DHA Supports Brain Development and Protects Neurological Function

By Russell L. Blaylock, MD

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One of the major building blocks of the brain, the omega-3 fatty acid docosahexaenoic acid (DHA) is critical for optimal brain health and function at all ages of life. Researchers are now finding that DHA provides brain-boosting benefits in infants and aging adults.

Recognizing DHA's crucial role in neurological and visual development in infants, manufacturers are rushing to incorporate DHA into infant formulas and baby foods. Similarly, adults seeking to stave off psychiatric and neurological ailments such as depression, post-traumatic stress disorder, and Alzheimer's disease are now paying careful attention to their DHA intake. Here, we'll discuss DHA's integral role in ensuring optimal cognitive and neurological health.

Multiple Benefits of Omega-3 Oils

Most scientists and medical authorities agree that a higher intake of omega-3 oils is important for good health. This is based on a large number of well-conducted studies in humans and animals, which have shown that omega-3 oils improve brain function, decrease inflammation, reduce the incidence of fatal heart attacks and ischemic strokes, improve the outcome of autoimmune diseases, and improve vision.

Of particular interest are the beneficial effects of omega-3 oils on neurological function and brain protection. For instance, a number of studies have shown that higher intakes of omega-3 oils significantly reduce the incidence of Alzheimer's disease as well as vascular dementia, and improve quality of life and memory in those affected by dementia.1

Although there is general agreement about the health benefits of omega-3 oils, few appreciate the differences in their various components called eico-sapentaenoic acid (EPA) and docosahexaeonic acid (DHA). These two components make up the bulk of the omega-3 oils. The ratio of EPA and DHA can vary considerably in commercial products, however, most of which have much higher concentrations of EPA, mainly because it is less expensive to manufacture and has a less fishy odor than DHA. Yet, studies have shown that most of the neurological benefits of omega-3 oils are derived from the DHA component rather than the EPA component.

In both the Chicago2 and Rotterdam studies,3 researchers found a 60% reduction in the incidence of Alzheimer's disease in those eating at least one fish-containing meal a week. In the Chicago study, DHA exerted a strong protective effect, which was not seen with EPA. Furthermore, this study found that intake of the plant-derived omega-3 fatty acid, alpha-linolenic acid, was associated with a reduction in the risk of Alzheimer's disease in subjects carrying the APOE4 gene, which is a powerful indicator of the disease.

People with Alzheimer's disease have dramatically lower levels of DHA in the neurons of their hippocampus, an area of the brain severely affected in the disease. This area is vital to creating recent memories (so-called working memory or declarative memory).4 Prasad and co-workers from the University of Kentucky found that phospholipids such as phosphatidyl-ethanolamine (PE), which normally contain the highest levels of DHA, are severely depleted in those regions of the brain most affected by Alzheimer's disease.5

DHA supplementation not only improves memory in cases of Alzheimer's disease but has also been shown to improve age-related memory loss as well.6 Animal studies have shown that DHA-supplemented diets can counteract learning difficulties when soluble amyloid-beta (the most injurious form of Alzheimer's-associated amyloid) is infused into the animals' brains.7

Animal studies, both in mice and non-human primates, also show that DHA-depleted diets impair learning and memory, and that re-feeding DHA-containing diets reverses these impairments.8-9 Feeding rats diets high in DHA improves both working memory (very short-term memory) and reference memory (longer-term) in both old and young animals.8,10,11

Reisbick and co-workers at the Oregon Health Sciences University found that rhesus monkeys fed a long-term omega-3-deficient diet began to show stereotyped behaviors during early life.12 These are the type of repetitive behaviors seen with social deprivation and autism.

Clearly, omega-3 oils such as DHA play essential roles in learning, memory, and behavior. Next, we'll look at their role in supporting nervous system development.

DHA and Brain Development

A growing number of studies in both human infants and animals are showing a strong correlation between the intake of omega-3 oils, especially DHA, and cognitive function, visual acuity, and overall brain development.13-15 In the human infant, brain development undergoes its most rapid and complex growth during the last trimester of pregnancy and the first two years after birth. This means that during this period the child's eventual neurological development is highly dependent on its dietary intake of essential nutrients, especially omega-3 oils.

Because the fetal and infant brain is unable to convert enough alpha-linolenic oil (an omega-3 oil found in some plant oils) into DHA, the baby almost totally depends on its mother for its supply.16 There is good evidence that the placenta selectively takes up DHA so as to ensure an adequate supply for the growing baby.17,18 Some 70% of energy supply during fetal development is devoted to brain development, and lipids make up 50 to 60% of the structure of the brain, with DHA making up 30% of the brain and 50% of the retina's structure. However, since the baby depends on the mother for its supply of DHA, omega-3 deficiencies in the mother can lead to increases in DHA deficiency in the infant brain with each successive birth. Studies have shown that brain DHA deficiency is limited to about 30% with the first generation, but by the third generation, brain DHA levels can fall by as much as 85%.19

The average DHA and EPA intake combined in the USA is about 100-200 mg/day, far below the 650 mg of DHA plus EPA that experts recommend for healthy individuals.20 Furthermore, it has been shown that after birth, DHA levels fall between the ages of 6 and 12 months mostly due to low DHA content in most baby foods and formulas,21 which can have a profound effect on postnatal brain development. A study that measured the impact of DHA on visual development in 6-month-old infants found that retinal and visual cortex maturation was greatly improved in infants receiving DHA-enriched egg yolk versus control infants who were deficient in DHA. In fact, the researchers found that even in breast-fed infants, DHA levels fell, whereas levels rose by 34% in the supplemented infants.21

In developing babies, higher levels of DHA levels are needed for the growth of neuronal cells than other brain structures.22 The composition of the membranes of neural cells is under constant reconstruction, and can change drastically with changes in diet. It has been shown that while other fatty acids plateau at birth, DHA levels actually double, mainly during periods of intense nerve cell development, that is, during intense brain growth.

Overwhelming evidence for the benefits of DHA comes from a recent review of some 50 studies, which concluded that higher DHA in babies' diets translates into better brain function, especially for cognitive and visual function.23 Further evidence that DHA may promote healthy nervous system development comes from a recent study in which researchers divided 53 normal, healthy infants into those exclusively breast-fed and those exclusively bottle-fed with a formula containing no DHA. Using assessments of visual, auditory, and sensory perception, they found definite abnormalities in all three tests in the bottle-fed babies at one year of age.24

A devastating consequence of low DHA status is its impact on the development of neurological abnormalities. In another study, researchers measured DHA, essential fatty acids, trans fatty acids, and arachidonic acid levels in the umbilical artery and vein of infants. They found that infants with neurological abnormalities at birth had significantly lower levels of arachidonic acid and DHA and higher trans fatty acid levels.25 In contrast, infants with higher arachidonic acid, DHA, and essential fatty acid levels had more normal neurological function. Editor's note: While excess levels of arachidonic acid contribute to chronic inflammation in aging humans, arachidonic acid is a critical building block to developing brains.

In a further test of cognitive development in infancy, researchers found that maternal and fetal DHA levels measured at birth correlated with attention and distractibility at 12 and 18 months, with those having higher DHA levels fairing better than those with low levels.26 It is also interesting to note that DHA plays a major role in muscle function and coordination in developing infants. A recent study using newborn baboons revealed that the highest levels of DHA are found in the motor control areas of the brain,27 which also play a major role in memory, social development, and behavior.

So we see that adequate DHA in the mother's diet is critical for normal brain development in her babies, and that with the first baby, her DHA level will fall even more because the placenta will preferentially extract the mother's DHA for the baby. This means that subsequent babies will have even lower DHA levels as the mother's DHA is further depleted.

The big question is, can developmental problems triggered by low DHA levels be reversed? The evidence seems to indicate, yes. For example, in one study, rats fed low-DHA diets for three generations from birth (producing severe deficiencies in brain DHA levels) and then fed a DHA-enhanced diet for six weeks achieved the same level on testing of spatial learning as animals maintained on an omega-3-adequate diet for three generations.28 A DHA-enriched diet for less than six weeks had no effect.

However, the rate of recovery of brain DHA varies among studies, depending on the experimental animal model and other variables. In another study, rat pups that were fed DHA-depleted diets for two generations followed by an omega-3-containing diet beginning at 15 days after birth began to regain DHA in essential brain structures within one day, but full recovery took one month.29 This slow recovery in rats was confirmed by other scientists.30 In the rhesus monkey, recovery of brain DHA can take as long as 12 weeks.31

In addition, the brain recovers its lost DHA slower than peripheral tissues. In one study, the rate of recovery of brain DHA went from 19% at one week, to 35% at two weeks, and to 80% at eight weeks in rats. In the retina, which has an even higher DHA content than the brain, recovery was faster than the brain, reaching 72% at four weeks, and was fully recovered at eight weeks.32 Recovery of DHA by the adult brain, however, is slower and less complete than the infant brain.33

DHA and the Adult Brain

While DHA is essential for the proper development of the infant brain, it also plays a vital role in the ongoing structure and function of the adult brain. It is a component of several important phospholipids in the brain, with the highest levels of DHA being found in phosphatidylethanolamine (PE) and phosphatidyl-serine (PS).34,35 Lower levels exist in phosphatidyl-cholines (PC). Structurally, DHA comprises 22 carbons and six double bonds, making it the most unsaturated fatty acid in cell membranes and an important ingredient in increasing the fluidity of cell membranes.

Changing the fluidity of cell membranes alters their physical properties, such as permeability and protein activity. This change can drastically alter cell signaling and plays a major role in increasing membrane permeability of cancer cells, making them more susceptible to immunologic and chemothera-peutic killing.36 EPA, however, has much less effect on membrane fluidity than DHA.37

It has also been shown that a greater incorporation of DHA into cell membranes results in dramatically less susceptibility to lipid peroxidation and oxidative stress in cells, especially neurons.38

Although many view the brain as a stable structure that changes little after adolescence, it is in fact always in a state of flux, not only by forming millions of new nerve connections, but also by replacing and altering its biochemical makeup, especially membrane lipids. Connected with this constant turnover of brain lipids are the phospholipase enzymes, which can release arachidonic acid and DHA from the cell membrane.39 Dietary changes can therefore drastically alter brain lipids, which can significantly alter brain function, even worsening neuropsychiatric disorders.40

Furthermore, there is evidence that as we age, the distribution of DHA in the brain changes.41 For example, during infancy the highest levels are found in the striatum (associated with motor control) and are lower in the hypothalamus (linking the nervous and endocrine systems) and hippocampus (associated with memory). In adults, the highest levels are in the cortex (essential to cognition) and lowest in the medulla (crucial for autonomic function). With aging, the highest levels are in the cortex and cerebellum (involved in motor control). An example of this regional specificity was seen in a recent study when scientists restored dietary DHA to rats that had been deprived of the nutrient. They found that all areas of brain DHA were restored after 12 weeks, except for the medulla, which recovered only 62% of its DHA.41 These findings therefore provide plentiful evidence that consuming enough DHA may be essential for upkeep of the adult brain.

DHA and Cell Signaling

In the past, a lot of attention has been paid to the effects of omega-3 oils on membrane properties, which are very important to the brain's healthy functioning. After all, membranes regulate entry into the cell as well as control receptor function, which facilitates cellular communication. More recently, however, researchers have discovered that omega-3 oils, especially the DHA component, also affect cell signaling.

DHA and Cell Signaling

Hundreds, if not thousands, of special molecules are involved in cell signaling, which control not only the cell's internal communication with the outside, but also communication within the cell. A group of special transcription molecules allows cells to communicate with the genes as well.

The vast array of cell-signaling molecules allows the signals to be fine-tuned and alternately switched to an assortment of functions—such as regulating cellular energy via the mitochondria, activating or silencing genes, generating specialized proteins, ion regulation, and regulating inflammatory mediators (see figure 1 on page 50). The complexity of actions within a cell is therefore carefully regulated by cell-signaling molecules.

Numerous enzymes, such as adenyl cyclase and protein kinase A involved in energy regulation, are upregulated by DHA. The DHA omega-3 also reduces proinflammatory mediators such as prostaglandin E2, thromboxanes, and leukotrienes, and increases the production of anti-inflammatory compounds such as lipoxins and resolvin along with substances that protect brain cells called neuroprotectins (see figure 3 on page 51).42

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cellular energy levels is particularly important in preventing excitotoxicity (a pathological process that damages or kills nerve cells), since low energy can dramatically increase sensitivity to this destructive process.

Another essential cognitive process controlled by DHA is regulating the brain's concentration of phosphatidylserine (PS), which is also vital for cell survival.45 Diets low in DHA reduce brain PS, which affects cell signaling for survival through enzymes including Na+/K+ ATPase and calcium uptake. Calcium is one of the most common and versatile cell-signaling systems. DHA, but not EPA, has been shown to be a major regulator of calcium oscillations (waves within cells),46 which regulate a vast array of cellular functions, including neurotransmitter release, mitochondrial function, gene activation, oxidative stress, and, in the developing brain, neuron migration and maturation.47 Low DHA levels are also known to lower brain and cellular growth factors, such as brain-derived growth factor.

Another detrimental effect of low DHA is to increase neuronal death. An observation of this was seen in a lab study, which revealed a dramatic increase in DNA fragmentation of DHA-depleted neurons in cell culture. Enriching this cellular medium with DHA protected the neurons,48 an effect that appeared to operate through phosphatidylserine (PS) via its actions on cell-signaling survival pathways.

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One of the principal cell-signaling pathways affected by both EPA and DHA is the peroxisome proliferator-activated receptors, or PPARs. When activated, this pathway inhibits proinflammatory cytokine production, thus greatly reducing inflammation, both systemically and in the brain. This could play a major role in reducing the damage generated by a host of disorders such as diabetes, atherosclerosis, autoimmune diseases, brain aging, autism, and the neuro-degenerative disorders.

Studies have shown that EPA and DHA activate PPARs, which in turn suppress nuclear factor-kappab (NF-kb), the main transcription system that activates inflammation.50 Thus, DHA, which is more potent than EPA in activating PPARs, may have important implications for reducing inflammation in the brain. A high intake of DHA and EPA also reduces inflammation by displacing arachidonic acid (a proinflammatory precursor) and cholesterol from the cell membrane, reducing the starting material used to make inflammatory mediators. Furthermore, DHA inhibits inflammatory eicosanoid production induced by the release of arachidonic acid from cell membranes. As we age, brain inflammation progressively increases, but a diet higher in DHA relative to other fatty acids may reduce this age-related brain inflammation.

WHAT YOU NEED TO KNOW

DHA

*The omega-3 fatty acid docosahexaenoic acid (DHA) is crucial for the healthy structure and function of the brain. An optimal intake of DHA is especially essential for pregnant and nursing mothers to ensure adequate brain development in their children.

*DHA is essential for the adult brain, where it impacts the brain's structure and signaling systems.

*DHA helps promote nervous system development and optimal memory function.

*DHA deficiency has been linked with many psychiatric disorders such as depression, suicidal behavior, anger, and hostility.

*Evidence suggests that adequate DHA intake may help prevent age-related memory decline and Alzheimer's disease.

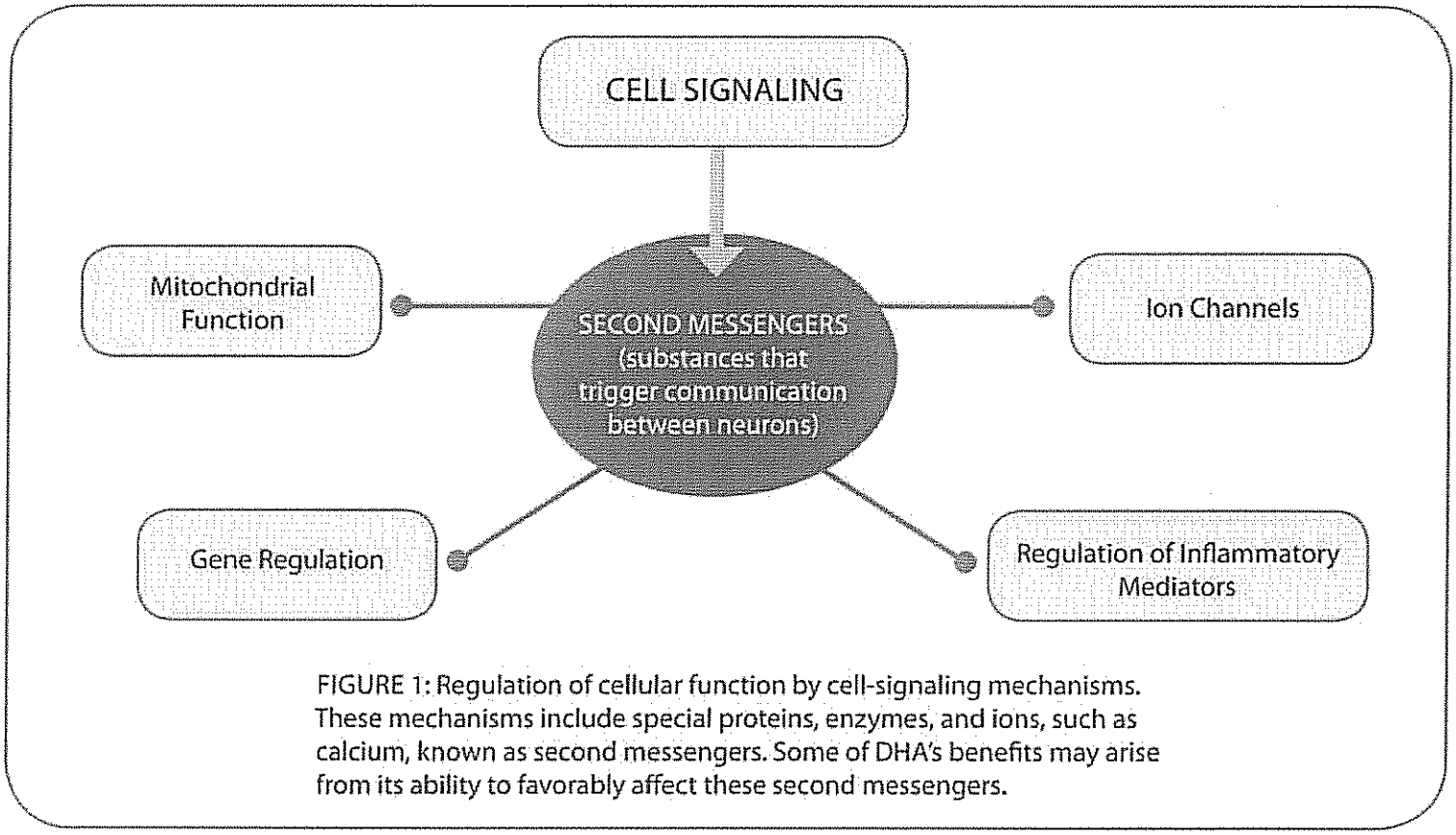


FIGURE 1: Regulation of cellular function by cell-signaling mechanisms. These mechanisms include special proteins, enzymes, and ions, such as calcium, known as second messengers. Some of DHA's benefits may arise from its ability to favorably affect these second messengers.

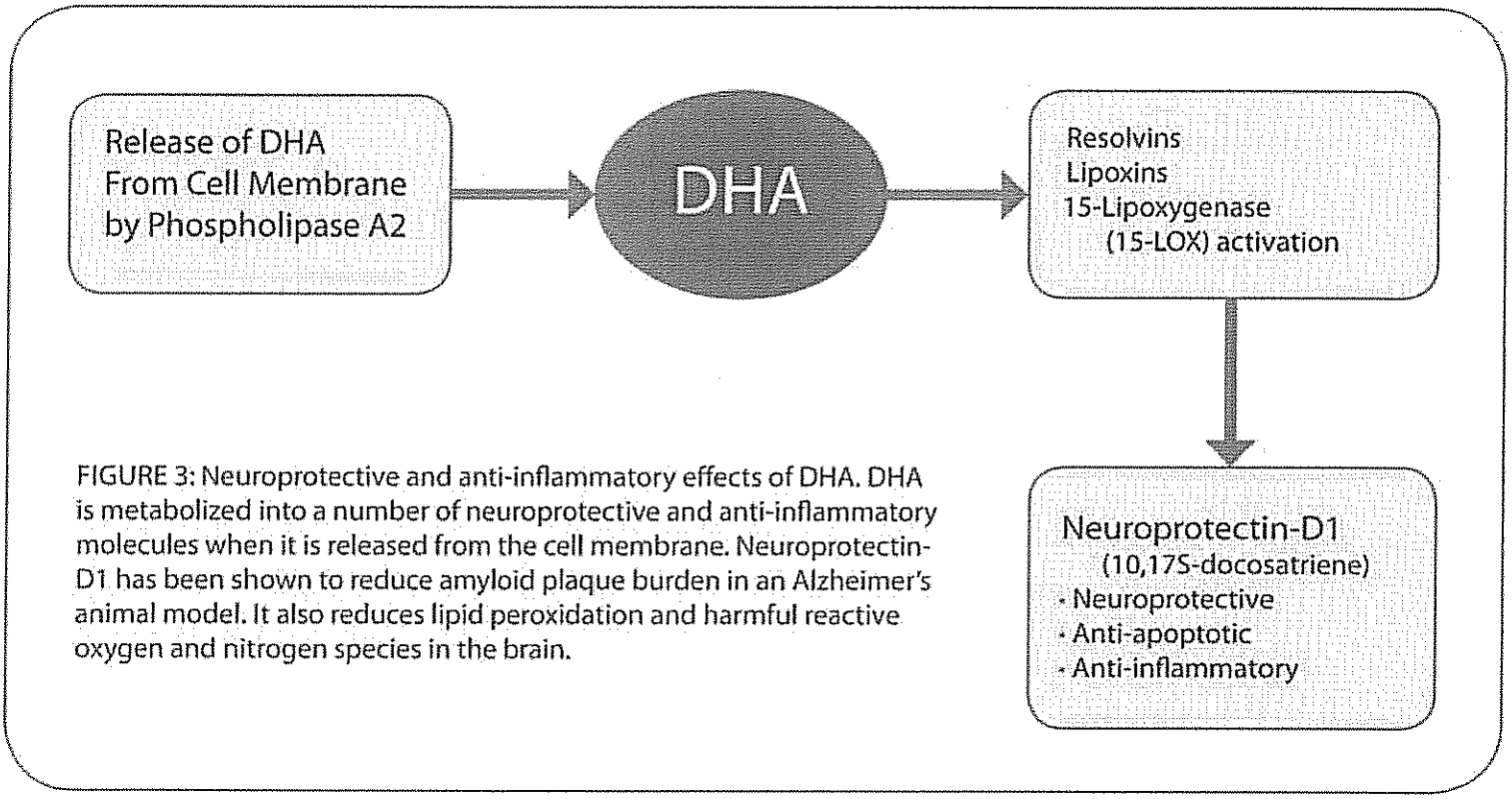


FIGURE 3: Neuroprotective and anti-inflammatory effects of DHA. DHA is metabolized into a number of neuroprotective and anti-inflammatory molecules when it is released from the cell membrane. Neuroprotectin-D1 has been shown to reduce amyloid plaque burden in an Alzheimer's animal model. It also reduces lipid peroxidation and harmful reactive oxygen and nitrogen species in the brain.

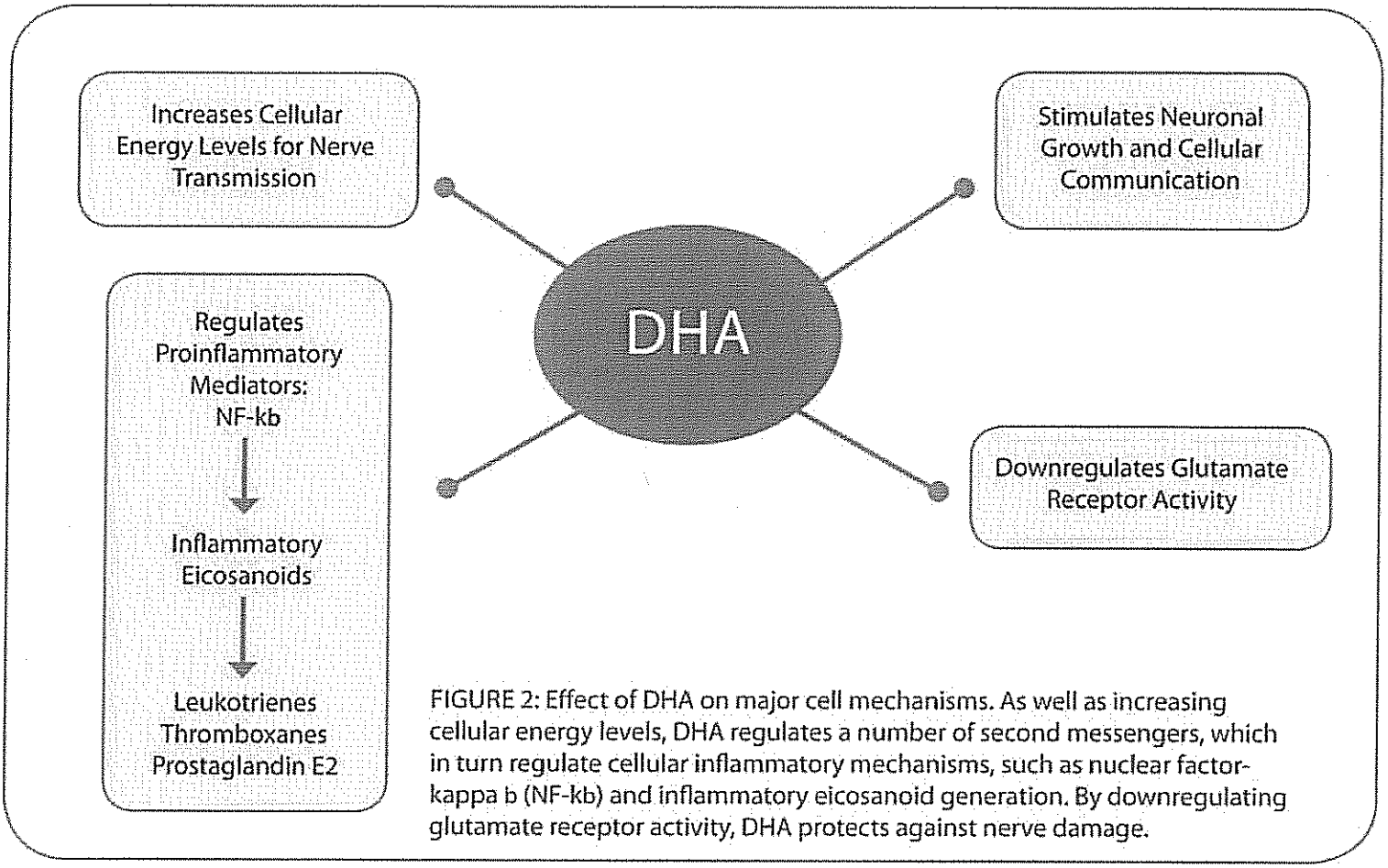
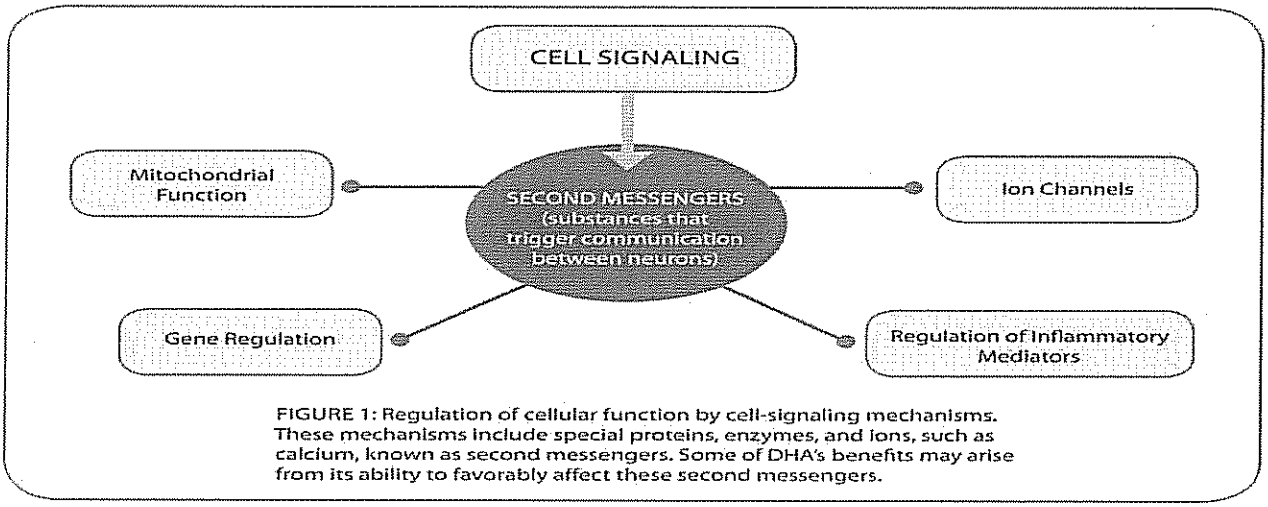


FIGURE 2: Effect of DHA on major cell mechanisms. As well as increasing cellular energy levels, DHA regulates a number of second messengers, which in turn regulate cellular inflammatory mechanisms, such as nuclear factor-kappa b (NF-kb) and inflammatory eicosanoid generation. By downregulating glutamate receptor activity, DHA protects against nerve damage.



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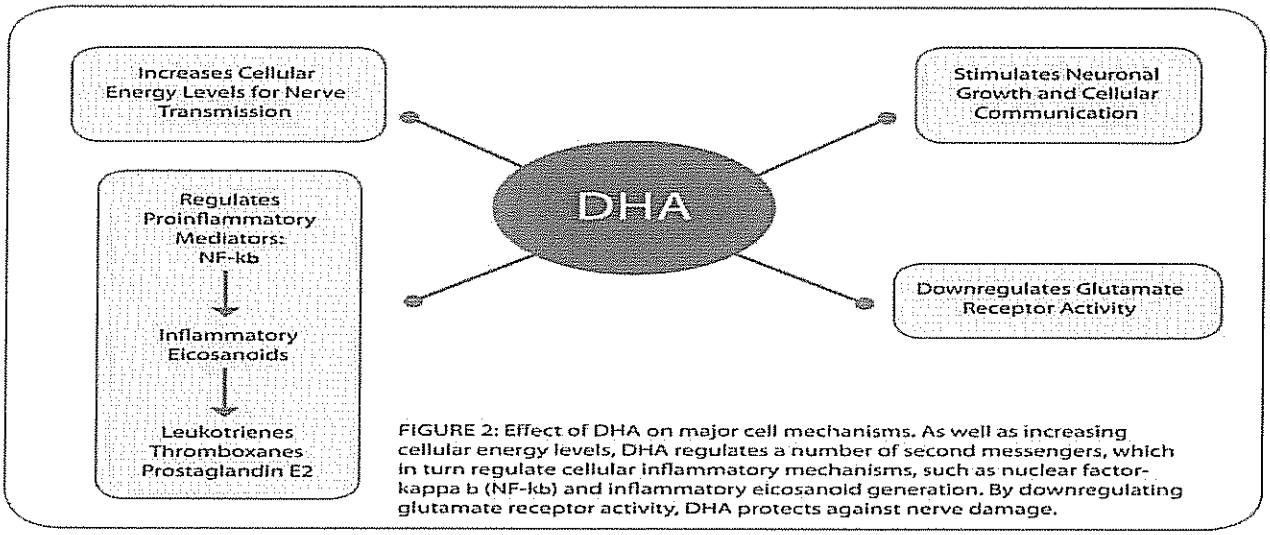

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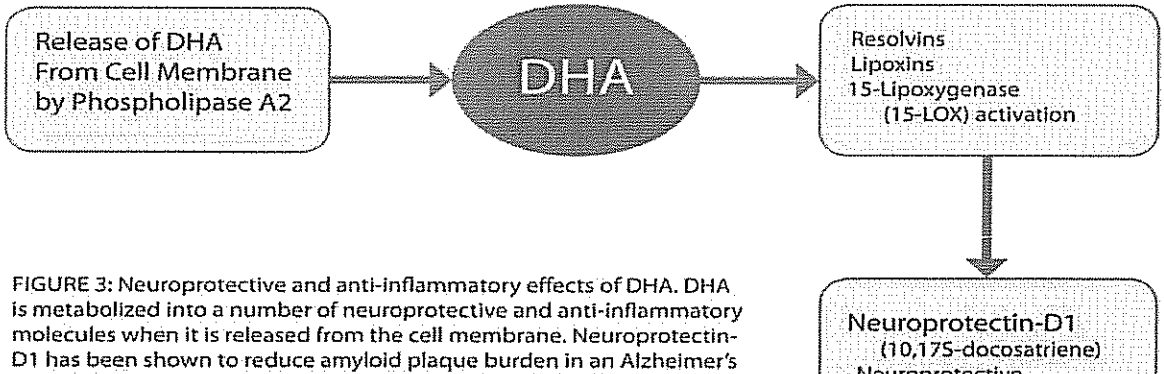

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