:					
EPQ II (89)	4.26±3.24 (27)	7.39±4.54 (62)	$t=-3.23$	87	0.000
BIS-11 (87)	57.42±7.47 (26)	64.18±9.91 (61)	$t=-3.12$	85	0.002
Other:					
Spielberger Trait Anxiety (88)	31.59±6.97 (27)	40.25±12.36 (61)	$t=-3.40$	86	0.000

categorical variables were tested by chi-square, and group differences in continuous variables were tested by *t*-test with follow-up multivariate analysis of variance (ANOVA) and partial correlation analyses as appropriate. Probability levels were set at a two-tailed alpha value of 0.05.

3. Results

Table 1 presents demographic, biological, and behavioral data for both the normal control and personality-disordered subjects. Group differences were found in age and, as expected, in dimensional measures of psychopathology and GAF. Regardless, no differences were noted in platelet 5-HT content between the groups.

3.1. Relationship between platelet 5-HT content and aggression expressed dimensionally and categorically

Despite the lack of a difference in platelet 5-HT content between the groups, an inverse relationship between platelet 5-HT content and LHA Aggression was found among all subjects ($r=-0.27$, $n=88$, $P=0.012$). This relationship was due to the inverse correlation in the personality-disordered sample ($r=-0.34$, $n=63$, $P=0.007$; Fig. 1) and not in the normal control sample ($r=-0.09$, $n=25$, $P=0.67$). Within the personality-disordered group, platelet 5-HT content was also reduced as a function of the lifetime diagnosis of IED-IR (IED-IR: 940.64±135.01 ng/mg protein vs. non-IED-IR: 1430.53±115.14 ng/mg protein, $P=0.02$). Despite the moderately strong relationship between LHA and BDHI Motor Aggression ($r=0.60$, $n=60$, $P<0.001$) in these subjects, the correlation with BDHI Motor Aggression was smaller in magnitude and did not quite reach statistical significance ($r=-0.22$, $n=68$, $P=0.071$). Finally, while platelet 5-HT content was lower as a function of history of suicide attempt, this result was not statistically significant (SA+: 1036.9±985.3 ng/mg protein vs. SA−: 1261.6±816.3 ng/mg protein; $t_{75}=0.76$, $P=0.45$).

Across all subjects, platelet 5-HT content varied significantly as a function of race (white: 939.4±686.7 ng/mg protein vs. non-white: 1662.0±720.0 ng/mg protein: $F_{1,98}=22.34$, $P<0.001$) but not as a function of age, gender, socioeconomic status, GAF score, season of study, or smoking status. While subsequent analyses, controlling for race, reduced the significance level of the platelet 5-HT content/LHA Aggression

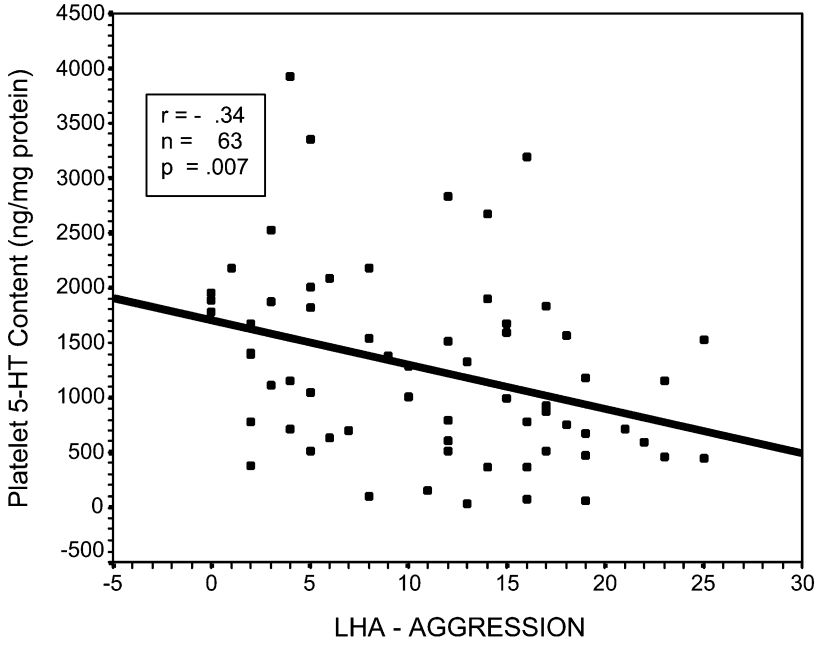

Fig. 1. Inverse correlation between platelet 5-HT content (raw data) and life history of aggression in 63 personality-disordered subjects.

relationship in the full sample to a trend ($r_{partial} = -0.20$, d.f. = 85, $P = 0.060$), this relationship remained statistically significant in the personality-disordered sample ($r_{partial} = -0.28$, d.f. = 60, $P = 0.028$). ANOVA using lifetime IED-IR and race as separate factors reduced the significance level for this analysis to that of a trend ($F_{1,73} = 3.44$, $P = 0.068$). Finally, analysis of data in the personality-disordered sample revealed no significant relationships between platelet 5-HT content and lifetime (or current) anxiety disorder, substance (alcoholism or non-alcoholic) use disorder or any of the three personality disorder clusters. While significant, or near significant, relationships were found between platelet 5-HT content and current ($t_{75} = 1.68$, $P < 0.10$) or lifetime ($t_{75} = 2.79$, $P < 0.01$) unipolar mood disorder (major depression or dysthymia), these relationships were due to a shared relationship with race (e.g. race: $F_{1,70} = 9.72$, $P = 0.003$ vs. Lifetime Mood Disorder: $F_{1,70} = 1.83$, $P = 0.18$).

3.2. Relationship between platelet 5-HT content and impulsivity and related personality/behavioral variables

Despite the significant relationships between LHA Aggression and EPQ-II Impulsivity in the personality-disordered sample ($r = 0.40$, $n = 53$, $P = 0.003$), platelet 5-HT content did not correlate with impulsivity assessed by EPQ II ($r = -0.05$, $n = 62$, $P = 0.71$) or BIS-11 ($r = -0.12$, $n = 61$, $P = 0.37$). Platelet 5-HT content also did not correlate with general personality variables such as EPQ-I Neuroticism, Psychoticism, or Extraversion ($r = -0.07$, 0.07 and -0.02, respectively) or EPQ-II Venturesomeness or Empathy ($r = -0.14$ and 0.10, respectively). Finally, platelet 5-HT content did not correlate with Spielberger Trait Anxiety ($r = -0.11$, $n = 61$, $P = 0.41$).

4. Discussion

These results provide evidence for an inverse relationship between platelet 5-HT content and life

history of aggression (but not impulsivity), assessed both dimensionally and categorically, in personality-disordered subjects. Although platelet 5-HT content has been reported to vary as a function of a variety of factors such as age (Jernej et al., 2000), gender (Muck-Seler et al., 1996), cigarette smoking (Racke et al., 1992) and season of study (Sarrias et al., 1989), platelet 5-HT content did not vary as a function of any of these variables in the present group of subjects. Platelet 5-HT content also did not vary as a function of global psychosocial functioning or as a function of most Axis I and II disorders. Platelet 5-HT content did vary as a function of race in this sample, with platelet 5-HT content being lower in whites than in non-white subjects. This observation is consistent with that of at least one previous study (Pfeffer et al., 1998). Regardless, the relationship between platelet 5-HT content and LHA Aggression continued to be statistically significant after accounting for the influence of race; the relationship with IED-IR was reduced to a statistical trend after controlling for race, consistent with the fact that categorical variables are statistically less powerful than dimensional variables. Finally, while personality-disordered subjects with life histories of unipolar mood disorder had lower platelet 5-HT content than personality-disordered subjects without such a history (and as consistent with Mann et al., 1992), this difference was fully accounted for by the variation in platelet 5-HT content associated with race.

The inverse relationship between platelet 5-HT content and LHA Aggression scores is consistent with the finding of an inverse relationship between the number of platelet 5-HT transporter sites in personality-disordered subjects (Coccaro et al., 1996) and the observation of an inverse correlation between platelet 5-HT uptake (V_{max}) and Barratt Impulsivity scores in male outpatients with episodic aggression (Brown et al., 1989). Taken together, these findings suggest that decreased platelet 5-HT content in these types of subjects may result from dysfunctional platelet 5-HT uptake. This finding is also consistent with low platelet 5-HT content reported as a function of suicide attempt history in depressed patients (Mann et al., 1992; Muck-Seler et al., 1996) and in a variety of patients with history of violent suicide attempt (Alvarez et al., 1999; Spreux-Varoquaux et al., 2001) since suicidal behavior is typically correlated with aggressive behavior (Brown et al., 1982; Coccaro et al., 1989). While we did not observe a statistically significant difference in platelet 5-HT content as a function of suicidal behavior, the small number of suicidal subjects in the sample did demonstrate a modest reduction in platelet 5-HT content compared with non-suicidal subjects. Given the effect size of this difference (0.27 S.D.), however, the number of subjects required for this study to demonstrate a statistically significant difference in this parameter, with 80% power, would have been 440.

However, these findings are in contrast to those reported in impulsive (Askenazy et al., 2000) and conduct-disordered (Pliszka et al., 1988; Unis et al., 1997) adolescents and in 21-year-old adults with significant histories of aggression (Moffitt et al., 1998). While several methodological issues (e.g. differences in sample size and use of different measures) may account for this disparity, the most salient factor is likely developmental in nature, since relationships between measures of central 5-HT function and aggression are typically reversed as a function of age. That is, while the 5-HT/aggression relationship is typically inverse in adult samples, this relationship is typically direct in younger samples (Castellanos et al., 1994; Halperin et al., 1997; Pine et al., 1997). While this may not appear to fully explain the variance of this report with that of the study of Moffitt et al. (1998) exclusively involving 21-year-old males, the subjects of the present study were considerably older than those in the study of Moffitt et al. (mean: 34.2 ± 9.4 vs. 21 years). In addition, the assessment of aggression in this study included behaviors that occurred long after the subjects were 21 years of age, and this, too, may have affected the results.

While we found a significant correlation between LHA aggression scores and platelet 5-HT content, no significant relationships were noted with impulsivity or other personality or behavioral variables assessed. Although this is not consistent with one recent study reporting a direct correlation between platelet 5-HT content and a dimensional

measure of impulsivity in adolescents, it is consistent with the absence of a platelet 5-HT content/impulsivity relationship reported in two other studies in the adult literature (Alvarez et al., 1999; Spreux-Varoquaux et al., 2001). It is also consistent with the absence of correlation between platelet [^{3}H]paroxetine binding parameters and impulsivity scores in similar personality-disordered subjects (Coccaro et al., 1996).

The interpretation of platelet 5-HT content levels as a peripheral index of central serotonergic function should be made with caution because the microenvironment of central neurons is absent in circulating platelets. However, reports indicating that the structure of the 5-HT transporter of neurons and platelets is identical (Lesch et al., 1993), and that the uptake of 5-HT into platelets is a direct function of the number of platelet 5-HT transporter sites (Maguire et al., 1993), provide support for the idea that the content of 5-HT in the peripheral blood platelet may reflect central 5-HT processes, at least in terms of a trait characteristic of central 5-HT function. Given these considerations, the present data may be consistent with other findings of an inverse relationship between central 5-HT indices and aggression in selected samples of psychiatric subjects (e.g. Brown et al., 1979, 1982; Linnoila et al., 1983; Coccaro et al., 1989). Accordingly, a reduction in platelet 5-HT content may suggest reduced 5-HT uptake by platelets secondary to a reduction in platelet 5-HT transporter sites (Coccaro et al., 1996). If a similar explanation is applied to central serotonergic neurons, reduced uptake of 5-HT into 5-HT neurons, secondary to a reduction of neuronal 5-HT transporter sites, may be associated with reduced turnover of 5-HT to 5-HIAA (e.g. reduction in CSF 5-HIAA levels as reported in aggressive subjects; Brown et al., 1979, 1982; Linnoila et al., 1983). This hypothesis is consistent with the fact that blockade of 5-HT uptake by selective serotonin reuptake inhibitors results in a reduction in CSF 5-HIAA concentrations (De Bellis et al., 1993) and in a reduction in platelet 5-HT content (Alvarez et al., 1999).

In conclusion, platelet 5-HT content was inversely correlated with life history of aggression in personality-disordered subjects. This finding may reflect parallel alterations in central 5-HT system function as suggested by other, more invasive measures of 5-HT function (e.g. Linnoila et al., 1983; Coccaro et al., 1989; Tiihonen et al., 1997; Siever et al., 1999). If so, the assessment of platelet 5-HT content may serve as a viable alternative to more invasive measures of 5-HT function in studies where large numbers of subjects are required for study (e.g. large family/pedigree, epidemiological survey, or twin studies) and/or in subjects where more invasive assessments of 5-HT function are neither practical nor desirable (e.g. studies of small children).

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