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Correction of Fatty Acids Metabolism as Treatment Strategy of Autism

Afaf El-Ansary and Hanan Qasem

Additional information is available at the end of the chapter

Abstract

Autism is a neurodevelopmental disorder clinically presented as abnormalities in social interaction and communication, repetitive behaviors, usually accompanied by various neurobehavioral disorders, such as learning disability, hyperactivity and anxiety.

It is well known that more than 50% of human brain weight is composed of lipids with a remarkably high content of long-chain polyunsaturated fatty acids (LCPUFA). Adequate supply of different fatty acids and lipids is critically needed by developing brain to achieve normal growth. Essential polyunsaturated fatty acids (PUFAs) are critical for normal pre-natal brain development. There has been increasing evidence that impairment of PUFAs metabolic pathway could affect the normal function of nervous system which is related to pathogenesis of autism.

Studies have demonstrate that autistic patients may exhibit abnormal PUFAs metabolism, which manifests as varying impaired levels of lipid mediators such as prostaglandins, eicosanoids, and isoprostanes in serum and plasma of autistic patients.

Consequently, interventions related to metabolic correction of fatty acids, phospholipids, prostaglandins, eicosanoids, and isoprostanes as fatty acids–derived signaling molecules were discussed in details with special reference to Omega-3 Fatty Acids supplementation and its recognized role in the correction of oxidative stress, neuroinflammation, glutamate excitotoxicity as ascertained etiological mechanisms in autism.

Keywords: fatty acids, omega-3, omega-6, prostaglandins, eicosanoids, isoprostanes

1. Introduction

In the last decades, researchers have been focused on lipids to make clear idea about it in both physiological and disease sides. Until now, 600 molecular species have been discovered from human plasma described as lipidome [1, 2]. Lipidome provides a comprehensive classification of lipids with their structure and function. About 60% of dry human brain is composed approximately from lipids with over 20% polyunsaturated fatty acids [3, 4].

From biochemistry point, PUFAs are type of simple lipid that contain one or more double bonds in *Cis* configuration. PUFAs are two classes omega-3 and omega-6 and these classes do not convert to other forms and play important roles in biochemical changes in the body. Omega-3 and omega-6 are dietary essential fatty acids because they cannot be synthesized by human body beside they can prevent deficiency symptoms [5]. The main sources of Omega-3 fatty acids are vegetable oil and fishes. Docosahexaenoic acid (DHA, 22:6ω3) and eicosapentaenoic acid (EPA, 20:5ω3) are omega-3 fatty acid with 22 carbons and 6 double bonds (22:6n-3). While vegetables are the main sources of omega-6, arachidonic acid (AA; 20:4ω6) is an omega-6 fatty acid with 20 carbons and 4 double bonds. These two fatty acids are the predominant long-chain (20 and 22 carbons) PUFAs in human brain [6].

In the last years, the interest in the health consumption for Omega-3 has led to more researches and manufacturing of these fatty acid as supplement foods. The European committee has been suggested that the minimum requirement of omega-3 and omega-6 is approximately 0.5 and 1% of energy intake, respectively. PUFAs are now regarded as nutritionally essential fatty acids [7]. Deficiency in these fatty acids causes dermatitis, growth retardation and infertility. They play critical role as second messengers in the process of signal transductions, structural component of ceramide and specific role in membrane function. These essential fatty acids found in the diet in the form of α-linolenic acid LA (n-3) and linoleic acid LNA (n-6). These fatty acids contain 18 carbon atoms which can be metabolized to more highly unsaturated members of their family mainly arachidonic [8] and docosahexaenoic acid [1]. The pathway takes place mainly in the liver and may be occur in the other tissues as well. In endoplasmic reticulum, the conversion of LA to AA occurs, this step consists of sequential alternating elongation and desaturation reactions catalyzed by fatty acid elongase and desaturase. DHA metabolic process occurs via separate channeled carnitine-dependent mitochondrial pathway. The outer mitochondrial membrane could well be the sole site for DHA. PUFAs accumulate in brain during myelination process. The turnover of PUFAs is unknown, but studies suggest that it is high because the huge demand of them especially in developmental stage of brain. The most important PUFA for infants is DHA. Clinical studies have shown that infants who feed milk-containing DHA in it have higher neurodevelopmental scores compare to other who do not have DHA in their feed. AA and DHA do not accrete in adult brain and plasma AA and DHA only need to replace brain consumption. About 18 and 4 mg/day are the estimate AA and DHA that up taken by brain from plasma unesterified form, respectively. Phospholipases family is responsible for releasing of AA and DHA from brain phospholipid membrane.

2. The importance of the omega-6 and omega-3 ratio

The differences between omega-6 and omega-3 acids are very small and may be insignifi-
cant. They exert opposite effects, ω-3 PUFAs work as anti-inflammatory agent and ω-6
PUFAs as pro-inflammatory agent. These opposing effects are not easily explained. It was
suggested that the variation between ω-6 and ω-3 PUFA is based on the molecular basis in
particular, to recognize various PUFAs [9]. The dietary deficiency of ω-3 fatty acids, as well
as the particular roles of ω-6 and ω-3, becomes an important subject, and their ratio takes
a deeper look into the disease issues. The optimal recommended ratio between ω-6 and
ω-3 fatty acids has many aspects. One aspect is the recommendation for total daily dietary
intake in various phases of life (e.g., infancy, pregnancy, adulthood and old age). Another
aspect is the optimal ratio of PUFAs as a food supplement or treatment [10]. PUFAs are
used in the body in a variety of conditions, such as in dermatological diseases and in car-
diovascular disorders. One particular area is the role of PUFAs in the brain and the utility of
PUFA to protect and stabilize the neuronal membrane in health and in disease. PUFAs play
a critical role in the central nervous system (CNS) and CNS conditions. Many researchers
have demonstrated that various PUFAs mediate a lot of process in brain. Some studies
examine the best ratio between ω-6 and ω-3 PUFAs to help body to do its role in good way.
The required ratio of ω-6 and ω-3 may differ when used for different tissues or functions.
1:1 is the optimal ratio for preventing cardiovascular diseases. 4:1 is the optimal ratio for
brain-mediated functions and has protective and stabilizing effects on the neuronal mem-
brane. The ratio between those PUFAs should be stable to maintain human health [11]
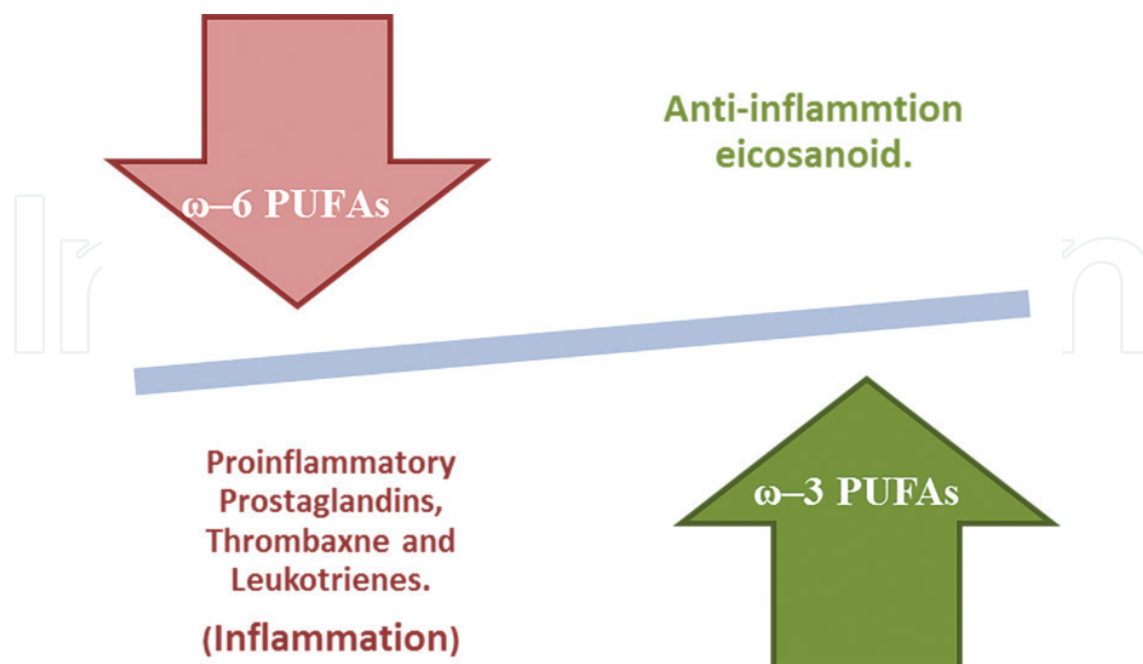(**Figure 1**).

Figure 1. The optimal omega-6 to omega-3 PUFAs balance in the body.

Recently, it is well accepted that early alterations of the intestinal microbiota composition with environmental factors such as Cesarean delivery, bottle feeding, diet and abuse of antibiotic, can induce gut dysbiosis that might be linked to abnormal neurodevelopment and brain dysfunction [12]. The role of gut-brain axis in the etiology of autism is ascertained and related to intestinal dysbiosis as autistic feature [13]. Based on the fact that gut microbiota are greatly affected with diet, it was interested to discuss the role of ω-3/ω-6 PUFAs on microbial composition of the gut. While some studies demonstrate that ω-6-rich diet shows negative impact on gut microbiota through the induction of overgrowth of Bacteroidetes and Firmicutes as bacterial species related to gastrointestinal inflammation frequently occurs in autistic patients [14, 15], ω-3 was proved to induce the growth of bifidobacteria and Lactobacillus as bacterial species that dampening inflammatory responses [16].

3. Lipid mediators

The releasing of AA happens in response to inflammation, ischemia and excitotoxicity, while DHA release occurs in response to ATP, Bardykinin and cholinergic and serotonergic receptors. These 20 carbon atoms are precursor of lipid mediators that regulate inflammation and immune system. These mediators include eicosanoids and docosanoid and synthesized by many different enzymes and contribute or protect from the risk of inflammation [17, 18]. Cyclooxygenase [19], lipooxygenase (LOX) and cytochrome P450 are the main enzymes involved in lipid mediator's synthesis [17]. COX facilitates conversion of AA to prostaglandin E2 (PGE2). There are two types of COX: COX-1 and COX-2 and their expression differ according to tissues and body situation. Expression of COX-1 occurs in all tissues, while basal COX-2 expression in neurons or in response to inflammation [20, 21] (**Figure 2**).
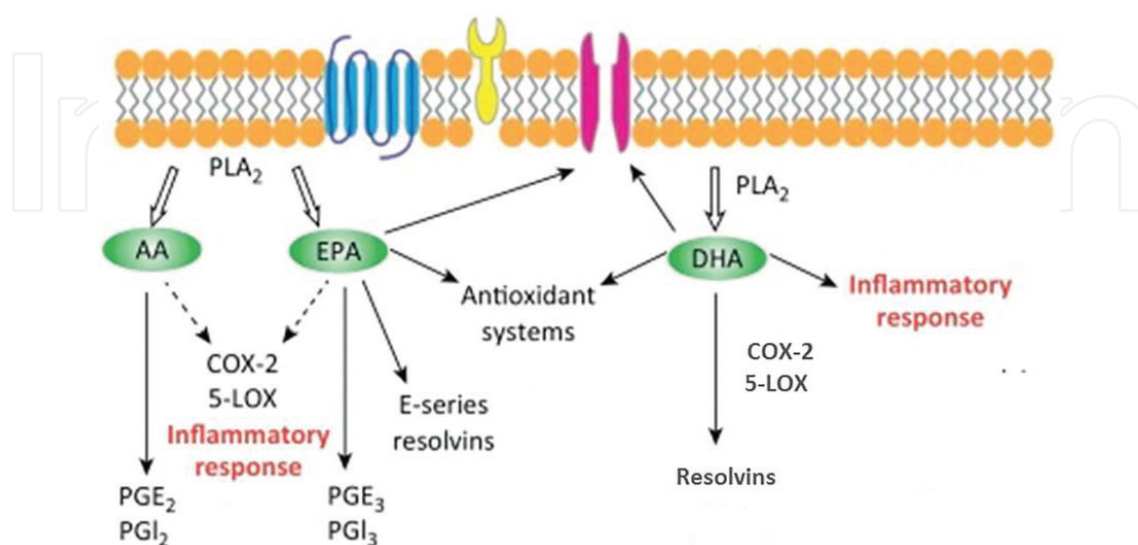

Figure 2. Polyunsaturated fatty acid and their metabolites.

Fatty acids and their mediators have numerous functions in the central nervous system (CNS), including a role in inflammation, glucose production, food intake and in analgesia, beside synaptic function; they activate or suppress neurotransmitter release including glutamate, GABA, monoamine neurotransmitters, opioids and acetylcholine. They also lead to microglia activation and the production of pro-inflammatory cytokines in the hippocampus.

Experimental studies have indicated that DHA is involved in learning and memory, but the real mechanisms underlying these effects are not well studied. It has protection effect by enhancing neuronal survival neurogenesis. DHA is the main PUFA in phosphatidylserine. It plays role in suppression of inflammatory cytokine expression and can invade macrophage and microglia. It also blocks macrophage and microglia-induced activation of NF-κB in the CNS of rodents with neuroinflammation [22].

AA and DHA are rapidly incorporated in the nervous tissue of retina and brain during the brain's growth spurt, which mainly takes place from the last trimester of pregnancy up to 2 years of age. Beyond development of the central nervous system, AA and DHA fatty acids may influence brain function throughout life by modifications of neuronal membrane fluidity, membrane activity-bound enzymes, number and affinity of receptors, function of neuronal membrane ionic channels, and production of neurotransmitters and brain peptides.

4. Abnormal fatty acid metabolism as etiological mechanism in autism

To understand the effect of DHA and AA on brain development and cognition, a lot of interests have been given to the role of PUFAs in infancy and early childhood life. Brain development in infants and children occurs in specific stages during early life. Unesterified ω-3 and ω-6 fatty acid content of the brain increase considerably during development. For proper CNS function high demand, sufficient supply of the essential PUFAs and proper ratio of AA to DHA are needed as critical process in the early life.

Many studies have observed a relationship between plasma or serum n-3 and n-6 PUFAs imbalances and neurodevelopmental disorders such as autism [23]. As mentioned above, DHA and AA play an important role in the nervous system, including retinal development and vision, neurogenesis and neuronal differentiation, neural plasticity, signal transduction, inflammation, learning and memory. These functions may be regulated by a number of gene products activated by PUFAs during development. Some clinical trials have been conducted on the beneficial effect of dietary ω-3 PUFA supplementation on behavior in various neurodevelopmental disorders, including autism [24], but trials with larger sample size are critically requested [3].

There is emerging evidence that fatty acid metabolism and homeostasis are altered in autism due to genetic defects, dietary insufficiency and abnormality in the fatty acid metabolizing

enzymes [25–27]. It is well known that alterations of fatty acid metabolism can affect the normal brain function especially during the development. A direct relationship between impaired fatty acid metabolism at various sites and pathophysiology of autism was repeatedly documented.

PLA 2 is an important enzyme that maintains the membrane phospholipids. It catalyzes the release of AA, a precursor of key lipid mediators such as PGs from the *sn-2* position of phospholipids [28, 29], and it has been shown to play a critical role in neuronal plasticity [30]. Activation of PLA 2 with the excitatory neurotransmitter glutamate usually resulted in a remarkable increase of AA with concomitant impairment of membrane phospholipids [31]. Additionally, both DHA and AA can be released in the presence increased levels inflammatory cytokines [32]. ω-3 PUFA supplementation appears to provide a promising neuroprotective treatment strategy related to the reduction of neuro-progression mediated by excitotoxicity and oxidative damage (PLA$_2$ and PUFA supplementation in UHR individuals) [33].

COX-2 has been widely studied as important enzyme that plays critical role in the body. COX-2 is highly expressed in tissues that under stress of inflammation or neurotoxicity. In study done by Boudrault et al. [34], COX-2 was shown to be modulated by ω-3 PUFA in mice brains beside its ability to control ω-6 PUFA level. These results suggest a potential mechanism by which ω-3 PUFA mediates its biological effects on inflammation or neurotransmission. ω3 PUFA suppresses the production of interleukin 1 (IL-1β) by suppressing the IL-1β mRNA, as well as the expression of Cox2 (cytooxygenase) mRNA that is induced by IL-1β [10].

LOX is a group of iron-containing dioxygenases that catalyze the addition of oxygen to AA, DHA and other PUFAs [35]. LOXs have different isoforms according to the type of tissue where they are located. 5-LOX has been shown to play important roles in human pathology by virtue of its central role in leukotriene biosynthesis. Leukotrienes have attracted much attention because of their powerful biological effects in vitro and in vivo. These lipid mediators are active in the low level and elicit a cellular proinflammatory and immune modulatory responses. 5-LOX and leukotrienes have been proved to play role in the pathogenesis of many human acute and chronic inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis, dermatitis, nephritis, atherosclerosis, autism and cancer [36–39]. The anti-inflammatory properties of ω3 PUFAs, especially EPA, are due to competition with AA as a substrate for 5-lipoxygenase. The eicosanoids are considered a link between PUFA, inflammation and immunity. In addition, ω3 PUFAs have effect on reduce leukotrienes level [10]. From molecular genetic studies of the Icelandic population, variant 5-LOX genotypes were found to be associated with increased atherosclerosis, and dietary ω6 PUFAs promoted, whereas marine ω3 PUFAs inhibited, this effect [40].

PGE 2 is a signaling molecule that diffuses rapidly through the membranes and exerts its diverse effects in the brain via four G-protein coupled EP receptors: EP1, EP2, EP3 and EP4 [41, 42]. The role of PGE 2 signaling in early brain development including formation of dendritic spines and neuronal plasticity is also documented [43, 44]. Tamiji and Crawford [45] reported that expression of the four G-protein coupled EP receptors was found to be significantly increases in the mouse brain during early neurogenesis (11–15 embryonic day). This might indicate that the PGE 2 signaling pathway may have an important role during early

brain development. Early brain pathology demonstrates abnormality of certain brain regions in autism [46–48]. Among these regions are cerebellum, medulla and pons which start to develop at the early stages of the neurogenesis (embryonic day 12), in addition to thalamus, hypothalamus, hippocampus and entorhinal cortex that begin developing at around day 15 [49]. A direct involvement of COX-2/PGE 2 signaling pathway in the development of these structures still remains to be ascertained.

The first reaction of mitochondrial fatty acid β-oxidation (FAO) in mitochondria is catalyzed by acyl-CoA dehydrogenase. Four different dehydrogenases participate in the complete degradation of fatty acids in mitochondria. They are flavin adenine dinucleotide (FAD)-containing enzymes which are structurally and functionally related only differ in their substrate specificities. These are, short-chain acyl-CoA dehydrogenase (SCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain acyl-CoA dehydrogenase (LCAD) and very long-chain acyl-CoA dehydrogenase (VLCAD), reflect the acyl chain lengths of their preferred substrates. Deficiency of long-chain acyl-CoA dehydrogenase (LCAD), as one of these dehydrogenases, is suspected to have a link with the development of autism [50].

Fatty acid β-oxidation is the major pathway to produce ATP and reducing power from different chain lengths of fatty acids [51, 52]. Transport of fatty acids from the cytoplasm into mitochondria is rate limiting step of FAO, and it requires carnitine as acyl carrier and carnitine palmitoyltransferase I (CPT1), which catalyzes the first regulatory reaction in this process. Trimethyllysine hydroxylase (TMLHE) is a second enzyme that catalyzes the first step of carnitine biosynthesis [53]. It is very interesting that several studies had reported that mutation of TMLHE is present in human population with high rate [54]. There is great evidence demonstrating an association between impaired FAO and autism [50, 55, 56]. Individuals with autism show altered levels of blood or plasma carnitine and acyl-carnitine, as a phenotype related to impaired long chain FAO. On the other hand, FAO-deficient children exhibit autistic features such as developmental delay [57]. Recently, Xie et al. [58] reported that efficient FAO is critically needed for the maintenance of neuronal stem cell (NSC) homeostasis in the mammalian embryonic neocortex. They suggested that linkage of NSC homeostatic mechanisms with inborn errors of metabolism (IEM) of developmental brain disorders has clinical implications. An increased risk of autism was found to be associated with TMLHE deficiencies [54, 59]. They also recorded that enhanced oxidative stress was observed in NSC mitochondria with impaired FAO activity, suggesting that impairment of NSC self-renewal occurs due to oxidative stress as an accepted etiological mechanism in autistic children [26, 27, 60].

Another evidence for fatty acids metabolic disturbances as one potential etiological mechanism in autism is the remarkable increase of adipic and suberic acids, as two dicarboxylic acids produced by the omega (ω)-oxidation pathway, a minor catabolic pathway for medium-chain fatty acids that becomes more important when β-oxidation is impaired [51, 61] (**Figure 3**). Based on the previously discussed association between impaired FAO and autism [50, 56, 62, 63], it was suggested that altered β-oxidation can increase the activity of ω fatty acid oxidation, thus leading to increased production of adipic and suberic acid [58, 61]. There is a strong body of evidence between mitochondrial dysfunction and PUFAs transport and metabolism in autism. For this reason, shifting from β to ω-oxidation pathway considering as an emergency pathway that protect cell from deleterious effects of mitochondrial enzyme
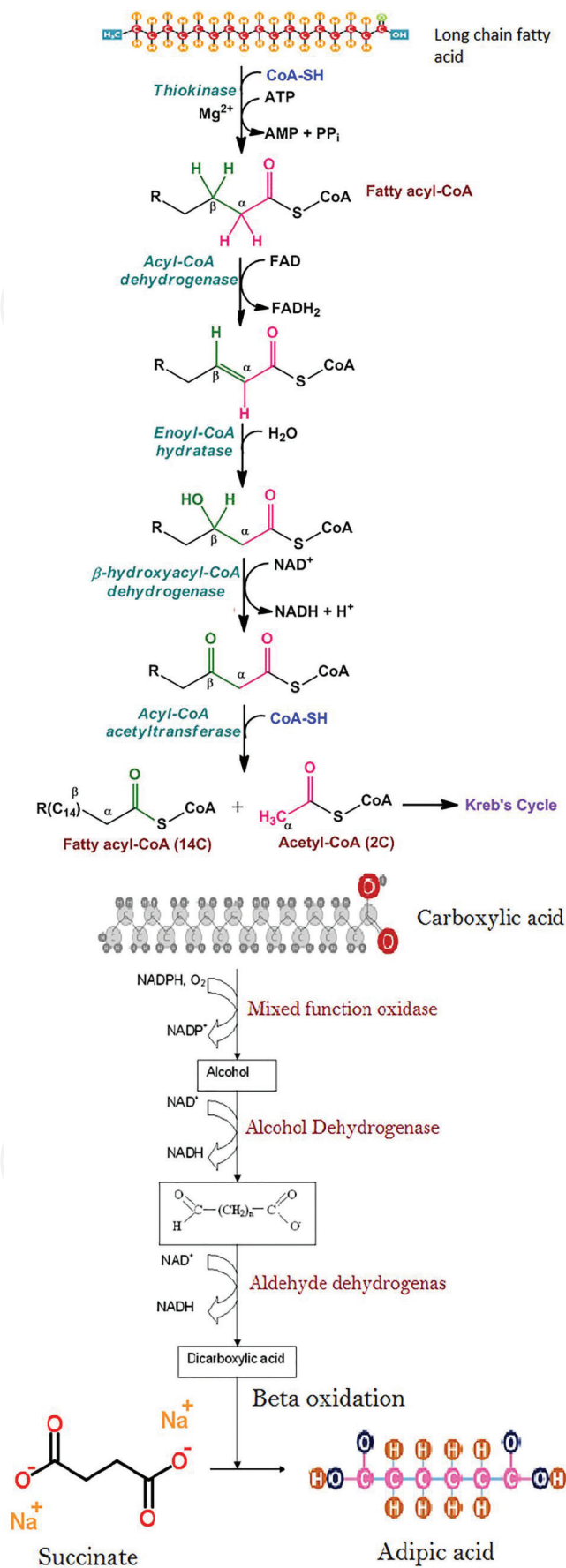
Figure 3. Beta oxidation (up) and omega oxidation [44] of fatty acids.

dysfunctions. So, researchers those days are looking for biomarkers that help to understand the activity of this pathway. The attention has focused in adipic and suberic acid measurements and their correlation with other important determiners that defined in autism.

Increased level of adipic acid has shown to inhibit the activity of both ʟ-glutamate decarboxylase [64] and GABA transaminase [65], leading to impaired glutamate/GABA ratio that might induce glutamate excitotoxicity, as consistent autistic feature in animal model and individuals with autism, through the overstimulation of glutamate receptors [66–69].

5. Fatty acids and brain neurochemistry

5.1. Serotonin

The reported impaired profile of PUFAs and their related lipid mediators in autistic children can be related to their abnormal neurotransmitter physiology. In animals studies, feeding on essential fatty acids diet resulted in serotonin depletion in the frontal cortex of pre-adolescent but not in post-pubescent rats, suggesting a role of n-3 DHA and n-6 AA in neurotransmitter synthesis or turnover [70]. Based on this lower n-3, DHA can be related to the absence of age-dependent changes of brain serotonin synthesis in autistic children and hyperserotonemia as biomarker of clinical severity of autism [71].

5.2. Gamma-amino butyric acid (GABA)

Takeuchi et al. reported that ω-3 DHA deficiency is related to the altered GABAergic activity in autistic patients [72]. This might be through the prevention GABAA receptor blocking repeatedly reported in this disorder [73]. This provides an important link between PUFAs and pathogenesis of autism [74, 75]. A second mechanism of interaction between PUFAs and GABA neurotransmission is through the actions of phospholipase A2 (PLA2) a membrane phospholipid hydrolyzing enzyme. PLA2 is thought to inhibit GABAA receptor function by reducing chloride flux in the cerebral cortex [76]. Based on this, ω-6 AA usually induces neuronal excitability through the activation of PLA2 or phospholipase C (PLC) and inhibition of GABAA receptors [77]. This can be easily related to the imbalanced GABAergic/glutamatergic in autistic patients [66].

5.3. Glutamate

Multiple early studies demonstrated that activation of postsynaptic glutamate receptors by glutamate induces release of AA from membrane phospholipids either directly, by activation of phospholipase A2, or indirectly from degradation of diacylglycerol [78, 79]. On the other hand, AA has been shown to increase glutamate release from synaptosomes [80, 81] through the stimulation of the inositol phospholipid metabolism or activation of protein kinase C.

Elevation of AA can be easily related to glutamate excitotoxicity and glutathione depletion as etiological mechanisms of autism. Recently, elevation of PLA2 was recorded in plasma of autistic patients compared to healthy controls [66, 82]. This enzyme is involved in the selective release of AA from phospholipids such as PC, PS and PE [36, 83]. Higuchi et al. [84] proved

that AA is involved and related to glutamate-induced glutathione depletion and the subsequent cell death through the accumulation of hydroperoxy eicosatetraenoic acids (HPETE) as AA reactive oxygen species (ROS) or hydroperoxides. This can be supported by the recent record of Gebremedhin [85] which reported that astrocytes of neonatal rat brain express message and protein for cytochrome P450 4A ω-hydroxylase CYP4A2/3 and synthesize 20-HETE when incubated with AA and this usually enhanced through the activation of metabotropic glutamate receptors.

5.4. Dopamine

Omega-3 intake has shown therapeutic effects through dopamine neurotransmission in major depression. The antidepressant efficacy of ω-3 supplementation may raise the possibility that they may have specific value for major depressive disorder with a dopaminergic system deficit [86]. This finding may have important implications for therapeutic strategies involving augmentation of standard antidepressant medications with fish oil. ω-3 has beneficial effect as detoxification agent that remove bad effect of reactive oxygen species in Parkinson disease [87]. PUFAs have been specially associated with dopamine activity in frontal lobe of brain. In adolescents, dietary n-3 PUFA deficiency produced a modality selective and task-dependent impairment in cognitive and motivated behavior distinct from the deficits observed in adults. This deficiency affected expression of dopamine-related proteins. Adolescent behavior and dopamine availability are uniquely sensitive to dietary omega-3 fatty acid deficiency [88].

6. PUFAs and BDNF interact with each other

Brain-derived neurotrophic factor (BDNF) showed alteration levels in sample of autistic patients, and it is involved in the regulation of neuronal development and plasticity and has a role in learning and memory. In first several years, serum BDNF concentrations increased in healthy children and then slightly decreased after reaching the adult level. In the patients with autism, mean levels were significantly lower in children compared with healthy adults [89]. Many researches [90–92] indicated that BDNF plays a critical role in the diagnosis of autism. PUFAs and BDNF interact with each other since PUFAs are known to augment the levels of BDNF in the brain [93]. PGE2 derived from AA, induced release of BDNF from glial cells and astrocytes through a G-protein-coupled receptor and then affect on the whole signaling pathway inside cell [94]. PGE2 contributes to BDNF upregulation in neurons following nerve injury in animal models, which facilitates the synthesis of BDNF in primary sensory neurons to initiate repair of damaged neurons and neuronal regeneration [95]. Other PUFA metabolites especially lipoxin A4 (LXA4), resolvins and protectins interact with BDNF. These interactions provide anti-inflammatory effect when the body needs it [96]. Deficiency in ω-3 PUFA intake is linked to decreased BDNF content, and low BDNF levels have been described after prenatal stress [97] (**Figure 4**). Glucocorticoids have been related to such an effect, since corticosterone is able to down-regulate both mRNA and protein BDNF [98]. Over-expressing of glucocorticoids showed an increased anxiety-like behavior [99]. Larrieu and colleagues have clarified that n-3 PUFA deficiency can influence neuronal cortical morphology and depressive-like
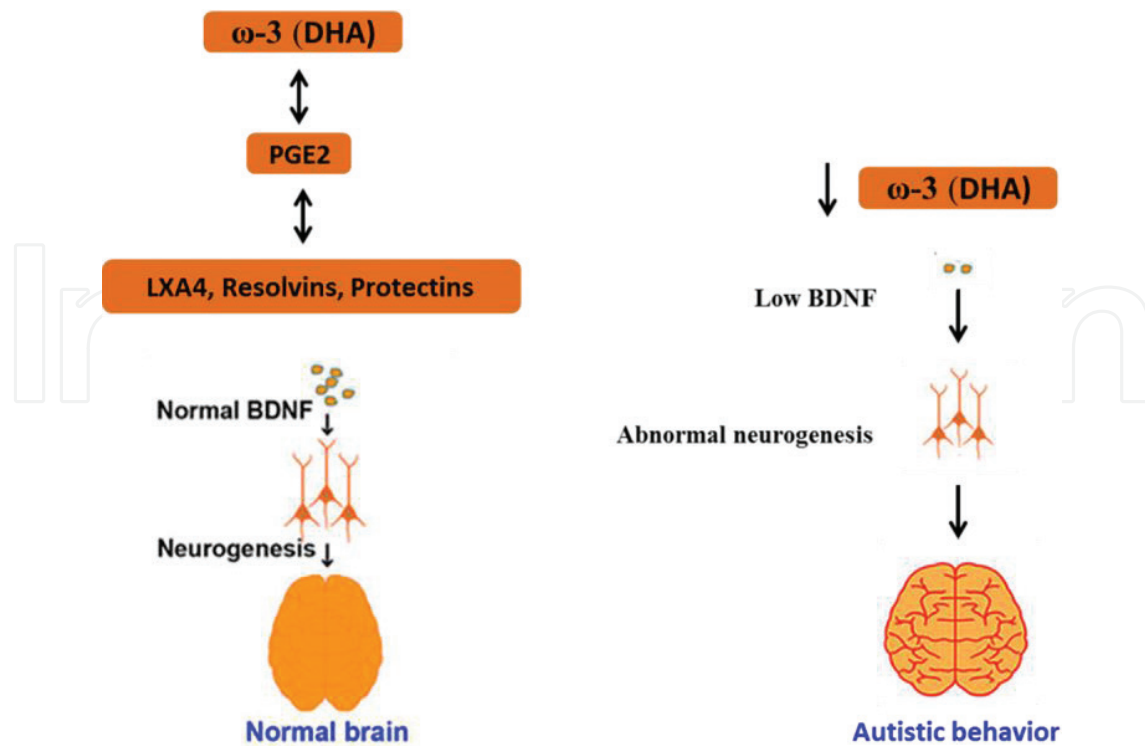
Figure 4. Interaction between PUFAs metabolites and BDNF.

behavior through corticosterone secretion. Furthermore, they showed that diet with low ω-3 induces a phenotype of social deficits and emotional behavior which is observed in autistic patients [100].

7. Amelioration of impaired lipid metabolism as treatment strategy of autism

It is well accepted that imbalances in ω-3 and ω-6 fatty acids are one of the etiological mechanisms in autism and are directly related to the abnormal behavioral severity of these patients. Interestingly, omega-3 and omega-6 fatty acids supplementation resulted in increased level of these fatty acids in the blood, reduced the elevated AA:DHA ratio ameliorates some behavioral deficits such as eye contact, hyperactivity, concentration and motor skills in autistic patients [101]. This can find support in the more recent study of Yui et al. [102, 103] which proved that large doses of AA added to DHA may improve impaired social interaction in individuals with autism, and Amminger et al. [104] who suggest that the use of pure omega-3 PUFAs (without any AA) may be beneficial in autism.

In a recent report of Klein and Kemper [105], supplementation with ω-3 fatty acids is more effective than risperidone as pharmacological drug with side effects. ω-3 fatty acids demonstrate many ameliorating effects presented as more social interaction, less irritability and more flexibility [106]. Due to the lack of evidence of effectiveness from large randomized clinical

trials, the safety, and low cost of ω-3 fatty acids, clinicians can encourage families' use of supplemental ω-3, but more frequent and completely blind trials are requested to move ω-3 fatty acids from tolerated to recommended supplement for the treatment of autistic patients [105].

Due to the strong interaction between diet and the gut microbiota, it has been suggested that the role of dietary changes in influencing brain biochemistry and behavior may be mediated through changes in gut microbiota composition and function [107]. In addition to improving brain function, n-3 PUFA can be used as treatment strategy of autistic patients through its beneficial impact on restoring healthy gut-microbiota by inducing bifidobacteria, and lactobacillus growth, and inhibiting enterobacteria growth with subsequent anti-inflammatory responses [16].

Mediterranean diet as good source of ω-3 usually recommended as a healthy diet [108]. It consists mainly of cereals, vegetables, nuts and fruits, with moderate amount of fish and poultry and low amount of red meat. Polyphenols as major ingredients of olive oil, a common component of Mediterranean diet is known to promo its protective effect by modulating different signaling cascades among which is nuclear factor-kappaB (NF-kB), pro-inflammatory response and oxidative stress response as three etiological mechanisms repeatedly recorded in autism [109].

Moreover, carnitine supplements, as a compound normally required for fatty acids metabolism, and significantly reduced in some children with autism [55], it was effective in improving the remarkably reduced DHA and very long-chain fatty acid level of autistic subjects [110]. Unlike autistic children, ω-3 supplementation showed no beneficial effect on severe autistic adults [24, 111].

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