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Lower docosahexaenoic acid concentrations in the postmortem prefrontal cortex of adult depressed suicide victims compared with controls without cardiovascular disease

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ABSTRACT

Background: A growing body of evidence suggests that deficits in long-chain omega-3 (LC*n*-3) fatty acids may contribute to major depressive disorder (MDD) and principal causes of excess mortality including suicide and cardiovascular disease. In the present study we compared concentrations of docosahexaenoic acid (DHA, 22:6*n*-3), the principal LC*n*-3 fatty acid in brain, in the postmortem prefrontal cortex (BA10) of adult depressed suicide victims and controls with and/or without cardiovascular disease.

Methods: DHA concentrations (μmol/g) in the prefrontal cortex (PFC, BA10) of adult male and female suicide victims ($n = 20$) and controls with ($n = 8$) or without ($n = 12$) cardiovascular disease were determined by gas chromatography.

Results: There was a non-significant trend for lower DHA concentrations in suicide victims compared with all controls (−10%, $p = 0.06$, $d = 0.5$). Significantly lower DHA concentrations were observed in suicide victims compared with controls without cardiovascular disease (−14%, $p = 0.03$, $d = 0.7$) but not controls with cardiovascular disease (−4%, $p = 0.71$, $d = 0.1$). There was a non-significant trend for lower DHA concentrations in controls with cardiovascular disease compared with controls without cardiovascular disease (−11%, $p = 0.1$, $d = 0.6$).

Conclusions: Adult depressed suicide victims exhibit lower postmortem PFC DHA concentrations compared with controls without cardiovascular disease. These data add to a growing body of evidence implicating DHA deficits in the pathophysiology of MDD, suicide, and cardiovascular disease.

1. Introduction

Major depressive disorder (MDD) is associated with excess premature mortality primarily due to suicide and cardiovascular-related diseases (Angst et al., 2002; Osby et al., 2001). A growing body of evidence has emerged over the past two decades that suggest that a deficiency in dietary essential long-chain omega-3 (LC*n*-3) fatty acids, eicosapenaenoic acid (EPA) and docosahexaenoic acid (DHA), may represent a modifiable risk factor for depression and comorbid cardiovascular disease (McNamara, 2009). The principal LC*n*-3 fatty acid found in mammalian gray matter is DHA (Chen et al., 2011; Carver et al., 2001), which preferentially accumulates in gray matter synaptasomal and mitochondrial membranes (Suzuki et al., 1997). DHA is mobilized from membrane phospholipids by the calcium-independent phospholipase A_2 ($iPLA_2$) isoform (Farooqui and Horrocks, 2004) and free DHA is a substrate for anti-inflammatory docosanoids (Groeger et al., 2010; Hong et al., 2003). We originally reported that MDD patients exhibit significant and selective DHA deficits in postmortem prefrontal cortex (PFC) (Brodmann area, BA 10) (McNamara et al., 2007). However, other postmortem studies did not observe lower DHA levels in the PFC of adult or adolescent suicide victims with or without comorbid MDD (Lalovic et al., 2007; McNamara et al., 2009a; Tatebayashi et al., 2012), and a number of different pre and postmortem variables may contribute to this discrepancy (McNamara and Jandacek, 2011).

A large percentage of control subjects typically used in post-mortem brain studies died from cardiovascular-related diseases which may represent a potential confound, particularly when

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investigating DHA levels. Cardiovascular disease is associated with low erythrocyte DHA levels similar to those observed in MDD patients (Block et al., 2008; McNamara, 2009), and erythrocyte DHA levels are positively correlated with frontal cortex DHA levels (Carver et al., 2001; Connor et al., 1990). Furthermore, low DHA levels are associated with clinical depression in patients with cardiovascular disease (Frasure-Smith et al., 2004; Parker et al., 2006). The primary goal of the present study was to determine DHA concentrations in the postmortem PFC (BA 10) of adult MDD patients that died from suicide and controls with and/or without cardiovascular disease. Based on this evidence, our *a priori* prediction was that depressed suicide victims would exhibit DHA deficits compared with controls dying from non-cardiovascular related diseases, but not compared with controls dying from cardiovascular disease.

2. Methods and materials

2.1. Postmortem brain tissues

Frozen, unfixed, postmortem prefrontal cortex (BA 10) tissue from adult suicide victims ($n = 20$) and adult controls ($n = 20$) were obtained from the Maryland Brain Collection at the Maryland Psychiatric Research Center, Baltimore, MD. Brain samples were free of neuropathologic abnormalities and human immunodeficiency virus antibodies. All subjects in this study were diagnosed using the Schedule for Clinical Interviews for the DSM-IV (SCID) (First et al., 1997). The SCID was administered by a trained interviewer using a family member as an informant and included a review of all obtainable medical and psychiatric records. The SCID diagnoses were validated by two trained psychiatrists (Kappa >0.9). This has been found to be a very accurate way to make diagnoses (Ramirez Basco et al., 2000). All procedures were approved by the University of Maryland Institutional Review Board.

2.2. Gas chromatography

DHA concentrations were determined using the saponification and methylation methods described previously (McNamara et al., 2009a). A known mass (0.5 mg) of heptadecanoic acid (17:0, 99%, Matreya LLC Inc., Pleasant Gap PA) was added to each sample prior to adding the saponification solution, and tissue fatty acid concentrations (μmol/g tissue weight) calculated from the relative mass of the heptadecanoic acid peak. Samples were analyzed with a Shimadzu GC-2010 equipped with an auto-injector (Shimadzu Scientific Instruments Inc., Columbia MD). The column was a DB-23 (123-2332): 30 m (length), I.D. 0.32 mm wide bore, film thickness of 0.25 μM (J&W Scientific, Folsom CA). Fatty acid identification was determined using retention times of authenticated fatty acid methyl ester standards (Matreya LLC Inc., Pleasant Gap PA). Analysis of fatty acid methyl esters is based on areas calculated with EZstart 7.4 software. Both DHA composition (mg fatty acid/100 mg fatty acids) and concentration (μmol/g) data were obtained. All samples were processed by a technician that was blind to subject diagnosis.

2.3. Statistical analysis

For the *a priori* analysis, case–control differences in DHA concentrations were evaluated with a one-tailed *t*-test ($\alpha = 0.05$). Analysis of gender effects was performed with a two-way ANOVA using gender (male, female) and cause-of-death (suicide, control) as the main factors. Parametric linear regression analyses were performed to determine the relationship between DHA concentrations, postmortem tissue variables, and selected demographic variables ($\alpha = 0.05$). Effect size was calculated using Cohen's *d*, with small, medium, and large effect sizes being equivalent to *d*-values of 0.30, 0.50, and 0.80, respectively (Cohen, 1997). All statistical tests were performed with GB-STAT software (Dynamic Microsystems, Inc., Silver Springs MD).

3. Results

3.1. Demographic variables

A comparison of subject and tissue variables is presented in Table 1, and a list of individual subject demographic, clinical, and toxicological variables are presented in Supplemental Table 1. The majority ($n = 19/20$) of suicide victims had a history of MDD, and $n = 1$ had a history of bipolar disorder. Controls were verified as free from psychiatric illness and substance abuse. A subset of controls died from atherosclerotic cardiovascular disease ($n = 7$) or cardiac arrhythmia ($n = 1$), and remaining controls ($n = 12$) died from non-cardiac causes. There were no significant differences between depressed suicides and controls dying from non-cardiovascular-related diseases in age ($p = 0.83$) or gender ($p = 0.72$), or between depressed suicides and controls dying from cardiovascular-related diseases in age ($p = 0.46$) or gender ($p = 0.19$). DHA concentrations were not correlated with age in suicides ($r = +0.30$, $p = 0.2$), controls ($r = -0.16$, $p = 0.5$), or when both groups were combined ($r = +0.08$, $p = 0.6$).

3.2. Postmortem variables

Within the control group ($n = 20$), there were no significant correlations between DHA concentrations and brain pH ($r = -0.11$, $p = 0.64$) or postmortem interval ($r = -0.03$, $p = 0.89$). Within the suicide group ($n = 20$), there were no significant correlations between DHA concentration and brain pH ($r = +0.30$, $p = 0.2$) or postmortem interval ($r = +0.29$, $p = 0.21$). After combining control and suicide groups ($N = 40$), there were no significant correlations between DHA concentration and brain pH ($r = +0.12$, $p = 0.49$) or postmortem interval ($r = +0.11$, $p = 0.48$). There were no significant differences between depressed suicides and controls dying from non-cardiovascular-related diseases in pH ($p = 0.97$) or postmortem interval ($p = 0.76$), or between depressed suicides and controls dying from cardiovascular-related diseases in pH ($p = 0.27$) and postmortem interval ($p = 0.77$).

Table 1
Demographic and tissue characteristics.

	Controls ($n = 20$)	Suicides ($n = 20$)	*P*-value[a]
Subject characteristics			
Age at death, mean ± *S.D.*	41.5 ± 16.1	39.9 ± 15.7	0.75
Male	39.1 ± 15.1	44.9 ± 13.7	0.83
Female	51.8 ± 14.7	37.8 ± 16.5	0.39
Gender (*n*)	5F, 15M	9F, 11M	0.32
Race (*n*)	14C, 6AA	18C, 2AA	0.23
Cause of death (*n*)			
Suicide	0	20	–
Cardiovacular disease	8	0	
Other	12	0	
Diagnosed with MDD	0	19	–
Diagnosed with bipolar disorder	0	1	–
Tissue characteristics			
Brain hemisphere	18R/2L	14R/4L/2UN	0.23
Postmoretm Interval (mean hrs ± *S.D.*)	18.3 ± 7.4	19.1 ± 6.7	0.72
Tissue pH (mean ± *S.D.*)	6.2 ± 0.4	6.2 ± 0.6	0.55

Race: C = Caucasian, AA = African American, UN = Unknown.
[a] Two-tailed *t*-test or Chi-squared test.