

Omega-3 fatty acid deficiencies in neurodevelopment, aggression and autonomic dysregulation: Opportunities for intervention

JOSEPH R. HIBBELN, TERESA A. FERGUSON, & TANYA L. BLASBALG

National Institute on Alcohol Abuse and Alcoholism, Bethesda, USA

Summary

Mechanisms by which aggressive and depressive disorders may be exacerbated by nutritional deficiencies in omega-3 fatty acids are considered. Early developmental deficiencies in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may lower serotonin levels at critical periods of neurodevelopment and may result in a cascade of suboptimal development of neurotransmitter systems limiting regulation of the limbic system by the frontal cortex. Residual developmental deficits may be manifest as dysregulation of sympathetic responses to stress including decreased heart rate variability and hypertension, which in turn have been linked to behavioral dysregulation. Little direct data are available to disentangle residual neurodevelopmental effects from reversible adult pathologies. Ensuring optimal intakes of omega-3 fatty acids during early development and adulthood shows considerable promise in preventing aggression and hostility.

Introduction

Increased risk for two of the most prevalent afflictions in the world, aggression and depression, may in part be explained as pathologies of the brain (Liu & Wuerker, 2005), potentially exacerbated by nutritional deficiencies. Violent and excessively aggressive behaviors are significant threats to public health, and the prevention of injury has been identified as a policy priority by the US Surgeon General (Satcher, 1995; US Department of Health and Human Services, 2005). In 2000, major depression was identified as the fourth leading cause of disease burden in the world (Ustun, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). It is anticipated that by 2020, neuropsychiatric disorders will account for 14% of the global burden of disease (World Health Organization, 2005). While other major morbidities, such as cardiovascular disease, have been linked to dietary factors (Hu & Willett, 2002), data regarding the role of nutrition in psychiatric disorders has only recently begun to emerge (Casper, 2004; Hallahan & Garland, 2004; Hibbeln & Salem, 1995; Salerno-Kennedy & Cashman, 2005). The identification of nutrients that could treat or prevent depressive and aggressive disorders would be extremely useful because of their low cost and global applicability.

Omega-3 fatty acids, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are now widely recognized as having important biological roles in reducing cardiovascular

mortality, and the American Heart Association includes them in their dietary recommendations (Krauss et al., 2000). However, we are only beginning to understand the role of omega-3 essential fatty acids in psychiatric disorders. Omega-3 fatty acids are thought to be important in psychiatric disorders both because they are selectively concentrated in the brain, and also because they may alter the neurochemical pathways involved in the pathophysiology of several psychiatric illnesses (Hibbeln & Salem, 1995; Hibbeln et al., 2000; Stoll et al., 1999). Here we will examine the hypothesis that omega-3 fatty acid deficiency in at least two developmental periods increases risk for aggressive and depressive behaviors. First, deficiency in long-chain essential fatty acids during critical periods of prenatal and childhood neurodevelopment may result in a residual predisposition towards aggressive and depressive behaviors, possibly by impairing neuronal migration, connectivity, timed apoptosis, and dendritic arborization, such that there is an irreversible disruption in the neuronal pathways that regulate behavior. Second, omega-3 fatty acid deficiency in early life may result in neurotransmitter alternations in the short term, further compounding the predisposition of otherwise healthy adults with additional genetic vulnerability to exhibit depression or aggressive behaviors when under stress.

We examine a conceptual framework for the role of deficiencies of long chain omega-3 fatty

acids during neurodevelopment and the later development of aggression and depression. First, data suggesting that interventions involving omega-3 fatty acid supplementation may have direct clinical benefits on aggression and depression are examined. Next, we survey the literature describing the early neurodevelopmental insults that increase predisposition to later aggression and depression. Finally, we discuss whether increasing omega-3 fatty acid levels alter the neurochemical mechanisms associated with impulsive and depressive states. Both the acute and residual effects of omega-3 fatty acids on two surrogate markers of aggression, serotonergic neurotransmission and autonomic nervous system reactivity—specifically heart rate variability—will be examined.

Although it is well established that omega-3 fatty acids are important for optimal brain function during infancy (Willatts, Forsyth, DiModugno, Varma, & Colvin, 1998), data regarding the persistence of these neurodevelopmental effects into childhood and/or adulthood are just beginning to emerge in the literature. It is unknown if the neurodevelopmental abnormalities that result from omega-3 fatty acid deficiency in infancy are reversible by adequate intake in childhood or adulthood. Furthermore, there are a growing number of controlled clinical trials of the short-term influence of omega-3 fatty acid supplementation in adult psychiatric populations with promising but limited results. For example, studies utilizing supplements with DHA alone, or with DHA amounts exceeding EPA amounts, do not appear to treat depression, while treatments containing amounts of EPA greater than DHA appear to be effective.

Aggression, violence, and omega-3 status

In epidemiological studies homicide can be considered as a surrogate measure of aggression as it is an extreme case of violent behavior. Mortality data are particularly useful as the definition of homicide is consistent across countries and data are prospectively collected for whole populations. Cross-national ecological data indicate that there is an inverse relationship between seafood consumption, a surrogate of omega-3 intake, and rates of death by homicide ($r=0.63$, $p<0.0006$, $n=36$ countries) (Hibbeln, 2001). Whereas tissue compositions of EPA and DHA can be increased by greater seafood consumption, these levels can be decreased by greater consumption of competing omega-6 fatty acids, in particular linoleic acid, found principally in seed oils (Lands et al., 1992). In addition, greater linoleic acid consumption, estimated from economic disappearance data, has been found to have a direct

relationship with homicide rates across five countries ($r=0.93$, $p<1\times 10^{-40}$) between 1960 and 1999 (Hibbeln, Nieminen, & Lands, 2004.) Differences in apparent intake of linoleic acid ranged from approximately 1% of calories in the UK in 1960 to nearly 10% of calories in the USA in 1999 and represent the world's diversity of linoleic acid intake (Hibbeln et al., 2004). Higher adipose concentrations of linoleic acid were strongly associated with Type A personality among Cretan adults (Mamalakis, Kafatos, & Board, 1994). We note that these studies demonstrate correlation, not causation, and that several other confounding variables have not been evaluated, such as socioeconomic status and firearm laws. We are aware of one animal study in which the effects of differences in linoleic acid consumption on aggression were assessed. Mice fed a diet of 43% soy oil exhibited 3–4 fold more aggression than mice fed a diet of 16% soy oil (Raygada, Cho, & Hilakivi-Clarke, 1998). Finally, it should be noted that cross-national study designs do not account for the varying levels of EPA and DHA intake for individuals over the course of their lifetime, making it impossible to distinguish between the acute effects of omega-3 fatty acids in adults and the residual neurodevelopmental effects of childhood deficiencies.

Observational and intervention studies of human subjects are consistent with the cross-national data described above, suggesting that low omega-3 levels are associated with aggression. Virkkunen and others were the first to report that violent and impulsive offenders had lower plasma concentrations of DHA than non-impulsive offenders and healthy controls (Virkkunen, Horrobin, Jenkins, & Manku, 1987). Stevens, Zentall, Abate, Kuczek and Burgess (1996) showed that a greater number of behavior problems, temper tantrums and sleep problems were reported in 6 to 12-year old boys with lower total omega-3 fatty acid concentrations than in controls. The CARDIA study found that greater seafood consumption amongst 4000 subjects was associated with lower scores on the Cook-Medley hostility scale, irrespective of gender or ethnicity (Iribarren et al., 2004). Several double-blind, placebo-controlled intervention trials have been conducted to assess the efficacy of omega-3 fatty acids in reducing hostility, an affective state closely related to anger and aggression. Although not specifically designed to assess psychometric changes, hostility and depression scores were reduced by a high fish diet over the course of five years (Weidner, Connor, Hollis, & Connor, 1992). Hamazaki, Sawazaki and Kobayashi (1996), reported that 1.5–1.8 g/d of DHA reduced measures of hostility in a picture frustration test among Japanese students, indicating that omega-3 fatty acids may reduce aggression during stress in normal subjects. It is interesting to note that the

baseline plasma DHA composition of this group was 3.0%, compared to typical American levels of approximately 1.5%.

Thienprasert et al. (2000) reported small decreases in hostility measures compared to placebo among Thai University employees after two months of supplementation with 1.5 g/d of DHA. Investigators in Boston (Zanarini & Frankenburg, 2003) reported large decreases in verbal and physical aggression among women with borderline personality disorder with EPA monotherapy. Although not primarily examining aggression, investigators at Oxford, UK (Richardson & Montgomery, 2005) found decreases in disruptive behavioral disorders among children with developmental coordination disorders and a high prevalence of attention deficit hyperactivity disorder upon supplementation of 558 mg/d EPA and 174 mg/d DHA. In a study of Japanese children (9–12 years old), Itomura et al. (2005) supplemented one group with fortified foods providing 840 mg/week EPA and 3600 mg/week DHA, while the control group ate unfortified foods. Measures of hostility and symptoms of attention deficit hyperactivity increased in girls in the control group who had no changes in EPA and DHA from baseline, but whose RBC linoleic acid levels increased. These data may indicate that foods low in EPA/DHA and high in linoleic acid increase the risk of hostility and attention deficit hyperactivity disorder. One of the most provocative reports has been that a cocktail of multivitamins, mineral and essential fatty acids (including about 180 mg of EPA plus DHA) reduced felony level violence among prisoners by 37% (Gesch, Hammond, Hampson, Eves, & Crowder, 2002). These studies suggest that residual behavioral problems may be reduced or reversed in childhood, adolescence and adulthood or at least concurrently treated by the use of essential fatty acids.

Depression and omega-3 fatty acid tissue composition

Several recent reviews (Bodnar & Wisner, 2005; Hibbeln, 1998; Freeman, 2000) and an evidence-based medicine evaluation (Schachter et al., 2005) point to an emerging body of epidemiological and intervention trial data indicating that suboptimal omega-3 levels may be a treatable risk factor for major depression. A large body of data also suggests that depression and aggression frequently coexist and may be linked by low serotonergic activity (Bjork, Dougherty, & Moeller, 1997; van Praag, 1986, 1998). Some theories of aggression suggest that negative affect (including depression) predisposes an individual to respond aggressively to provocation (Berkowitz, 1990). Since depression frequently

is found in aggressive individuals, and depression may improve with fatty acid supplementation, it is interesting to assess depression as a covariate measure when considering the effects of EPA and DHA levels on aggression. One consideration is whether acute intervention with omega-3 fatty acids selectively improves aggression and hostility, or if supplementation has a more general effect by reducing negative affect and perhaps improving positive affect as has been reported in healthy volunteers under stress (Bradbury, Myers, & Oliver, 2004).

Predictors of aggression during early development

While our review of the acute effects of omega-3 fatty acid intervention suggests clinical benefits in aggression and depression, it is important to also consider another mechanism by which low omega-3 fatty acid tissue composition may affect behavioral outcomes. Deficiencies in long-chain essential fatty acids during neurodevelopment may result in a residual predisposition which increases risk, but is not necessarily the sole cause of aggression and depression. Several examples have established that early neurodevelopmental insults increase risk for later aberrant behavioral outcomes. First, maternal exposure to organic solvents during pregnancy has been associated with worse neurobehavioral outcomes in children. Results indicated increased scores on both the Externalizing and Internalizing scales of the Child Behavior Checklist (CBCL) and an increased prevalence of mild-to-severe behavioral problems in the exposed group compared to controls (Till, Koren, & Rovet, 2001). A second factor considered in the development of aggressive behaviors is prenatal exposure to alcohol. A review of this research by Kelly, Day and Streissguth (2000) reports differences in aggression outcomes in relation to prenatal exposure for both peri-adolescence and adulthood. Adolescents exposed to alcohol during development, compared to those who were not, exhibited more social difficulties as measured by behavioral checklists such as the CBCL. In adulthood, prenatal exposure to alcohol was related to high rates of trouble with the law, inappropriate sexual behavior, depression, suicide, and failure to care for children (Kelly et al., 2000). We note that chronic ethanol exposure depletes DHA from frontal cortex (Pawlosky & Salem, 1995), thus low omega-3 intake could potentially exacerbate fetal alcohol effects.

Serotonergic function in aggression, depression and impulsiveness

Suboptimal concentrations of central serotonin and 5-hydroxyindoleacetic acid (5-HIAA), a metabolite

of serotonin, in cerebrospinal fluid (CSF) have been repeatedly implicated in the pathophysiology of aggression, depression, and impulsivity (Linnoila et al., 1983; Mann, 1998; Mann, Oquendo, Underwood, & Arango, 1999; Roy, Virkkunen, & Linnoila, 1987; Stanley et al., 2000; Virkkunen et al., 1994; Virkkunen, Goldman, Nielsen & Linnoila, 1995). Both animal and human studies have sought to explore the early developmental predictors of later aggressive behavior with some focus on neurochemical correlates and measures of heart rate variability. Neurochemical factors of interest include serotonin and its metabolite 5-HIAA, vasopressin, and brain-derived neurotrophic factor (BDNF). Animal studies have shown that vasopressin facilitates aggression, while serotonin inhibits aggression by blocking vasopressin activity (Lyons et al., 1999). Mice deficient in BDNF lost serotonergic synaptic density in the frontal cortex and became significantly more aggressive (Lyons et al., 1999). In the absence of sufficient BDNF, mice developed enhanced intermale aggressiveness and hyperphasia, behavioral abnormalities associated with serotonin dysfunction.

In another study, the stress of emotional and physical insult on these neurochemical systems was assessed during adolescence and related to aggressive behavior in adulthood in male hamsters. It was determined that stress in the form of threat or attack in adolescence altered the balance between vasopressin and serotonin, followed by the emergence of inappropriate aggressive behavior in early adulthood (Ferris, 2000). Adequate omega-3 tissue composition normalizes BDNF levels after traumatic injury (Wu, Ying, & Gomez-Pinilla, 2004) which is suggestive of a clinical role for omega-3 sufficiency.

Support for the role of low CSF 5-HIAA concentrations in predicting aggressiveness has been shown in a study involving 49 free-ranging, 2-year-old male rhesus monkeys. Low 5-HIAA concentrations in CSF collected in early development were predictive of future excessive aggression, risk taking, and premature death among the non-human primate males (Higley et al., 1996). In a two-year prospective study of children and adolescents with disruptive behavior disorders, low 5-HIAA concentrations predicted higher degrees of severity of physical aggression during follow-up interviews (Kruesi et al., 1992). In an earlier report, Kruesi et al. (1990) showed evidence that in children and adolescents with at least one major disruptive behavior disorder, CSF-5HIAA concentrations were significantly lower than for a matched group of children and adolescents with obsessive-compulsive disorder. Others (Schulz et al., 2001) reported no clear evidence for a relationship between serotonin function and aggression in disruptive boys. These authors also reported that two other

hypothesized explanations, age and the presence of ADHD, did not influence the relationship between serotonin and childhood aggression.

Aggressive and impulsive behaviors may be explained, in broad terms, by suboptimal regulation of the limbic system by the frontal cortex, which has been shown to regulate both impulsive behaviors and cardiovascular reactivity (Bechara, Tranel, Damasio, & Damasio, 1996; Bechara, Damasio, & Damasio, 2000). Therefore, the relationship between serotonin concentrations and decreased EPA and DHA may be of importance when considering later behavioral outcomes. Developmental models are particularly useful for studying the relationship between brain DHA and neurotransmitter changes because the developing brain is particularly vulnerable to dietary deficiencies of omega-3 fatty acids. Serotonergic and dopaminergic neurotransmission in the frontal cortex can be affected by dietary essential fatty acids during infancy. These results are consistent with the findings of Austed, Innis and de la Pressa Owens (2000), who reported changes in concentrations of both serotonin and CSF 5-HIAA in the frontal cortex of piglets given control and DHA/AA supplemented formulas; the concentration of serotonin increased, while that of the metabolite, CSF 5-HIAA, decreased. de la Pressa Owens and Innis (1999) fed 24 piglets controlled infant formulas starting a birth. One group received formula supplemented with arachidonic acid (AA) (0.2%) and DHA (0.16%), while the other group received unsupplemented formula containing the same baseline levels of linoleic and linolenic acids. Frontal cortex concentrations of serotonin, tryptophan, dopamine, homovanillic acid (HVA) and norepinephrine (NE) were nearly double in the AA plus DHA group over 18 days. These investigators followed-up this finding and reported residual increases in serotonin and dopamine levels in infants resulting solely from supplementation of mothers during pregnancy (Innis & de la Pressa Owens, 2001). Kudas et al. (2004) reported that serotonin release stimulated by fenfloramine, was decreased four-fold among rats fed low EPA and DHA diets. Deficits in serotonin levels and release were reversible only up to 21 days of life.

Serotonin acts a critical neurodevelopmental signaling molecule in early neurodevelopment, long lasting deficits in neuronal architecture may occur if serotonin activity is impaired. Serotonin (5-HT) has been described as the phylogenetically most ancient neurodevelopmental signal critical in initiating neurodevelopment, and in promoting neuronal cell differentiation, migration and synaptogenesis in glutaminergic and monoaminergic neurons (Lauder, 1990; Lieth, McClay, & Lauder, 1990; De Vitry, Hamon, Catelon, Dubois, & Thibault, 1986).

Serotonin is a tropic factor during neurogenesis for the development of 5-HT neurons as well as guiding the migration of glutamatergic, GABAergic, noradrenergic and other neurons. Early deficits in serotonin result in residual deficits in levels of several neuropeptides including vasopressin and vasointestinal peptide in the superchiasmatic nucleus (Mirochnik, Bosler, Tillet, Calas, & Ugrumov, 2005). Deficits in serotonin have been linked to an increased risk of autism and other neurodevelopmental deficits (Whitaker-Azmitia, 2001; Whitaker-Azmitia, Druse, Walker, & Lauder, 1996). Serotonin guides the innervations of glutamatergic neurons from the striatum to layer VI of the prefrontal cortex linking cortical and limbic systems (Lauder, 1990; Whitaker-Azmitia, 2001; Whitaker-Azmitia et al., 1996). Impairment or suboptimal development of cortical regulation of the limbic system by the frontal cortex could potentially result in impaired regulation of impulsivity and aggression.

Human and primate studies of fatty acid supplementation effects

Correlational data from human studies suggest that increasing omega-3 fatty acid levels may change neurotransmitter metabolite concentrations. Plasma concentrations of DHA and AA were associated with CSF 5-HIAA and HVA concentrations in 234 subjects investigated at the National Institute on Alcohol Abuse and Alcoholism (Hibbeln et al., 1998a, b), revealing a direct relationship between DHA and CSF 5-HIAA in healthy control subjects and late onset alcoholics. This finding has been replicated in 104 adult rhesus monkeys, with both DHA and EPA in plasma positively correlating with CSF 5-HIAA (Hibbeln et al., unpublished). Among these animals, higher EPA and DHA plasma concentrations were also associated with more functional dominance behaviors. While falling short of proving causality, these correlational findings suggest that increasing omega-3 fatty acid intake may increase brain serotonin concentrations. Data demonstrating that increasing EPA and/or DHA levels directly changes CSF 5-HIAA concentrations in humans are sparse. Nizzo et al. (1978) reported that a six hour intravenous infusion of DHA contained in 200 mg bovine cortex phospholipids (BC-PL) increased CSF 5-HIAA and homovanillic acid (HVA) concentrations in human subjects. Unfortunately, this study was poorly controlled and examined few subjects. In terms of alternate neurotransmitter systems, Sawazaki, Hamazaki, Yazawa and Kobayashi (1999) reported that concentrations of norepinephrine were significantly reduced after administration of 1.5 g of DHA in subjects who were under long-lasting psychological stress. To our knowledge, changes to

serotonergic function with fatty acid supplementation have not yet been assessed in a randomized placebo controlled trial in humans.

Animal studies of fatty acid supplementation effects

A number of animal studies have provided insight into how dietary omega-3 fatty acids may influence neurotransmitter concentrations in humans. Deficiencies in omega-3 fatty acids have been shown to impact monoaminergic neurotransmission in the frontal cortex of pigs and rats (de la Pressa Owens & Innis, 1999; DeLion, Chalon, Guilloteau, Besnard, & Durand, 1996; Olsson, Shoaf, & Salem, 1998). Omega-3 deficient rats have also exhibited significant reductions in the number of dopaminergic synaptic vesicles in the frontal cortex (Zimmer et al., 2000a, b). This dietary deficiency also resulted in a 90% reduction in the quantity of dopamine released after tyramine stimulation in rats (Zimmer et al., 2000a, b). Chalon et al. (1998) found that dopamine levels were 40% greater in the frontal cortex of rats fed fish oils compared to those fed a control diet. While animal studies have most strongly documented improvements in dopaminergic function with omega-3 fatty acid supplementation, they have also indicated that the function of serotonergic neurons may be altered in adult animals depending on omega-3 tissue composition. Olsson et al. (1998) reported that a diet low in omega-3 fatty acids decreased serotonin and 5-HIAA concentrations in several brain regions of the rat, including the frontal cortex. DeLion et al. (1996) reported that in addition to lowering levels of endogenous dopamine in the frontal cortex of rats by 40–75%, chronic dietary deficiency in omega-3 fatty acids induced an 18–46% increase in the density of type 2 serotonin receptors (5-HT₂) in the frontal cortex, with no change in binding affinity and without variation in serotonin levels. Stanley, Mann and Durand (1983) found a 44% increase in 5HT₂ receptor density, with no change in binding affinity in the frontal cortex. In addition, Heron, Shinitzky, Hershkovitz and Samuel, (1980) demonstrated that changing the fatty acid composition of membranes altered their biophysical properties, resulting in markedly distorted serotonin receptor binding. These observations support the assertion that greater omega-3 fatty acid intake may increase serotonergic neurotransmission. One consideration in comparing animal models is that rodents have less frontal cortex mass, and less serotonergic innervation compared to piglets and primates, which may, in part explain differences in findings regarding dopaminergic and serotonergic neurotransmission.

We postulate three mechanisms by which omega-3 fatty acid insufficiency may reduce serotonergic

function, particularly in the frontal cortex, and thereby influence the development of a predisposition towards aggressive behaviors through dysregulation of the limbic system. First, the number of serotonergic neurons and synapses may be decreased as a result of omega-3 fatty acid deficiency in critical developmental periods. Docosahexaenoic acid supplementation promotes neurite outgrowth (Calderon & Kim, 2004; Ikemoto et al., 2000; Innis et al., 2001), inhibits apoptosis (Kim, Akbar, Lau, & Edsall, 2000), and regulates the composition of polysialylated oligosaccharides (Yoshida et al., 2001), which are important to synaptogenesis. In addition, DHA promotes synaptic growth cone formation (Martin, Wickham, Om, Sanders, & Ceballos, 2000). Furthermore, omega-3 deficiency decreases concentrations of nerve growth factor (NGF) by nearly 50% (Ikemoto et al., 2000). Thus, a DHA insufficiency could possibly lead to reduced numbers of serotonergic neurons and synapses. Second, omega-3 insufficiency may reduce serotonin function by regulating metabolism and catabolism. Membrane fatty acid composition can affect the metabolism of serotonin by regulating the activity of tryptophan hydroxylase (Mandell, 1984), monoamine oxidase (DeLion et al., 1997), the serotonergic reuptake pump (Block & Edwards, 1987), and serotonergic receptors. Third, DHA may also improve depression and aggression through global effects, such as improved cerebral blood flow (Tsukada, Kakiuchi, Fukumoto, Nishiyama, & Koga, 2000), as assessed by Positron Emission Tomography.

Aggression and cardiovascular physiology

Abnormalities of autonomic nervous system function have been repeatedly described in aggressive and violent subjects (Pine et al., 1996a, b; Raine, Lencz, Bihle, LaCasse, & Colletti, 2000; Scarpa & Raine, 1997). For example, low autonomic arousal measured at age 15 predicted with 75% accuracy incarceration by age 24 in a nine-year prospective study of the siblings of juvenile delinquents (Raine, Venables, & Williams, 1990). These abnormalities, which include low heart rate, low heart rate variability and slow skin conductance in response to emotional stimuli, appear to indicate deficits in the central nervous system regulation of autonomic functioning, and have been associated with a lack of inhibition and fearlessness (Akselrod et al., 1985; Mezzacappa et al., 1996; Raine, Brennan, Mednick, & Mednick, 1996; Raine, 1996). Another manifestation of autonomic dysregulation related to aggression is excessive or inappropriate response to stress (Haller, Mikics, Halasz, & Toth, 2005).

Several investigators have reported that, among healthy subjects, supplementation with EPA and DHA decreases excessive releases of epinephrine or cortisol and may blunt excessive responses of blood pressure (Delarue et al., 2003; Hamazaki, Itomura, Sawazaki, & Nagao, 2000; Hamazaki et al., 2005; Sawazaki et al., 1999). Although not a direct measure of autonomic hyperactivity, residual elevations in blood pressure resulting from prenatal deficiencies in long chain omega-3s have been reported (Weisinger et al., 2001). We have previously proposed that deficiencies in omega-3 may link hostility and depression to increased risks of cardiovascular disease (Hibbeln & Salem, 2001).

Suboptimal regulation of the sympathetic nervous system has been a focus of intense interest in predicting sociopathy and aggression. In a study comparing low resting heart rate at age 3 years to aggression at age 11 years, Raine et al. (1997) reported that aggressive children had lower heart rates than non-aggressive children, and that children with low heart rates were more aggressive than those with higher heart rates. Another study tested the hypothesis that psychopathology in school-aged children is associated with reduced heart period variability. This study found that boys with the lowest heart period variability exhibited the highest scores on both the Externalizing and Internalizing scales of the Child-Behavior Checklist (CBCL) (Pine et al., 1998). Finally, in a study of very low birth weight children, the neonatal respiratory sinus arrhythmia (RSA) maturation, a measure of heart rate variability, provided an early risk index for later social behavioral problems. Children with low RSA maturation scores were at risk for later behavioral difficulties (Doussard-Roosevelt, McClenny, & Porges, 2001).

One critical question is whether there is evidence that nutritional interventions of any kind early in development might improve measures of autonomic reactivity and potentially reduce the risk of future sociopathic behavior. We know of no data that directly address this issue. However, we do note that the educational and nutritional enrichment of children aged 3–5 years was associated with increased autonomic arousal at age 11 (Raine et al., 2001). We note that the 100 children in the enrichment group received a diet high in fish. It would be of interest to continue investigation of heart rate variability as a marker for later aggressive behavior, in addition to continuing investigation of the role of the serotonergic system in behavioral outcomes.

Several lines of evidence suggest that a reduction in prefrontal cortex gray matter, which is common in subjects with antisocial personality disorder, may be responsible for the reduced autonomic nervous system arousal associated with aggression and violence (Raine et al., 2000). Studies of subjects

that have suffered damage to the prefrontal cortex in adulthood have provided unique insights into the role of emotions in appropriate social and moral decision-making. Although these subjects have otherwise normal intelligence and normal neuropsychological profiles, they lack the ability to project the emotional consequences of their current behaviors into the future (Bechara et al., 1996). When it is pointed out that their judgment was poor, they can often recognize the social or moral error (Bechara, Damasio, Damasio, & Anderson, 1994). However, when children suffer damage to the prefrontal cortex as toddlers, they appear never to develop appropriate social and moral behavior. This apparently occurs because they cannot connect feelings of guilt and other emotional responses to the consequences of their behavior (Anderson, Bechara, Damasio, Tranel, & Damasio, 2000a; Anderson, Damasio, Tranel, & Damasio, 2000b). These diminished emotional responses are reflected in several measures of reduced autonomic nervous system arousal, such as diminished skin conductance, reduced heart rate, and reduced heart rate variability. These same measures are consistently found in subjects with antisocial personality disorder, which is marked by aggression and violence (Raine et al., 2000).

Heart rate variability and serotonergic control

Central serotonergic activity is important in the regulation of heart rate variability. Activation of serotonin 5-HT₃ receptors with ketamine resulted in decreased heart rate variability in rhesus monkeys, while administration of ondansetron, a 5-HT₃ receptor antagonist, attenuated this response (Hibbeln et al., 2000). The nucleus tractus solitarius is rich in 5-HT₃ receptors, indicating that the brain stem may be the seat of serotonergic control of heart rate. Rabinowitz and Lown (1978) used tryptophan loading to elevate serotonin concentrations globally in the CNS of dogs, which caused diminished sympathetic neuronal activity and increased the threshold of cardiac ventricular instability by 50%. Lehnert et al. (1987) found similar results with 5-l-hydroxytryptophan loading in cats, which induced a 42% increase in the ventricular fibrillation threshold and suppression of efferent sympathetic activity. Finally heart rate variability in depressed patients improved with a successful antidepressant treatment that affected serotonergic function (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Khaykin et al., 1998). Although these data are far from conclusive, they suggest that reduced serotonergic function decreases heart rate variability. As reviewed above, low EPA and/or DHA tissue composition may reduce serotonergic function, which suggests low EPA and/or DHA levels might in turn

be associated with reduced heart rate variability and reduced autonomic nervous system activity.

Omega-3 fatty acid tissue composition and heart rate variability

Several studies have suggested that omega-3 fatty acid supplementation leads to increased heart rate variability. Four double-blind placebo-controlled clinical trials of adult subjects have documented increases in heart rate variability after treatments with omega-3 fatty acids during 24-hour monitoring (Christensen et al., 1996, 1997, 1998; Christensen, Christensen, Dyerberg, & Schmidt, 1999). Even though these human intervention trials suffer from several methodological problems, including a lack of correction for post hoc comparisons, additional primate data support the results. Heart rate variability under stress was significantly higher among adolescent rhesus monkeys that were fed formulas containing DHA and AA as infants, as compared to monkeys fed standard formula (Hibbeln et al., 2000). In future human intervention trials, it will be important to utilize sound statistical analysis and also to assess how individual differences in baseline aggressiveness and depression relate to cardiovascular reactivity.

A final point to be stressed on neurodevelopment and aggression is that all aspects of the development of aggressive and depressive behaviors must be considered, including psychosocial, biological, and environmental factors. For example, Raine et al. (1997) found that early maternal rejection in combination with birth complications predicted violent offenses among men during late adolescence and up to age 34. These two factors may be part of a larger body of data suggesting that childhood trauma in general may predispose children to a maladaptive way of dealing with stress and trauma later in life, manifested in a variety of outcomes. For example, Perry and Pollard (1998) review data on the role of caregivers in early development. Responsive, predictable caregivers provide children with a healthy stress-response neurobiology, developing resistance to earlier trauma by having a stable base to return to when overwhelmed. On the other hand, children exposed to chaotic or threatening caregiving develop a sensitized stress-response system, which may later negatively affect emotional, behavioral, and cardiovascular reactivity. In another study by Raine et al. (1996), 397 male subjects were studied using obstetric and early neuromotor measures collected during their first year of life, family, social, demographic, and behavioral measures from ages 17–19, and criminal data from ages 20–22. Cluster analyses revealed three distinct groups. When the neuromotor deficits and negative family factors were clustered

together into one group (labeled 'biosocial'), these individuals had more than double the adult violence, theft, and total crime rates of the other two groups (obstetric risk factors only and poverty risk factors only). In addition, the biosocial group had significantly more behavioral and academic problems in adolescence (Raine et al., 1996). Collectively, while the data on the neurodevelopmental interplay of serotonergic systems, cardiac systems, and DHA and EPA levels suggest multiple roles for these factors in the development of residual aggressive and depressive behaviors, there are still several biological, psychosocial, and environmental factors that may also predispose children to these types of behaviors.

Summary and conclusions

Deficits in omega-3 fatty acid intake, particularly in prenatal periods, may impair serotonergic function and result in a cascade of suboptimal development of cortico-limbic regulation of other neurotransmitter systems. This suboptimal development may contribute to greater risks of deficits in cortical regulation of emotional responses that are in turn linked to autonomic hyper-reactivity. This conceptual model merits testing in non-human primates, which may best model the complex development of emotionally linked socially mediated responses. Although it appears that there are neurodevelopmental deficits induced by deficiencies of omega-3 fatty acid intake during critical time periods, these are not well characterized. In human adults and children, clinical studies suggest that supplementation with omega-3 fatty acids may reduce aggressive, impulsive, and depressive behaviors, which may be mediated by effects on neurological deficits. Reductions in depression and aggression as a result of omega-3 supplementation would be an important contribution to public health because these nutrients are inexpensive, non-toxic and readily available in specific foods. Negative results would provide guidance to physicians currently using these fatty acids to treat their patients, while positive findings would indicate that omega-3 fatty acids can increase heart rate variability, which is associated with a decreased risk of sudden cardiac death. Positive findings would suggest that a low omega-3 level is an important factor linking depression and aggression to increased cardiovascular risk. One future clinical application could be the treatment of patients identified with depression or hostility who are at greater risk of myocardial infarction. Critical examination of the consequences of the increase in omega-6 fatty acid intake in the USA during the last century is merited, in particular of the increase of linoleic acid intake from less than 0.5–10% of calories, as this change has functionally depleted omega-3s

from the food supply and may be linked to increased risk for homicide mortality.

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