Whole Blood Serotonin Relates to Violence in an Epidemiological Study

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Background: *Clinical and animal studies suggest that brain serotonergic systems may regulate aggressive behavior; however, the serotonin/violence hypothesis has not been assessed at the epidemiological level. For study of an epidemiological sample we examined blood serotonin, because certain physiological and behavioral findings suggested that it might serve as an analog marker for serotonergic function.*

Methods: *Whole blood serotonin was measured in a representative birth cohort of 781 21-year-old women (47%) and men (53%). Violence was measured using cumulative court conviction records and participants' self-reports. Potential intervening factors addressed were: gender, age, diurnal variation, diet, psychiatric medications, illicit drug history, season of phlebotomy, plasma tryptophan, platelet count, body mass, suicide attempts, psychiatric diagnoses, alcohol, tobacco, socioeconomic status, IQ, and overall criminal offending.*

Results: *Whole blood serotonin related to violence among men but not women. Violent men's mean blood serotonin level was 0.48 SD above the male population norm and 0.56 SD above the mean of nonviolent men. The finding was specific to violence, as opposed to general crime, and it was robust across two different methods of measuring violence. Together, the intervening variables accounted for 25% of the relation between blood serotonin and violence.*

Conclusions: *To our knowledge, this is the first demonstration that an index of serotonergic function is related to violence in the general population.* Biol Psychiatry 1998;43:446–457 *© 1998 Society of Biological Psychiatry*

Key Words: Serotonin, violence, aggression, platelet

Introduction

The serotonin (5-HT) system has been postulated to constrain or inhibit behavior (Depue and Spoont 1986; Soubrie 1986). Diminished serotonergic function is thought to disinhibit aggression against the self and others, perhaps by sharpening sensitivity to stimuli that elicit aggression and blunting sensitivity to cues that signal punishment (Plutchik and Van Praag 1989; Spoont 1992). This study was prompted by clinical reports that dysfunction of the serotonergic system of the brain compromises the regulation of human aggressive behavior (Coccaro 1989; Eichelman 1993; Virkkunen and Linnoila 1993). Technological developments in the measurement and interpretation of serotonin in whole blood allowed us to conduct the first test of the serotonin/violence hypothesis in an epidemiological sample. Although blood serotonin and brain serotonin differ in origin and function, they are connected by similarities in metabolic production, degradation, and storage. Thus the ease of measuring blood serotonin enabled us to test the hypothesis that whole blood serotonin would differ between young adults in the general population who have committed violent crimes and their nonviolent age peers.

The serotonin/aggression hypothesis has been studied in vivo among clinical subjects using three primary indices of serotonergic function: the primary serotonin metabolite in cerebrospinal fluid (CSF) [5-hydroxyindoleacetic acid (5-HIAA)], endocrine responses to drug challenges, and serotonin in blood (platelet 5-HT, whole blood 5-HT, or platelet 5-HT uptake). Although many experiments have shown that manipulations of the serotonergic system can influence aggression in rodents (Cases et al 1995; Eichelman 1993; Pucilowski and Kostowski 1983; Spoont 1992) and nonhuman primates (Brammer et al 1991; Chamberlain et al 1987), reviews of the few such experimental studies with human patients describe results as inconclusive (Coccaro 1989; Virkkunen and Linnoila 1993). In studies using nonexperimental designs, CSF 5-HIAA has been related to scales measuring hostility among normals (Roy et al 1988) and has been reported to discriminate between aggressive patients and matched controls (Coc-

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caro 1989; Virkkunen et al 1994a, 1994b). Within clinical samples of aggressive patients low CSF 5-HIAA has been empirically linked with impulsive varieties of antisocial behavior and has been shown to differentiate alcoholic, personality-disordered, and suicidal subgroups (Brown et al 1982a; Schalling 1993). Moreover, two longitudinal follow-up studies of patient samples have demonstrated that variation in CSF 5-HIAA can predict aggression over the course of 2–3 years in children (Kruesi et al 1992) and adults (Virkkunen et al 1989a). In research that assesses the serotonin system by challenging it with drugs such as fenfluramine, blunted plasma prolactin responses to the fenfluramine challenge have been linked to patients' suicide, alcohol history, and aggressive personality (Coccaro et al 1989), to antisocial personality disorder (Moss et al 1990; O'Keane et al 1992), and to problem behavior among family members of patients (Coccaro et al 1994). Blood studies have been far fewer and findings less consistent (Rogeness et al 1982), but blood 5-HT measures have been reported to relate positively to aggression in groups of inpatients with depression (Mann et al 1992), hyperactivity (Cook et al 1995), conduct disorder (Pliszka et al 1988; Unis et al in press), and episodic problem behavior (Brown et al 1989). These findings encouraged us to examine whole blood serotonin and violence in a human representative sample.

To date, the human samples used to test the serotonin/violence hypothesis have been constrained to inpatients as a consequence of the exacting and intrusive procedures and ethical considerations inherent in studying CSF 5-HIAA or conducting drug challenges. As a result, prior studies have had to rely on relatively small samples, which are further divided into multiple comparison groups (an average of 28 subjects and 4.6 comparison groups per report), perhaps compromising statistical power and heightening the risk of deductive error by conducting many statistical tests on few subjects. Not all studies of the serotonin/violence relation report consistent findings, and reviews implicate sampling as a source of the inconsistencies (Berman et al in press; Coccaro 1989). Analyses of variation within a patient sample can be distorted by the restricted range of scores, sometimes producing inaccurate estimates of the sensitivity of a biological marker (Berk 1983; Rasmusson et al 1990). Clinical studies that use matched nonpatient controls risk deductive error by failing to represent the healthy population as faithfully as they represent the population of patients (Mednick 1978). Further, clinical samples are known to be vulnerable to selection bias that may compromise the generalizability of findings (Cohen and Cohen 1984; Ransohoff and Feinstein 1978). A test of the serotonin/violence hypothesis in an epidemiological sample provides a timely complement to the clinical literature by addressing these methodological concerns about the external validity of clinical samples. Such a study can also provide new information about how abnormal the whole blood serotonin status of violent individuals is, when compared against the critical comparison standard of norms for the general population (Rasmusson et al 1990).

A test of the serotonin/violence hypothesis in an epidemiological sample was made feasible by the relative ease of sampling whole blood, which unlike CSF can be obtained from nonpatients. Serotonin in whole blood can be assayed quickly, inexpensively, and accurately (Yuwiler et al 1970). The assays are highly reliable; repeated measures show small intraindividual and large stable interindividual variation (Yuwiler et al 1981). As for interpretation (Anderson et al 1987; Hanna et al 1991; Unis et al in press), central serotonin indicators such as levels of 5-HIAA in CSF have generally related negatively to measures of aggressive behavior, whereas concentrations of serotonin in blood have generally related positively to aggressive behavior. This pattern has been reported consistently for samples of adults [although a recent review points out that serotonin studies of children yield less consistent findings (Pine et al 1996)]. In this study of adults then, we tested the hypothesis that violent adults would have higher concentrations of whole blood serotonin than nonviolent adults.

In this epidemiological study, measures of violence differ from the measures used in clinical studies. Clinical studies have variously defined aggression as high scores on personality checklists tapping irritable or hostile attitudes, as observed aggressive actions on the inpatient ward, or sometimes on the basis of the violent infraction that precipitated the current hospitalization or incarceration. Personality checklists and inpatient ward behaviors bear imperfect or unknown relations to potential for criminal violence in the streets or at home. Designations of violence that are based on the current infraction do establish the consequential nature of the violent offense, but they are subject to misclassification if the complete violent offending history is not assessed (Rasmusson et al 1990). In the present study, violence was assessed using cumulative court records of conviction from age 13 to age 21; age 21 is just past the peak age of risk for violent offending (Elliott et al 1986). Violence was also assessed by self-report interviews to allow study of the substantial number of repetitively violent individuals in the population who escape official identification (Elliott et al 1986). Thus, to supplement prior clinical samples, this research included violent individuals who have not, as well as who have, been convicted, incarcerated, or treated psychiatrically for their violent behavior. Because conviction records and self-reports suffer complementary measurement biases, the use of both in tandem affords the most

effective empirical strategy for violence research (Hirschi et al 1980).

This research was conducted as part of the Dunedin Multidisciplinary Health and Development Study; the multidisciplinary assessment design of the larger study allowed us systematically to examine a number of variables that might influence the serotonin/violence relation. Men and women were studied, to redress the dearth of studies of serotonin and violence among women (Raine 1993). Factors known or suspected to influence concentrations of whole blood serotonin were evaluated, including use of psychiatric medications, illicit drugs or tobacco (Mann et al 1992), season of venipuncture (Arora et al 1984; Badcock et al 1987; Brewerton et al 1988), blood platelet count (Ritvo et al 1971), and blood concentration of the precursor tryptophan (Chamberlain et al 1987; Fernstrom and Wurtman 1971). We examined body mass because it has been hypothesized that, if larger individuals are more likely to be violent, the serotonin/violence relation may be an artifact of the link between serotonin and somatostatin, a hormone that influences body mass (Raine 1993). Suicide attempts were assessed in an effort to place this research in the context of clinical studies reporting that serotonin relates to violence against the self as well as against others (Asberg et al 1986; Coccaro et al 1989; Nielson et al 1994). Psychiatric diagnoses were examined because serotonin has been linked to several disorders (van Kammen 1987). Alcohol dependence was examined because it has been shown to relate specifically to serotonin within antisocial clinical samples (Coccaro et al 1989; Linnoila et al 1983). Two known powerful correlates of violence (Lynam et al 1993) were also studied, socioeconomic status and IQ test scores, to ascertain their relation to whole blood serotonin. Finally, we tested the serotonin/violence hypothesis while controlling for frequency of overall criminal offending because virtually all violent offenders have lengthy careers of nonviolent property crime. Nonviolent crimes must be statistically controlled as a test to establish that a biological marker has specificity for violent behavior, as opposed to being more generally associated with an antisocial or illicit lifestyle.

Methods and Materials

Sample

Participants in this study were the 21-year-old members of an unselected cohort, born between April 1, 1972 and March 31, 1973 in a New Zealand city of approximately 120,000 inhabitants, and studied since birth in the Dunedin Multidisciplinary Health and Development Study. The history of the study has been described elsewhere (Silva 1990; Silva and Stanton 1996). This report presents findings from the most recent assessment, when the study members were 21 years old, conducted during 1993–1994. The investigation's standard procedure involves bringing participants to the Research Unit near their birthday for a full day of individual interviews, examinations, and laboratory studies presented as 50-min modules in counterbalanced order (e.g., IQ test, diagnostic mental health interview, physical examination, delinquency interview). Study members incarcerated for offending are brought to the research unit under guard or assessed at the unit after parole. Self-report interviews with participants are supplemented and validated by a search of official records and by questionnaires mailed to informants who know each participant well. Because confidentiality has never been violated, study members are by now willing to provide frank interview responses.

The base sample for the study comprises the 1037 individuals originally enrolled (52% male and 48% female). At age 21, 97% of the living study members participated, and blood serotonin samples were obtained from 781 participants, a compliance rate of 82% (17 subjects had died since infancy, 9 were not located, 19 refused the entire study, 42 were interviewed in the field where blood samples could not be taken, 169 came to the Unit but declined venipuncture). The original sample was representative of New Zealand's South Island in family socioeconomic status and in Caucasian European ethnicity; only 2% of participants were identified by their mothers at birth as half or full Polynesian. The sample of 781 individuals for the blood serotonin study did not differ from the unstudied members of the birth cohort on gender (chi-square = 1.4, $p > .20$), family socioeconomic status ($t = 1.2$, $p > .20$), or criminal conviction (chi-square = 0.66, $p > .40$).

Whole Blood Serotonin

Assays were performed on blood samples collected by venipuncture between 4:00 and 5:00 PM at the end of the 8-hour assessment day (with lunch served) that occurred within 60 days of each participant's 21st birthday. Thus, although laboratory studies suggest that whole blood serotonin is not affected after puberty by age (Badcock et al 1987; Ritvo et al 1971; Siefert et al 1980), recent diet (Badcock et al 1987; Kremer et al 1990; Ritvo et al 1970), or diurnal variation or activity level (Badcock et al 1987; Kremer et al 1990), these factors were controlled because not all reports agree (Wirz-Justice et al 1977). The blood was collected into lithium heparin (Vacutainer) tubes and stored in the dark at −20°C until the time of assay, from 1 to 12 months later. Storage under these conditions does not affect whole blood serotonin concentrations (Badcock et al 1987).

Blood 5-HT concentration was determined using a high-performance liquid chromatography (HPLC) procedure (Brammer, unpublished manuscript) that bears an essentially 1:1 relation to the fluorometric assay of Yuwiler et al (1970). A 100-μL portion of whole blood was diluted with 750 μL 3% freshly prepared ascorbic acid, and the mixture was treated with 100 μL 4 mol/L perchloric acid. The tubes were vortexed for 1 min and then centrifuged (13,000 $g \times 5$ min). The supernatant was withdrawn and held on ice until examination by liquid

chromatography. A mobile phase was prepared from an aqueous component of 33 mmol/L acetate, 33 mmol/L citrate, 33 mmol/L phosphate, and 0.27 mmol/L edetic acid (EDTA) adjusted to pH 4.1 with sodium hydroxide, which was then 0.2-μm filtered, and mixed with acetonitrile to 7%. A flow rate of 1.0 mL/min was maintained, and 50 μL of sample supernatant was injected. Serotonin was well resolved from tryptophan and tyrosine on an ODS analytical column (4.6 × 150 mm, 5-μm particle) and detected by fluorescence at 283-nm excitation and 330-nm emission. External standards were treated the same as samples. Results are expressed as ng serotonin per mL whole blood. In quality-control tests for this study, the within-day coefficient of variation (CV) was 4.3% (96.6 ± 4.2 ng/mL, $n = 20$). The between-day CV for a quality-control blood sample was 3.6% (119.8 ± 4.2 ng/mL, $n = 5$). The average between-day CV for 9 patients' blood samples taken on five occasions was 5.8% (range 3.1–7.8%), and recovery of added serotonin at low and high standards was greater than 97%.

Court Records

Court conviction criminal records for all courts in New Zealand and Australia were obtained by searching the central computer system of the New Zealand police, revealing that 141 study members had been convicted for some offense(s) by age 21. Of the sample members who had provided blood samples, 31 (26 men and 5 women) had been convicted of one or more of the following violent crimes: inciting or threatening violence ($n = 17$ incidents), using an attack dog on a person ($n = 1$), presenting an offensive weapon ($n = 13$), threatening a police officer ($n = 5$), rape ($n = 2$), manual assault ($n = 25$), assault on a police officer ($n = 5$), assault with a deadly weapon ($n = 5$), aggravated robbery ($n = 1$), and homicide ($n = 1$).

Self-Reports

Self-reports of criminal offenses committed during the past year were obtained in private standardized interviews at age 21 using the respected Self-Report Delinquency Interview developed for the U.S. National Youth Survey and National Institute of Justice multisite surveys (Elliott and Huizinga 1989). The interview assessed 41 different illegal offenses. In the Dunedin sample it yields an internal reliability alpha of .88, a 1-month test–retest reliability correlation of .85, and moderate correlations with informant reports and conviction records (Moffitt et al 1994). Serotonin assays and court conviction records were obtained only after all subjects had been interviewed, and thus self-report measures were blind and independent. Of the sample members who had provided blood samples, the 50 (36 men and 14 women) designated as self-reported violent participants had reported at least two of the following in the past 12 months: "attacked someone you lived with, with a weapon or with the idea of seriously hurting or killing them" ($n = 11$ study members), "attacked someone else with a weapon or with the idea of seriously hurting or killing them" ($n = 13$), "hit someone you lived with" ($n = 33$), "hit someone else" ($n = 39$), "used a weapon, force, or strongarm methods to rob a person" ($n = 2$), "were involved in a gang fight" ($n = 18$).

Potential Intervening Variables

On the basis of prior research, we examined 15 variables that might influence the serotonin/violence relation. *Psychiatric medications* taken in the past 12 months were recorded from study members' self-reports during the age-21 mental health interview. Medication was taken for a mental disorder by 4.1% of study members. *Illicit drug use history* was assessed by age-21 self-report of drugs used during the past 12 months: marijuana, stimulants, sedatives, cocaine, heroin, opiates, 1-(1-phenylcyclohexyl)piperidine/methylenedioxyamphetamine, psychedelics, inhalants, or other. Scores ranged from 0 to 10 drugs, with 20% of the sample using two or more types of drugs. *Season* of venipuncture was ascertained from subject's appointment date. *Tryptophan* assays were conducted as part of the assay for serotonin (Brammer, unpublished manuscript). Quality-control studies used the same procedures and subjects used for serotonin. The within-day CV was 1.3%, the between-day CV was 4.9%, the average between-day CV was 3.6% (range 2.3–5.3%), and recovery was greater than 95%. *Platelet counts* were carried out as part of a full blood count by the Coulter Principle on a Coulter STK-S electronic cell counter. *Body mass index* was calculated, using anthropometric measurements taken at the age-21 assessment, as measured weight, divided by measured height squared. *Suicide attempts* in the past 12 months were recorded from study members' self-reports during the age-21 mental health interview. Suicide was attempted by 19 study members (blood could not be sampled from the 1 study member who had died from suicide). Diagnoses of Axis I mental disorders during the 12 months preceding the age-21 assessment were made according to the criteria DSM-III-R (American Psychiatric Association 1987). Symptoms were privately assessed using the standardized Diagnostic Interview Schedule (Robins and Regier 1991). Reliability, validity, and prevalence rates of psychiatric diagnoses in the Dunedin sample have been reported elsewhere and match U.S. epidemiological surveys (Newman et al 1996). Disorders examined were: *depressive disorders* (depressive episode and dysthymia), *anxiety disorders* (generalized anxiety, obsessive–compulsive disorder, panic disorder, and phobias), *manic episode*, *alcohol dependence*, and *tobacco dependence*. Because of the youth and limited size of the sample, disorders with lifetime prevalence rates of 1% or lower were not assessed (e.g., the sample would yield too few definite schizophrenia cases by age 21 for analysis). *Socioeconomic status* (SES) was rated on a six-point scale used to measure the status of occupations in New Zealand, ranging from professional–administrative to unskilled (Elley and Irving 1985). University students, 20% of the sample, were rated as "highly skilled." Participants who were unemployed at the time of assessment, 14.8% of the sample, were rated on the last job they had held. *Intelligence quotients* were measured using the Wechsler Intelligence Scales (Revised), the most reliable and valid standardized individual test of intelligence (Wechsler 1974). Frequency of *nonviolent criminal conviction* and *self-reported nonviolent crime* were assessed as

previously described in the sections on measurement of violent conviction and self-reported violence.

Results

Whole Blood Serotonin and Measures of Violence

Student's *t* test was used to test for differences between means of violent versus nonviolent groups. Effect sizes are estimated according to the formula of Cohen (1988) as the distance between the mean scores of two groups, in standard deviation (*z*) units, where 0.2 SD is a small effect, 0.5 SD is a moderate effect, and 0.8 SD is a large effect. (Degrees of freedom vary in this report because the cases with present data varied by analysis, but no analysis had fewer than 98% of the study members who gave blood samples.)

AMONG WOMEN. Comparisons between violent and nonviolent women revealed that serotonin level was unrelated to women's violence whether measured by self-report ($t = 0.17$, 365 df, $p > .75$) or conviction ($t = 0.30$, 367 df, $p > .75$). The effect sizes among women were very small: .04 for self-reported violence and .13 for violent conviction. To examine whether or not menstrual fluctuations in platelet production might have introduced noise into the women's serotonin measure, we controlled for individual differences in platelet count while comparing violent and nonviolent women, but the effect sizes did not increase. Because serotonin was unrelated to women's violence in this sample, the women will not be described further in this report.

AMONG MEN. Comparisons between violent and nonviolent men revealed that serotonin level was related to men's violence whether measured by self-report ($t = 2.88$, 407 df, $p < .01$) or conviction ($t = 2.56$, 410 df, $p < .01$). The effect size among men was moderate: .50 for self-reported violence and .51 for violent conviction. Self-reported violence and conviction for violence overlapped in the sample of men (chi-square = 64.27, 1 df, $p < .001$). The odds of conviction were 12.7 times greater for men who self-reported violence than for men who did not, with a 95% confidence interval (CI) between 6 and 27. Given this overlap, a violent group was constituted as the men who had self-reported violence *or* been convicted for it. Of these 54 violent men, 70% had been convicted for violence by the courts, 13% had been remanded to prison, and 9% had been psychiatrically hospitalized during the past year. With respect to psychiatric diagnoses, 28% of the violent men were alcohol dependent, 42% were tobacco dependent, 27% had anxiety disorder, 23% had depressive disorder, and 4% had a manic episode. The 54 violent men had higher blood serotonin than the nonviolent men ($t = 3.87$, 408 df, $p < .001$). The effect size was moderate: .56.

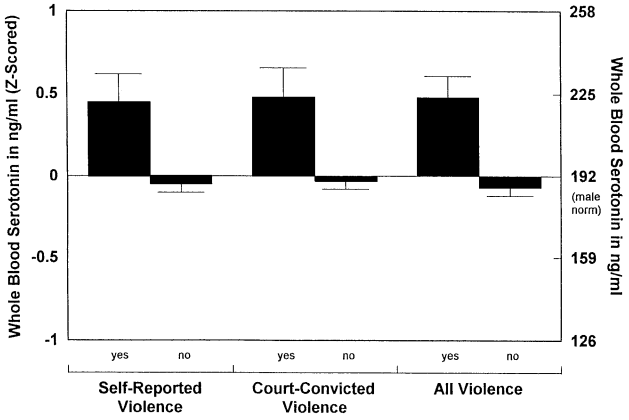

Figure 1. Mean whole blood serotonin levels for violent versus nonviolent men. The group differences are similar whether violence was measured by self-report, court conviction, or a combination of the two.

Figure 1 shows group means and standard errors. Because the sample is a representative epidemiological sample, and the serotonin scores formed an approximate normal distribution, the group mean in standard deviation (*z* score) units may be interpreted as the group's deviation from the population norm for young men. Figure 2 shows the distributions of serotonin scores for all sample men and for violent men. Examination of the distributions of serotonin scores shows that the relation between serotonin and violence was not an artifact of extreme cases at the tails.

Controlling for Potential Intervening Variables

Table 1 shows the mean levels of whole blood serotonin for violent and nonviolent men, before and after adjusting for the effects of other study variables. To test for

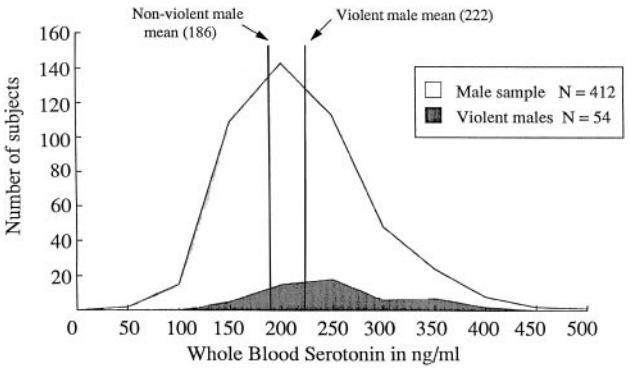

Figure 2. Distributions of whole blood serotonin scores within the sample of 54 violent men versus the full sample of 410 men. The violent and nonviolent group means differ, but the violent men's distribution overlaps the sample's normal distribution.

Table 1. Analysis of Variance for Whole Blood Serotonin (ng/mL) by Men's Violence before and after Controlling for Potential Intervening Variables

	Violent men's mean serotonin	Nonviolent men's mean serotonin	Effect size in SD	*F* value	*p* value
n of subjects	54	356			
Baseline comparison	222.18	185.75	0.56	14.97	.000
Adjusted means after controlling for					
Psychiatric medications	222.03	185.79	0.55	14.52	.000
Illicit drug use	219.41	186.16	0.51	11.30	.001
Season	221.59	185.83	0.54	14.61	.000
Tryptophan	220.89	185.94	0.53	13.98	.000
Platelet count	220.31	186.57	0.49	13.38	.000
Body mass	221.43	185.81	0.54	14.44	.000
Suicide attempts	224.56	185.40	0.60	17.09	.000
Depressive disorder	223.00	185.62	0.58	15.40	.000
Anxiety disorder	222.37	185.71	0.56	14.77	.000
Manic episode	219.27	186.56	0.50	11.47	.001
Alcohol dependence	220.54	185.98	0.53	13.25	.000
Tobacco dependence	218.21	186.57	0.49	9.38	.002
SES	222.24	185.72	0.55	13.66	.000
IQ	219.41	186.92	0.50	11.29	.001
Nonviolent convictions	216.86	186.55	0.46	8.81	.003
Self-reported nonviolent crime	227.73	184.98	0.65	14.81	.000

differences between means of violent versus nonviolent groups while controlling for potential intervening variables, we used analysis of covariance if the covariate was a continuously distributed variable, or multiple regression if the covariate was binary.

PSYCHIATRIC MEDICATIONS. The 10 men who had taken psychiatric medications in the past year had serotonin levels 0.48 SD lower than nonmedicated men, but the difference was not significant because statistical power was limited by the small number of medicated men (t = 1.5, 407 df, p = .13). Violent men were not more likely to have been medicated than were nonviolent men [3.7% (2 violent men) vs. 3.6%, chi-square = 0.01, 1 df, $p > .90$]. Moreover, as shown in Table 1, the serotonin difference between violent and nonviolent men remained after medication was entered as a covariate.

ILLICIT DRUG USE. Serotonin was weakly but significantly correlated with number of drugs used (r = .11, 409 df, $p < .05$). When violent participation was statistically controlled, the correlation between serotonin and drug use dropped to nonsignificance (beta = .05, $p > .20$); it appeared to be an artifact of disproportionate drug use by violent men; violent men used more than twice as many illicit drugs as nonviolent men (t = 8.04, 488 df, $p <$ .001); however, the serotonin difference between violent and nonviolent men remained after drug use was entered as a covariate.

SEASON. Levels of serotonin were 0.29 SD lower for men assessed in January, February, and March (summer in New Zealand) relative to other seasons (t = 2.48, 410 df, $p < .01$); however, the serotonin difference between violent and nonviolent men remained after season (coded as summer vs. nonsummer) was entered as a covariate.

TRYPTOPHAN. Serotonin was weakly but significantly correlated with tryptophan concentration (r = .14, 412 df, $p < .01$). Violent and nonviolent men did not differ significantly on tryptophan (t = 1.19, 408 df, $p >$ .2). The serotonin difference between violent and nonviolent men remained after tryptophan was entered as a covariate.

PLATELET COUNT. Serotonin was significantly correlated with platelet count (r = .20, 410 df, $p < .001$). Violent and nonviolent men approached a significant difference on platelet count (t = 1.92, 409 df, p = .06), violent men having more platelets. The serotonin difference between violent and nonviolent men remained after platelet count was entered as a covariate.

BODY MASS. Serotonin was weakly but significantly correlated with body mass (r = −.13, 410 df, $p < .01$). Violent and nonviolent men did not differ significantly on body mass (t = 0.19, 478 df, $p > .75$). The serotonin difference between violent and nonviolent men remained after body mass was entered as a covariate.

SUICIDE ATTEMPTS. The 9 men in our sample who had attempted suicide did not differ significantly from nonsuicidal men on serotonin level ($t = 1.5$, 409 df, $p = .13$). The mean serotonin level for 3 attempters who had been treated with psychiatric medications such as 5-HT reuptake inhibitors was 1.05 SD below the male norm, and the mean for the 6 unmedicated suicide attempters was 0.23 SD below the male norm. Violent men were 6.16 times more likely to attempt suicide than were nonviolent men (95% CI: 1.73–21.88, chi-square = 10.14, 1 df, $p < .001$). None of the violent suicidal men were medicated. Moreover, the serotonin difference between violent and nonviolent men remained after suicide was entered as a covariate.

PSYCHIATRIC DISORDERS. Depressed men did not differ from nondepressed men on serotonin ($t = .08$, 410 df, $p = .93$). Similarly, anxious men did not differ from nonanxious men on serotonin ($t = .58$, 410 df, $p = .56$); however, manic men did have higher serotonin concentrations than nonmanic men ($t = 2.16$, 408 df, $p = .03$). Violent men were 2.75 times more likely to have a depressive disorder than were nonviolent men (95% CI: 1.44–5.25, chi-square = 10.11, 1 df, $p < .01$), and 3.03 times more likely to have an anxiety disorder then were nonviolent men (95% CI: 1.65–5.58, chi-square = 13.72, 1 df, $p < .001$); however, violent men were not more likely to be manic than were nonviolent men (chi-square = 2.01, 1 df, $p = .15$). The serotonin difference between violent and nonviolent men remained after depression, anxiety, and mania were entered separately as covariates.

ALCOHOL. Alcohol-dependent men had higher blood serotonin concentrations than nondependent men ($t = 2.03$, 409 df, $p < .05$). Violent men were 3.15 times more likely to be alcohol dependent than were nonviolent men (95% CI: 1.72–5.75, chi-square = 15.15, 1 df, $p < .001$); however, the serotonin difference between violent and nonviolent men remained after alcohol dependence was entered as a covariate.

TOBACCO. Tobacco-dependent men had higher blood serotonin concentrations than nondependent men ($t = 1.93$, 390 df, $p = .06$). Violent men were 5.15 times more likely to be tobacco dependent than were nonviolent men (95% CI: 2.91–9.13, chi-square = 36.40, 1 df, $p < .001$); however, the serotonin difference between violent and nonviolent men remained after tobacco dependence was entered as a covariate.

Because diagnostic categories may not fully reflect variations in the distributions of symptom behaviors, we repeated the analyses for depression, anxiety, mania, alcohol, and tobacco using continuously distributed counts of symptoms and quantity measures of substance use. Results did not change.

SOCIOECONOMIC STATUS. Serotonin was not correlated with SES, $r = .05$. Violent men had lower SES ratings than nonviolent men ($t = 7.23$, 486 df, $p < .001$); however, the serotonin difference between violent and nonviolent men remained after SES was entered as a covariate.

IQ. Serotonin was weakly but significantly and negatively correlated with IQ ($r = -.12$, 401 df, $p < .05$), as previously reported (Cook et al 1988). Violent men had lower IQ scores than nonviolent men ($t = 5.24$, 477 df, $p < .001$); however, the serotonin difference between violent and nonviolent men remained after IQ was entered as a covariate.

CONTROLLING FOR INTERVENING VARIABLES SIMULTANEOUSLY. Five variables were related to both serotonin and to violence, at either conventional or marginal levels of significance: illicit drug use, platelet count, alcohol dependence, tobacco dependence, and IQ. When these five variables were entered simultaneously as covariates, the serotonin difference between violent and nonviolent men remained significant ($F = 5.92$, $p = .01$). After the mean serotonin scores of violent and nonviolent men were adjusted for these five covariates, the effect size decreased about one quarter, from .56 to .41.

FREQUENCY OF NONVIOLENT OFFENDING. Violent men had much higher rates of all types of crimes than did nonviolent men, whether measured by self-report ($t = 9.56$, 480 df, $p < .01$) or conviction ($t = 9.59$, 487 df, $p < .01$); however, as shown in Table 1, the serotonin difference between violent and nonviolent men remained after overall frequency of offending was entered as a covariate.

Discussion

In this study, elevated whole blood serotonin was characteristic of violent men. The violent men's mean serotonin level, 222 ng/mL, was 0.48 SD above the male sample norm and 0.56 SD above the mean of nonviolent men. The finding was specific to violence as opposed to antisocial activities in general, for it was unaltered when the frequency of overall offending was statistically controlled. The finding was robust across two different methods of measuring violence, self-report and court conviction. To our knowledge, this is the first study to demonstrate that a possible index of serotonergic function is related to violence in the general population. The epidemiological

serotonin effect was not small; it indicated a moderate effect size in the population. Moreover, the relation between serotonin and violence was not an artifact of cases at the extreme end of the distribution; however, the overlapping distributions shown in Figure 2 revealed that some nonviolent men showed higher levels of serotonin than the violent men. As such, although whole blood serotonin is sensitive to violence risk, it does not have enough specificity to serve as a marker for violence risk in the general population.

Observed elevated whole blood serotonin among violent men is consistent with the hypothesis that serotonergic dysfunction is associated with aggression. It must be emphasized, however, that even though the present results are not inconsistent with a serotonin dysfunction in the central nervous system, the association is certainly indirect and might even be fortuitous. Serotonin in blood is largely produced in the gut, wholly contained within platelets, and does not cross the blood–brain barrier. Thus, its relation to serotonergic function in the brain remains an empirical question (Rasmusson et al 1990; Sarrias et al 1990). One rationale for examining blood serotonin as a possible index of brain serotonin function is based on similarities in metabolic control of serotonin synthesis, similarities in the serotonin reuptake systems of platelets and neurons, and the presence of 5-HT_{2A} receptors on platelets. Thus both brain and blood indices are affected by treatments that load serotonin precursors, disrupt serotonin uptake and storage, and alter serotonin degradation (Cook et al 1994; Geller et al 1982; Given and Longenecker 1985; Kremer et al 1990; Mann et al 1992; Pletscher 1978; Raleigh et al 1984; Stahl 1985; Von Hahn et al 1980). For example, fenfluramine enhances whole blood serotonin levels (Geller et al 1982), and individual differences in such enhanced levels have been shown to correlate with individual differences in blunted prolactin release (McBride et al 1989). Specifically, it has been suggested that the pattern of antisocial behavior relating to low CSF 5-HIAA but to high whole blood serotonin may not be a paradox. The pattern could be explained if antisocial individuals' serotonergic neurons and platelets shared increased serotonergic transport (Cook et al 1993, 1995). The same pattern has been shown among monoamine oxidase-deficient patients (Brunner et al 1993; Lenders et al 1996). Interpretation of our findings will depend on the extent to which central and peripheral indices of the serotonin system are ultimately shown to be influenced by similar kinetic developmental defects or experimental interventions. Nonetheless, whatever the mechanism, this study illustrates that whole blood serotonin is related to behavior, and thus peripheral serotonin measures warrant more research.

Depending on the outcome of such research, whole blood serotonin could become a useful measure for epidemiological studies. Recent commentaries in the literature (Berman et al in press; Pine et al 1996; Stoff et al 1991) have blamed failures to replicate relations between measures of the serotonin system and behavior on small and idiosyncratic samples. These commentaries also advise researchers to address the developmental origins of links between serotonin and aggression by studying samples of children longitudinally with repeated behavioral and serotonin measures. If replicated, our findings suggest that whole blood serotonin may be a useful measure for studying larger, more representative samples, and may allow repeated measures in developmental studies.

The sampling design of the present study allowed comparison by gender. Individual differences in serotonin level were linked with violence only among men; the finding did not describe women. This observation agrees with the only prior study of women (Gardner et al 1990). There is evidence that whole blood serotonin may fluctuate slightly near the end of the menstrual cycle, perhaps from hormonal effects on platelet production (Ritvo et al 1971), although this fluctuation is not reported consistently (Ashcroft et al 1964). We had not assessed the women's menstrual cycles, but we were able to introduce statistical controls for platelet count, which did not alter the null relation between women's violence and serotonin. Nonetheless, it is possible that potential findings may have been obscured by noise in the women's serotonin data. Alternately, it is possible that women's violence differs from men's violence in its psychological meaning, and thereby has different biological correlates. For example, in one comparison of men and women who were matched on levels of violent behaviors against an intimate partner, male perpetrators were significantly more deviant than female perpetrators on several psychiatric and social correlates of violence (Magdol et al 1997).

The research procedures of the Dunedin study eliminated potential influences on blood serotonin from diurnal variation, recent diet, recent activity level, or age. The measurement design of the Dunedin study allowed statistical control for potential biasing effects on serotonin by variables suggested in the methodological literature. Although serotonin levels were indeed lower among study members who had taken psychiatric medications, lower in the austral summer, higher among illicit drug users and heavy smokers, and positively related to plasma tryptophan and platelet count, none of these effects influenced the relation between serotonin and violence. The serotonin/violence relation also survived statistical control for potential biasing effects of factors hypothesized to be related to violence: body mass, suicide attempts, psychiatric disorders, alcohol abuse, low socioeconomic status, and low IQ. In combination, control factors accounted for

about one quarter of the relation between serotonin and violence: adjusting simultaneously for alcohol, tobacco, and drug use, platelet count, and IQ, the violent men's mean serotonin concentration remained 0.41 SD above the mean of nonviolent men. Thus, the whole blood serotonin/violence relation in this sample is neither wholly mediated by these variables, nor is it an artifact of them.

The finding of this study is compatible with a growing clinical literature on serotonin and aggression. Elevated serotonin in blood has been reported for conduct-disordered (Cook et al 1995; Pliszka et al 1988; Unis et al in press) and aggressive (Brown et al 1989; Mann et al 1992) groups of patients. Consistent with these blood findings, low levels of 5-HIAA in cerebrospinal fluid have been reported for an aggressive subgroup within conduct-disordered patients (Kruesi et al 1990) and specific diagnostic subgroups within samples of criminal patients (Brown et al 1982b; Linnoila et al 1983; Virkkunen et al 1987, 1989b, 1994a, 1994b). Experimental challenge by a serotonin agonist affected alcoholic, suicidal, and aggressive subgroups within a patient sample (Coccaro et al 1989). These previous clinical reports, and literature reviews based on them, have speculated that dysfunction in the central serotonergic system will be limited to relatively circumscribed and sometimes rare subgroups of violent offenders (Asberg et al 1986; Eichelman 1993; Raine 1993; Rogeness et al 1992; Schalling 1993; Spoont 1992; Virkkunen and Linnoila 1993). Those subgroups have been variously, and somewhat inconclusively, proposed as personality disordered, pathologically violent, hostile/affective, suicidal, nonalcoholic, early-onset alcoholic, intrafamilially violent, impulsive, or mesomorphic in body build. If the serotonin/violence relation were specific to the subgroups we studied here, it should have been reduced to nonsignificance in the covariance analyses. The relation was not reduced, suggesting the hypothesis that the serotonin/violence relation in the general population may be robust across at least some implicated clinical subgroups. Research that combines brain measures of serotonin with epidemiological sampling frames is needed to determine if the serotonin/violence relation is limited to select subgroups or broadly applicable to most violent offenders.

The present investigation was cross-sectional, examining serotonin only in 21-year-olds. Laboratory studies suggest that individual differences in whole blood serotonin are stable over periods of a year or more (Badcock et al 1987; Ritvo et al 1970; Yuwiler et al 1981). Two previous clinical studies have shown that CSF serotonin indices can predict aggression and violence after 2–3 years of follow-up (Kruesi et al 1992; Virkkunen et al 1989a). In addition, in studies of monkeys, experimental manipulations of males' dominance hierarchies (Botchin et al 1994; Raleigh et al 1984) and infants' rearing experiences (Higley et al 1991, 1993) have documented that changes in social experience can bring about changes in the serotonin system, suggesting a need for prospective longitudinal research to test whether changes in violence status are accompanied by changes in serotonin among humans. The 21-year-olds in our sample were just past the peak age of violence in New Zealand; in the next 5 years some of the violent offenders will desist, while some now-nonviolent members of the sample will initiate violent offending. Future assessments in the Dunedin longitudinal study will allow us to test the long-term stability of individual differences in whole blood serotonin, to test whether whole blood serotonin levels can predict future violent outcomes, and to trace the serotonin/violence relation across adult development.

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