Omega-3 Status and Cerebrospinal Fluid Corticotrophin Releasing Hormone in Perpetrators of Domestic Violence

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Background: *Elevated levels of corticotrophin-releasing hormone in the cortical-hippocampal-amygdala pathway increase fear and anxiety, which are components of defensive and violent behaviors. Prostaglandins E_2 and $F_{2\alpha}$, which increase corticotrophin-releasing hormone RNA expression in this pathway, are reduced by dietary intakes of omega-3 fats.*

Methods: *Among 21 perpetrators of domestic violence, cerebrospinal fluid and plasma were assessed for corticotrophin-releasing hormone and fatty acid compositions, respectively.*

Results: *Lower plasma docosahexaenoic acid (wt% fatty acids) alone predicted greater cerebrospinal fluid corticotrophin-releasing hormone (pg/mL), in exponential ($r = -.67$, $p < .006$) and linear regressions ($r = -0.68$, $p < .003$ excluding four subjects with the highest docosahexaenate levels).*

Conclusions: *In this small observational study, low plasma docosahexaenoic acid levels were correlated to higher cerebrospinal fluid corticotrophin-releasing hormone levels. Placebo controlled trials can determine if dietary omega-3 fatty acids can reduce excessive corticotrophin-releasing hormone levels in psychiatric illnesses.*

Key Words: Corticotrophin releasing hormone, omega-3 fatty acids, docosahexaenoic acid, violence, stress

Activation of the cortical-hippocampal-amygdala pathway by elevated levels of corticotrophin releasing hormone (CRH), in addition to other mechanisms, has been repeatedly linked to exaggerated responses to stress, including persistent fear, depression, and violence (Ressler and Nemeroff 2000). Prostaglandin E_2 release not only stimulates this pathway but also plays a critical role in increasing the transcription of CRH messenger RNA (mRNA) and the activation of primary, early, and intermediate genes (Bugajshi et al 1996; Lacroix et al 1996). The activation of neurosecretory neurons that express CRH in response to interleukin 1-β within this pathway is dependent on prostaglandin E_2 (Ek et al 2000; Watanobe and Takebe 1994; Zhang and Rivest 1999). Prostaglandin E_2 release in the brain can be increased by omega-6 fatty acid rich diets (Hoffmann et al 1986) that raise the tissue concentrations of arachidonic acid, the precursor that is converted to prostaglandin E_2 and $F_{2\alpha}$ by cyclooxygenase enzymes (Cambronero et al 1992). The inducible isoform, cyclooxygenase-2, is expressed in brain selectively in neurons of the hippocampus, cerebral cortex, amygdala, and hypothalamus (Vidensky et al 2003). Greater dietary intake of long-chain omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid both decrease arachidonic acid levels and compete for cyclooxygenase enzymes, resulting in lower levels of prostaglandin E_2 and $F_{2\alpha}$ release in peripheral tissues (Endres et al 1989; Lands et al 1992). Thus, we postulated that low concentrations of long-chain omega-3 fatty acids in plasma would be associated with elevated concentrations of CRH in cerebrospinal fluid. We chose to examine subjects with a persistent history of violence, because excessive fear and anxiety responses have been implicated as important components of violent behaviors (George et al 2000; Van Praag 2001), and both CRH expression and CRH receptor subtypes appear to elicit a wide spectrum of autonomic and behavioral effects that appear to integrate the perception and manifestation of anxiety and fear responses (Charney and Deutch 1996; Risbrough et al 2004). In six placebo-controlled trials, supplementation of omega-3 fatty acids has reduced violent behaviors or measures of aggression (Gesch et al 2002; Hamazaki et al 1996, 2002; Hirayama et al 2004; Stevens et al 2003; Zanarini and Frankenburg 2003).

Methods and Materials

Subjects were perpetrators of domestic violence ($n = 21$) who we previously reported as having rage and panic-like responses to infusion with an anxiogenic agent, sodium lactate (George et al 2000). The DSM-III-R diagnoses were obtained using the Structured Clinical Interview (Spitzer et al 1992) and Hamilton Depression Rating Scale (Hamilton 1967). Written informed consent was obtained under continuous review by the National Institute of Alcohol Abuse and Alcoholism Institutional Review Board, National Institutes of Health (NIH) Clinical Center. Cerebrospinal fluid and plasma were obtained after 3 days on a low monoamine diet and an overnight fast on the research unit of the National Institute of Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland. Fatty acids were quantified as previously described (Hibbeln et al 1998). Cerebrospinal fluid CRH concentrations were quantified by radioimmunoassay (Banki et al 1992). Single and multiple regression models using linear and nonlinear Pearson and Spearman regressions were conducted using iterative curve fitting to determine the best nonlinear fit (Sigma Plot, V. 8, SPSS Inc, Chicago, Illinois, and Statview, Version 5.0.1, SAS Institute, Inc, Cary, North Carolina).

Results

Lower plasma docosahexaenoic acid (wt % of total fatty acids) alone correlated with lower cerebrospinal fluid CRH concentrations ($r = -.67$, $p < .006$, negative exponential regression) (see Figure 1). The four subjects with the highest concentrations of CRH (pg/mL) were strong determinants of this curvilinear regres-

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Received January 26, 2004; revised August 17, 2004; accepted August 30, 2004.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2004.08.021

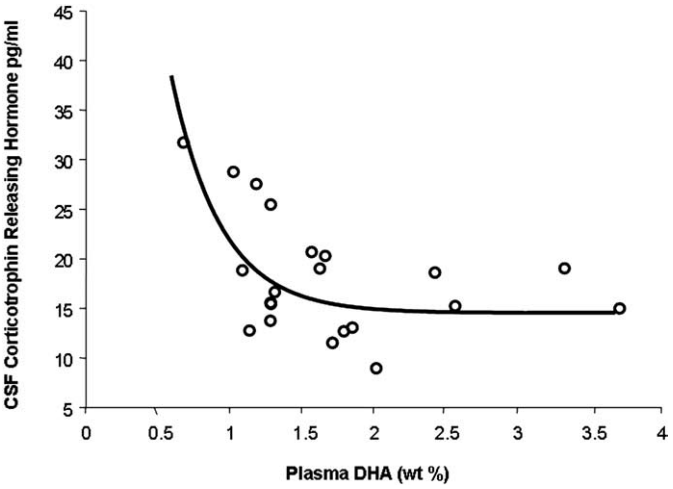

Figure 1. Lower plasma levels of docosahexaenoic acid (DHA) (wt % total fatty acids), an omega-3 polyunsaturated fatty acid, are correlated with higher concentrations of corticotrophin releasing hormone in cerebrospinal fluid (CSF) (pg/mL) among perpetrators of domestic violence ($r = -.67$, $p < .006$) in a nonlinear Pearsons product moment regression analysis.

sion fit. Plasma saturated, monounsaturated, eicosapentaenoic acid, arachidonic acid, and other polyunsaturated fatty acids were unrelated. The potentially confounding factors age, gender, smoking, alcohol consumption, diagnosis and severity of depression, and severity of violence were assessed in univariate and multivariate linear regressions and did not substantially contribute to these findings. These results were also robust after excluding four subjects with the highest plasma docosahexaenoic acid (wt % of total fatty acids) ($r = -.68$, $p < .003$, linear regression).

Discussion

To our knowledge, this is the first report that a low omega-3 fatty acid status may be associated with elevated CRH levels in humans, as previously proposed by Smith (1991). Omega-3 rich diets reduce the arachidonic acid available for prostaglandin E_2 and $F_{2\alpha}$ release (Endres et al 1989; Lands et al 1992). Reduced release of these eicosanoids, in turn, reduces CRH expression and activation of the cortical-hippocampal-amygdala pathway (Lacroix et al 1996). Down-regulation of this pathway would be expected to have clinical outcomes of reducing exaggerated fear responses and violent behaviors (Charney and Deutch 1996; Van Praag 2001). This proposition is consistent with the report that while an intracranial infusion of CRH had stress-inducing effects on behaviors including decreases of rearing, smelling, and feeding and increased face washing, the supplementation of docosahexaenoic acid significantly improved these distress behaviors (Takeuchi et al 2003). In a small number, supplementation with 7.2 g/d of fish oils has been reported to reduce sympathetic activation induced by mental stress, presumably through central mechanisms (Delarue et al 2003). The proposition that greater dietary intake of omega-3 fatty acids reduces violent and aggressive behaviors is also consistent with several epidemiologic, observational, and interventional studies. In double-blind, placebo-controlled trials, combinations of docosahexaenoic acid and eicosapentaenoic acid (together with a multivitamin) reduced felony-level violent offenses among 231 prisoners by 37% (Gesch et al 2002), reduced the increases in hostility measures seen in the placebo group of Japanese university students exposed to exam stress (Hamazaki et al 1996), and reduced verbal and physical aggression among women with borderline personality disorder (Zanarini and Frankenburg 2003). Higher rates of homicide were correlated with ($r = -.63$, $p < .0006$) lower rates of seafood consumption across a 20-fold difference in prevalence in a cross-national study (Hibbeln 2001). Among both cocaine attempters and subjects in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, subjects with lower docosahexaenoic acid status were more aggressive (Buydens-Branchey et al 2003; Iribarren et al 2004). The regression analyses reported here in this small observational study should be interpreted cautiously and not considered as evidence of a causal relationship. Randomized, placebo-controlled trials are needed to determine if supplementation with docosahexaenoic acid and eicosapentaenoic acid (Song and Horrobin 2004) can decrease elevated levels of CRH and improve behavioral outcomes among subjects with aggressive and violent behaviors. If effective, this novel nutritional approach may be developed into a therapeutic approach to regulate excessive CRH levels in other psychiatric illnesses adversely impacted by hyperactivity of the hypothalamic-pituitary-adrenal axis.

This study was funded by the Division of Intramural Clinical and Basic Science Research, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health.

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