ELSEVIER

Drug and Alcohol Dependence 71 (2003) 319–323

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Short communication

Polyunsaturated fatty acid status and aggression in cocaine addicts

Laure Buydens-Branchey [a,b,*], Marc Branchey [a,b], Dana L. McMakin [c], Joseph R. Hibbeln [c]

[a] *Department of Psychiatry, State University of New York—Health Science Center at Brooklyn, Brooklyn, NY 11209, USA*
[b] *Veterans Affairs New York Harbor Healthcare System, Brooklyn Campus (11S/BK), 800 Poly Place, Brooklyn, NY 11209, USA*
[c] *National Institute of Alcohol Abuse and Alcoholism, Rockville, MD 20852, USA*

Received 21 January 2003; received in revised form 10 April 2003; accepted 15 April 2003

Abstract

Background: There is mounting evidence that low levels of some polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of aggressive disorders. PUFA status is influenced by nutritional factors and because of our observation that some substance abusers have poor dietary habits, we explored the possibility that the fatty acids (FA) profiles of cocaine addicts with and without aggressive tendencies would differ. We also explored the possibility that their FA levels would change after a 2 week stay on an inpatient unit where a standard diet would be provided. *Methods:* Plasma levels of FAs were measured in 24 cocaine addicts admitted to an inpatient substance abuse unit. Six patients had a past history of aggression and 18 did not. *Results:* A comparison of the FA levels of aggressive and non-aggressive patients performed 3.7 ± 2.0 days after their admission did not reveal any significant difference in saturated FAs (SFAs) or monounsaturated FAs (MFAs). Aggressive patients had significantly lower levels of the n-6 PUFA docosapentaenoic acid (DPA), of total n-3 PUFAs and of the n-3 PUFA docosahexaenoic acid (DHA), and a marginally significant increase in the ratio of n-6 to n-3 PUFAs. Measurements performed 18.4 ± 1.3 days after admission showed that most FAs had increased in the two patient groups. Some PUFAs, especially those of the n-3 series, increased more sharply in the aggressive patients. As a result, PUFA differences between groups that were present shortly after admission became non-significant. *Conclusions:* These data suggest that patients' diets prior to their hospitalization were less than optimal and that the diet of the aggressive individuals might have been particularly deficient in n-3 rich nutrients. These data also give additional support to evidence indicating a possible link between an n-3 deficiency and aggression in humans.
Published by Elsevier Science Ireland Ltd.

Keywords: Cocaine addiction; Aggression; Polyunsaturated fatty acids

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 an n-3 deficiency or an increase in the n-6/n-3 ratio could play a role in the pathophysiology of depressive disorders, suicidal tendencies and aggressive disorders, including homicides. Associations between psychiatric disorders and PUFAs can be understood in light of the fact that some PUFAs, particularly arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3), are structural components of neuronal membrane phospholipids and influence neuronal function (Yehuda et al., 1999). The brain demand for PUFAs has to be supported by an exogenous supply. Dietary DHA, for example, is the main source of the DHA incorporated into neuronal membranes (Lauritzen et al., 2001).

Evidence linking low PUFA levels and violence or aggression is still scant. In a cross-national analysis of homicide mortality rates, based on a 1996 World Health

* Corresponding author. Tel.: +1-718-836-6600x6129; fax: +1-201-567-3726.
E-mail address: lbuydens@worldnet.att.net (L. Buydens-Branchey).

03765-8716/03/$ - see front matter. Published by Elsevier Science Ireland Ltd.
doi:10.1016/S0376-8716(03)00168-6

Organization report that included 26 countries, Hibbeln (2001) found that higher mortality rates due to homicide were significantly correlated with lower consumption of seafood, which is rich in n-3 PUFAs. Hamazaki et al. (1996, 1998) reported that the administration of DHA reduced measures of hostility in the Rosensweig Picture Frustration Test among Japanese students undergoing the stress of University exams but failed to reproduce these effects in students evaluated under non-stressful conditions. Associations between circulating levels of PUFAs and violence were studied by Virkunnen et al. (1987), who observed increases in levels of PUFAs of the n-6 series in habitually violent and impulsive offenders by comparison with healthy subjects. Gesch et al. (2002) have recently reported that felony level violent offences were reduced by 37% among prisoners supplemented with n-3 fatty acids (FA), multivitamins and minerals in a placebo-controlled trial.

High frequency and high severity violent or aggressive behaviors are extensively bound up with drug use (Blumstein et al., 1986). We have observed that the diet of some substance abusers is less than optimal because of lack of appetite, lack of interest in food while "high" or unwillingness to spend money for food instead of drugs (unpublished). It appeared thus of interest to study patients known to exhibit violence more frequently than the general population and whose dietary habits could result in alterations in FA profiles. The subjects of this study were cocaine addicts, with and without aggressive tendencies, admitted to an inpatient drug rehabilitation unit. They were chosen from sequential admissions to the unit. Their FA status was assessed shortly after their admission and again 2 weeks later. Our goals were (1) to compare the FA status of patients with and without aggressive tendencies (2) to explore changes in FAs after a stay of 2 weeks on a unit providing a drug-free environment and a standard diet.

2. Methods

2.1. Patients

Patients selected for participation in the study were 24 hospitalized men whose age (mean ± S.D.) was 39.0 ± 6.1 years. They were treatment seeking and hospitalization was part of their regular treatment. In order to ensure that they were kept in a drug free environment, they underwent a thorough search upon admission to the rehabilitation unit, were prevented from receiving visitors and were not allowed to leave the premises unless accompanied by a staff member. The unit was kept locked at all times. The study was approved by the institution IRB and written informed consent was obtained from all participating patients after the study had been fully described.

Patients were physically healthy. They did not receive any medication during their stay in the hospital. They were screened with the Structured Clinical Interview for DSM IV or SCID (First et al., 1997). Additional information was obtained about number of years of regular use of substances and amounts of substances consumed during the month preceding admission. Patients were enrolled in the study if they met DSM IV 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 0.8 g/kg BW of pure ethanol during the year preceding their admission were excluded from the study. Patients were also administered a slightly modified version of the Brown–Goodwin Assessment for Life History of Aggression (Brown et al., 1981). This assessment is aimed at obtaining information about the following behavioral categories: non-specific fighting; specific assaults on people, animals or property; school disciplinary problems; disciplinary problems at work; antisocial behavior not involving the police; antisocial behavior involving the police; military disciplinary problems not involving the military judicial system; military disciplinary problems involving the military judicial system. It comprises one other category, temper tantrums, that was not used in the present study. In each category, non occurrence is scored as 0, one event as 1, two events as 2, three, several or frequent events as 3 and four or more, many or numerous events as 4. Patients with a total score of 8 or more were considered to have a history of aggression.

2.2. Biochemical determinations

Blood samples were collected twice, after an overnight fast, 3.7 ± 2.0 and 18.4 ± 1.3 days after admission. Blood was centrifuged and FAs measured in plasma samples kept frozen at −80 °C from the time of collection until biochemical determinations were performed. Determinations of saturated FAs (SFAs), monounsaturated FAs (MUFAs), total n-6 PUFAs, linoleic acid (LA, 18:2n-6), AA, docosapentaenoic acid (DPA, 22:5n-6), total n-3 PUFAs, α-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3) and DHA were determined by gas chromatography at the NIAAA Laboratory of Membrane Biophysics and Biochemistry (Hibbeln et al., 1998a).

2.3. Data analysis

Differences between non-aggressive and aggressive patients' first and second measures were assessed with

two-tailed Student's t-tests. Percentages of increases of second measures over first ones were calculated for each patient. Means of these percentages were calculated for aggressive and non-aggressive patients and were compared with two-tailed Student's t-tests.

3. Results

3.1. Patient characteristics and drug use variables

None of the correlations between FA levels and patients' age, weight, number of years of cocaine use and amounts of cocaine used during the month preceding admission, when calculated in the entire patient group, were significant. Comparisons between the two patient groups were not significant but the aggressive patients were slightly younger (38.0 ± 5.3 vs. 39.6 ± 6.5 years), weighted less (71.9 ± 9.3 vs. 76.7 ± 10.1 kg), had used cocaine for a longer period (12.9 ± 5.5 vs. 11.0 ± 7.6 years) and had used more cocaine during the month preceding admission (50.9 ± 36.0 vs. 38.3 ± 19.1 g).

3.2. History of aggression

Six patients were determined to have had a history of aggression on the basis of their answers to the modified version of the Brown–Goodwin questionnaire. The aggression score of these patients was significantly higher than that of the non-aggressive patients (13.3 ± 4.8 vs. 3.1 ± 1.6, $P < 0.003$). All the aggressive patients had a history of assaultive behavior. These behaviors included hitting and kicking others, assaulting others with guns, knives, pipes and chains and beating girlfriends. All had been involved in property damage that included the breaking up of car windows, of radios, of TV sets, of furniture and the destruction of park benches. Other criminal behaviors included armed robberies, burglaries, or rapes. They had all been jailed. Only four of the 18 non-aggressive patients (20.2%) reported having assaulted others but their assaults were less frequent and of a less severe nature. Individuals in both groups reported having committed crimes that did not involve violence such as forgeries, receiving stolen property or thefts without confrontation of the victims but fewer non-aggressive patients reported having committed these crimes (27.7 vs. 100%).

3.3. Fatty acid measures

Comparisons of the aggressive and non-aggressive patients' first FA measures did not show any significant difference between groups in total FAs, SFAs, MUFAs, total PUFAs or total n-6 PUFAs (see Table 1). On the other hand, DPA, total n-3 PUFAs and DHA were significantly lower in the aggressive patients ($P = 0.047$; 0.039 and 0.004, respectively). The n-6/n-3 ratio was higher in the aggressive patients. A comparison of the two patient groups was marginally significant ($P = 0.055$).

During the 2 week interval separating the first and the second measures, most FAs increased in both groups but the increase in some FAs (especially the n-3 PUFAs) was more pronounced in the aggressive patients. One of the consequences of these FA changes over time was that the significant differences between patient groups that were present shortly after admission became non-significant.

Fig. 1 illustrates the percentages of changes in some PUFAs from first to second measures in aggressive and non-aggressive patients. This figure shows that the total n-3 PUFAs increased by 49.2% and DHA by 57.7% in the aggressive patients versus 11.7 and 7% in the non-aggressive patients ($P = 0.011$ and 0.001, respectively). There was a slight increase in the percentage of change in the n-6/n-3 ratio in the non-aggressive subjects but a significant decrease in this ratio in the aggressive individuals ($P = 0.032$), secondary to the increase in the n-3 PUFAs.

4. Discussion

In this study, FAs were measured in cocaine addicts shortly after their admission to an inpatient unit. Patients with a history of aggressive behavior were found to have significantly lower levels of DPA, of total n-3 PUFAs and of DHA and an almost significantly higher n-6/n-3 ratio when compared with patients with no aggression history. After 2 weeks of hospitalization, most PUFAs increased in the two patient groups but some PUFAs, especially those of the n-3 series increased more sharply in the group of aggressive patients. One of the consequences of PUFA changes over time was that the significant differences between aggressive and non-aggressive patients that were present shortly after admission became non-significant 2 weeks later.

These data give further support to evidence indicating a possible link between an n-3 deficiency or an increase in the n-6/n-3 ratio and violence and aggression in humans. Data derived from preclinical studies also indicate that increases in n-6 PUFAs influence aggressive behavior. Hilakivi-Clarke et al. (1996) observed that a diet rich in n-6 PUFAs increased the aggressive behavior of adult male mice and rats. An increase in aggressive behavior was also observed in the offspring of mice fed a diet supplemented with n-6 PUFAs during pregnancy (Raygada et al., 1998).

The increase in most FAs in the two patient groups after a stay of only 2 weeks on an inpatient unit where a standard diet was provided could indicate that, prior to their admission, patients had poor dietary habits. The

Table 1
FA values in non-aggressive and aggressive cocaine adddicts

	First measures (3.7±2.0 days after admission)			Second measures (18.4±1.3 days after admission)		
	Non-aggressive ($N=18$)	Aggressive ($N=6$)	Non-aggressive vs. aggressive (P value)	Non-aggressive ($N=18$)	Aggressive ($N=6$)	Non-aggressive vs. aggressive (P value)
Tot FA	2202±471	1879±222	ns	2374±589	2285±302	ns
SFA	727±180	600±107	ns	774±219	709±96	ns
MFA	545±146	459±101	ns	563±199	540±90	ns
PUFA	930±166	819±92	ns	1037±190	1036±158	ns
Tot n-6	870±153	774±87	ns	971±171	968±158	ns
LA	616±107	547±99	ns	695±119	698±146	ns
AA	171±36	152±39	ns	185±40	181±32	ns
DPA	5.65±1.49	4.18±0.87	0.047	7.02±1.99	6.67±0.98	ns
Tot n-3	59.7±15.1	45.6±5.8	0.039	66.2±22.5	67.5±10.3	ns
ALA	10.15±3.79	8.79±5.46	ns	11.75±4.59	14.64±5.22	ns
EPA	11.89±3.77	11.18±2.80	ns	12.90±5.92	12.81±2.05	ns
DHA	26.92±7.60	16.74±2.75	0.004	28.80±10.83	26.17±5.31	ns
n-6/n-3	14.93±2.40	17.05±1.50	0.055	5.49±3.01	14.70±3.76	ns
DPA/DHA	220±.067	267±.077	ns	260±.082	266±.061	ns

Abbreviations; Tot FA, total FAs; SFA, saturated FAs; MFA, monounsaturated FAs; PUFA, polyunsaturated FAs; LA, linoleic acid (18:2n-6); AA, arachidonic acid (20:4n-6); DPA, docosapentaenoic acid (22:5n-6); ALA, α-linolenic acid (18:3n-3); EPA, eicosapentaenoic acid (20:5n-3); DHA, docosahexaenoic acid (22:6n-3). Values (Means±S.D.) are expressed in ng/ml except for the ratios. The significance level of differences between groups was evaluated by two-tailed Student's t-tests. P values for three significant differences and one marginally significant difference are shown.

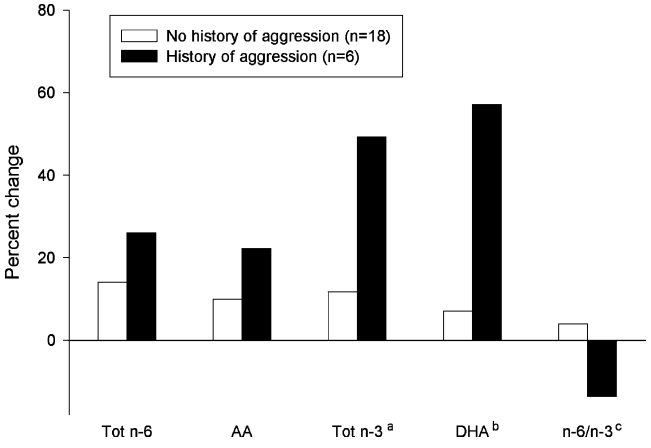

Fig. 1. Percentages of PUFA changes from first to second determinations in hospitalized cocaine addicts. PUFAs were measured 3.7±2.0 and 18.4±1.3 days following admission. Significant differences between patients with and without a history of aggression were found for (a) total n-3 PUFAs: $P=0.011$, (b) DHA: $P=0.001$ and (c) n-6/n-3 ratio: $P=0.032$. Abbreviations: PUFAs, polyunsaturated fatty acids; AA, arachidonic acid (20:4n-6); DHA, docosahexaenoic acid (22:6n-3).

more robust increase in the n-3 PUFAs in the aggressive patients could reflect the fact that their pre-admission diets were particularly deficient in n-3 rich nutrients. This is, however, speculative because dietary histories were not obtained in the course of the present study.

It is possible that dietary intake of AA, EPA and DHA may affect serotonergic function in the frontal cortex which is thought to be central to the pathophysiology of aggressive, suicidal and depressive behaviors (Mann, 1998). In the animal literature, it has been shown that diets either supplemented with or made deficient in PUFAs influence neurotransmitter levels. For the first 18 days after birth, de la Presa Owens and Innis (1999) fed piglets either standard infant formulas or formulas supplemented with AA and DHA and observed that the concentration of serotonin, tryptophan, dopamine, HVA and norepinephrine were nearly doubled in the frontal cortex of supplemented infants. These data are consistent with a human study which reported correlations between higher plasma concentrations of DHA and AA with higher concentrations of cerebrospinal fluid 5-hydroxy-indole-acetic acid (5-HIAA), central serotonin's main metabolite (Hibbeln et al., 1998b). Conversely, 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. These data suggest that the regulation of frontal cortex serotonergic function could be one mechanism linking PUFA status and aggression.

The present study has limitations. Dietary histories were not obtained and we did not determine whether changes in FA profiles were accompanied by behavioral changes. Confirmation of the benefits of increasing n-3 PUFA intake either through dietary modification or through the administration of supplements will necessi-

tate substantial further research. Future trials should include baseline dietary questionnaires and FA measurements in order to screen out individuals who are not FA deficient. These trials should also involve the monitoring of FAs and the assessment of clinical changes that may accompany or follow modifications in FA profiles. Future work in this area may yield inexpensive and well tolerated treatments for a variety of psychiatric illnesses, including the depressive episodes and suicidal and aggressive behaviors found to be frequently associated with the abuse of a variety of substances.

Acknowledgements

This work was supported by the Veterans Administration by NIDA and by the NIAAA.

References

Blumstein, A., Cohen, J., Roth, J.A., Visher, C.A., 1986. Criminal Careers and "Career Criminals". National Academy of Sciences, Washington, DC.

Brown, G.L., Ballenger, J.C., Minichiello, M.D., Goodwin, F.K., 1981. Human aggression and its relationship to CSF 5-HIAA, MHPG, and HVA. In: Sandler, M. (Ed.), Psychopharmacology of Aggression. Raven Press, New York, pp. 131–147.

de la Presa Owens, S., Innis, S.M., 1999. Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linoleic acid and alpha-linolenic acid deficient diet in formula-fed piglets. J. Nutr. 129, 2088–2093.

Delion, S., Chalon, S., Guilloteau, D., Besnard, J.C., Durand, G., 1996. α-Linolenic acid dietary deficiency alters age-related changes of dopaminergic and serotoninergic neurotransmission in the rat frontal cortex. J. Neurochem. 66, 1582–1591.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). American Psychiatric Press, Washington, DC.

Gesch, C.B., Hammond, S.M., Hampson, S.E., Eves, A., Crowder, M.J., 2002. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners: randomized, placebo-controlled trial. Br. J. Psychiatry 181, 22–28.

Hamazaki, T., Sawazaki, S., Itomura, M., Asaoka, E., Nagao, Y., Nishimura, N., Yazawa, K., Kuwamori, T., Kobayashi, M., 1996. The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. J. Clin. Invest. 97, 1129–1133.

Hamazaki, T., Sawazaki, S., Nagao, Y., Kuwamori, T., Yazawa, K., Mizushima, Y., Kobayashi, M., 1998. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. Lipids 33, 663–667.

Hibbeln, J.R., 2001. Homicide mortality rates and seafood consumption: a cross-national analysis. World Rev. Nutr. Diet 88, 41–46.

Hibbeln, J.R., Salem, N., Jr, 2001. Omega-3 fatty acids and psychiatric disorders. Current status of the field. In: Mostofosky, D., Yehuda, S., Salem, N., Jr (Eds.), Fatty Acids: Physiological and Behavioral Functions. Humana Press, Totowa, NJ, pp. 311–330.

Hibbeln, J.R., Linnoila, M., Umhau, C., Rawlings, R., George, D.T., Salem, N., Jr, 1998a. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. Biol. Psychiatry 44, 235–242.

Hibbeln, J.R., Umhau, J.C., Linnoila, M., George, D.T., Ragan, P.W., Shoaf, S.E., Salem, N., Jr, 1998b. A replication study of violent and non violent subjects: cerebrospinal fluid metabolites of serotonin and dopamine are predicted by plasma essential fatty acids. Biol. Psychiatry 44, 243–249.

Hilakivi-Clarke, L., Cho, E., Onojafe, I., 1996. High-fat diet induces aggressive behavior in male mice and rats. Life Sci. 58, 1653–1660.

Lauritzen, L., Hansen, H.S., Jørgensen, M.H., Michaelsen, K.F., 2001. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. Prog. Lipid Res. 40, 1–94.

Mann, J.J., 1998. The neurobiology of suicide. Nat. Med. 4, 25–30.

Olsson, N.U., Shoaf, S.E., Salem, N., Jr, 1998. The effect of dietary polyunsaturated fatty acids and alcohol on neurotransmitters levels in rat brain. Nutr. Neurosci. 1, 133–140.

Raygada, M., Cho, E., Hilakivi-Clarke, L., 1998. High maternal intake of polyunsaturated fatty acids during pregnancy alters offspring's aggressive behavior, immobility in the swim text, locomotor activity and brain protein kinase C activity. J. Nutr. 125, 2505–2511.

Stanley, M., Mann, J.J., 1983. Increased serotonin-2 binding sites in frontal cortex of suicide victims. Lancet 8318, 214–216.

Virkunnen, M.E., Horrobin, D.F., Jenkins, D.K., Manku, M.S., 1987. Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. Biol. Psychiatry 22, 1087–1096.

Yehuda, S., Rabinovitz, S., Mostofsky, D.I., 1999. Essential fatty acids are mediators of brain biochemistry and cognitive functions. J. Neurosci. Res. 56, 565–570.