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Research Brief

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Benefits of omega-3 supplementation: Effects on aggressive behavior and implications for autism spectrum disorders

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Summary: Here we look at the evidence and theoretical mechanisms for treating aggression with omega-3 fatty acids. Since aggressive behavior often accompanies autism, omega-3 fatty acids may be helpful in treating such behavioral difficulties. We conclude that omega-3 fatty acids may be helpful in treating aggression, but further research is required to confirm its effects. To date, the research on omega-3 fatty acids in relation to autism is severely limited, with only one study that directly investigated the effects of omega-3 supplementation in a small number of children with autism spectrum disorders (ASDs). We suggest this may be a fruitful area of study.

Why study omega-3 fatty acids in neuropsychiatry?

About half the brain is fat (Sastry, 1985), and up to 20% may be omega-3 fatty acids (Hulbert et al., 2002). Docosahexaenoic acid (DHA), an important omega-3 fatty acid found in fish oil, comprises approximately 32% of neuronal synaptic membranes (Cotman et al., 1969). If brain structure influences neural functioning, then omega-3 fatty acids may play a role in influencing psychological outcomes. Indeed, several studies have indicated reductions in red blood cell composition of fatty acids in neurological disorders, such as schizophrenia, attention deficit hyperactivity disorder, depression, and bipolar disorder (cited in Bell et al., 2004).

Background on Essential Fatty Acids

The benefits of essential fatty acids first received national recognition in a report from the Committee on Medical Aspects of Food Policy (Department of Health, 1994). Specifically, the long-chain omega-3 polyunsaturated fatty acids (PUFA) contained within fish oils were noted for their potential health benefits (Ruxton et al., 2004). Considerable evidence since emerged documenting numerous benefits of the omega-3 PUFAs found in fish oil.

Both DHA and another omega-3 called eicosapentaenoic acid (EPA) are PUFAs that are synthesized from the omega-3 precursor, alpha-linolenic acid (ALA). ALA is essential to the human diet because it cannot be synthesized within the human body.

Omega-3s have been shown in laboratory, observational and clinical studies to have a positive

impact on a variety of health factors, particularly cardiovascular health, psychological disorders, and numerous inflammatory diseases. Omega-6 fatty acids, however, appear to cause inflammation with possible detrimental health effects.

Studies show that as dietary omega-6 increases, the amount of omega-3s incorporated into tissues decreases (Holman, 1998), and it is the ratio of omega-6 to omega-3 that is thought to be important. Since it is difficult to overhaul personal diets in clinical studies, one option is to focus on increasing omega-3s to improve this ratio in order to enhance overall health.

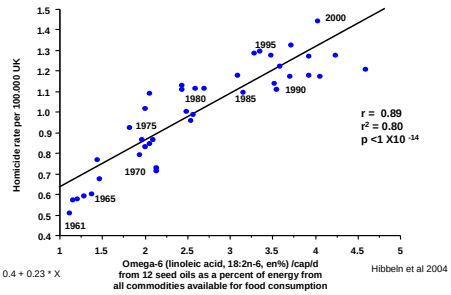
It has been suggested that imbalances in fatty acids may be linked to the development of pervasive developmental disorders (PDDs; Richardson & Ross, 2000). Little research has looked at the relationship between omega-3s and aggression in ASD, but the relationship between aggression and fatty acids in other contexts has been addressed. In light of the fact that aggressive behaviors are often associated with ASD, the following review presents data on the relationship between aggression and omega-3 fatty acids. The literature in this area may shed light on the potential benefits that omega-3s may have in addressing behavioral concerns and injurious behavior in people with PDDs.

The data do not conclusively indicate that consuming more omega-6 *causes* aggression, or that omega-3s prevent it; they just indicate that a relationship might exist and provide cause for further study.

Ecological Studies

Ecological studies, by design, provide a very broad view of the possible relationships between environmental factors (such as diet) and health at the population level. Several studies show that populations who consume a lot of omega-6 fatty acids are more likely to have high rates of homicide than those who consume less omega-6 (Hibbeln et al., 2006). In contrast, in countries where a lot of long chain omega-3s are consumed, murder rates are lower (Hibbeln, 2001). It is also true that as omega-6 fatty acid consumption has increased in the United States, the United Kingdom, Australia, Canada and Argentina over time, rates of murder have increased in a way that closely correlates with the changes in dietary omega-6 (see Figure 1 for data on the United Kingdom; Hibbeln et al., 2004). It is interesting to note that rates of autism have been increasing during this same period, though the cause of this increase is not clear (Fombonne, 2003). It is important to keep in mind that such reported correlations between markers of aggression and increased consumption of omega-6 do not indicate causation. That is, the data do not conclusively indicate that consuming more omega-6 *causes* aggression, or that omega-3s prevent it; they just indicate that a relationship might exist and provide cause for further study.

Figure 1: Homicide mortality in the United Kingdom and availability of Omega-6 fats (18:2n-6) in the food supply 1961-2000

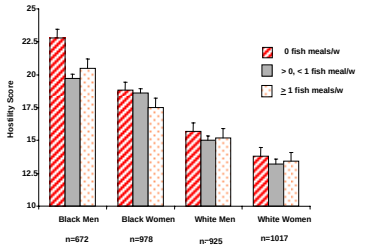


Case-Control and Prospective Studies

Case-control and prospective studies involve designs that come closer to ascertaining causality than ecological studies. The CARDIA study was a prospective observational study of risk factors associated with cardiovascular disease. It was found that among the young urban adults who were

studied, eating fish decreased the likelihood of being very hostile by 18% (see Figure 2; Iribarren et al., 2004). A case-control study compared 100 suicide attempters to 100 controls, and found that EPA was 25% higher in the controls (Huan et al., 2004). Similarly, patients with autism were found to have levels of omega-3s in plasma that were 20% lower than in controls (Vancassel et al., 2001). This finding was confirmed in another study, which found that Autism and Asperger's disorder in children corresponded with clinical signs of essential fatty acid deficiency and reduced red blood cell omega-3s (Bell et al., 2004).

Figure 2: Lower Cook-Medley hostility scores associated with more frequent fish consumption. The CARDIA STUDY



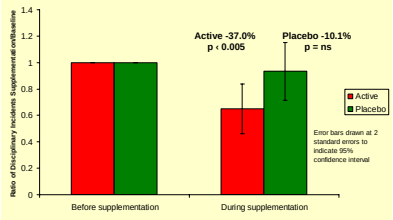
Irribaren, Hibbeln et al Eu J Nutr 2004; 58: 24-31

Randomized Placebo-Controlled Trials

Some of the strongest evidence on the relationship between diet and aggressive behaviors has been obtained from randomized controlled trials. Typically, in a clinical trial, participants are randomly assigned to a treatment group or a non-treatment control group. A recent study of rats by DeMar and colleagues (2006) found that deprivation of omega-3 fatty acids was related to a two-fold increase in aggressive behaviors compared to rats that were not deprived. Similar results in humans have also been documented:

- In children with disruptive behaviors, a 560 mg omega-3 fatty acid supplement daily for 4 months led to improvement in oppositional behaviors for more patients than a placebo. The magnitude of change correlated with increases of EPA (Stevens et al. 2003).
- In school children consuming fish oil-fortified foods contributing 4.4 g DHA+EPA daily for 3 months, changes in physical aggression were related to the changing ratio of EPA/AA. (Itomura et al., 2005).
- Stress-related aggression decreased in Japanese university students given 1.5-1.8 g DHA/day for 3 months, but aggression increased in the placebo group (Hamazaki et al., 1996, 1999, 2000).
- Consuming 1.5 g DHA/day for 2 months decreased aggression in stressful situations in elderly white collar workers in Thailand (Hamazaki et al., 2002).
- A cholesterol-lowering diet, which included high fish consumption, resulted in a reduction of aggressive hostility in adults (Weidner, 1992).
- In women with borderline personality disorder, 1 g ethyl-EPA for 2 months was superior to placebo in reducing aggression (Zanarini & Frankenberg, 2003).
- Reductions in violent offenses were documented among British prisoners in a placebo-controlled trial of a multivitamin/mineral and essential fatty acid supplement (see Figure 3; Gesch et al., 2002).

Figure 3: Reductions in felony level violent offences among prisoners in placebo controlled trial of recommended daily amounts of vitamins, minerals and essential fatty acids



338 offences among 172 prisoners over 9 months treatment in a UK maximum security prison compared to 9 months baseline. Analysis: Negative binomial mixed Poisson regression analysis
Gesch et al. Br J Psychiatry 2002, 181:22-28

Autism and Asperger's disorder in children corresponded with clinical signs of essential fatty acid deficiency and reduced red blood cell omega-3s.

A current study underway at the National Institute of Health (NIH) explores the relationship between aggression and the omega-3 fatty acid status of alcoholics.

Autism Studies

There has been one randomized placebo-controlled pilot study on the effects of omega-3 supplements in youth with autism. The study found a trend toward reducing hyperactivity and stereotypy (repetitive thought, motion or speech), but the number of subjects was small and the findings were not statistically significant (Amminger et al., 2006). As a pilot study, however, these results provide reason to pursue larger trials. Another study showed that fish oil supplementation in children with autism increased red blood cell levels of omega-3 fatty acids while reducing omega-6s. These changes were accompanied by improvements in general health, cognitive skills, and sociability, as well as reductions in irritability, aggression, and hyperactivity, according to parental reports (Bell et al., 2004). Among children with developmental coordination disorder, which is common among patients with autism, omega-3 supplementation improved reading, spelling and disruptive behaviors (Richardson & Montgomery, 2005).

Current Research at the NIH

A current study underway at the National Institute of Health (NIH) explores the relationship between aggression and the omega-3 fatty acid status of alcoholics, who undergo accelerated depletion of DHA from the brain due to alcohol exposure (Pawlosky et al., 2001). Pilot analyses, presented at the International Society for Research on Aggression biannual conference in 2006, indicated that supplementation of aggressive alcoholics with omega-3s yielded a 33% decrease in anger compared to placebo over a 12 week period. Also, alcohol and substance abuse decreased for the participants who took omega-3s (Hibbeln et al., unpublished). Findings from this study specifically with aggression and various psychiatric outcomes are expected in the next year as the clinical protocol reaches its conclusion.

Possible Mechanisms

The mechanisms by which omega-3s might influence aggression have not been fully elucidated, and there is much work to be done in this area. However, evidence has accumulated in recent years leading to the conclusion that omega-3s act via many different pathways. Some of these theories are covered here, although a full discussion of how omega-3s affect processes in the brain and body is beyond the scope of this article.

First, omega-3 fatty acids play a role in regulating the activity of cell membranes and the structures contained within those membranes. The structure of DHA differs enough from the fats that replace it in when DHA is in short supply (i.e. dietary deficiency) to have a profound effect on membrane fluidity. Membrane fluidity, in turn, influences the activity of receptors and enzymes contained within the membrane. This might have an effect on glucose metabolism in neurons (i.e. energy usage) and on neurotransmitter function (Sinclair & Wesinger, 2004). Hibbeln et al. (1998) have found that healthy human subjects who have higher levels of plasma DHA have higher levels of 5-HIAA, a metabolite of the neurotransmitter serotonin, and higher levels of HVA, a metabolite of dopamine, in their cerebrospinal fluid, an indication of the amount of the metabolites in the brain. Serotonin, dopamine, and their respective metabolites have also been found to be increased in the brains of piglets that were fed infant formula supplemented with essential fatty acids (de la Presa

Owens & Innis, 2000). Relatively high levels of 5-HIAA and HVA have been associated with decreased aggression, and it is also of note that deficits in serotonin are also linked to an increased risk of autism and other developmental disorders (Hibbeln, Ferguson & Blasbalg, 2006).

Second, essential fatty acids play an important role in modulating inflammation in the body through the production of molecules called eicosanoids. Eicosanoids are made from whatever omega-6 AA or the omega-3 EPA lipids are available in a certain part of cell membranes. Eicosanoids made from the former are highly inflammatory while those from the latter are much less so. These molecules may have additional functions that only recently gained the attention of scientists (Calder, 2006). The effect of inflammation on brain function and psychiatric outcomes is not known, but may be significant.

Third, omega-3 fatty acids have been found to influence gene transcription, determining what genes get expressed and to what extent they are turned on or off. A study in rats has shown that dietary omega-3s influence the expression of at least 40 different genes in the brain (Kitajka et al., 2004). The full implications of these genetic changes are not yet known, but are likely very significant to brain function and psychiatric outcomes.

Finally, it may be through a combination of the mechanisms described above that omega-3 fatty acids help maintain the integrity of neurons. Evidence derived from cell culture experiments suggests that neural outgrowth and dendritic proliferation is enhanced by DHA, increasing the number of synapses formed in the neural network (Calderon & Kim, 2004). Also, omega-3 supplementation prevents neuronal cell death (Sinclair & Wesinger, 2004).

Recommendations and Conclusions

Long chain omega-3's (EPA and DHA) are found primarily in fatty fish and certain marine algae. Fish oil capsules are a good source for supplementation, but it is important to read labels to make sure the product delivers a high potency of EPA and DHA. The shorter chain, ALA, is found in nuts and seed oils. However, conversion to the long chain DHA in humans is poor (maximum 15%), and ALA is often accompanied by omega-6 fatty acids in food sources. Thus, ALA supplementation is not recommended at this point.

In conclusion, omega-3s may be an important dietary consideration in improving brain functioning and subsequently reducing aggressive behaviors, though further research is needed to understand its mechanisms. To date, only one study, with limited methodology, looked at the effect of omega-3s on aggression and other behaviors specifically in individuals with ASDs, and there are no randomized controlled trials that directly support a recommendation of omega-3 consumption by children with ASDs. However, the overall benefits suggest that the supplement can lead to the reduction of associated aggressive symptoms. Further, there is no apparent harm associated with omega-3 supplementation. As with any form of supplementation, the decision to use omega-3s in children with autism should be made in conjunction with a primary care provider. The growing research in the behavioral benefits of omega-3s suggests this would be a fruitful area of study.

In conclusion, omega-3s may be an important dietary consideration in improving brain functioning and subsequently reducing aggressive behaviors.

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