Plasma Phospholipid Essential Fatty Acids and Prostaglandins in Alcoholic, Habitually Violent, and Impulsive Offenders

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Plasma phospholipid essential fatty acids and some of their main metabolites, prostaglandins, were measured among habitually violent and impulsive male offenders, who all had alcohol abuse problems, and nonviolent control persons. Linoleic acid (18 : 2n-6), the precursor of the n-6 fatty acids, was below normal in intermittent explosive disorder, but the dihomogammalinolenic acid (DGLA) (20 : 3n-6) and some subsequent n-6 acids were at the same time elevated among all offenders. Also, a monounsaturate, oleic acid (18 : 1n-9) was elevated. The high DGLA correlated with low cholesterol level in intermittent explosive disorder. The arachidonic acid metabolites PGE_2 and TxB_2 were elevated in violent antisocial personality. The PGE_1/DGLA ratio was low in intermittent explosive disorder. The number of registered violent crimes and violent suicidal attempts correlated with high phospholipid DGLA values. The possibility that the high phospholipid DGLA is connected with low free DGLA pool, and therefore low PGE_1 formation, among these offenders is discussed.

Introduction

During recent years evidence has accumulated that in habitual violence and impulsiveness biological factors may play a central role in etiology. First, among habitually violent military men (Brown et al. 1979, 1982), violent offenders with XYY chromosome (Bioulac et al. 1980), impulsive homicidal offenders (Linnoila et al. 1983a; Lidberg et al. 1984, 1985; Virkkunen et al. 1987), and impulsive arsonists (Virkkunen et al. 1987), there is a low cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) level, possibly as a result of low brain serotonin turnover. Similar findings have been obtained in "violent," impulsive suicidal persons (Asberg et al. 1976; Traskman et al. 1981).

Second, among habitually violent and impulsive offenders who have usually committed their crimes under the influence of alcohol, there is a tendency to a low blood glucose nadir in the Glucose Tolerance Test (GTT) (Virkkunen 1982, 1984, 1986a,b; Virkkunen and Huttunen 1982). This seems to depend at least on enhanced insulin secretion (Virk-

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kunen 1983a, 1986a,b). Even among normal students, the aggression scores in valid psychological questionnaire tests are increased in this phase of a Glucose Tolerance Test (Benton et al. 1982).

Third, among habitually violent and impulsive homicidal offenders, the cholesterol level is often significantly below normal, especially in younger age groups (Virkkunen 1983b). Also, among those adolescents who have an aggressive conduct disorder with attention deficit disorder, cholesterol levels are lower than in those without the aggressive conduct disorders (Virkkunen and Penttinen 1984).

In this study, we have measured plasma phospholipid essential fatty acids and levels of some of their main prostaglandin metabolites in groups of habitually violent and impulsive offenders and control male psychiatric personnel in a forensic psychiatric department. As essential fatty acids, and especially dihomogammalinolenic acid (DGLA), lower plasma cholesterol levels (Horrobin and Manku 1983), it was hypothesized that they also might be abnormal in habitually violent and impulsive individuals. Moreover, a major metabolite of DGLA, PGE_1, has been found to increase brain serotonin levels (Debnath et al. 1978), and to be involved in the regulation of insulin secretion (Robertson 1979, 1983; Giugliano et al. 1983). Formation of DGLA, and hence of PGE_1, is also increased by active insulin secretion (Brenner 1981). The outline of essential fatty acid metabolism can be seen in Table 1.

Methods

Subjects

In the Mental Examination Department of the Psychiatric Clinic of the Helsinki University Central Hospital, 34 consecutive habitually violent and impulsive male offenders were investigated. Every one of these had committed at least one violent crime and also had at least two discrete episodes of loss of control of aggressive impulses, resulting in serious assault or destruction of property. These actions had usually been grossly out of proportion to any precipitating psychosocial stressor and also had usually happened under the influence of alcohol. Of these individuals, 15 had had enough conduct disorder problems in childhood to fulfill the criteria of antisocial personality in DSM-III (Group B). There were 19 persons who had habitually violent and impulsive problems only in adulthood, and then usually under the influence of alcohol, so that they fulfilled the criteria of intermittent explosive disorder (Group A). Among Group A, the severity of the explosive

Table 1. Outline of Essential Fatty Acid (EFA) Metabolism

	n-6 EFAs		n-3 EFAs	
Linoleic (LA)	18:2n-6		18:3n-3	Alpha-linolenic (ALA)
	↓	delta-6-desaturase	↓	
Gamma-linolenic (GLA)	18:3n-6		18:4n-3	
Dihomogammalinolenic (DGLA)	20:3n-6		20:4n-3	
	↓	delta-5-desaturase	↓	
Arachidonic (AA)	20:4n-6		20:5n-3	Eicosapentaenoic (EPA)
Adrenic	22:4n-6		22:5n-3	
	↓	delta-4-desaturase	↓	
	22:5n-6		22:6n-3	Docosahexaenoic (DHA)

tendencies and the number of registered violent crimes varied considerably, but every individual fulfilled the DSM-III criteria for an intermittent explosive disorder. Of the group, four were impulsive arsonists, although they also tended to display similar behavior in interpersonal relations under the influence of alcohol. Altogether, 11 had had more than 2 registered violent crimes.

Due to the presence of many kinds of impulse-control problems, all the offenders with antisocial personality and 14 of the most severe cases with intermittent explosive disorder also fulfilled the criteria for borderline personality disorder. One person who had committed many acts of arson and a homicide had grand-mal epilepsy.

Those who were retarded (IQ under 68) or who had a chromosome abnormality (XYY or XXY) were excluded. Also excluded were those persons who had an antisocial personality without any habitually violent tendency (usually habitual thieves), or who had schizophrenia. Two of those who had an intermittent explosive disorder also fulfilled the criteria for paranoid personality disorder. Altogether, nine of the subjects had also been aggressive to themselves and had committed violent, impulsive suicidal attempts. All fulfilled the criteria for alcohol abuse in DSM-III, but not one had liver disease as shown by either physical examination or routine laboratory tests for liver enzymes (SGOT and SGPT).

The offenders had been in prison and thus without alcohol for several months (average 5) prior to the measurements. All offenders were hospitalized at least 3 days prior to the study and were given a diet with a minimum of 48%–55% of calories as carbohydrate and 37%–38% as fat, which is a standard in the University Central Hospital. In prison, during the preceding months, they had ingested a diet with the same composition.

The control group for comparison consisted of 16 healthy men from the personnel of the Psychiatric Clinic of Helsinki University Central Hospital (Group C). They were matched as closely as possible for age and weight with the offenders. None of the controls had any kind of aggression or alcohol abuse problems. They were advised to keep to their normal diet during the 3 days preceding the experiments. During these days, the controls were without alcohol and ate the main meals in the hospital, the meals being similar in composition to those of the offenders. The subjects and the controls had not taken any kind of medicine during the 3 days prior to the sample collections.

The mean age of all offenders was 33.2 ± 14.0 years (Group A 28.5 ± 12.9; Group B 36.8 ± 16.4) and of the controls was 33.0 ± 11.1 years. The mean weight of all offenders was 72.8 ± 9.1 kg (Group A 71.5 ± 9.3; Group B 73.2 ± 9.0) and of the controls 73.8 ± 8.0 kg.

Sample Collection and Analysis

After an overnight fast, blood was collected into glass vacutainers containing EDTA and was transferred immediately into siliconized glass tubes that contained 10 mg indomethacin in order to block ongoing prostaglandin synthesis. The blood was centrifuged and the plasma separated and frozen at −70°C. Once all the samples had been collected, they were sent in a single batch by air in dry ice to the Efamol Research Institute, Kentville, Nova Scotia, Canada. They remained frozen during the journey and were not thawed until analysis. Part of the plasma was used for analysis of fatty acids and part for analysis of prostaglandins.

For fatty acid analysis, the plasma samples were extracted with chloroform/methanol (2 : 1). The extract was filtered through sodium sulfate, evaporated to dryness, and taken

up in 0.5 ml chloroform/methanol. The various lipid fractions were then separated by thin-layer chromatography on silica gel plates. The phospholipid fraction was scraped off and methylated using boron trifluoride/methanol. The resulting methyl esters of the fatty acids were separated and measured using a Hewlett-Packard 5880 gas chromatograph (Hewlett-Packard, Palo Alto, CA) with a 6-ft column packed with 10% silar on Chromosorb WAW 106/230. The carrier gas was helium (30 ml/min). Detector temperature was 200°C, and injector temperature 220°C. Retention times and peak areas were automatically computed by a Hewlett-Packard Integrator. Peaks were identified by comparison with standard methyl fatty acid esters from NuChek Prep Inc., Elysian, MN.

For prostaglandin analysis, 1-ml plasma samples were acidified to pH 3 and extracted 3 times with ethyl acetate. The supernatants were pooled, evaporated to dryness, and reconstituted in phosphate buffer. PGE_1 (Institut-Pasteur), PGE_2 (Institut-Pasteur), and TxB_2 (Seragen, Boston) antisera were appropriately diluted in phosphate-buffered saline. Aliquots (0.1 ml) of the appropriate antibody solution were mixed with standard or samples and the appropriate tritiated prostanoids (New England Nuclear, Boston, MA). After incubation, the protein-bound material was separated by adding dextran-coated charcoal suspension, and the tubes were centrifuged. The supernatants were decanted into scintillation vials with 10 ml of a scintillation cocktail (Aquasol-2; New England Nuclear), and the radioactivity determined in a liquid scintillation counter. All radioimmunoassays were carried out in duplicate. The results were automatically calculated by computer.

Statistical Analysis

Analyses of Variance (ANOVA) were carried out, and if significant interactions were identified, the two-tailed *t*-tests were used in comparisons between groups. In separate analyses, Pearson's product-moment correlations (r) were computed to assess the relationships between plasma cholesterol and DGLA values and the numbers of registered violent crimes or the presence of violent impulsive suicidal attempts and DGLA among habitually violent and impulsive offenders.

Results

There were many significant differences from normals in fatty acid levels (Table 2). In summary, the most important abnormalities were as follows.

1. Levels of the main dietary essential fatty acid, linoleic acid (18 : 2 n-6), the precursor of the n-6 fatty acids, was below normal in intermittent explosive disorder.
2. Dihomogammalinolenic acid (DGLA) (20 : 3n-6) and some subsequent n-6 essential fatty acids (22 : 4n-6 and 22 : 5n-6) were elevated at the same time.
3. Of the n-3 metabolites of α-linolenic acid, docosahexaenoic acid (22 : 6n-3) was present at a low level in violent antisocial personality.
4. The monounsaturate, oleic acid (18 : 1n-9), was significantly elevated in both groups of habitually violent and impulsive offenders.

It therefore appeared that the conversion of linoleic acid to its n-6 metabolities was increased, especially so in intermittent explosive disorder.

The DGLA values correlated positively with plasma cholesterol levels in intermittent explosive disorder, but not in antisocial personality (Figure 1).

Among those habitually violent and impulsive offenders who had committed only one or two registered violent crimes, the DGLA value was 3.1 ± 0.6; but among those who

Table 2. Plasma Phospholipid Essential Fatty Acids among the Habitually Violent and Impulsive Male Offenders and the Male Controls

Fatty acids	Group A (n = 19)	Group B (n = 15)	Group C (n = 16)
16:0	28.26 ± 1.37	27.44 ± 1.24[c]	28.31 ± 1.18
18:0	10.30 ± 2.32	10.67 ± 2.01	10.14 ± 1.44
18:1	13.30 ± 1.62[a]	12.83 ± 1.13[a]	11.39 ± 1.09
18:2	21.20 ± 2.70[a]	23.11 ± 3.21	24.76 ± 3.54
18:3n6	0.08 ± 0.10	0.09 ± 0.09	0.06 ± 0.08
20:3n6	3.36 ± 0.67[b]	3.17 ± 0.52[c]	2.71 ± 0.52
20:4n6	9.09 ± 1.56	8.86 ± 1.55	9.21 ± 1.15
22:4n6	0.34 ± 0.07[d]	0.35 ± 0.17[e]	0.27 ± 0.09
22:5n6	0.10 ± 0.08[d]	0.12 ± 0.08[a]	TR
18:3n3	0.34 ± 0.07	0.42 ± 0.15	0.36 ± 0.12
20:5n3	1.91 ± 0.66	1.80 ± 0.64	2.19 ± 1.53
22:5n3	1.19 ± 0.31	1.16 ± 0.17	1.11 ± 0.17
22:6n3	5.93 ± 1.41	5.56 ± 1.16[c]	6.47 ± 0.81

The results show the concentration of each fatty acid in the phospholipid fraction in mg/100 mg total lipid present.

Group A, habitually violent and impulsive male offenders with intermittent explosive disorder; Group B, habitually violent and impulsive male offenders with antisocial personality; Group C, male controls without this kind of tendency.

[a] $p < 0.001$; [b] $p < 0.002$; [c] $p < 0.01$; [d] $p < 0.02$; [e] $p < 0.05$ (two-tailed t-test), significantly different from Group C.

had committed more, it was 3.6 ± 0.4. The difference was statistically significant ($t = 2.65$, $p < 0.02$). Impulsive, explosive arsonists had unusually high DGLA values (4.5, 3.7, 3.3, and 4.3). One of these was the epileptic (4.3).

Among those habitually violent and impulsive offenders who had committed violent, impulsive suicidal attempts, the mean DGLA value was 3.7 ± 0.4, whereas among those who had not committed these attempts, it was 3.1 ± 0.6. This difference was also statistically significant ($t = 2.76$, $p < 0.01$). Thus, it seemed that aggression, whether directed against other persons, the self, or the environment, was associated with high DGLA values.

Mean plasma cholesterol values did not differentiate between those who had committed many violent crimes ($t = 1.21$, $p = 0.23$) or who had made violent suicidal attempts ($t = 1.04$, $p = 0.31$).

With respect to PGE_1 derived from DGLA, it was increased in proportion to the DGLA levels in Group B (Table 3). PGE_1 was significantly lower in Group A than in Group B, and the ratio of PGE_1 to DGLA was significantly less in Group A than in either Group B or the controls. This suggests that conversion of DGLA to PGE_1 was below normal in Group A.

With regard to the two series products derived from arachidonic acid, PGE_2 and TxB_2, PGE_2 plus TxB_2 were higher in Group B than in either the controls or Group A. As arachidonic acid levels were similar in all three groups, this suggests enhanced formation of these substances in group B. 6-Keto-PGF_1-alpha levels were, however, significantly lower in both offender groups than in controls.

Discussion

Linoleic acid (18 : 2n-6), which was present in low concentration, and oleic acid (18 : 1n-9), which was found at a high level, are metabolized by the same series of enzymes. The first step is desaturation by the enzyme delta-6-desaturase. This enzyme preferentially

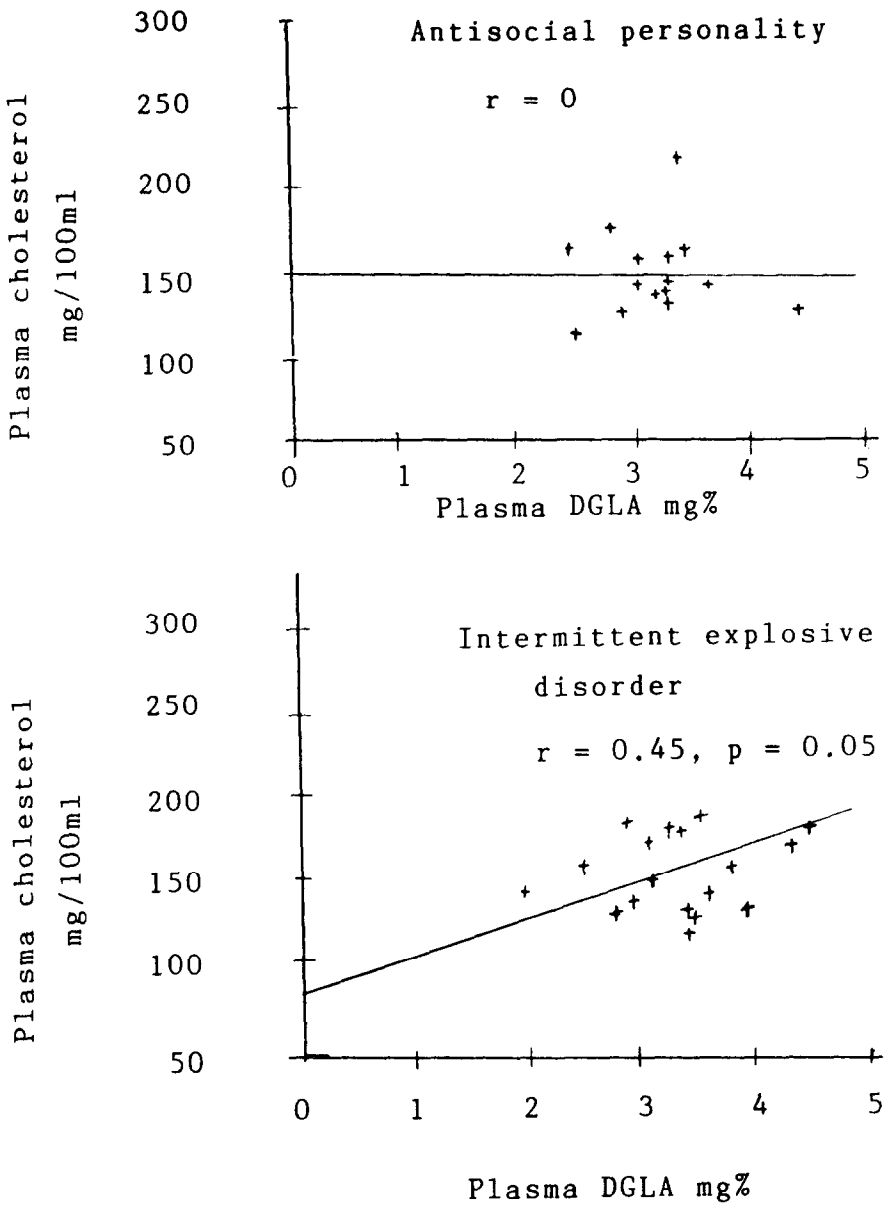

Figure 1. Correlation between plasma cholesterol and DGLA values.

metabolizes linoleic acid, and when this is present in adequate amounts, n-6, but not n-9, metabolites are formed. The pattern of fatty acids suggests increased activity of this enzyme among habitually violent and impulsive offenders. This is consistent with the high levels of insulin present in habitually violent and impulsive offenders and also with their low cholesterol levels: insulin activates, whereas diabetes and high cholesterol concentrations inhibit, the enzyme (Peluffo et al. 1970; Brenner 1981; Horrobin 1983;

Table 3. The Main Prostaglandins and Their Precursor Plasma Phospholipid Essential Fatty Acids among the Habitually Violent and Impulsive Male Offenders and the Male Controls

	Group A (n = 19)	Group B (n = 15)	Group C (n = 16)
Fatty acids			
DGLA (mg/100 mg)	3.36 ± 0.67[a]	3.17 ± 0.52[a]	2.71 ± 0.52
AA (mg/100 mg)	9.09 ± 1.56	8.86 ± 1.55	9.21 ± 1.15
Prostaglandins			
PGE_1 (ng/ml)	0.72 ± 0.6[b]	1.03 ± 0.9[b]	0.84 ± 0.4
PGE_2 (ng/ml)	1.33 ± 1.0[b]	2.61 ± 1.7[a,b]	1.62 ± 0.7
TxB_2 (ng/ml)	0.24 ± 0.1[a,b]	0.63 ± 0.5[a,b]	0.31 ± 0.1
6-Keto-PGF_1-alpha	0.95 ± 0.7[a]	1.01 ± 0.9[a]	1.55 ± 0.6
PGE_1 + 6-keto-PGF_1-alpha	1.67 ± 1.4[a,b]	2.04 ± 1.7[a,b]	2.39 ± 1.0
PGE_2 + TxB_2	1.57 ± 1.2[a,b]	3.24 ± 2.0[a,b]	1.93 ± 0.8
Prostaglandins/precursor phospholipid essential fatty acids			
PGE_1/DGLA	0.21	0.32	0.31
PGE_2 + TxB_2 + 6-keto-PGF_1-alpha/AA	0.28	0.48	0.38

Group A, habitually violent and impulsive male offenders with intermittent explosive disorder; Group B, habitually violent and impulsive male offenders with antisocial personality; Group C, male controls without this kind of tendency.

Analysis of Variance (ANOVA): [a]$p < 0.05$, significantly different from Group C (two-tailed t-test); [b]$p < 0.01$, offenders groups significantly different (two-tailed t-test).

Jamal et al. 1986). There is increased free insulin secretion during glucose tolerance testing in individuals with violent antisocial personality and especially with intermittent explosive disorder (Virkkunen 1983a, 1986a,b).

In those with a violent antisocial personality, there is decreased urinary cortisol secretion, whereas there is normal secretion in intermittent explosive disorder (Virkkunen 1985). Glucocorticoids induce the synthesis of an intracellular protein lipocortin, which then acts as an inhibitor of phospholipase A-2 and thereby reduces the release of arachidonic acid (Danon and Assouline 1978; Blackwell et al. 1980; Fuller et al. 1984). Thus, one expected that the effect of decreased cortisol production would be an increased formation of PGE_2 and TxB_2, as was found in the antisocial personality group. However, it had been shown earlier that PGE_2 and TxB_2 were also elevated in the serum of depressive patients (Lieb et al. 1983; Calabrese and Gulledge 1984), as was PGE_2 in the cerebrospinal fluid of women patients with unipolar depression with "character disorders" (Linnoila et al. 1983b). Gerner and Merrill (1983), who did not assay PGE_1 and PGE_2 separately, but PGE as a group, could not find any PGE abnormalities in the CSF.

Is there any rational explanation for the fact that high DGLA levels correlated with the number of violent crimes, and thus, with dangerous propensities? First, it is likely that this high value is correlated more with impulsiveness than with aggression, as the impulsive explosive arsonists in the sample had very high values. Moreover, among impulsive arsonists, the CSF 5-HIAA is still lower than among habitually violent and impulsive offenders, although the level is below normal in both groups (Virkkunen et al. 1987). Usually, arsonists are more impulsive than violent. Second, as habitually violent and impulsive offences usually happen under the influence of alcohol, what happens to essential fatty acids and

prostaglandins in this situation may be a major factor. Alcohol usually enhances the conversion of DGLA to PGE_1 at clinically relevant concentrations (Manku et al. 1979; Rotrosen et al. 1980; Segarnick et al. 1985). However, the effect of alcohol on DGLA is only in the free form: it does not enhance the conversion of phospholipid-bound DGLA to PGE_1 (Segarnick et al. 1985). The action of alcohol on arachidonic metabolism is considerably more variable and usually occurs only at rather high concentrations.

The effects of alcohol on CNS functions are mediated in part by its actions on EFA and PG metabolism and are in part dependent on these actions. For example, in mice, the effects of alcohol on sleep seem to be entirely dependent on PG formation, whereas those on balance seem to be independent of PGs (Segarnick et al. 1982).

There are two alternative interpretations of the likely effects of alcohol on PGE_1 in our groups of habitually violent and impulsive offenders. The first is that high levels of DGLA in phospholipids will also be associated with an above normal pool of free DGLA: in this case, alcohol would be expected to have a considerably greater effect than normal on PGE_1 and PGE_1-related behavior. The second dramatically opposite and more probable interpretation is that the phospholipid DGLA concentration is high because DGLA is being incorporated into the phospholipid from the free DGLA pool and is not being metabolized. In this case, free DGLA concentrations would be low, and the effect of alcohol on PGE_1 and PGE_1-related behavior would be less than normal. These aspects require further study.

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