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Polyunsaturated fatty acid status and relapse vulnerability in cocaine addicts

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Abstract

There is mounting evidence that low levels of some polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of depressive and aggressive disorders, including homicides. There is also evidence derived mostly from the animal literature that PUFAs could play a role in the abuse of substances through their action on central serotonergic and dopaminergic systems that are both known to play a role in reward mechanisms. In this study, we explored the possibility that the relapse rates of cocaine addicts discharged after a period of detoxification on an inpatient unit would be associated with their PUFA status. Thirty-eight patients were enrolled in the study. PUFA status was assessed only at baseline, shortly after admission. Resumption of substance use was assessed 3 months, 6 months and 1 year following discharge. Thirty-two patients remained available for follow-up for the duration of the study. Subjects who relapsed at 3 months had significantly lower baseline levels of total n-6 PUFAs, linoleic acid (LA, 18:2n-6), arachidonic acid (AA, 20:4n-6) and total n-3 PUFAs when compared to non-relapsers by ANCOVAs with age and weight as covariates. Lower baseline total n-6 PUFAs, LA and AA continued to predict relapse 6 months and 12 months following discharge. Age, marital status, educational level, cocaine use parameters or psychopathology did not differ between relapsers and non-relapsers. In conclusion, low PUFA status at baseline was a better predictor of relapse than cocaine use, sociodemographic or clinical parameters. These data suggest, but do not prove, the existence of a causal relationship between n-6 or n-3 status and relapse vulnerability in cocaine addicts, and provide a rationale for the exploration of possible relationships between relapse to addictive disorders and PUFA status in observational and interventional trials.

Keywords: PUFAs; Cocaine abuse; Recurrence

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1. Introduction

There is mounting evidence that low levels of some polyunsaturated fatty acids (PUFAs) are associated with various psychiatric disorders. Data available to date, derived from epidemiological studies focusing on the consumption of foods rich in n-3 PUFAs such as fish, from concomitant assessments of circulating levels of PUFAs and psychopathology and from the effects of PUFA supplementation on psychiatric symptoms, have recently been reviewed by Hibbeln and Salem (2001). These data seem to indicate that alterations in some PUFAs could play a role in the pathophysiology of depressive disorders, suicidal tendencies and aggressive disorders, including homicides.

The adult brain contains approximately 50–60% of its dry weight as lipids and close to 35% of these lipids are PUFAs. Fatty acids (FAs) are long chains of hydrocarbons connected by double bonds that are not saturated with hydrogen or single bonds saturated with hydrogen. PUFAs contain two or more double bonds between carbons, monounsaturated fatty acids (MUFAs), one, and saturated fatty acids (SFAs), none. Both major families of PUFAs are essential as mammals cannot place a double bond in the third carbon from the methyl end of the hydrocarbon chain (n-3 PUFAs) or the sixth carbon from the methyl end (n-6 PUFAs). Two PUFAs are highly concentrated in synaptic neuronal membranes, the n-6 PUFA arachidonic acid (AA or 20:4n-6) and the n-3 PUFA docosahexaenoic acid (DHA or 22:6n-3). Deficiencies in AA and DHA alter basic neuronal processes such as neurite outgrowth, synaptic growth formation, G protein coupled signal transduction, vulnerability to apoptosis and membrane physical properties (for review, see Salem et al., 2001). These biochemical and biophysical alterations result in functional deficits that include learning deficits among animals and impaired neurodevelopment among human infants (Salem et al., 2001). The central nervous system appears to have basic nutritional requirements for essential PUFAs, and many of the factors that link PUFA deficiencies to an increased vulnerability to affective and impulsive disorders may also increase vulnerability to addictive disorders.

To the best of our knowledge, evidence linking PUFA status and substance abuse is almost nonexistent. One observational study performed in heroin addicts showed that the ratio of n-6 to n-3 PUFAs was higher in the red blood cells of addicted individuals than in normal volunteers (Wannasirindr et al., 2000). Addictive disorders have a relapsing character, and sizable percentages of cocaine users resume cocaine use after periods of total interruption of drug use, for example, after stays on inpatient units. In light of the apparent increased vulnerability to the development of behavioral problems and psychiatric disorders of individuals with low PUFA status, we wondered whether decreases in some PUFAs at admission would be associated with the relapse rates of cocaine addicts after their discharge from a 3-week inpatient treatment program.

2. Methods

2.1. Patients

Participating patients were physically healthy. They did not have major abnormalities on liver function tests. They did not receive any medication during their stay in the hospital. They were screened with the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1990). Patients were enrolled in the study if they met DSM-III-R criteria for cocaine dependence but did not meet criteria for any other Axis I disorder (including dependence on any substance besides cocaine) as determined by the SCID. Patients with a history of intravenous use of any substance, patients who had used opiates in any form during the year preceding their admission and patients who had used on a daily basis more than 1 g/kg body weight (BW) of pure ethanol during the year preceding their admission were excluded from the study. The presence of Axis II disorders was not an exclusionary criterion. Patients were enrolled after the study was explained to them and after written informed consent was obtained.

2.2. Follow-up assessments

Patients were discharged after a stay of 3 weeks on the inpatient unit. Follow-up interviews were

scheduled 3 months, 6 months and 1 year after discharge. The interviews were structured and aimed at eliciting information about resumption of use of substances. Urine drug screens were used to support interview data. Relapse was defined as follows: (1) Use of cocaine for at least 5% of the time elapsed between two interviews. (2) Inpatient admission for cocaine abuse during the same period. (3) Average daily intake of more than 1 g/kg BW of pure ethanol during the time elapsed between two interviews. (4) Inpatient admission for alcohol abuse during the same period.

None of the patients had used heroin during the follow-up period. Once a patient was considered to have relapsed during any of the time intervals surveyed, he was considered to have relapsed for the duration of the follow-up period.

2.3. Biochemical measurements

Fasting plasma samples were collected 2 weeks after patients had been admitted to the hospital and FAs measured at the NIAAA Laboratory of Membrane Biophysics and Biochemistry. Measurements included total SFAs; total MUFAs; total PUFAs; total n-6 PUFAs; linoleic acid (LA: 18:2n-6); arachidonic acid (AA, 20:4n-6); docosapentaenoic acid (DPA, 22:5n-6); total n-3 PUFAs; α-linolenic acid (ALA, 18:3n-3); eicosapentaenoic acid (EPA, 20:5n-3); and docosahexaenoic acid (DHA, 22:6n-3). The method used involved lipid transmethylation and extraction, followed by gas chromatographic determination. A direct methylation procedure, carried out in 5.0-ml methanol–acetyl chloride (50:1 v/v), followed by extraction with hexane, was performed on 200-μl aliquots of plasma, to which methyl tricosanoate (23:0) had been added as an internal standard (Lepage and Roy, 1988). Fatty acid methyl esters were then analyzed, according to the method of Moriguchi et al. (2000), on a gas chromatograph (Model 5890; Hewlett–Packard, Palo Alto, CA, USA) equipped with a flame ionization detector and fused silica capillary column (DB-FFAP; 30 m×0.25 mm×0.25 μm; J and W, Folsom, CA, USA), with a carrier gas (hydrogen) at a linear velocity of 50 cm/s. Injector and detector temperatures were set to 250 °C and the oven temperature program was as follows: 130 to 175 °C at 4 °C/min, 175 to 210 °C at 1 °C/min, and then to 245 °C at 30 °C/min with a final hold for 15 min. The fatty acid methyl esters from 10:0 to 24:1n-9 were identified by comparison with the retention time of a standard mixture (462; Nu-Check-Prep, Elysian, MN, USA). The concentrations of individual and total fatty acids were quantified by comparison with the 23:0 internal standard. Intra-assay and inter-assay coefficients of variance were less than 3% and less than 5%, respectively.

2.4. Statistical analysis

Calculations were made with data collected in the patients available to follow-up for the entire 1-year period. Comparisons of relapsers' and non-relapsers' demographic and clinical data were made with two-tailed Student's *t*-tests, chi-square tests or Fisher's exact tests. Fatty acid levels were those obtained while the patients were hospitalized. Comparisons of these levels in relapsers and non-relapsers were performed 3 months, 6 months and 1 year after discharge with analyses of covariance (ANCOVAs) using age and weight as covariates.

3. Results

Out of the 38 patients who participated in the study, six patients (13%) were lost to follow-up during the 1-year period that followed their discharge from the hospital. Fig. 1 shows the percentages of those who relapsed among the 32 patients who remained available to follow-up for the duration of the study. Nine of these patients (28%) had relapsed when interviewed 3 months after their discharge. The relapse rate continued to increase during the following 9 months but did so more slowly. After 1 year, only three additional patients (9%) had relapsed. A total of 12 patients (37% of the population surveyed) had thus resumed drug use within 1 year of discharge from an inpatient unit. Six of the 12 relapsers had to be rehospitalized for drug-related problems.

The demographic and clinical characteristics of the 32 individuals who remained available to follow-up for 1 year are presented in Table 1. There were no significant differences between non-

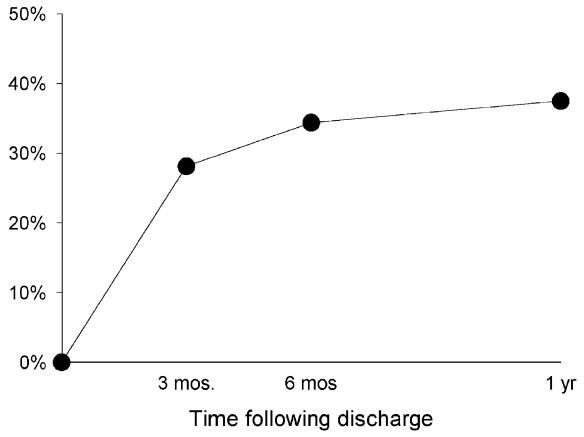

Fig. 1. Cumulative percentages of cocaine addicts who relapsed during a 1-year follow-up period.

relapsers and relapsers in age, marital status, educational level, cocaine use variables, alcohol use variables or Axis II diagnoses.

The FA values of non-relapsers and relapsers are shown in Table 2. Total SFAs and total MUFAs were higher in non-relapsers, but differences between the two groups did not reach statistical significance. However, comparisons between the two groups showed significantly lower levels of total PUFAs, total n-6, LA, AA and total n-3 in relapsers 3 months following their discharge. Significant differences between the two groups in total PUFAs, total n-6 PUFAs, LA and AA were still present 6 months and 1 year following discharge, but the differences between total n-3 PUFAs were no longer significant.

4. Discussion

In this study of non-opiate and non-alcohol dependent cocaine addicts whose FAs had been determined during a 3-week stay on an inpatient unit, the PUFA profile of those who relapsed was significantly different from that of non-relapsers. Three months after their discharge, patients who

Table 1
Demographic and clinical characteristics of non-relapsers and relapsers during a 1-year follow-up period

	No relapse ($n=20$)	Relapse ($n=12$)	P value
Age	36.95±7.48	35.25±7.07	NS
Marital status			
% Never married	30.0 (6/20)	25.0 (3/12)	NS
% Married	25.0 (5/20)	16.7 (2/12)	NS
% Separated/divorced	45.0 (9/20)	58.3 (7/12)	NS
Educational level (years)	12.0±0.43	11.6±0.94	NS
Cocaine use			
Number of years of use	5.65±5.04	7.93±5.06	NS
Maximum daily amount (in grams)	2.87±2.57	2.44±1.49	NS
Average daily amount (in grams)	2.01±1.80	1.92±1.53	NS
Alcohol use			
% with no use	25.0 (5/20)	25.0 (3/12)	NS
% using 0.5 g/kg/day or less	30.0 (6/20)	41.7 (5/12)	NS
% using from 0.5 to 1 g/kg/day	45.0 (9/20)	33.3 (4/12)	NS
Personality disorders			
% with any personality disorder	60.0 (12/20)	58.3 (7/12)	NS
% with antisocial personality disorder	50.0 (10/20)	58.3 (7/12)	NS
% with borderline personality disorder	15.0 (3/20)	25.0 (3/12)	NS

Comparisons between the two groups were made with two-tailed Student's *t*-tests, chi-square tests with Yates' continuity correction or Fisher's exact tests, as appropriate.

Table 2
Index admission PUFA levels in cocaine addicts who did and did not relapse following discharge

	Time following discharge								
	3 Months			6 Months			1 Year		
	No relapse ($n=23$)	Relapse ($n=9$)	*P*	No relapse ($n=21$)	Relapse ($n=11$)	*P*	No relapse ($n=20$)	Relapse ($n=12$)	*P*
Total SFAs	789±255	675±141	NS	799±264	677±128	NS	812±265	666±128	NS
Total MUFAs	633±248	511±129	NS	643±257	513±118	NS	654±258	505±116	NS
Total PUFAs	1104±175	945±109	0.005	1109±182	963±106	0.032	1116±184	964±101	0.035
Total n-6	1030±162	884±96	0.006	1037±168	897±91	0.024	1043±170	899±87	0.016
LA	739±132	634±58	0.015	743±138	646±58	0.050	748±140	646±55	0.035
AA	209±37	175±37	0.013	212±37	176±33	0.016	212±38	179±34	0.032
DPA	7.01±2.09	7.00±2.95	NS	7.14±2.12	6.74±2.73	NS	7.23±2.13	6.63±2.63	NS
Total n-3	74.1±16.1	60.2±17.5	0.033	72.6±16.0	65.7±19.8	NS	72.9±16.4	65.8±18.9	NS
ALA	14.3±5.6	11.1±2.7	NS	14.1±5.5	12.2±4.2	NS	14.1±5.7	12.2±4.0	NS
EPA	14.3±4.4	11.9±3.8	NS	14.2±4.6	12.5±3.7	NS	14.4±4.6	12.3±3.6	NS
DHA	32.2±10.2	26.3±11.6	NS	31.2±10.0	29.2±12.7	NS	31.1±10.2	29.4±12.1	NS
n-6/n-3	14.2±2.1	15.4±3.0	NS	14.5±1.9	14.6±3.4	NS	14.6±1.9	14.5±3.2	NS

Values (means±S.D.) are expressed in μg/ml, except for ratios.
Comparisons between groups were made with ANCOVAs, using age and weight as covariates.

relapsed were found to have significantly lower levels of total PUFAs, total n-6 PUFAs and total n-3 PUFAs while hospitalized. Among individual PUFAs, LA and AA, which were significantly lower in relapsers, differentiated the two patient groups. Significant differences between the two groups in total PUFAs, total n-6 PUFAs, LA and AA were still evident 6 months and 1 year following discharge. This was not the case for n-3 PUFAs, which were lower in those who relapsed 6 months and 1 year following discharge but not significantly so. Although total SFA and total MUFA levels were higher in non-relapsers, differences between the groups did not reach statistical significance. Moreover, it is presently believed that it is mostly changes in AA and in DHA that alter neuronal processes because of their concentration in neuronal membranes (Yehuda et al., 1999).

PUFAs were better predictors of relapse than a number of sociodemographic and clinical data. Comparisons of age, marital status, educational level, cocaine and alcohol use variables and number of Axis II diagnoses did not reveal any significant difference between those who relapsed and those who did not, although relapsers were more frequently divorced or separated and had used cocaine for a longer period prior to their admission. The role of Axis I diagnoses in substance use resumption could not be assessed because patients with these diagnoses were excluded from the study. The absence of significant associations between relapse vulnerability and sociodemographic, substance use or clinical data found in this study can be viewed in the context of existing literature indicating a lack of agreement about the predictive value of these baseline variables for long-term outcome in cocaine addicts.

There is mounting evidence that PUFAs could influence serotonergic and dopaminergic neurotransmission, which are both known to play a role in reward mechanisms. Higher concentrations of plasma DHA were found to predict higher levels of CSF 5-HIAA in healthy controls and late onset alcoholics (Hibbeln et al., 1998). This finding suggests that increasing DHA consumption may increase brain serotonin and thus decrease depression, impulsive tendencies and aggressive behavior. Two recent double-blind placebo-controlled studies demonstrated the efficacy of n-3 PUFAs in the treatment of depression. Nemets et al. (2002) reported highly significant benefits of the addition of EPA to antidepressant treatment in as little as 3 weeks in treatment-resistant depressives and Peet and Horrobin (2000) reported that the depressive

symptoms of up to 70% of treatment-resistant subjects who received EPA improved by 50%. One study demonstrated the efficacy of n-6 and n-3 PUFAs in the treatment of violence. Gesch et al. (2002) recently reported that felony level violent offences were reduced by 35% among prisoners supplemented with n-6 and n-3 fatty acids, multivitamins and minerals in a placebo-controlled trial.

Preclinical studies have also shown that modifying the FA composition of the diet can influence neurotransmitter level. The addition of AA and DHA to the diet of piglets increased the frontal cortex concentrations of 5-HT, tryptophan, dopamine and homovanillic acid (de la Pressa Owens and Innis, 2000). A decrease in FA levels was found to affect 5-HT as well. Rats fed a diet deficient in n-3 FAs had an increase in 5-HT receptor density in the frontal cortex with no change in binding activity (Delion et al., 1996). These changes were similar to those reported by Stanley and Mann (1983) among suicide victims. Olsson et al. (1998) observed that rats fed a diet low in n-3 FAs had decreased concentrations of 5-HT and 5-HIAA in several brain regions including the cortex. Diets supplemented with or made deficient in FAs affect the dopaminergic system. Dopamine levels were 40% greater in the frontal cortex of rats fed fish oil by comparison with those fed a control diet (Chalon et al., 1998). Conversely, rats fed a diet deficient in n-3 FAs had lower levels of endogenous dopamine and decreased numbers of D_2 receptors in the frontal cortex (Delion et al., 1994). They also had a decrease in the number of dopaminergic vesicles in presynaptic terminals (Zimmer et al., 2000b) and a significant reduction in the amount of dopamine released after tyramine stimulation (Zimmer et al., 2000a).

Other studies did not evaluate the effects of dietary modifications on dopaminergic function but assessed the effects of some FAs (mostly AA) on the dopamine transporter whose blockage by cocaine plays an important role in the cocaine-induced euphoria. These experiments were acute and their clinical relevance is not presently known. The dopamine transporter is a member of the family of Na^+, Cl^- dependent transporters. In oocytes expressing the human dopamine transporter, both AA and DHA, acutely and exogenously added, increased the transporter cation conductance 50-fold (Ingram and Amara, 2000). It is thus possible that, in addition to its many effects on neurons, AA may also alter neuronal signaling through its action on the dopamine transporter. AA was found to inhibit dopamine reuptake (Zhang and Reith, 1996; L'hirondel et al., 1995) and to stimulate its release (L'hirondel et al., 1995). On the basis of these studies, it could hypothesized that in cocaine addicts with lower levels of AA, less dopamine is released and more dopamine is transported back into neurons than is the case for addicts with higher AA levels. This could lead those individuals with lower AA levels to consume larger amounts of cocaine in order to increase the amount of dopamine in the synaptic cleft and obtain the desired effect.

The present study has methodological limitations. Fatty acids were measured only once, 2 weeks after patients were admitted to an inpatient unit. No measurement was obtained during the follow-up period. A single FA measure probably represented a useful (although not optimal) measure of preadmission FA status and FA status following discharge as dietary habits are usually well established by adulthood and do not tend to vary greatly over time, especially with regards to PUFA composition. Some PUFA values were nevertheless significantly associated with relapse risk for up to 1 year following discharge. It should also be pointed out that we selected cocaine abusers whose alcohol consumption was non-existent or moderate and who did not have important abnormalities on liver function tests. It is possible that our findings could not be generalized to groups of cocaine addicts who consume larger amounts of alcohol.

Available evidence does not permit us to conclude that a causal relationship exists between n-6 or n-3 PUFA status and risk for developing addictive disorders, but it provides a rationale for further exploration of links between these disorders and PUFA deficiencies as well as for interventional trials. Work in this field could lead to the use of treatments that are both well tolerated and inexpensive.

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