A Replication Study of Violent and Nonviolent Subjects: Cerebrospinal Fluid Metabolites of Serotonin and Dopamine Are Predicted by Plasma Essential Fatty Acids

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Background: *Among an independent group of subjects selected for their history of violent, impulsive behaviors and nonviolent control subjects, we attempted to replicate the finding that plasma docosahexaenoic acid concentrations were negatively correlated with cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) concentrations.*

Methods: *CSF 5-HIAA and homovanillic acid (HVA), fasting total cholesterol, and plasma fatty acid concentrations were examined in violent and nonviolent subjects matched for their severity of alcohol dependence.*

Results: *Violent subjects had significantly higher lifetime violence and hostility ratings and lower concentrations of CSF 5-HIAA than nonviolent subjects. Plasma docosahexaenoic acid was negatively correlated with CSF 5-HIAA only among violent subjects.*

Conclusions: *This observational study suggests that dietary essential fatty acids may change neurotransmitter concentrations. Prospective dietary intervention trials will be required to determine if increasing dietary intake of docosahexaenoic acid will increase or decrease either CSF 5-HIAA concentrations or impulsive and violent behaviors.* Biol Psychiatry 1998;44:243–249 © *1998 Society of Biological Psychiatry*

Key Words: Alcoholism, cholesterol, docosahexaenoic acid, polyunsaturated fatty acids, serotonin, suicide, violence, 5-hydroxyindoleacetic acid, arachidonic acid, essential fatty acids, depression

Introduction

There is international concern for the widespread problem of alcohol-related violence (Norton and Morgan 1989). In a 1-year period, episodes of alcohol-related violence occurred among 12% of people aged 22 years and younger and among 3% of the general population (Rossow 1996). Violent behaviors are not only associated with acute alcohol intoxication. A genetic risk for the development of alcohol dependence appears to be linked to a pattern of violent and impulsive behaviors among male alcoholics with an early onset of dependence (Goldman 1996). An onset of alcohol dependence before a person's 20th birthday doubles their likelihood of incarceration for acts of criminal violence and quadruples their likelihood of attempted suicide (Buydens-Branchey et al 1989). In two large Swedish adoption studies, Sigvardsson et al (1996) reported a high genetic loading for early onset of alcoholism, which was also characterized by male gender and a high frequency of impulsive behaviors manifested as criminal and aggressive acts and suicide attempts. These shared clinical and genetic characteristics that predispose toward violent impulsive behavior and early-onset alcoholism appear to be linked by reduced central serotinergic functions (Goldman 1996; Roy et al 1987).

Impulsive violence, suicidal and aggressive behaviors, and early onset of alcoholism have been repeatedly linked to low concentrations of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) (Mann 1995), a metabolite that reflects serotonin turnover predominantly in the frontal cortex (Stanley et al 1985). Low concentrations of CSF 5-HIAA have been reported in early-onset alcoholics (Fils-Aime et al 1996), impulsive homicidal offenders (Linnoila et al 1983), and impulsive fire setters (Virkkunen et al 1994). Low concentrations of CSF 5-HIAA have also predicted aggression and lack of social competence among nonhuman primates (Higley et al

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1996), patients with personality disorders (Brown and Goodwin 1984), and those with high hostility scores among healthy volunteers (Roy et al 1988). Low CSF 5-HIAA concentrations among suicide attempters with depression, personality disorders, or alcoholism is one of the most replicated findings in biological psychiatry (Roy et al 1991).

Previously we postulated (Hibbeln and Salem 1995) that the serotonin turnover rate in the central nervous system may be modulated by docosahexaenoic acid, a polyunsaturated essential fatty acid that is a critical component of synaptic membranes (Salem 1989). We recently found that higher concentrations of plasma docosahexaenoic acid and arachidonic acid predicted higher concentrations of CSF 5-HIAA among healthy volunteers (Hibbeln et al 1998). Our finding was consistent with the report of Hamazaki et al (1996) that docosahexaenoic acid reduced hostility among healthy Japanese students in a double-blind placebo-controlled supplementation trial. This finding was striking, considering that the Japanese students had plasma docosahexaenoic acid concentrations of 3% at baseline, and 6% after supplementation, whereas typical plasma concentrations for Americans are 1% or less (Hibbeln et al 1998); however, we found that plasma concentrations of docosahexaenoic acid were inversely correlated with CSF 5-HIAA concentrations among early-onset alcoholics, who are at risk for violent and impulsive behavior (Hibbeln et al 1998). Thus, we sought to replicate the negative correlation between plasma docosahexaenoic acid and CSF 5-HIAA in a second observational study of an independent group of subjects selected for their history of violent, impulsive behaviors and in a set of nonviolent control subjects. Thus violent and nonviolent groups each included a similar number of subjects with and without alcohol dependence to control for the possible confounding effects of alcohol-induced hepatic damage while isolating violent behavior as a variable.

Methods and Materials

All subjects were admitted to the inpatient research ward of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health Clinical Center in Bethesda, Maryland. Both violent subjects and nonviolent comparison subjects were recruited by newspaper advertisements. Inclusion criteria for violent subjects consisted of having a lifetime history of more than five episodes of violent, physical aggression that had clear potential to cause, or actually caused, bodily harm. Examples of these episodes included pushing someone downstairs, punching someone in the face or body, kicking, stabbing, or threatening with a gun in a fit of anger. All these subjects reported having recent episodes of violent behavior (within the last 3 months) or isolated themselves from significant relationships to avoid such episodes. All violent subjects reported at least one episode of violence that occurred while they were neither intoxicated, nor in alcohol withdrawal. Exclusion criteria for both violent and nonviolent subjects included a history of a major psychotic or a major affective disorder, panic disorder, seizure or other neurological disorder, history of head trauma that resulted in a loss of consciousness for more than 1 hour, lifetime history of amphetamine, hallucinogen, or opiate dependence, and current dependence on cocaine or other illicit drugs. The absence of major medical problems was confirmed by clinical chemistry and physical examination. All subjects completed the Structured Clinical Interview for DSM-III-R (SCID) administered by a research social worker (Williams et al 1992). Interviews were blind rated by a different research social worker and a psychiatrist under the supervision of a senior research psychiatrist. No subjects were included from the previous study (Hibbeln et al 1998). Nonalcoholic volunteers were paid for their participation.

Table 1. Descriptive Statistics

	Nonviolent group	Violent group	
n	31	27	
Male	22	21	
Female	9	6	
Current alcohol dependence	13	13	
Never alcohol dependent	18	14	
Age (years)	39.9 (8.0)	38.5 (6.4)	ns
Height (cm)	172.8 (15.5)	174.7 (9.6)	ns
Weight (kg)	80.3 (13.5)	77.4 (16.8)	ns
Hollingshead socioeconomic scale	4.1 (.6)	3.9 (1.3)	ns

Mean (SD). Nonparametric Mann–Whitney comparisons between groups indicated by ns (nonsignificant) or relevant *p* value.

Thirteen of 27 violent subjects met diagnostic criteria for current alcohol dependence, which is a prevalence typical of violent populations (Norton and Morgan 1989; Rossow 1996; Linnoila et al 1983; Virkkunen et al 1994). We designed the nonviolent comparison group to contain a similar number of subjects with and without current alcohol dependence compared to the violent group (Table 1). Subjects were excluded from the nonviolent comparison group if during their adult lifetime they reported having, or were found to have had even one episode of violent, physical aggression, as described above. Alcohol-dependent subjects in both the violent and nonviolent groups met Research Diagnostic Criteria (RDC) (Spitzer et al 1978) and DSM-III-R criteria (American Psychiatric Association 1987) for alcohol dependence and had been abstinent for between 21 and 63 days at the time of the study, confirmed by random breath and urine drug testing. All subjects were medication free at the time of the study, and none received monoamine oxidase or serotonin reuptake inhibitors in the 3 months prior to the study. Michigan Alcoholism Screening Test (MAST) scores, CAGE scores, derived from the MAST (Strogaad et al 1994), and Hollingshead ratings of socioeconomic class were obtained for all subjects. Subjects completed Brown–Goodwin Lifetime Aggression rating scales (Brown and Goodwin 1984) and Buss–Durkee Hostility

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Inventory rating scales (Buss and Durkee 1957). Information on recent and chronic alcohol consumption was obtained from a structured research questionnaire completed by the subjects (Eckardt et al 1978). All subjects provided written informed consent for the study as approved by the National Institute on Alcohol Abuse and Alcoholism Institutional Review Board protocol #91-AA0237.

All subjects were maintained on a low-monoamine diet (Muscettola et al 1977) for a minimum of 3 days prior to the lumbar puncture and blood sampling. This diet did not restrict fish, meat, poultry, or oil consumption. Lumbar punctures were performed after an overnight fast as previously described (Fils-Aime et al 1996). Fasting plasma samples used to quantify total cholesterol concentrations and total fatty acid profiles were obtained within 1 week of CSF collection. CSF and plasma samples were frozen at −70°C until analysis, except for total cholesterol, which was analyzed on fresh samples.

Quantitative Biochemical Assays

Concentrations of the major metabolites of serotonin (5-HIAA) and dopamine [homovanillic acid (HVA)] were quantified in the CSF by gas chromatography–mass spectroscopy using deuterated internal standards (Polinski et al 1988). Within- and between-run coefficients of variance were less than 5%, as previously reported (Polinski et al 1988). Plasma fatty acid composition was quantified using internal standards, as previously reported (Hibbeln et al 1998). An automated calorimetric cholesterol esterase assay was performed on fresh samples by the clinical laboratories at the Clinical Center of the National Institutes of Health (Hitachi 917, Boehringer and Mannheim, Inc.). This assay was standardized to Centers for Disease Control authentic standards.

Statistical Analyses

Statistical analyses were computed using Statistica for Windows 1.0 (Statsoft, Tulsa, OK) and Statview 4.1 (Abacus Concepts, Berkeley, CA). Differences between groups were examined with nonparametric Mann–Whitney tests. In separate analyses, Pearson product–moment correlations were computed to assess the relationships between each CSF monoamine metabolite concentration and liver enzymes, frequency, quantity and years of excessive alcohol consumption, age, height, weight, CAGE, and Hollingshead social class scores. Tests for correlational relationships to CSF neurotransmitter metabolites were performed only on long-chain essential fatty acids specifically selected on the basis of our previous work (Hibbeln et al 1998) to avoid bias of multiple testing.

Results

The violent group had significantly higher scores of lifetime aggression on the Brown Goodwin Lifetime History of Aggression Scale and the Buss Durkee Hostility Inventory than the nonviolent group (Figure 1). The groups did not differ in age, quantitative measures of alcohol consumption, or indices of alcohol-related liver damage (Table 2). These measures might have been confounding factors in the relationship between plasma lipids and CSF neurotransmitter metabolites. No differences were found in the concentrations of any individual fatty acid or total plasma cholesterol comparing the violent to the nonviolent group (Table 3). The violent group had significantly lower concentrations of CSF 5-HIAA than the nonviolent group.

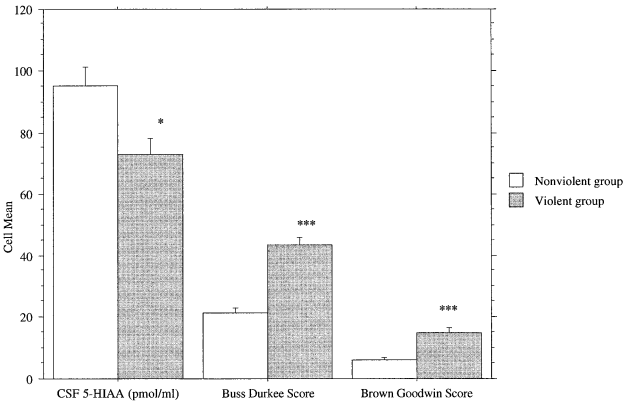

Figure 1. Means and standard errors for cerebrospinal fluid 5-HIAA concentrations, and Buss Durkee Hostility Inventory and Brown Goodwin Lifetime History of Aggression scores. Analysis of variance comparisons of violent and nonviolent groups are indicated at $*p < .02$ and $***p < .0001$.

Correlational Analysis

Age, height, weight, plasma total cholesterol, frequency and quantity of alcohol consumed, lifetime alcohol consumption, Hollingshead socioeconomic scale, and MAST and CAGE score were not significantly correlated to CSF 5-HIAA or CSF HVA, nor to cholesterol, nor to plasma fatty acids including docosahexaenoic acid. Thus, these factors could not influence the relationship between plasma docosahexaenoic acid and either CSF 5-HIAA or CSF HVA concentrations. In this study, neither CSF 5-HIAA nor CSF HVA were correlated with the total score of the Buss Durkee Hostility Inventory, nor the Brown Goodwin Lifetime Aggression score, nor any subscale score in either rating instrument, in either group or when the groups were combined. Among the violent group, CSF 5-HIAA showed a trend to predict the total Buss–Durkee score ($r = -.42$, $p < .0509$). Plasma total cholesterol was not correlated to CSF 5-HIAA or CSF HVA or the Buss Durke Hostility Inventory score or the Brown Goodwin Lifetime Aggression score, in either group.

In this study we tested the a priori hypothesis that the violent patients have a negative correlation between

Table 2. Alcohol-Related Variables and Neurotransmitter Metabolites

	Nonviolent group	Violent group	
MAST score	18.3 (30.1)	19.2 (19.9)	ns
Frequency (days/last 180)	39.2 (57.4)	48.7 (62.2)	ns
Quantity (g/day)	49.8 (78.5)	23.9 (30.4)	ns
Lifetime drinking history (kg)	158 (257)	208 (256)	ns
CAGE	1.3 (1.8)	1.5 (1.6)	ns
AP (U/L)	71 (16)	67 (21)	ns
AST (U/L)	19 (7)	18 (5)	ns
ALT (U/L)	23 (17)	21 (20)	ns
LDH (U/L)	144 (618)	138 (20)	ns
CSF HVA (pmol/mL)	158.0 (72.5)	152.1 (71.4)	ns
CSF 5-HIAA (pmol/mL)	95.4 (33.6)	73.1 (28.3)	$p < .02$

Mean (SD). Nonparametric Mann–Whitney comparisons between groups indicated by ns (nonsignificant) or relevant *p* value. AP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

plasma docosahexaenoic acid and CSF 5-HIAA concentrations similar to the relationship previously observed among early-onset alcoholics (Hibbeln et al 1998). Thus, the correlational testing of CSF 5-HIAA concentrations was limited to plasma lipid variables defined by our previous study, plus a few important controls, i.e., 20:4n6, 18:3n3, 22:6n3 (docosahexaenoic acid), total plasma fatty acids, and total cholesterol concentrations. Results of these univariate analyses are described in Table 4. CSF 5-HIAA and CSF HVA were significantly intercorrelated ($r = .78$, $p < .001$), consistent with previous reports (Agren et al 1986; Linnoila et al 1983). The test of equality of correlations was applied only to the relationship between CSF 5-HIAA and plasma docosahexaenoic acid comparing the two groups ($p < .05$). The negative correlation between docosahexaenoic acid and CSF 5-HIAA concentrations ($r = -.46$, $p < 0.02$) (Figure 2) was of a similar magnitude to our previous finding of a negative correlation between docosahexaenoic acid and CSF 5-HIAA concentrations ($r = -.33$, $p < .005$) among early-onset alcoholics (Hibbeln et al 1998).

Discussion

In this study, we replicated our previous finding that high plasma concentrations of docosahexaenoic acid, a polyunsaturated omega-3 fatty acid, predict low concentrations of a metabolite of serotonin, CSF 5-HIAA, among violent, impulsive subjects. Low concentrations of CSF 5-HIAA have been repeatedly and robustly linked to suicidal and violent behavior (Mann 1995; Fils-Aime et al 1996; Linnoila et al 1983; Virkkunen et al 1994; Higley et al

Table 3. Plasma Fatty Acid Composition

	Nonviolent group	Violent group	
Total cholesterol (μg/ml)	172 (40)	171 (24)	ns
Total fatty acids (μg/ml)	1876 (880)	1687 (322)	ns
Saturated total (μg/ml)	635 (644)	511 (205)	ns
Monounsat. total (μg/ml)	445 (267)	384 (111)	ns
n-6/n-3 ratio	13.1 (4.5)	13.9 (3.5)	ns
AA/EPA ratio	16.4 (6.5)	15.5 (6.1)	ns
20:3n9 (μg/ml)	2.1 (1.9)	1.3 (0.8)	ns
18:2n6 (μg/ml)	537.6 (109.5)	551.3 (85.7)	ns
18:3n6	8.9 (6.1)	9.3 (4.1)	ns
20:2n6	4.5 (1.7)	4.6 (1.5)	ns
20:3n6	27.2 (8.2)	25.1 (6.9)	ns
20:4n6	122.0 (28.6)	112.5 (31.3)	ns
22:4n6	4.8 (1.8)	4.4 (1.2)	ns
22:5n6	4.1 (1.4)	3.7 (0.9)	ns
18:3n3 (μg/ml)	11.5 (7.4)	10.3 (4.6)	ns
22:5n3	9.1 (3.2)	8.3 (2.2)	ns
20:5n3	9.3 (6.5)	8.6 (5.2)	ns
22:6n3	30.8 (14.3)	27.2 (11.7)	ns

Mean (SD). Nonparametric Mann–Whitney comparisons between groups indicated by ns (nonsignificant) or relevant *p* value.

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Table 4. Correlational Relationships of Plasma Lipid Variables with CSF 5-HIAA and CSF HVA

	r	
	CSF HVA	CSF 5-HIAA
Violent group		
Total cholesterol (mg/dL)	.08 ns	.12 ns
20:4n6 (μg/mL)	.15 ns	.08 ns
18:3n3 (μg/mL)	.06 ns	.27 ns
22:6n3 (μg/mL)	−.33 ns	−.46 $p < .02$ ($r^2 = .21$)
Nonviolent group		
Total cholesterol (mg/dL)	.12 ns	.34 ns
20:4n6 (μg/mL)	.20 ns	.01 ns
18:3n3 (μg/mL)	.01 ns	.30 ns
22:6n3 (μg/mL)	.13 ns	.17 ns

Pearson univariate correlations indicated by *r* values and variance by r^2, for plasma variables selected as significant in a previous study. ns indicates nonsignificant at $p < .05$.

1996; Brown and Goodwin 1984; Roy et al 1988). Consistent with these reports, violent subjects had low concentrations of CSF 5-HIAA and higher hostility and lifetime aggression scores compared with the nonviolent group. In comparing violent and nonviolent groups, no mean differences were found in age, prevalence of alcohol dependence, level of alcohol consumption, or markers of hepatic damage. Furthermore these variables had no correlational relationship to either plasma docosahexaenoic acid or CSF 5-HIAA. Thus, it is unlikely that the negative correlation between plasma docosahexaenoic acid and CSF 5-HIAA concentrations was due to alcoholic hepatitis or the disruption of apolipoprotein-mediated polyunsaturated fatty acid transport by alcohol, which would have had similar effects on both violent and nonviolent groups. Plasma contains a transient, rapidly turning over pool of fatty acids, which generally reflects dietary intake but is susceptible to wide variability as a result of differences in dietary intake and metabolism (Anderson et al 1996). Considering this variability, replication of a finding of any correlation between a plasma essential fatty acid and CSF neurotransmitter metabolite concentrations in an observational study is remarkable.

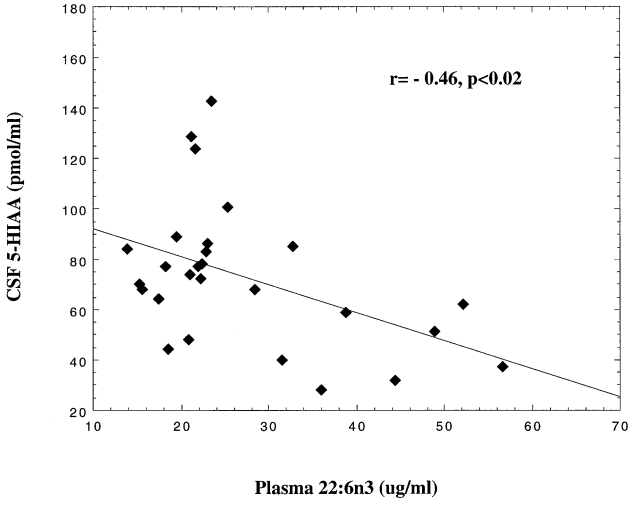

Figure 2. Scattergram of plasma docosahexaenoic acid and CSF 5-HIAA among violent subjects. The negative correlation is similar among early-onset alcoholics, as described in Hibbeln et al (1998, Figure 1).

The relatively robust and replicated findings of correlational relationships between plasma docosahexaenoic acid and CSF 5-HIAA concentrations in healthy volunteers, early-onset alcoholics (Hibbeln et al 1998), and violent subjects suggest, but do not demonstrate, a causal relationship between plasma concentrations of docosahexaenoic acid and alterations of serotonin function in the central nervous system. This interpretation assumes that concentrations of plasma docosahexaenoic acid reflect adult brain docosahexaenoic acid concentrations, and that brain docosahexaenoic acid concentrations affect serotonin concentrations or metabolism. Chronic alcohol use did lower docosahexaenoic acid concentrations in both plasma and brain among both adult felines and juvenile rhesus monkeys (Pawlosky and Salem 1995, 1996). During development and during refeeding with docosahexaenoic acid after a prenatal omega-3 deficiency, low plasma docosahexaenoic acid concentrations reflected low brain concentrations among infant rhesus monkeys (Connor et al 1990). In frontal cortex, rats with low brain concentrations of docosahexaenoic acid were found to have a 44% increase in serotonin$_{2A}$ receptor number (DeLion et al 1994), a potential marker of reduced serotonin function (Mann 1995). In frontal cortex from suicide victims, strikingly similar increases in serotonin$_{2A}$ receptor number have been repeatedly described (Mann 1995).

Violent subjects, early-onset alcoholics, and suicidal patients may share a defect in the mechanisms that regulate the transportation and selective concentration of docosahexaenoic acid into the brain. Such a defect would result in the accretion of docosahexaenoic acid in plasma and not reflect brain concentrations. An abnormality in apolipoprotein-mediated polyunsaturated fatty acid and cholesterol transportation has been described among violent prisoners; compared to nonviolent controls they had higher concentrations of apolipoprotein A-IV and apolipoprotein E (Corrigan et al 1997). These differences were highly statistically significant. High dietary doses of docosahexaenoic acid may compensate for a defect in apolipoprotein-mediated selective concentration of docosahexaenoic acid into the brain and may potentially normalize serotonin function among impulsive, violent subjects. Alternatively, early-onset alcoholics may have a genetic variant of essential fatty acid regulation of seroto-

nin synthesis, release, metabolism, or uptake. Caution must be exercised, as the negative correlation between plasma docosahexaenoic acid and CSF 5-HIAA in violent subjects may suggest that elevating plasma docosahexaenoic acid concentrations could directly reduce central serotonin concentrations, lower CSF 5-HIAA concentrations, and increase impulsive behavior in violent subjects and genetically similar populations.

The negative correlation between plasma docosahexaenoic acid and CSF 5-HIAA (Hibbeln et al 1998) appears to be specifically related to violent and impulsive behavior, not alcohol consumption, as the violent and nonviolent groups were specifically matched for alcohol use in this study. Although we previously found a positive correlation between arachidonic acid and both CSF 5-HIAA and CSF HVA concentrations in healthy volunteers, we did not find a significant correlation between plasma 20:4n6 concentrations and CSF 5-HIAA or CSF HVA concentrations in the nonviolent group (Hibbeln et al 1998). The nonviolent group had a smaller number of subjects and was not diagnostically equivalent to the healthy volunteers, which may explain these differences. Contrary to the hypothesis suggested by Endelberg (1992), we also replicated our previous finding that plasma total cholesterol fails to predict CSF 5-HIAA concentrations, among both violent and nonviolent subjects. This study replicates our previous findings (Hibbeln et al 1998) and is consistent with our prior hypothesis that low plasma docosahexaenoic acid concentrations, rather than low plasma cholesterol concentrations, may increase predisposition to hostility and depression (Hibbeln and Salem 1995). The findings presented here are also consistent with a report that abnormalities in essential fatty acid metabolism may be present in violent offenders (Virkkunen et al 1987). We caution that these data have not demonstrated that changes in dietary intake of polyunsaturated essential fatty acids can cause changes in central serotonergic function or alter impulsive or depressive behaviors. Well-controlled clinical trials are required to determine if such relatively inexpensive interventions will be effective in changing CSF neurotransmitter metabolite concentrations and reduce risk of violent, impulsive behaviors, or be destructive and increase risk of such behaviors.

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