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EFFECT OF OMEGA-3-FATTY ACIDS ON DIFFERENT NEURONAL DISORDERS; A MOLECULAR APPROACH

Meghoparna Kundu, Jeenatara Begum *, Tamalika Chakraborty, Surya Shiskha Baidya, Suparba Tribedy and Nabamisha Chatterjee

Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Road, Panihati, Kolkata - 700114, Bengal, India.

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Correspondence to Author:
Jeenatara Begum

Guru Nanak Institute of Pharmaceutical Science and Technology, 157/F, Nilgunj Road, Panihati, Kolkata - 700114, Bengal, India.

E-mail: jeenatara.begum@gnipst.ac.in

ABSTRACT: Omega-3 fatty acids are essential fatty acids present in regular animal and plant food diets. They play a key role in different body functions. Omega-3 fatty acids help to prevent central nervous system diseases. In this paper, we have shown the molecular basis of this effect. There isa number of studies showing the role of omega-3 fatty acids in the prevention of different central nervous system disorders. Omega-3 fatty acid plays a key role in brain development even during embryogenesis. It mainly shows a preventive effect against CNS disorders due to its anti-inflammatory action. Parkinson's disease, migraine, schizophrenia, dementia and psychosis are some of the most abundant CNS disorders which are difficult to cure completely, especially in advanced stages. Omega-3 fatty acids, which can be obtained from a regular diet plan, have the potential to prevent and sometimes cure these disorders. Although in some cases the appropriate database is not available, all in all, it can be said that omega-3 fatty is plays a preventive role in most CNS diseases.

INTRODUCTION: Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) with a double bond after the third carbon atom in the carbon chain. They contain more than one *cis* double bond. All omega-3 fatty acids (ω3 or n-3) have one or more double bonds between the third and fourth carbon atom (counting from the methyl end of the fatty acid). Mainly there are three types of omega-3 fatty acids:

- Alpha Linolenic Acid [ALA]
- Eicosapntanoic Acid [EPA]
- Docosahexaenoic acid [DHA

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ALA is mainly obtained from plant oils such as flaxseed, soybean, and canola oils. Fish and other sea foods are the sources of DHA and EPA [1]. They are fats that are commonly found in marine and plant oils. Despite being considered essential fatty acids, they are one of the most essential sources of energy in daily diet. Consuming omega-3 fatty acids versus other fatty acids as a supplement helps reduce the risk of cancer, cardiovascular disease, inflammation, hypothyroidism and brain aging disorders. They are needed for normal metabolism [2].

Consumption of Omega 3 fatty acids potentiates the body's responses to pathogens and foreign particles. Omega-3 fatty acids change cell membrane lipid composition and alter signal transduction and modulate gene transcription. A favorable omega-6 to omega-3 polyunsaturated fatty acids ratio and have a protective effect against many decrepitude. Eating a diet high in long-chain

omega-3 fatty acids decrease the risk of stroke. Omega 3 fatty acids play an important role in increasing the amount of good cholesterol i.e., low-density lipoprotein (LDL) cholesterol, and decreasing creasing blood pressure. Omega 3 fatty acids also maintain the balance of the neurotransmitter system in the brain. Thus, it has the potential to show activity against developmental disorders, psychiatric disorders and cognitive aging. Consuming omega-3 fatty acids may prevent or reduce symptoms of some developmental disorders. With cognitive aging such as the degradation of neurogenesis, which is how neurons are generated, omega-3 may enhance the process of neurogenesis [2].

Effect of Omega 3 Fatty acid on Neurons and Brain Gene Expression: Omega 3 fatty acids (ALA, DHA, EPA) play a critical role in the development of neurons as well as the healthy function of the Central Nervous System. They play a crucial role in controlling learning skills and memory.[3] Omega-3 acids are involved in maintaining the balance of neurotransmitter systems in the brain. In a study, a nutrigenomic approach with high-density microarrays was used to detect the changes in brain gene expression as a response to different PUFA-enriched diets in rats.

In a study on aged rats fed throughout life with PUFA-enriched diets, genes with altered expressions play important roles in synaptic plasticity and learning. The effect of Omega 3 fatty acid is pleiotropic resulting in changes in neurotransmitter synthesis, release, and reuptake. Any misbalance in omega 3 fatty acid concentration may disrupt normal brain function resulting in many neuronal disorders [4]. Regulation of gene expression by omega 3 fatty acid takes place through interactions with specific or nonspecific ligands that bind to regulate factors acting on cis-regulatory elements of the gene affecting mRNA synthesis. For example, omega-3 fatty acids (ALA, EPA and DHA) can directly interact with transcription and translation factors, like peroxisome proliferator-activated receptors (PPAR), which directly modulate the expression of target genes. A large amount of DHA present in the breast milk of a breastfeeding mother is responsible for the healthy neurons and brain development of infants. A good amount of DHA also helps in better visual development in children [3]. It is important that, during the time of embryogenesis, the brain is supplied with adequate intakes of omega 3 fatty acids for its functions. In several studies, it is reported that omega-3 fatty acids activate several genes. For example, ALA and DHA activate some genes in other tissues like the liver, adipose tissue, *etc*. One of the first observations that dietary fat influenced brain gene expression was reported by DeWille and Farmer [4].

They found that the mRNA level of several genes involved in myelination, such as those coding for proteolipid protein and myelin basic protein, were affected by a diet lacking essential omega-3 fatty acids. DNA micro rays or real-time PCR techniques are now capable of estimating brain gene expression by the action of omega 3 fatty acids. ALA and DHA are not only the main fatty acids in grey matter but also required for balanced neurotransmitter release. The level of DHA strictly controls the CNS any deviation from the required level can cause cognitive disorders. Animals and humans having ALA and DHA deficiency in their diet had a decreased concentration of ALA and DHA in the brain and retina which results in impaired neuronal and visual functions. The study has shown that about 55 genes were upregulated and 47 genes are downregulated by omega 3 fatty acids in the brain. It is reported that molecules rich in essential omega 3 fatty acids directly incorporate with neuronal energy metabolism and ATP generating machinery [3].

Ongoing aging of the brain is associated with a decreased level of omega-3 fatty acids. Aging can significantly affect the enzymes responsible for acylation and phosphorylation. Impairments, such as loss of memory and learning disabilities, are also common phenomena in aged animals and humans [3].

Omega-3 fatty acids are involved in maintaining the balance of neurotransmitter systems in the brain. Multiple animal-based studies have confirmed that omega-3 fatty acid deficiencies during development results in disruptions of dopaminergic, serotonergic, and cholinergic signal transmission. The effect of omega 3 fatty acid is pleiotropic, resulting in changes in neurotransmitter synthesis, release, and reuptake. However, gene expression may also depend on the approach of the

experiment. And also same levels of omega 3 fatty acid shows different effects in different regions of the brain, and control different type of functions. This may lead to different regulatory pathways and different sensitivities of the brain regions [4]. Recent studies have shown the altered expression of genes due to the effect of omega-3 fatty acids including transthyretin, alpha-synuclein and calmodulins which plays important role in synaptic plasticity and learning ability. Among the down-regulated genes were a kainate glutamate receptor and a DEAD-box polypeptide and the up-regulated genes were a chemokine-like factor, a tumor necrosis factor receptor, and cytochrome c. Omega 3 fatty acids also have effects on different regions of the brain (especially the cerebrum and hippocampus). They have direct effects on transcriptional modulators; the downstream developmentally and tissue-specifically activated elements might be one of the clues to understanding the beneficial effects of the omega-3-fatty acids on the nervous system [5].

DHA plays a crucial role in gene expression not only in the brain but in many tissues. It can alter membrane receptors such as rhodopsin, which results in the permeability blood-brain barrier. It can regulate the activity of membrane-bound enzymes (Na/K-dependent ATPase), ionic channels and dopaminergic and serotoninergic neurotransmission, most probably by changing membrane fluidity and it can alter signal transduction through effects on inositol phosphates, diacylglycerol and protein kinase [4]. At the cellular level, DHA can protect neural cells from apoptotic death, stimulate neuron outgrowth in PC12 cells, induce synaptic growth factors during neuronal development, enhance synaptic functions, regulate nerve growth factors, and influence neuron size. Regulation of gene expression by omega 3 fatty acid can occur through interactions with specific or nonspecific ligands that bind to response factors acting on cis-regulatory elements of the gene, which finally turn on or off mRNA synthesis. For example, PUFA can directly interact with transcription factors, like peroxisome proliferator-activated receptors (PPAR) that directly modulate the expression of target genes in the CNS [1].

Effect of Omega 3 Fatty Acids on Inflammation and Oxidative Stress: Inflammation is the body's immune response to an irritant which is regulated by several chemicals like cytokines, histamine, bradykinin, prostaglandin, *etc*. Excessive, inappropriate, and uncontrolled inflammation can lead to many human diseases. Eicosapentaenoic acid [EPA] and Docosaheptanoic acid [DHA] are Omega 3 fatty acids that are capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, production and release of prostaglandin and production of pro-inflammatory cytokines. EPA gives rise to eicosanoids that may interact with many inflammation-inducing factors that functionally and significantly inhibit inflammatory processes. Studies have shown a significant down regulation of the gene expression of TNF-α.

Mechanisms underlying the anti-inflammatory actions of EPA and DHA include altered cell-matrix phospholipids fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kb so reducing expression of inflammatory genes, and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ. Animal experiments demonstrate the benefit of EPA and DHA in a range of models of inflammatory conditions. Human trials demonstrate the benefit of oral omega-3 fatty acids in stabilizing advanced atherosclerotic plaques. Intravenous omega-3 fatty acids may have benefits in critically ill patients through reduced inflammation. The anti-inflammatory and inflammation-resolving actions of EPA, DHA and their derivatives are of clinical compliance [5].

Elevated levels of several inflammation markers, such as C-reactive protein (CRP), fibrinogen, and various cytokines have been reported and omega-3 fatty acids interact with these markers which leads to reduced levels of these markers there by reduction of inflammation [4]. Oral or IV administration of Omega 3 fatty acids is proven to reduce inflammatory conditions in many auto-immune diseases, arthritis and serious infections in patients [4]. DHA is crucial for cell signaling through a variety of bioactive mediators. These mediators include oxylipins derived from cyclooxygenases (COX), lipoxygenases (LOX) and cytochrome

P450 (CYP) pathways that are involved in the regulation of inflammation and phagocytic activity of immune cells [4]. Omega-3 fatty acids are known to be anti-inflammatory and to alter gene expression within the cells. Omega 3 fatty acids promote an anti-inflammatory environment within the body with different complexes. Eicosanoids produced from arachidonic acid plays vital roles in inflammation.EPA also gives rise to eicosanoids and these have different characteristics from arachidonic acid-derived eicosanoids. EPA and DHA give rise to resolvins which have anti-inflammatory properties. Eicosanoids, which include PGs, thromboxanes, LTs and other oxidized derivatives are generated from arachidonic acid by the metabolic processes. Eicosanoids generally oppose the intensity and duration of inflammatory responses having cell and stimulus-specific sources. EPA also acts as a substrate for the cyclooxygenase and lipoxygenase enzymes that produce eicosanoids, but it produces mediators having a different structure and potency from those arachidonic acid-derived ones.

EPA and DHA also play a role in the production ofresolvins and related compounds (*e.g.*, protectins) through cyclooxygenase and lipoxygenase enzymes pathways. These mediators have proven anti-inflammatory or inflammation-resolve properties. For example, resolvin E1, resolvin D1 and protectin D1 inhibit transendothelial migration of neutrophils. Thus, it prevents neutrophilic infiltration at sites of inflammation, resolvin D1 inhibits IL-1β production and protectin D1 inhibits TNF and IL-1β production.

The role of resolvins and related compounds may be very important because the resolution of inflammation is important in shutting off the ongoing inflammatory process and in limiting tissue damage. Several studies have demonstrated a time-dependent decrease in chemotaxis of human neutrophils and monocytes towards various chemoattractants including LTB_4, bacterial peptides, and human serum in presence of omega 3 fatty acids. A dose-response study by Schmidt *et al* suggests that near-maximum inhibition of chemotaxis occurs at an intake of 1.3 g EPA+DHA/day. The mechanism of the inhibition of chemotaxis by n-3 PUFAs is not clear. Sometimes it is related to reduced expression or antagonism of receptors for chemoattractants. DHA and EPA havealso been shown to alter the production of inflammatory proteins including chemokines, cytokines, growth factors, and matrix proteases. The mechanism of this effect isthe alteration of activation of key transcription factors involved in regulating inflammatory gene expression. There are two transcription factors that are likely to play a role in inflammation i.e., nuclear factor κ B (NFκB) and PPAR-γ. NFκB is activated as a result of a signaling cascade triggered by extracellular inflammatory stimuli and involving phosphorylation of an inhibitory subunit which then allows translocation of the remaining NFκB dimer to the nucleus. The second transcription factor, PPAR-γ, actsas an anti-inflammatory substance. PPAR-γ directly regulates inflammatory gene expression. It also interferes with the activation of NFκBand creates an intriguing interaction between these two transcription factors. Both NFκB and PPAR-γ may be regulated by omega-3 fatty acids [4, 5]

Moreover, the anti-inflammatory effects provided by the omega 3 fatty acids are-

- Increase production of weakly inflammatory or anti-inflammatory eicosanoids from EPA.
- Increase production of anti-inflammatory and inflammation resolving resolvins from EPA and DHA.
- Decrease production of pro-inflammatory cytokines and other pro-inflammatory proteins induced *via* the NFκB system.
- Decrease chemotactic responses of leukocytes.

Further, marine n-3 PUFAs decrease mortality due to cardiovascular disease this may be, in part, due to the stabilization of atherosclerotic plaques against rupture which again has an inflammatory component. Thus, the anti-inflammatory effects of omega 3 fatty acids may contribute to their protective actions against atherosclerosis, plaque rupture, and COPD.

Effect of Omega 3 Fatty Acid in Parkinson's disease: Parkinson's disease (PD) is one of the most common neurodegenerative disorders and its

prevalence increases with age. Worldwide aging of the population has thus drawn attention to the need for developing therapeutic strategies that could delay the onset of neurodegenerative disorders, or even halt the progression of such diseases [6]. So, far, no formal clinical assessment of the impact of n-3 PUFAs on motor symptoms in Parkinson's disease patients has been reported. However, the effect of DHA in this can be extrapolated from studies in monkeys exposed to the neurotoxin MPTP and consequently developing Parkinson's syndrome. It is observed that there is no effect of the subcutaneous DHA treatment on motor symptoms, probably due to the nearly complete obliteration of the dopaminergic system in the non-human primate model. It is critical to elucidate its potential as a disease-modifying approach in early PD-diagnosed patients and a thorough clinical assessment of the effect of n-3 PUFA supplementation against PD symptoms is needed [7].

Besides motor features, there are non-motor symptoms in PD, which include sleep abnormalities, autonomic system failures, mood disorders and cognitive deficits. Depression and related symptoms affect over 40% of PD cases. Intervention studies with n-3 PUFAs in patients suffering from depression had mostly positive outcomes, while some have reported a lack of clinically significant improvements compared to placebo. It is generally accepted that the consumption of n-3 PUFAs from fish is associated with a lower risk of developing dementia [8].

PD is a very complex neurodegenerative disorder. The clinical benefits of levodopa treatment are often short-lived and lead to important motor complications such as dyskinesia. Since, PD manifests have reached more than 50–70%, the identification of biological biomarkers to diagnose PD earlier is generally considered a priority in parallel to the development of neuroprotective strategies. The distinction between DHA, EPA and ALA effects should also be further evaluated to establish which n-3 PUFA should be prioritized, therefore, warranting further investigation regarding the potential benefits of n-3 PUFA for patients [9].

Effect of Omega-3-fatty Acid on Migraine: Migraine is a progressive and prevalent paroxysmal neurological disorder characterized by headache, which attacks in phases of 4–48 hours. Nausea and vomiting, photosensitivity, phonophobia, flashes of light, vertigo, and loose motions are also common for moderate and severe migraine. Headache is accompanied by neurological symptoms in migraine with aura or classical migraine. Common migraine is milder than classical ones. Severe migraine pain is generally caused by pulsatile dilatation of certain large cranial vessels. Neurogenic inflammation followed by vasoconstriction in carotid arteriovenous anastomoses starts the attack by producing cortical ischemia. Vasoconstriction can be mediated by 5-HT, neurokinin, substance P, calcitonin gene-related peptide (CGRP), nitric oxide, *etc*. Increased levels of glutamate in the attack phase, magnesium deficiency, monoaminergic pathway disorders, and mitochondrial disorders can also lead to the prophylaxis of migraine pain [10, 11].

It is esteemed that the heritability of migraine is 30 to 60%. It can be considered a polygenic disorder. A study shows that different genes are responsible for different types of migraine. A casual gene responsible for typical migraine with aura is KCNK18. A frameshift mutation in the TRESK potassium channel, especially the down regulation of TREK1 and TREK2 potassium channels is responsible for this type of migraine. The CACNA1A gene is responsible for familial hemiplegic migraine (FHM) and spinocerebellar ataxia type 6 (SCA6) by regulating Ca^{++} channels [12].

Long-chain n-3 polyunsaturated fatty acids (PUFAs) especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inhibit the production of proinflammatory mediators like cytokines from macrophages by producing resolvin. Thus, it shows an anti-inflammatory effect and reduces the intensity and frequency of migraine attacks [11, 13]. Otherwise, it can show an anti-inflammatory effect by targeting lipo-polysaccharides (LPS) surface receptors. In the rat, PUFA significantly decreases the production of ROS in glial cells [11]. A study done on 105 people, it is shown that persons with low EPA and DHA suffer from more frequent and severe migraine attacks [13].

In a systemic review, eight out of ten studies show a decrease in frequency and severity of migraine when omega-3-fatty acid is used alone or in a combination with curcumin, nano-curcumin, or migraine prophylactic treatment [14].

Effects of Omega-3 Fatty Acid in Schizophrenia: Schizophrenia is a serious long-term psychological disorder affecting about 1% of the population worldwide. It is typified by positive symptoms (such as hallucinations and delusions), negative symptoms (including anhedonia, alogia, abolition, *etc*.), severe behavioral problems, and cognitive function deficits (*e.g.,* impaired psychological functioning). Nonetheless, those people with defective genes may be more vulnerable to various environmental risk factors and develop the disease [15]. The fact is that a significant reduction of omega-3 PUFA levels is seen in plasma, red blood cells (RBC), and the brain. In patients with schizophrenia, has led to several open-label and randomized clinical trials examining whether dietary supplementation with omega-3 PUFAs could improve the course of illness in patients with schizophrenia [16].

However, results from many studies examining the effects of Omega-3 supplementation on symptoms in schizophrenia were inconsistent. Some show reduced conversion rate to psychosis in UHR individuals, incidence rate and improved prognoses[1)] with greater efficacy over placebo in the first episode and chronic patients, while others showed no differences between schizophrenia and control groups. One study reported worse symptoms. Several meta-analyses and an early review of these clinical trials failed to make plausible conclusions concerning the therapeutic benefit of omega-3 PUFA supplements in this disease [17].

[2)]

However, a Very recent review has shown favorable impacts of dietary supplementation of omega-3 fatty acids as a therapeutic option in mental disorders. The dietary supplementation with DHA improves memory and cognitive functions in healthy elderly subjects and patients with mild cognitive impairment. Omega-3 supplementation effectively reduces severe psychotic symptoms. It suggests that patients with predefined lipid levels might benefit from lipid treatments, but more controlled clinical trials are warranted [18].

Effect of omega-3-fatty Acid on Dementia: Dementia is a progressive disease that is mainly associated with memory loss and poor cognitive health. Alzheimer's disease (AD) is considered one of the foremost causes of dementia in late adult life. It is a progressive neurodegenerative disorder that is characterized by the sudden incidence of memory loss (dementia) and impaired higher intellectual function. The involvement of β amyloid protein is seen in this disease. Aggregation, deposition and decreased clearance of β amyloid protein lead to interference in neurotransmission and neuronal death. Pathophysiologically it is characterized by Intracellular neurofibrillary tangles (NFTs) and extracellular amyloidal protein deposits [19].

Intake of omega-3 fatty acids may decrease the risk of the incidence of Alzheimer's disease. Omega-3 fatty acids show pleiotropic effects on the cardiovascular and central nervous systems (CNS) [20]. Some studies showed fish consumption was associated with a reduced risk of Alzheimer's dementia. AD is initiated by β amyloid (Aβ) peptide. Inhibition of Aβ production is a potential treatment approach for AD. Many studies show the efficacy of DHA in reducing Aβ production and accumulation in vitro and in animal models. There can be two mechanisms,

Studies showthat omega-3 fatty acids can increase neuronal expression of Soria/ LR11 *in-vitro* and *in-vivo*. SorLa is an amyloid precursor sorting protein. It has shown the property to limit Ab production by trafficking amyloid precursor proteins away from the secretases that make Aβ. It has shown diminished expression levels early stages of late-onset AD [20].

Phospholipase A_2 and membrane-bound DHA produce neuroprotection D1 (NAD1). NAD1 downregulates the production of pro-inflammatory proteins (COX-2, IL-1B, *etc*.) and pro-apoptotic proteins (Bcl-2, Bcl-xl) and upregulates the production of anti-apoptotic proteins (Bad, Bax, *etc*). Thus, it can prevent apoptosis and neuronal degeneration [21].

According to some studies, DHA has protective properties against Ab oligomer toxicity and caspase activation *in-vitro* [22]. The literature has estimated a

daily intake of 180 mg per day of DHA is sufficient to improve cognitive health [23]. On the contrary, a randomized study with cognitive function data of 3536 participants at the final follow-up showed no effect of omega-3 PUFA on incident dementia [24]. Several other studies are showing these kinds of negative results [20].

Effect of omega 3 Fatty Acids on ADHD: Attention deficit hyperactivity disorder (ADHD) is a type of neurodevelopmental disorder.

It interferes with development and functioning in multiple cognitive domains. It is characterized by trouble focusing on tasks, physical agitation and poor decision-making abilities [25, 26].

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) breaks ADHD into three subtypes according to the behavioral symptoms [27]:

- Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Type
- Attention-Deficit/Hyperactivity Disorder Predominantly Hyperactive-Impulsive Type
- Attention-Deficit/Hyperactivity Disorder Combined Type

ADHD shows a high rate of comorbidity with other mental health disorders such as learning disability, conduct disorder, anxiety disorder, major depressive disorder, bipolar disorder and substance use disorders in both adults and children [28]. In childhood, these most commonly include conduct and/or oppositional disorders as well as many forms of specific learning difficulties such as dyslexia (specific reading disabilities), developmental language disorders, the autistic spectrum of disorders (ASD) and dyspraxia (developmental coordination disorder or DCD). Young adults (22.3 to 24.3 years) found the proportion of omega- 3 fatty acids was significantly lower in the plasma phospholipids and red blood cells of ADHD participants [21].

The genetic and environmental factors contributing to ADHD are relatively unknown, but endophenotypes offer a potential middle ground between genes and symptoms. ADHD is commonly linked to "core" deficits involving "executive function," "delay aversion," or "activation" theories that attempt to explain ADHD through its symptomology. On the other hand, Endophenotypes purport to identify potential behavioral markers that correlate with specific genetic etiology. Inhibition of prepotent responses is linked with deficits in pre-frontal cortex (PFC) functioning, which is a common dysfunction associated with ADHD and other impulse-control disorders [28].

Gene Responsible for ADHD [29]:

Dopamine D4 Receptor Gene (DRD4): The DRD4 gene is on chromosome 11p15.5. Both dopamine and noradrenaline bind with the D4 receptor. The first meta-analysis of the DRD4 gene in ADHD founda significant association between the 7-repeat allele.

Dopamine Transporter Gene (SLC6A3 or DAT1): The dopamine transporter gene on chromosome 5p13.3 was initially considered to be the responsible gene for ADHD as it is responsible for the reuptake of dopamine in the presynaptic cleft. It is one of the major targets of stimulant medication.

Catechol-O-Methyltransferase (*COMT*): The gene encoding COMT is an enzyme that catalyzes the degradation of dopamine, adrenaline and noradrenaline which is present on chromosome 22q11.2. The polymorphism in COMT is an SNP resulting in a valine to methionine substitution, which isfunctional with the val/ val genotype increasing enzyme activity.

The Synaptosomal Associated Protein of 25kD (*SNAP25*): SNAP25 is a neuron-specific protein which is involved in the regulation of neurotransmitter release. Omega-3 fatty acids are dietary essentials that are critical to brain development and function. The deficiency of omega-3 may contribute to many psychiatric and neurodevelopmental disorders. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two omega-3 fatty acids that are highly concentrated in the brain, exhibiting antioxidative, anti-inflammatory, and anti-apoptotic effects, with these contributing to neuron protection [30]. The precursor α-linolenic acid (ALA) is a type of ω-3 PUFAs.

This precursor is converted into docosahexaenoic acid (DHA), which plays an important role in the production of phospholipids in neuronal membranes in the brain. DHA maintains the fluidity and permeability of the neurolemma. High concentrations are found particularly in synapses, which makes DHA necessary for the function of neurons. Eicosapentaenoic acid (EPA), being an important mediator, is responsible for the production of eicosanoids. These eicosanoids can function as anti-inflammation signaling molecules.

Effect of Omega-3-fatty Acid on Bipolar Disorder: Bipolar disorder (BD) (manic-depressive illness) is a severe, chronic affective, neuropsychiatric disorder, associated with significant disability, morbidity, and premature mortality. Along with the core dysfunction in mood regulation, the clinical manifestation of BD includes anxiety, psychosis, impulsivity, disturbances in cognition and circadian rhythm (*e.g.,* sleep-wake cycle) [31]. According to the National Institute of Mental Health (NIMH), it is characterized by extreme changes in mood, energy, and activity levels, which range from elevated or irritated manic episodes to depressive episodes. If the elevated mood is severe or associated with psychosis, it is called mania and if it is less severe, it is called hypomania. Bipolar Disorder is classified into [32].

- **Bipolar I Disorder (BD-I):** It is a type of bipolar spectrum disorder characterized by the occurrence of at least one manic episode, with or without mixed or psychotic features.
- **Bipolar II disorder (BD-II):** It is a mood disorder on the bipolar spectrum, characterized by at least one episode of hypomania and at least one episode of major depression.
- **Cyclothymic Disorder (Also Called Cyclothymia): It is** defined by periods of hypomanic symptoms as well as periods of depressive symptoms lasting for at least 2 years.

Mood stabilizers such as lithium carbonate and certain anticonvulsants such as valproate carbamazepine and antipsychotics such as aripiprazole are the primary pharmacological intervention, both in the treatment of acute episodes and in prophylaxis. Antipsychotics are primarily given during acute manic episodes. Mood-stabilizing drugs that are currently available have inhibitory effects on neuronal signal transduction systems. The ingestion of large amounts of omega 3 fatty acids is associated with a general dampening of signal transduction pathways which is also associated with phosphatidylinositol and arachidonic acid.

So, the Omega 3 fatty acids may be useful in bipolar disorder where the pathophysiological process may involve over activity of cell signal transduction. Bipolar disorders affect both children and adults cross-culturally and are associated with impaired cognitive, social and occupational functioning [33].

BDNF (Brain-derived neurotrophic factor) is an interesting candidate gene for bipolar disorder. It is acommon mediator of the potential benefits that may be obtained with multimodal interventions in bipolar disorder. Omega-3 fatty acids play important rolein BDNF synthesis and intracellular signaling in neurons. DHA (Docosahexaenoic acid) increases neurotrophic signaling by activating one branch of the classical BDNF signaling via PI3-K/Akt pathways. It also increases BDNF synthesis by activating MAPK signaling. Activated MAPK phosphorylates CREB, which translocates into the nucleus and activates *BDNF* gene transcription [31].

Gene Responsible for Bipolar Disorder:

ZNF804A Gene [34]: The ZNF804A (zinc finger protein 804A) gene has been often related to bipolar disorder. ZNF804A gene is predominantly expressed in the brain. The rs1344706 SNP at chromosome 2q32.1 of ZNF804A is the first risk factor for bipolar disorder. Polymorphisms in this gene are thought to confer an increased predisposition to schizophrenia, bipolar disorder, and Heroin addiction.

ANK3 (Ankyrin 3) [35]: The protein Ankyrin-G is required in the clustering of sodium voltage-gated channels in nodes of Ranvier and axonal segments. It is involved in different biological functions as well as in the maintenance of membrane domains. This modular protein resulted in being an essential factor for enabling the propagation of action potentials in myelinated neurons.

ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) [34]: ERBB2 gene encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases 86. The importance of ERBB2in bipolar disorder is supported by a genome-wide significant association finding and by the observation of dysregulatedERBB2 expression in the dorsolateral prefrontal cortex.

POU3F2 (POU Class 3 Homeobox 2) [34]: POU3F2 is a protein-coding gene. The POU3F2 protein is associated with bipolar disorder. It is involved in the neocortex development in mice and is linked to a single nucleotide polymorphism.

Omega-3 fatty acids are an essential dietary supplement that is used for brain development and function. Relative lack of omega-3 may contribute to many psychiatric and neurodevelopmental disorders and it may inhibit neuronal signal transduction pathways. Omega-3 fatty acids are mainly used for the treatment of mental health conditions because there is a growing recognition that inflammation may play a role in mood disorders. In bipolar disorder (manic depression), the omega-3 fatty acid may be most effective for the depressed phase rather than the manic phase of the illness [31].

Effect of Omega-3-fatty Acid on Impulsive Behavior: Impulsive behavior is a construct that encompasses a wide range of what are often considered maladaptive behaviors. It refers to a personality trait that leaves you prone to acting on your impulses over thinking things through and considering the consequence. It is associated with many psychiatric disorders. Impulsive behavior is not always maladaptive and is advantageous in situations in which it is important to respond rapidly and take advantage of unexpected opportunities. It is an emergent function modulated by the prefrontal cortex (PFC) that helps to dampen risky behaviors during adolescence [36].

Development of cortical gray matter follows a regionally-specific, non-linear maturation pattern, whereby gray matter volume generally increases in childhood, peaks in late childhood or early adolescence and declines into young adulthood. It is associated with improvements in cognitive function and behavior. Within the PFC, these dynamic developmental processes occur rapidly during the adolescent years and are thought to underlie improvements in executive function, including impulse control [36].

Serotonin helps to inhibit impulsive aggression including suicide. Depleting brain serotonin levels has also been shown to cause loss of inhibitory behavior against adverse consequences, which is linked to recidivism [37].

Omega-3 fatty acids are considered essential dietary nutrients. This study examined whether intake of energy-adjusted long-chain omega-3 fatty acids [eicosapentaenoic acid (EPA) C docosahexaenoic acid (DHA)] was related to variation in impulse control and PFC activity during performance of an inhibitory task in adolescents enrolled in a longitudinal neuroimaging study [37]. Docosahexaenoic acid helps to developcritical neuronal functions. DHA promotes membrane fluidity and the interaction of embedded proteins neuronal signaling and the resolution of inflammation which is associated with greater neuronal size. Low levels of omega-3 fatty acids reduce DHA incorporation in synaptic membranes which may be detrimental to the function of the PFC and inhibitory control over the lifespan. Insufficiency of dietary omega-3 fatty acids during this developmental period may be a factor that hinders the development of behavioral control [38].

Gene Responsible for Impulsive Behavior [38]:

Serotonin Transporter: Serotonin transporter (5-HTT) is a transmembrane protein responsible for the reverse transport of serotonin from the synaptic cleft to the pre-synaptic neuron. The SLC6A4 gene encoding serotonin transporter is located on chromosome 17q11.2 A functional insertion-deletion polymorphism 5-HTTLPR was present in the promoter region of the SLC6A4 gene.

Serotonin Receptors: 5-HTR1A and 5-HTR1B genes are encoding the serotonin receptors 1A and 1B.These genes are responsible for impulsive behavior. The human intronless 5-HTR1A gene is present on chromosome 5q11.2-q13. The 5-HTR1B gene was present in human chromosome 6q13. A functional polymorphism G861C (rs6296), alters the affinity of the ligand-receptor interaction in the molecule of 5-HTR1B. A polymorphic nucleotide

substitution A(−161)T modulates the transcriptional activity of the 5-HTR1B promoter by affecting the sequence of the binding site for transcriptional factor SP-1(Specificity protein-1).

Monoamine Oxidases A and B: Monoamine oxidases A and B (MAOA and MAOB) are two enzymes encoded by two adjacent genes that are located on chromosome Xp11.3 and share a common promoter. Both these enzymes play a crucial role in the metabolism of biogenic amines in the central and peripheral nervous systems.

Dopamine Transporter: Dopamine transporter (DAT1) is encoded by the SLC6A3 gene located on chromosome 5p15.3. It is a membrane protein that is responsible for the transfer of dopamine from the synapse to the presynaptic neuron.

CONCLUSION: Omega-3 fatty acid shows a remarkable effect on brain development. A daily diet including most crop seeds, vegetable oils (canola, soybean, corn, and sunflower oils) and green leafy vegetables are the plant sources of omega-3 fatty acids. Animal sources include fish and fish oil, especially marine fishes, beef and lamb[39]. The development of learning new skills is enhanced by this diet. Many central nervous system diseases can be prevented by consuming omega-3 fatty acids daily. There is insufficient clinical data on the effect of omega-3 fatty acids on Perkinson's disease. Mild cognitive impairment and psychotic disorder can be improved by omega-3 fatty acids. Study shows intake of omega-3 fatty acids decrease the risk of incidence of dementia and severity of migraine Although in some cases the appropriate database is not available, all in all, it can be said that omega-3 fatty is plays a preventive role in most CNS diseases.

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