Feature

Omega-3 and treatment implications in Attention Deficit Hyperactivity Disorder (ADHD) and associated behavioral symptoms

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Summary

Attention Deficit Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder with core symptoms of inattention, hyperactivity, and impulsivity. Marked impairments in self-regulatory and executive function skills are associated with distractibility, disorganization, working memory, goal-directed behaviors and maintaining motivation, focus and effort. Another recognized feature of ADHD is the concept of emotional dysregulation which is the inability to regulate emotional processes and can often manifest as instability in temperament, and explosive temper. Although there is a high degree of heritability for symptoms of ADHD, somewhere in the region of 65–75%, most of the genetic effect is considered accountable by gene/environmental interactions. One plausible environmental postulation is the hypothesis of inadequate neuronal levels of omega-3 highly unsaturated fatty acids (HUFAs) leading to abnormalities in dopamine-related neurotransmission in the frontal cortex and reward-related pathways in the ventral striatum regions. Neuroimaging studies have confirmed that these brain networks are impaired in ADHD compared to control counterparts during a range of tasks measuring motivation and reward management processes. Omega-3 highly unsaturated fatty acids have critical roles throughout the central nervous system featuring in complex structural and functional processes related, but not restricted to myelination, cell-signaling, gene expression and in the regulation of mood and affect. This article will present and discuss evidence from several clinical studies and raise questions regarding future research directions.

Introduction

ADHD is defined by the Diagnostic and Statistical Manual of Mental Disorders (V) as a complex, multi-faceted, behavioral disorder often co-occurring with externalizing disorders including oppositional and conduct disorders. Typical behaviors of inattention (e.g., as seen in Attention Deficit Disorder/ADD) and/or the combined hyperactive-impulsive (ADHD sub-type) are present before the age of 12 and often observable in children as young as 2 years. In regards to the hyperactive-impulsive nature of ADHD, typical behaviors include an inability to sit still for any period of time; fidgeting, tapping and squirming and general restless behavior. Children will lose interest quickly in assigned tasks and are unable to follow through on instructions. They are prone to talking excessively, and making frequent and repetitive interruptions during the conversations of others. Often children with ADHD are unable to play quietly, and are constantly on the go as if driven by a motor. The inattentive subtype (ADD) is characterized by an inability to pay close attention to detail. Children will often make careless mistakes in school and homework. They have difficulty paying attention and appear not to be listening even when spoken to directly. Consequently, they fail to complete school and homework and/or chores around the home instead wondering off easily distracted. Children and adults with ADD also persistently loose items necessary for everyday functioning and are often messy, disorganized with little or no concept of time. The disorder, although typically diagnosed in childhood, frequently persists into adulthood and places those affected at risk for a variety of irregularities in personality development. Clinicians agree that symptoms of hyperactivity diminish with age with inattentiveness persisting into adulthood. It is thought that somewhere in the region of 50% of children with ADHD also display symptoms of related disorders including mood, bi-polar, anxiety, and/or depressive disorders. In the United States, the financial burden associated with ADHD is staggering and calculated in the region of tens of billions of U.S. dollars per annum [1]. Several lines of research have suggested a role of omega-3 highly unsaturated fatty acids as an alternative treatment intervention for children with ADHD; either as a mono-therapy for treatment resistant children or as an adjunct to pharmacological interventions. A recent meta-analysis by Bloch and Qawasmi (2012) evaluated the outcomes of 10 dietary omega-3 clinical intervention trials (n = 699) in children with ADHD. The reported that EPA-rich preparations (eicosapentaenoic acid is a highly unsaturated fatty acid) were significantly associated with clinical efficacy [2].

Unmanaged ADHD and associative risk factors

The developmental trajectory of unmanaged ADHD is precarious. Often adolescents with ADHD, primarily as a direct result of lack of educational support and/or persistent fixed term and permanent school exclusions will gravitate towards delinquent peer groups. This places them at risk for conduct disorder-related, anti-social behaviors and the development of addictions to nicotine, alcohol, marihuana and cocaine. The addictive nature of ADHD is described as the gateway hypothesis and is theorized as a form of self-medicating. Among the prison population, increasing research studies are reporting a disproportionate number of inmates meeting criteria for ADHD but not having received a diagnosis in childhood. For example, a recent Swedish prison study found approximately 40% of the adults met criteria for ADHD. Comparatively, a study conducted in a women’s prison in Rhode Island found 46% of the in-
mates met criteria for childhood ADHD. Likewise, an Icelandic study found that 50% of males recently incarcerated met DSM-IV criteria for ADHD. Gow and colleagues (2013) recently reported an association between lower blood levels of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA, 20:5n-3) and higher scores of callous-unemotional (CU) traits in male children with ADHD. CU traits are considered a considerable risk factor for the later development of conduct disorder and psychopathy. The clinical measurement of these traits in children with symptoms of ADHD, in addition to testing for low omega-3 status, may pose to be a meaningful preventative tool given the implications of unmanaged ADHD. Omega-3/6 fatty acids in conjunction with multi-vitamins and minerals have already found to be significantly effective in reducing anti-social and violent incidents in young adult prison populations [3].

Omega-3 highly unsaturated fatty acids (HUFAs)

Omega-3 HUFAs, including docosahexaenoic acid (DHA: 22:6n-3), EPA, docosapentaenoic acid (DPAn-3: 22:5n-3) and omega-6 HUFAs, most notably arachidonic acid (AA: 20:4 n-6) are consumed preformed or produced from the essential fatty acid precursors α-linolenic acids (ALA: 18:3n-3) and linoleic acid (LA: 18:2n-6) respectively. The main sources of DHA and EPA are marine fish/seafood and as the essential fatty acids cannot be synthesized de-novo these must be sourced via the diet.

DHA and AA are selectively concentrated into central nervous system phospholipid pools as acyl chains. There is a molecularly specific requirement not only for critical biophysical functions as major constituents of neuronal membranes, but also for diverse biological activities. HUFAs are major structural components of neuronal membranes, essential for cell signalling and brain function. In addition, they are involved in nerve function, cell division and growth and are found in high concentrations in the brain. DHA increases neuronal responses by enhancing the flexibility of cell membranes and as a result improving magnocellular functions [4]. DHA is abundant in the central nervous system and plays a pivotal role in serotonergic and dopaminergic function. Most of the accumulation of DHA takes place during prenatal and early postnatal development, which coincides with synaptic formation [5]. The negative impact of inadequate DHA during critical periods of brain development has been well studied in animals and, to a lesser extent, in humans. Maternal nutritional deficiencies during neurogenesis and angiogenesis have long been associated with behavioral impairments in both animal models [6] and in humans [7]. In animal studies, prenatal and postnatal DHA insufficiency has been associated with a variety of structural changes, including delayed neuronal migration, disrupted dendritic arborization, abnormal neuronal development in the hippocampus, and abnormalities in timed apoptosis. It appears that HUFA insufficiency during lactation can lead to some irreversible changes [8], presumably due to impaired connectivity. EPA converts into signaling molecules called eicosanoids which are generated by the oxygenation of twenty-carbon essential fatty acids. There are four families (thromboxanes, prostaglandins, leukotrienes and resolvins) of eicosanoids which derive from either an omega-6 or omega-3 fatty acid. They possess varying complex functions including inflammation, immunity and messengers in the central nervous system.

Importantly, there is also an association between ADHD and a dysregulation of noradrenergic function and faulty neurotransmitter systems, especially, of the dopaminergic system involving the dorsolateral prefrontal cortex networks. These catecholamine networks are also known to be altered, in some cases permanently, as a result of omega-3 deficiency in utero. It is well documented that the psycho-stimulant methylphenidate is able to reverse some of the neuropsychological deficits observed in ADHD patients whilst in healthy adults it can improve reaction time, working memory and vigilance by directly impacting on dopamine and noradrenaline release in the prefrontal cortex [9]. In a similar way, omega-3 modifies the activity and production of neurotransmitters and signal transduction. Behavior pathologies reflecting self-harm, aggression, increased anxiety, decreased goal-directed behavior, increased

Figure 1. The relationship between omega-3 EPA (upper left panel), total n-3 (lower left panel), DHA (upper right panel), total n-6 (lower right panel) shown as percentage levels of plasma choline phosphoglycerides (PC) and mean scores for callous and unemotional traits in children/adolescents with ADHD (n = 29) group. The p values are corrected for multiple testing.

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Table 1. Mean fatty acids (% levels) in plasma choline phosphoglycerides in ADHD and Healthy Control children/adolescents

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 38)</th>
<th>ADHD (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Omega 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C18: 2n-6 (LA)</td>
<td>24.8</td>
<td>3.44</td>
</tr>
<tr>
<td>C18: 3n6</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>C20: 2n6</td>
<td>0.31</td>
<td>0.07</td>
</tr>
<tr>
<td>C20: 3n6</td>
<td>3.66</td>
<td>0.96</td>
</tr>
<tr>
<td>C20: 4n6 (AA)</td>
<td>11.6</td>
<td>2.25</td>
</tr>
<tr>
<td>C22: 4n6</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>C22: 5n6</td>
<td>0.25</td>
<td>0.08</td>
</tr>
<tr>
<td>Total n6</td>
<td>41.1</td>
<td>3.39</td>
</tr>
<tr>
<td>Omega 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C18: 3n (ALA)</td>
<td>0.34</td>
<td>0.13</td>
</tr>
<tr>
<td>C20: n3</td>
<td>0.13</td>
<td>0.04</td>
</tr>
<tr>
<td>C20: 5n3 (EPA)</td>
<td>0.99</td>
<td>0.45</td>
</tr>
<tr>
<td>C22: 5n3</td>
<td>1.06</td>
<td>0.31</td>
</tr>
<tr>
<td>C22: 6n3 (DHA)</td>
<td>3.71</td>
<td>0.92</td>
</tr>
<tr>
<td>Total n3</td>
<td>6.23</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Note: *p < .05, **p < .01

Adhd and Implicated Brain Regions

Adhd and Implicated Brain Regions

(FunCtion and structure)

Neuroimaging studies have reported structural abnormalities in ADHD in fronto-cerebellar circuits in particular the dorsolateral-prefrontal cortex, cerebellar vermis and caudate nucleus compared to controls. Other structural differences between ADHD and controls include: reduced brain volumes in the ventral striatum; global reductions in gray matter volumes and the size of right-hemispheric fiber tracts in the cingulum bundle connecting the anterior cingulate with the dorsolateral prefrontal cortex as well as in fronto-striatal fiber tracts and the superior longitudinal fasciculus that link prefrontal and parietal regions.

During tasks measuring brain function differences have also been reported between ADHD and controls characterized by under-activation during inhibitory [15], sustained attention [16] and temporal processing tasks [17] implicating the striatum, caudate nucleus and basal ganglia.

Abnormalities in reward processes

A common phenomenon in children with ADHD is a greater tendency towards smaller, immediate rewards over larger, delayed ones. The role of the ventral striatum has been implicated in reinforcement mechanisms and alterations in the reward processes leads to delay aversion [18]. It has also been proposed that the nucleus accumbens (chiefly the ventro-striatal nucleus) is implicated in coding and computing the value of future rewards and orchestrating the performance of goal-directed actions. Hypo-activation of the ventral striatum has been persistently reported during tasks of reward processing in adults with ADHD [19]. Abnormalities in reward management processes are thought to derive from alternations in DA-mesolimbic circuits [20]. D2 receptors are highly present in the striatum, ventral tegmental area (VTA), and substantia nigra (SN). Furthermore, the mesolimbic tract is formed by dopaminergic neurons which project to the amygdala and hippocampus. Both mesocortical and mesolimbic tracts are involved in affect and motivation regulation. Neuroimaging studies have persistently demonstrated that addiction is associated with a significant decrease in striatal dopamine transmission as measured as dopamine D2 receptor binding and pre-synaptic dopamine release [21]. Impulsivity, addiction to drugs of abuse and disorders such as ADHD are all associated with comparable deficits in striatal dopamine signaling suggesting that these biomarkers (poor D2 receptor binding and dopamine release) occur prior to drug exposure but may play a role in the development of addictive behaviors [21]. Animal studies have demonstrated that DHA deficiency significantly decreases the density of ventral striatal D2-like receptors [22]. It may be that dietary supplementation with high doses of omega-3 HUFAs can restore the ventral striatal D2 receptor signaling pathways and in doing so mediate the responses to reward and behaviors commonly associated with ADHD.

Assessments of brain function and role of omega-3 in ADHD: What we know so far

To date, there are no published data from functional or structural neuroimaging omega-3 intervention trials in children or adults with ADHD. A clinical trial by McNamara and colleagues (2010) using functional magnetic resonance imaging (fMRI) reporting changes in cortical attention networks in healthy boys following supplementation with DHA. Little attention has also been paid to emotional dysregulation in children with ADHD despite the evidence that emotion dysfunction exists on several levels. Namely, (1) in animal models omega-3 deficiency depletes dopamine by 40–60% in the frontal cortex; (2) that supplementation with EPA/DHA can improve mood and symptoms of depression [23] and (3) children with ADHD have been reported to demonstrate an inability to correctly identify the facial expressions of others especially emotions of fear, anger and sadness. Facial expressions provide significant non-verbal social cues to affective states and are immediate indicators of emotional dispositions in other people. In ADHD, impaired interpersonal relationships are common and in children these are manifested within peer, sibling, teacher and parental relationships.

There are only two studies published to date investigating emotion-elicited event-related potential (ERPs) neuronal activity and omega-3 fatty acids in children with ADHD [14]. Event related potentials (ERPs) are an imaging technique with a high temporal resolution which is advantageous for the study of emotion processing and allows the investigation of automaticity during different, temporally separate, stages of emotion processing. The first study by Gow et al., (2009) reported positive associations between omega-3 fatty acids and event related P300 responses to positive stimuli (faces depicting happiness) relative to negative emotional stimuli (facial expressions of fear and anger) in male children with symptoms of ADHD. The associations implied that the greater the blood
levels of omega-3 fatty acids the greater the neuronal responsive to positive emotional expressions. However, these associations were observed in a very small sample size with no comparison to a healthy control group.

The second study by Gow et al. (2013) recruited 63 male children/adolescents (31 with ADHD and 32 healthy control children with a mean age of 14 years) and recorded their event related potentials during an emotion processing task, in addition, to collecting a blood sample to measure the mean percentage levels of both omega-3 and 6 essential fatty acids. The study adopted a well-known model of emotion processing by Halgren and Marinkovic (1994). The model describes 2 stages of emotion processing captured by two waveforms; N200 which is a negative-going wave occurring approximately 200 milliseconds after the presentation of the emotional expression and N400, also a negative going wave occurring approximately 400 milliseconds after the presentation of the emotion. The N200 wave is thought to be particularly altered by emotional expressions, and captures the early orienting stage during which the participant is encoding and deciphering the emotion. The N400 wave reflects semantic processing and the later contextual evaluation stage of the emotion processing model. During the EEG recording, the child/adolescent is instructed to pay attention to the presentation of different facial expressions appearing on a computer screen for approximately 500 milliseconds. Each face depicts an emotion comprising happiness, fear, anger, disgust, sadness or a neutral face. The results of the study found that both N200 and N400 waves were significantly different between the children with ADHD compared to the control group. At both these time points, the healthy control children produced larger negative-going activity than the children with ADHD. In addition to lower levels of plasma choline phosphoglycerides including EPA and DHA, the children with ADHD produced significantly less negative-going electrical activity in response to the emotional expressions compared to the healthy controls. There were also significant associations between higher omega-3 levels and greater N400 responses to happy faces suggesting that as omega-3 increased the responses to the ADHD also increased and were more similar to the responses generated by the healthy control group. The key finding of this study was that both the orienting and contextual evaluation stages of the emotion processing model were impaired in children with ADHD. As the children with ADHD had significantly lower levels of omega-3, it was theoretically postulated that the lower omega-3 may be affecting neurotransmitter functions which were reflected in the inability to generate the same neuronal responses as seen in the healthy control group. It remains unseen as to whether supplementation with omega-3 is able to modulate neurotransmitter functions in humans.

Future randomized, placebo-controlled, clinical trials would need to investigate whether omega-3 supplementation is able to normalize some of the neuronal deficits observed in this study.

Conclusion

In studies with human participants, cumulative evidence suggests that low omega-3 HUFA levels may be linked with behavioral problems commonly associated with ADHD including the presence of callous and unemotional traits. Several research trials have found supplementation with omega-3 fatty acids to be advantageous in reducing symptoms of ADHD, child depression and anti-social and violent behaviors. There is therefore plausible and theoretical evidence to suggest the necessity for larger, clinical intervention trials with high-doses of EPA and potentially other trace elements/multivitamins preferably using neuroimaging techniques such as fMRI. It may be that high dose supplementation with EPA/DHA are able to restore the ventral striatal D2 receptor signaling pathways and in doing so mediate the responses to reward and addictive behaviors commonly associated with ADHD.

References

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