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Roles and Mechanisms of Docosahexaenoic Acid (DHA) in Neurodevelopment, Neuronal Functions, Learning and Memory

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ABSTRACT

Docosahexaenoic acid (DHA) is an omega-3 fatty acid which is a major constituent of the brain, retina and skin in terms of structure. DHA can be produced from the metabolic synthesis of alpha linolenic acid (ALA) or gotten from breast milk, fatty fishes, or oil from algae. Studies have shown that DHA is an essential nutrient for normal functioning of the brain. It is the major omega-3 fatty acid present in brain tissues and is known to have effects on neurotransmitters, synaptic transmission, and signal transduction. Also, certain DHA metabolites are biologically active molecules that protect the tissues from oxidative injury and stress. DHA is also known to carry out important membrane neuronal functions such as Phospholipid synthesis, membrane fluidity, neuronal survival, regulation of gene expression and modulation of enzyme activity in the brain. Therefore, DHA needs to be taken at developmental stages of human life such as period of pregnancy, lactation and even childhood for proper development and functioning of the brain.

Keywords**:** Docosahexaenoic acid, Brain, Neuron, Learning, Memory, Cognition, Neurotransmitters

1. INTRODUCTION

Docosahexaenoic acid (DHA) is an omega-3 fatty acid which is a major constituent of the brain, retina and skin in terms of structure. Its shorthand name is 22:6(n-3). DHA can be produced from the metabolic synthesis of alpha linolenic acid (ALA) or gotten from breast milk, fatty fishes, or oil from algae[7]. DHA in fish and multi-cellular organisms originates from

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microalgae. DHA can also be commercially produced from microalgae particularly from *Crypthecodinium cohnii* and *Schizochytrium*. For organisms that do not consume or eat algae or animal produce that contain DHA, they biosynthesize their own DHA from Alpha linolenic acid, which is an omega-3 fatty acid sourced from plants and also present in produce from animals that are obtained from these plants.. DHA present in breast milk is essential for the proper development of a child[54]. The rate of DHA synthesis is 15% higher in women than in men[30]. Docosahexaenoic acid is a main fatty acid constituent in the phospholipids of the brain and the retina (Figure 1).

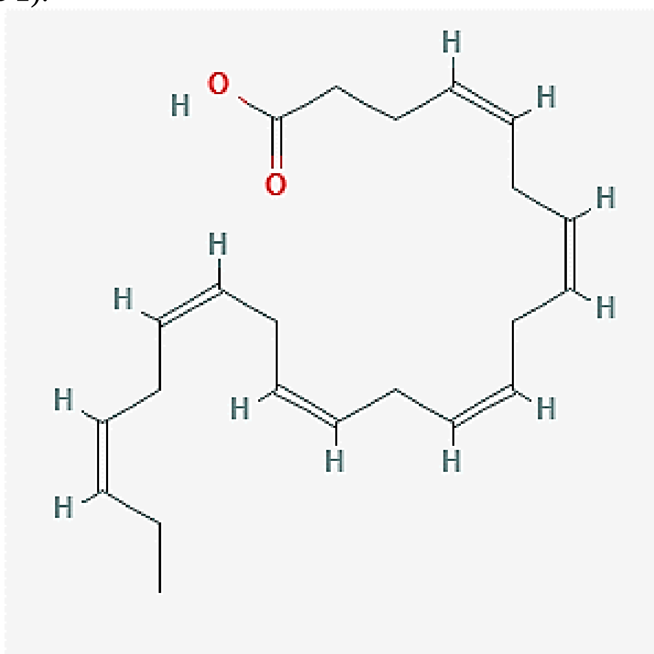

Figure 1. Structure of DHA (Biochemistry, Metabolism and Nutrition, 2013)

1. 1. Metabolic synthesis

In humans, DHA can either be gotten from the diet or may be synthesized from by denovo synthetic pathway from alpha-linolenic acid as illustrated below Figure 2.

1. 2. Sourcesof docosahexaenoic acid

As earlier discussed, DHA can be sourced from the diet. Some of the dietary sources include:

- Algae - Some algae are natural sources of DHA and EPA. The algae in the diet of certain fatty fishes make them to be good sources of omega 3 fatty acids.
- Fatty fishes such as mackerel, tuna, salmon, anchovies, herring and halibut.
- Eggs: Eggs contain small quantities of DHA in them, but there are now eggs that are fortified with DHA with an amount up to 57mg of DHA per egg.
- Infant Milk e.g Peak 123 and 456.
- Flaxseed oil, soyabean oil, canola oil, walnuts, and walnut oils are rich sources of alpha linoleic acid (precursor of DHA).

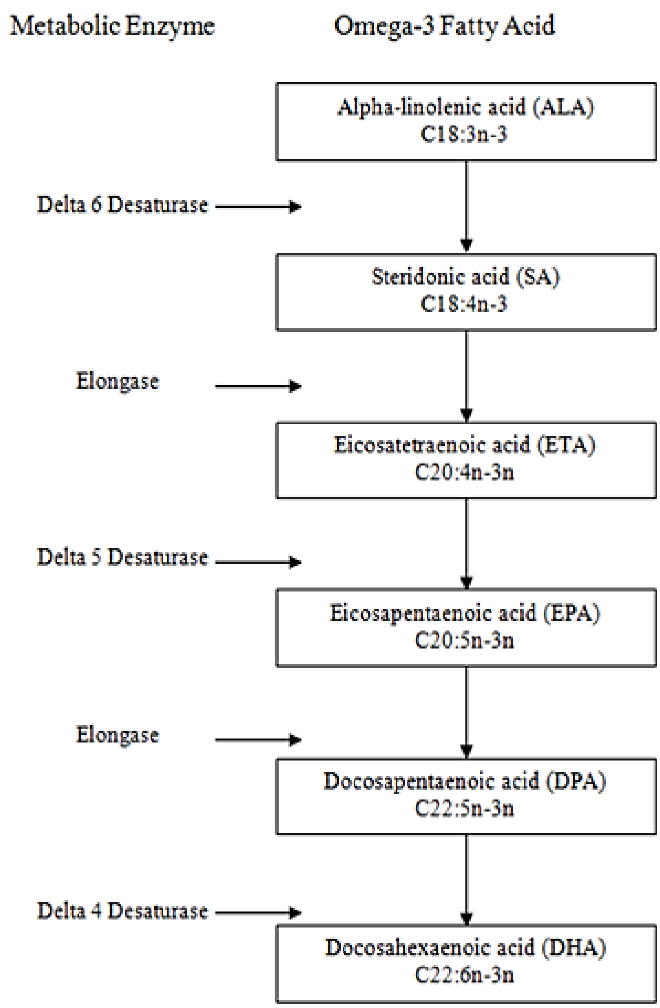

Figure 2. Pathway of metabolic synthesis of DHA[44].

1. 3. Function of DHA

- DHA helps in the maintenance of normal blood pressure[50].
- DHA plays a vital role in the maintaining the normal brain function of the brain.
- It helps in visual maintenance.
- EPA and DHA also play a role in the normal functioning of the heart and reduce the risk of heart diseases[50].
- Intake of Docosahexaenoic acid (DHA) by a pregnant and lactating mother helps in the development of the brain and vision of a growing fetus and infant that is breastfeeding.
- Dietary intake of DHA is a necessity for brain function and vision to modulate some key properties of the neuronal membranes [10, 35].
- It is the major omega-3 fatty acid of all fatty acids present in the brain which makes it a key component of the brain's structure[40].

2. THE BRAIN

The brain is one of the components of the central nervous system. The second being the spinal cord. The brain is consists of three major parts namely the cerebrum, the cerebellum and the brainstem. It controls most of the activities in the human body like processing and coordination of information or signals from the sense organs, making of decisions and reasoning. The brain is a complex structure that is found in and protected by the skull.

The brain is suspended in a fluid known as the cerebrospinal fluid, and sheltered from the blood owing this to the blood–brain barrier. This does not imply that the brain is not susceptible to injury or damage. Damages can be as a result trauma to the brain, or inadequate supply of blood to be brain resulting in stroke as well as neurodegenerative illnesses such as Parkinson's disease, multiple sclerosis and Alzheimer's disease. Some conditions like schizophrenia and depression otherwise known as clinical depression are linked to brain malfunctioning.

The study of the anatomy of the brain is known as neuroanatomy, while the study of the function of the brain is called neuroscience. Some methods have been used to study the rate of brain functions. Research carried out on the brain has advanced from time to time philosophically, experimentally, and theoretically in different phases per time. The next phase of research has been foreseen to be one of feigning the activity of the brain[23].

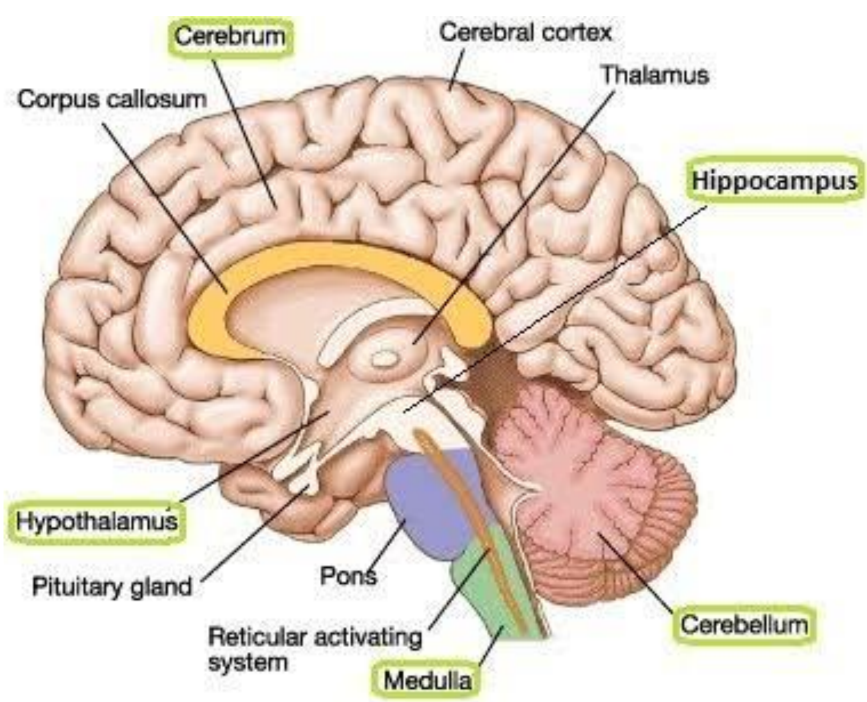

Figure 3. Structure of The Brain (Source: https://www.steemit.com)

3. DHA IN BRAIN CELLS

In the neuronal membranes, DHA is majorly concentrated as phospholipids such as phosphatidylethanolamine and phosphatidylserine. Phosphatidylserine is the key phospholipid that is acidic in nature and found in membranes of the neurons [11]. Phospholipids are part of the constituents of the brain's solid matter and are responsible for neuronal functions. DHA makes up about 15-20% of the fatty acid present in the brain cortex. When it is synthesized into phospholipids, it enhances the efficiency of the synaptic membrane, which is important for neurotransmission process [74]. DHA also plays a key role in synaptic signaling.

3. 1. The role of DHA in neurodevelopment and neuronal functions neuronal phospholipid synthesis

DHA stimulates an increase in the production of some particular phospholipids which is one of the mechanisms for neuritogenesis [55]. In the biosynthesis of phospholipids in the neurons, there is an addition of an acyl group to DHA yielding phosphatidic acid. The major part of the phosphatidic acid is then dephosphorylated to produce diacylglycerol, that undergoes further metabolism to yield phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine. Phosphatidylethanolamine is usually biotransformed to form phosphatidylserine by exchanging its nitrogen with serine (Base Exchange reaction) [60].

3. 2. Improved membrane neuronal function via membrane fluidity

The flexibility or rigidity of a molecule is determined by the number of double bonds present in it. Saturated fatty acids such as palmitic acid (16:0) or stearic acid (18:0) are rigid naturally. This rigidity makes them fatty acids to constrict forming a solid structure. The phospholipids derived from these fatty acids have a rigid structure. DHA having six double bonds may take many conformations because the molecule can rotate freely around C-C bonds but cannot rotate around the rigid C=C bonds [26].

This extremely flexible of DHA inhibits the constriction of phospholipids containing DHA. This results in a substantial increase in fluidity of the membranes. Membranes that have high DHA content may also have high fluidity which is vital in neurotransmission process [80]. Also, an increase in membrane fluidity is said to be necessary for increasing the rate of protein-protein interaction in the membrane within the neuronal phospholipid bilayer.

3. 3. Modification of neuronal enzyme activity

DHA has a profound effect on the functioning of receptors and the activation of membrane proteins. DHA contained in a Diacylglycerol molecule may boost the activation of the protein kinase C (PKC) [17]. Protein kinase C (PKC) signalling which is regulated by phospholipid, is also known to be involved in processes associated with the brain such as modulation of ion channel, regulation of receptor activity, release of neurotransmitters, neuronal survival and synaptic plasticity.

Na^+/K^+ ATPase, also known as sodium pump is also modulated by DHA via essential enzyme in the neuronal membrane. The key function of these enzymes in the neurons is generation and maintenance of Na^+ and K^+ gradients which are important for maintenance of the resting potential of the neuronal membrane. Sodium pump also controls intercellular electrical impulses.

3. 4. Inhibition of neuronal apoptosis

Movement of Phosphatidylserine (PS) to the external of the plasma membrane is one of the early signs of apoptosis. Cell death by apoptosis is caused by the stimulating the action of caspase-3 enzyme [62, 81]. Phosphatidylserine (a DHA containing phospholipid) prevents cell death by stimulation of the Phosphoinositide 3-kinase (PI 3)/ Protein kinase B (Akt) and increasing the rate of translocation of Rapidly Accelerated Fibrocorma (raf-1 kinase) into the plasma membrane. This process is necessary for the activation of these kinases in the plasma membrane. Their activity is improved by higher levels of phosphatidylserine. These activities reduce the activation of caspase-3 causing neuronal survival.

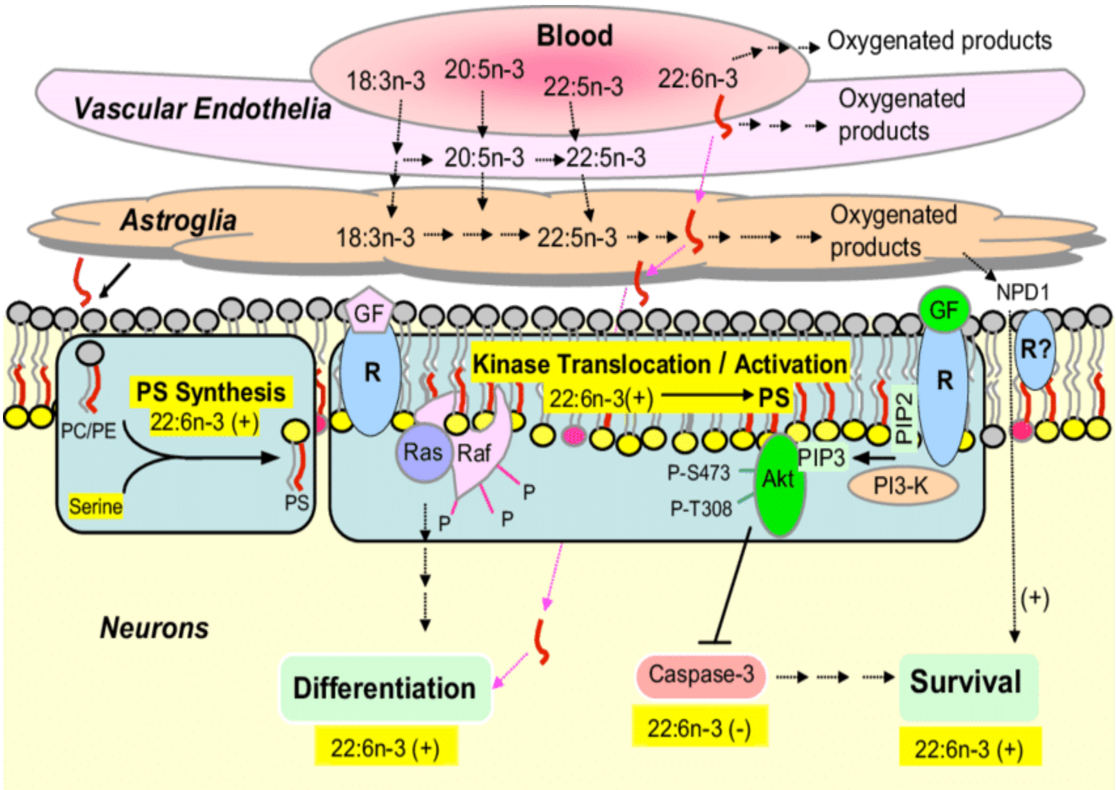

Figure 4. Illustration showing DHA modulated Neuronal survival [46].

3. 5. Neuronal regulation of gene expression

Polyunsaturated omega-3 fatty acids alter the expression of genes by cleavage to specific receptors and transcription factors. Receptor activation modulated by DHA includes retinoid X receptor. The brain contains substantial levels of retinoid X receptor and DHA is a ligand and activator of the retinoid X receptor protein [52].

Alteration of gene expression involved in lipid metabolism results in achieving an ideal atmosphere for neurite outgrowth during neuronal differentiation and brain formation. This may be as a result of DHA stimulation of the gene expression in synthesis of phospholipids [6, 71].

3. 6. DHA metabolities as signaling molecules

Phospholipids are also important sources of second messengers that are involved in intracellular and intercellular signaling. Studies showed that various Phospholipid species are specially used to produce these molecules.

Phospholipase A2 enzymes from phospholipids releases Arachidonic Acid (AA) and Eicosapentaenoic acid (EPA)/Docosahexaenoic acid(DHA) and converts them to powerful signaling molecules through the action of cyclooxygenases, lipoxygenases and cytochrome P450 monooxygenases.

Also, docosanoids which are also DHA metabolites, protect the neurons from oxidative stress [7, 61].

3. 7. Effects of DHA on neurotransmitters

Glutamate

DHA improves synaptic activities with an associated rise in synapsin and glutamate receptor expression in the hippocampus [45]. DHA umpires the activities of glutamate transporters such as GLT1, GLAST, and EAAC1. DHA fuels GLT1 and EAAC1 transporters via a mechanism that involves the activity of extracellular Ca^{2+}, CaM kinase II, and protein kinase C.

Dopamine (DA)

Deficit in DHA in the brain caused by poor DHA supplementation can lead to redeployment of dopamine vesicles in presynaptic terminals, increase in extracellular dopamine concentrations and reduction in elevations in extracellular dopamine concentrations in brain tissues [16]. These findings point to the fact that changes in DHA in the synaptic membrane can have an effect on brain functions such as synaptic neurotransmission and plasticity mediated by dopamine [24].

Serotonin

Deficiency of Omega 3 polyunsaturated fatty acids can lead to changes in serotonin and dopamine vesicles, thereby inducing various regulatory processes like modification of cerebral receptors in some areas of the brain [16]. Prolonged omega-3 polyunsaturated fatty acid dietary deficiency causes alterations in the levels of serotonin in the synapse and after activating it with fenfluramine.

Acetylcholine

The incorporation of DHA into synaptic membrane phospholipids is increased after activation of choline [41]. Acetylcholine is a neurotransmitter that has memory boosting and learning functions

3. 8. DHA in learning and memory

Synaptic plasticity

Synaptic plasticity which is synaptic connectivity between neurons is one of the mechanisms of action that triggers learning and memory. Long-term potentiation mediates synaptic plasticity (LTP) [59]. This is a process involving an interface between a ligand usually an extracellular ligand and receptors in the neuronal membrane through signaling activities in postsynaptic neurons and consequently degenerating signals in the presynaptic cells. These events are important for synthesis of new proteins, formation of new synapses, and increase in the neuron connection. New structures are formed in the synapse to enhance memory capacity by changing the synaptic functions over periods of time. Memory is said to be formed at this point.

Long term potentiation is the basis of memory formation. It can be induced by activating the N-Methyl-D-Aspartate receptor (NMDAR). The NMDAR subunits NR2A and NR2B are linked to the receptor activity. NMDARs relate with the Brain- derived neurotrophic factors (BDNF) and Tyrosine receptor kinase B (TrkB) pathway to enhance synaptic plasticity [82]. NMDARs remain attached to Post synaptic density protein (PSD-95), which aid in signaling of NMDARs and control of long- term potentiation. Synaptophysin increases memory [29]. Research has demonstrated that DHA leads to increase in expression levels of all these receptors levels which may be the reason for the increase in memory function.

Neurogenesis and neuronal differentiation

The dentate gyrus in the hippocampus is accountable for formation of spatial memories. It is a region where neural cells continuously undergo neurogenesis i.e produce new neurons, which now merge into the new neural system forming synapses alongside other neurons. Neurogenesis is suggested to take part in memory and learning function [32]. The molecular mechanism is yet to be elucidated.

DHA stimulates the differentiation of neural stem cells into neurons by facilitating their leaving the cell cycle and inhibiting apoptosis. During differentiation, the cells need to be stopped at the phase G1, and without going through the restriction point of the cell-cycle must get to the G0 phase. DHA increases the rate at which neural cells undergo differentiation by stimulating some transcription factors such as neurogenin. They cease the cell cycle at the G0 phase.

This shows that DHA has an influence on neural stem cells, controlling their differentiation and conversion into new neurons leading to neuronal maturity, which now leads to formation of synapses to increase the connectivity between them (circuitry), therefore, resulting in memory and learning formation [ss].

3. 9. Other benefits of DHA

Maternal benefits of DHA

- DHA supplementation is said to function in the prevention and management of depression after childbirth. An analysis by Hibbeln of the data pooled from several countries showed a negative correlation between the prevalence of postpartum depression and either sea food consumption or breast milk DHA concentration [37].
- DHA reduces the risk of developing pre eclampsia in pregnant women.
- DHA reduces the risk of recurring miscarriage happening in women due to anti-phospholipid syndrome [73].
- Evidence from studies suggested that higher intake of DHA during pregnancy may lead to increase in gestational period and also a possible increase in birth weight [66]. The mechanism for the extension of pregnancy period is due to decline in the production of the prostaglandins PGE2, and PGF2 due to the reduced content of arachidonic acid of the cell membrane as a result of DHA intake [22].

Pediatric benefits

- Improved cognition in infants up till of 4 years of age.
- Developed intelligence quotient (IQ) in children.
- Developed motor and social capability.
- Developed visual maturity and clarity.
- Enhanced attention capacity of the child at one year of age.

DHA deficiency

- Reduced visual clarity
- Altered vision.
- Attention deficit hyperactivity disorder (ADHD)
- Optic fibrosis
- Depression
- Aggressive hostility
- Cognitive deterioration.

For this reason, the mother and child must take adequate amounts of DHA [21].

4. OTHER FOOD NUTRIENTS LINKED TO BRAIN DEVELOPMENT

Protein-energy malnutrition

The brain's cortex and hippocampus are the most susceptible to protein-energy malnutrition [51]. Protein-energy malnutrition usually takes place between twenty four and forty four weeks post conception. Fetal protein-energy malnutrition leads to a condition where the fetus does not grow to normal weight during pregnancy (intrauterine growth retardation) and is in most cases linked to hypertension or severe malnutrition in pregnancy [53].

Iron

Iron is accumulated by the growing fetus in the last three months of pregnancy and is vital for key processes in the neurons such as formation of myelin sheath, energy metabolism and synthesis of neurotransmitters [9].

Zinc

Fetuses of mothers who are zinc-deficient display declined fetal movement and variation of heartbeat. This suggests autonomic nervous system instability [57]. However IQ is not affected.

Copper

Copper is essential for the proteins involved in the metabolism of brain-energy, antioxidant activity, metabolism of dopamine and accumulation of iron in fetuses and neonates brain [68, 69].

Other nutrients

Some other food nutrients influence brain development like iodine and selenium [4, 58]. Other nutrients are folate and choline [27, 18] and Vitamins A and B_6.

5. CONCLUSION

Nutrition generally, has a major role to play in the development and proper functioning of the central nervous system. Research has shown that malnutrition leads to lifetime cognitive and behavioral deficits. It is therefore a necessity for adequate intake of DHA in the formative years of human such as pregnancy, lactation and childhood.

Recommendations

- Pregnant women and nursing mothers should take foods rich in DHA (100-300 mg/day) to meet the nutritional requirement of the fetus and baby respectively.
- Exclusive breastfeeding for six months.
- Infant formula, milk that are DHA fortified should be given to the child after six months of exclusive breastfeeding.
- Weaning foods should be DHA-rich foods to enable proper brain functions and general body well-being of the child.

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