THE USE OF OMEGA-3 PUFAS IN PAIN THERAPY

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Submission: June 26, 2017; **Published:** July 14, 2017

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Abstract

Acute and chronic pain afflicts millions of patients each year worldwide. However, inadequate management of acute pain negatively impacts numerous aspects of patient health and may increase the risk of developing chronic pain, which can have a profound impact on the body's endocrine, neurologic, musculo-skeletal, cardiovascular and immune systems. Although opioids are the preferred treatment for most moderate to severe acute and chronic pains, their side effects can interfere with and thus limit their clinical effectiveness. Morphine is one of the most used opioids for the acute and chronic control of moderate to severe pain. However, side effects are frequently observed in patients receiving morphine during chronic pain treatment, which can lead to the interruption of treatment.

Recently, an increasing number of preclinical and clinical studies have demonstrated the beneficial effects of omega-3 PUFAs in different clinical situations with inflammatory pain. This review examines a number preclinical and clinical studies using omega-3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid) as a monotherapy or as an adjunct to morphine in the treatment of pain and suggests a role for omega-3 PUFAs as adjuncts to opioids in pain therapy, which might contribute to a reduction in the occurrence of typical side-effects common to morphine use.

Keywords: Docosahexaenoic acid; Eicosapentaenoic acid; Omega-3 polyunsaturated fatty acid; Pain; Nutraceuticals

Abbreviations: AA: Arachidonic Acid; ALA: Alpha-Linolenic Acid; ASICs: Acid-Sensing Ion Channels; DGLA: Dihomo-γ-linolenic Acid; DHA: Docosa Hexaenoic Acid; EFAs: Essential Fatty Acids; EPA: Eicosa Pentaenoic Acid; EDP: Epoxy Docosa Pentaenoic Acid; EEQ: Epoxy Eicosatetraenoic Acid; GLA: γ-linolenic Acid; GPR40: G-Protein-Coupled receptor 40; LA: Linoleic Acid; LOX: Lip Oxygenase; PLA2: Phospho Lipase A2; omega-3 PUFAs: omega-3 Poly Unsaturated Fatty Acids; omega-6 PUFAs: omega-6 Polyunsaturated Fatty Acids; RvE: Resolvin E; RvD: Resolvin D; TRPV1: Transient Receptor Potential Vanilloid type 1

Introduction

The Fatty acids (FA) are lipids that represent a significant percentage of the daily caloric intake in the diet of mammals. All FA are carboxylic acids (carboxylic group) with hydrocarbon chains of 4 to 36 carbon, with the physical and chemical characteristics of the FA (eg, their melting point or solubility in water) and also their nutritional properties (energy content, digestibility, metabolic effects, etc.) depending on the number of carbon atoms in each molecule, the number of double bonds that they possess (double bonds between carbons), the position occupied by their double bonds in the chain and their isomerisms (cis or trans).

FA can be classified according to the length of the chain, the number, position and configuration of the double bonds, as well as the additional existence of other functional groups.

With respect to the carbon chain length, the FAs are classified as: short chain (less than 10 carbons), medium chain (12 or 14 carbons) or long chain (16 carbons or more).Also, fatty acids are classified as saturated fatty acids that have no double bonds or unsaturated fatty acids that have double or triple bonds. Based on the number of double bonds present, unsaturated fatty acids are further divided into monounsaturated fatty acids with only one double bond and polyunsaturated fatty acids (PUFAs) with two or more double bonds. When the first double bond is located between the 9 -10 carbon atoms (counting from the terminal methyl group), these molecules originate the family or series of FA called omega-9.When the double bond is between the 6 -7 carbon atoms, this originates the omega-6 family, and for the double-bond between the 3- 4 carbon atoms , the family omega-3arises (Figure 1).

Figure1: Classification of Fatty Acids.
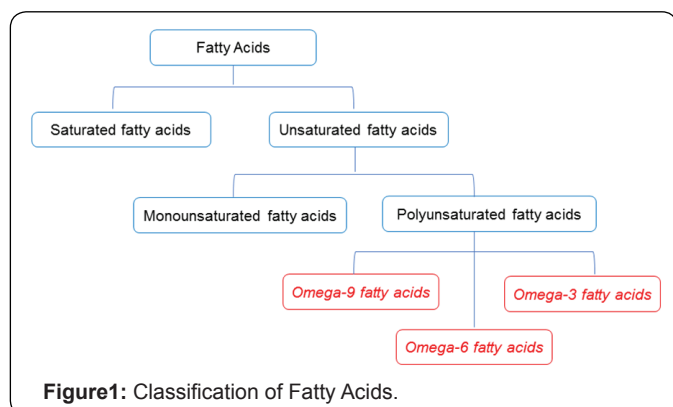
Dietary sources of Omega-3 PUFAs

Some marine species, such asmammals, fish and crustaceans, are characterized by accumulating in their tissues relatively large amounts of omega-3 PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).These animals can incorporate these fatty acids mainly with the food, since they have an inefficient biosynthesis of EPA and DHA from ALA [1]. The marine food chain depends on primary producers such as marine phytoplankton and zooplankton, because they can cumulative omega-3 PUFAs [2,3].These primary marine producers can effectively incorporate PUFAs with long chains from ALA and LA via a series of desaturation and elongation reactions, such as EPA and DHA. An increase in the fat content of marine animals indicates a resulting higher content of EPA and DHA in their meat and the oil obtained from them.

EPA accumulates mainly in adipose tissue, while 90% or more of DHA constitutes the nervous tissue of these animals, mainly in the form of phosphatidylserine and phosphatidylethanolamine. In this way, fish such as tuna, herring, mackerel, sardine, jurel, salmon and anchovy are important sources of EPA and DHA [4]when consumed as meat or in the products of their industrialization (mainly flour and oil).Other sources of omega-3 PUFAs are vegetables, with vegetable oils being the main source of ALA, such as linseed and primrose. In particular, ALA is present in the chloroplast of green leaves of vegetables and contain only shorter-chain omega-3 PUFAs and low or absent levels of EPA and DHA [5,6].

Essential Fatty Acids

Essential fatty acids (EFAs) correspond to both the n-6 and n-3 series, as in linoleic acid (LA) and alpha-linolenic acid (ALA), respectively [7].They are called essential because they are indispensable for human life and man cannot synthesize them, so their incorporation with the diet is required in a daily proportion of 1 to 2% of the total lipids consumed [8]. A lack of EFAs, AL and ALA is manifested by specific signs, including lack of growth, skin lesions, less pigmentation of the skin, loss of muscle tone, degenerative changes in the kidney, lung and liver, an increase in basal metabolism [9], and is also a possible cause of hyperactivity in children [10] Moreover, it

can produce alterations in cell permeability, water balance disorders, increased susceptibility to infections and changes in electroencephalogram and electrocardiogram [11,12]. The common signs of EPA and DHA deficiency are much less obvious than for ALA. These include heart problems and/or poor circulation, visual disturbances, changes in the skin (dry skin), eczema or hair loss, poor memory, peripheral neuropathies, behavior problems and learning difficulties. Many visual and nervous system disorders are also probably due to DHA deficit [13].
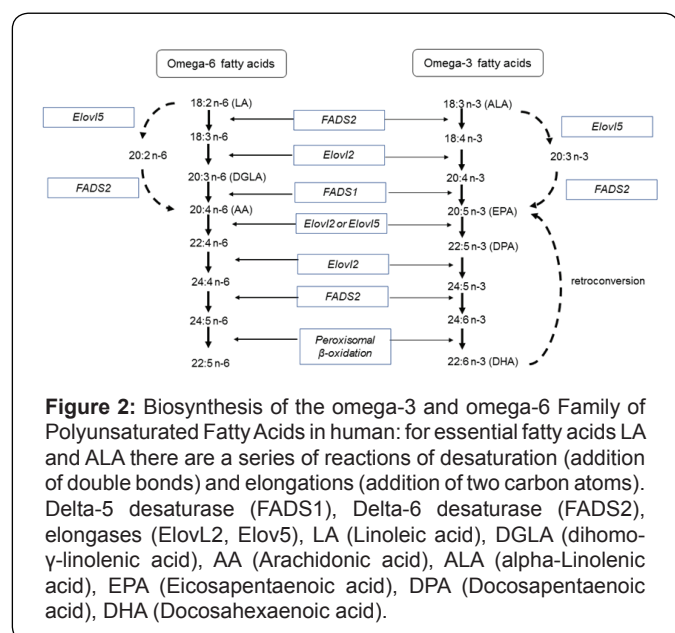
Biosynthesis of the omega-3 PUFAs family

The biosynthesis process of omega-3 PUFAs generates a series of metabolites, polyunsaturated fatty acids with higher carbon numbers, and a greater number of double bonds from ALA. Once absorbed from the diet, the EFAs LA and ALA are primarily metabolized in the liver, although it is also possible that this takes place in other tissues [14]. The biochemical process of AL and ALA elongation and desaturation occurs in the endoplasmic reticulum and also in the peroxisomes of liver cells or hepatocytes [15]. Linoleic acid (LA) can be metabolized to other more unsaturated long-chain members of the n-6 family by the insertion of additional double bonds during consecutive elongation and desaturation mechanisms. The initial phase of LA (18:2 n-6) to GLA (γ-linolenic acid, 18:3 n-6) conversion is by the enzyme delta-6-desaturase (FADS2) [16] and this is then converted to DGLA (dihomo-γ-linolenic acid 20:3 n−6) by elongation of elongases (ElovL2). Subsequently, DGLA, by the action of delta-5 desaturase (FADS1), is transformed into AA [17]. Finally, a cycle of elongation, desaturation by Delta-6 desaturase (FADS2) and peroximal beta-oxidation generates docosapentaenoic acid (22:5 n−6) [18].

ALA (omega-3 PUFA) is desaturated to 18: 4 n-3 (stearidonic acid) by delta-6 desaturase, elongated to 20: 4 n-3 (eicosatetraenoic acid) and then converted to 20: 5 n-3 (EPA) in the endoplasmic reticulum (RE) by delta-5 desaturase. Subsequently, EPA by action of elongase is transformed into 22: 5 n-3 (docosapentaenoic acid), which continues to elongate at 24: 5 n-3 (tetracosapentaenoic acid), followed by desaturation by delta-6 desaturase of 24: 6 n-3 (tetracosahexaenoic acid). Subsequently, this acid is transferred to the peroxisomes, and finally converted to 22: 6 n-3 (DHA) by removing 2 carbons from the chain by beta-oxidation (Figure 2). Aretroconversion of DHA to EPA omega-3 PUFAs is also possible, although this type of metabolic process is relatively limited in man [19]. Retroconversion includes a beta-oxidation cycle with some auxiliary enzymes [20], but Brossard et al. [21] calculated that the retro conversion rate of DHA to EPA in humans receiving normal dietary amounts of DHA is only ≈1.4%.

While dietary ALA can be converted to DHA and EPA, this is a slow process [22,23] and the extent of this conversion appears to be minimal during common intake [24,25] in humans as well as in rodents and other mammals [26,27]. ALA is metabolized

to EPA and DHA more efficiently in women than the men. The female capacity to convert ALA to EPA is ≈ 21%,with ≈ 9% being converted to DHA, and a concomitant reduction in the rate of ALA oxidation (≈22% compared with ≈33% in men) [25,28,29]. These differences in metabolism may be attributed to the regulatory effects of estrogens [30], and this ability to increase the conversion of ALA in women possibly being important to meet the demand for DHA in the neonate and fetus [31]. It is well established that DHA can be biosynthesized from the short chain precursor ALA, through the elongation and desaturation processes of its hydrocarbon chain [32] (Figure 2). LA and ALA are metabolized by the same enzymes and therefore compete for them, with these metabolic processes not being interchangeable [33]. The Omega-3 and omega-6 PUFAs compete for the desaturase enzymes (FADS1 and FADS2) and have a higher affinity for ALA than LA [22,23,34].

Figure 2: Biosynthesis of the omega-3 and omega-6 Family of Polyunsaturated Fatty Acids in human: for essential fatty acids LA and ALA there are a series of reactions of desaturation (addition of double bonds) and elongations (addition of two carbon atoms). Delta-5 desaturase (FADS1), Delta-6 desaturase (FADS2), elongases (ElovL2, Elov5), LA (Linoleic acid), DGLA (dihomo-γ-linolenic acid), AA (Arachidonic acid), ALA (alpha-Linolenic acid), EPA (Eicosapentaenoic acid), DPA (Docosapentaenoic acid), DHA (Docosahexaenoic acid).

Omega-3 PUFAs and pain

The diet should not only provide EFAs, but also the omega-3 and omega-6 PUFAs, with the balance between these PUFAs being critical as it greatly influences human health.Omega-3 and Omega-6 PUFAs compete with same metabolic enzymes and position of the phospholipids, but they often have important opposing physiological effects [35]. AA is a major intermediate omega-6 PUFA that competes with DHA for the same elongation and desaturation enzymes. However, a diet with ALA (omega-3 PUFA) induces suppressive effects on the metabolism of omega-6 PUFAs, whereas omega-6 PUFA has a 10-fold suppressive effect lower on the metabolism of omega-3 PUFAs [36]. Therefore, an abundant diet of LA produces a suppression of the ALA to DHA conversion [37]. Also, AA competes with DHA for the sn-2 position of phospholipids in cellular membranes [38].

The omega-6 PUFAs produce metabolites with inflammatory, procoagulant and vasoconstrictor actions, processes that are vital for the body's immune system's ability to repair and protect itself. In contrast, omega-3 PUFAs metabolites counteract the effects of omega-6, being anti-inflammatory, anticoagulant, and vasodilators [39-41]. The high LA content of modern industrialized diets can generate a physiological situation that favors chronic inflammation, heart disease, diabetes, autoimmune arthritis and impaired neuronal functioning, including mental disorders [42-45] and the development of chronic pain [46].

When humans ingest fish or fish oil, the EPA and DHA from the diet partially replace the omega-6 PUFAs (especially AA) in the membranes of probably all cells, but especially in the membranes of platelets, erythrocytes, neutrophils, monocytes, and liver cells (reviewed in (541) [47]. Clinical studies have shown some benefits resulting from the use of omega-3 PUFAs (EPA and DHA) for different inflammatory pains, such as inflammatory joint pain, inflammatory bowel disease, chronic headaches, knee osteoarthritis, rheumatoid arthritis, neck or back pain, neuropathic pain, musculoskeletal injury and dysmenorrheal [48]. In addition, some studies have demonstrated that omega-3 PUFAs can significantly reduce then onsteroidal anti-inflammatory drug (NSAIDs) requirement in patients with mild rheumatoid arthritis [49-62].
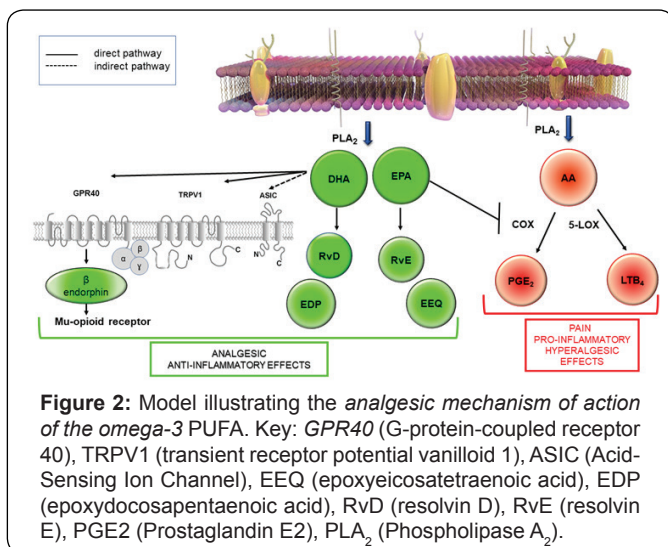
The role of omega-3 PUFAs in pain has also been investigated in rodents, with Yehuda et al. [63] being one of the first to report on the effects of how diet can modify the response of rodents to acute and chronic nociceptive stimuli. In this investigation, animals fed on a soybean oil diet with polyunsaturated vegetable fat for three weeks demonstrated an increase in the pain threshold. Furthermore, these authors reported the effect of different omega-3: omega-6 ratios in the diet and found that an increase inALA-omega-3 PUFA led an analgesic effect.

Other investigations using fish oil (18% EPA and 12% DHA) and fish oil concentrate (46.5% EPA and 37.5% DHA) have demonstrated an antinociceptive effect after their chronic administration [64,65], including after acute oral administration at low doses [66]. Related to this, some studies have shown antinociceptive effects against various pain stimuli (thermal and chemical nociception) after acute administration of DHA in mice [67-69]. In an experimental animal model of Complete Freund's Adjuvant-induced knee arthritis, the chronic administration of chronic DHA produced antinociceptive and anti-inflammatory effects [70]. However, no data are available about EPA alone in pain treatment.

Although the exact mechanisms by which omega-3 PUFAs reduce pain is still not fully defined in molecular terms, recent studies have revealed that the antinociceptive effect ofomega-3 PUFAs occurs through the following different mechanisms:

a) Inhibition of the production of the lipid mediator from the arachidonic acid cascade, as the latter contributes to pain and inflammation (PGE_2) [71] and hyperalgesia(LTB_4) [72,73].

b)   Production of lipid mediator from EPA and DHA withanalgesic action, such as the E-series (RvE1, RvE2) and D-series (RvD1, RvD2) resolving, respectively, which are potent analgesics [74-78].

c)   Regulation of both the peripheral and central transient receptor potential of vanilloid 1 (TRPV1) and acid-sensing ion channels (ASICs).The TRPV1 receptor is a lig and-gated non-selective caution channel activated by heat (>43 degrees C), low pH and endogenous lipid molecules, with TRPV1 receptor stimulation by endocannabinoids or by capsaicin leading to analgesia [79]. ASICs are permeable to cations and are activated by extracellular acidosis. As ASICs are known to contribute to pain, the stimulation of ASICs in either the CNS or the PNS produces this [80]. Interestingly, whereas DHA is a potent TRPV1 agonist, EPA inhibits the activation of this caution channel by various agonists [81].

d)   Release of β-endorphin by action of DHA through the G-protein-coupled receptor 40 (GPR40 signaling, which finally induces antinociception by the stimulation of the μ- and δ-opioid receptors [68,69].

e)   Release of the epoxidized metabolites derived from omega-3 PUFAs DHA (epoxydocosapentaenoic acid, EDP) and EPA (epoxyeicosatetraenoic acid, EEQ), which have an analgesic action [82,83] (Figure 3).

Figure 2: Model illustrating the *analgesic mechanism of action of the omega-3 PUFA*. Key: *GPR40* (G-protein-coupled receptor 40), TRPV1 (transient receptor potential vanilloid 1), ASIC (Acid-Sensing Ion Channel), EEQ (epoxyeicosatetraenoic acid), EDP (epoxydocosapentaenoic acid), RvD (resolvin D), RvE (resolvin E), PGE2 (Prostaglandin E2), PLA$_2$ (Phospholipase A$_2$).

Morphine therapy in cancer and non-cancer pain

The prevalence of cancer has been increasing, with a projection estimated by 2020 of 2017 million new cases [84], which implies that there will be a corresponding increase in individuals of pain caused by the disease and by its treatments [85]. In fact, approximately 50% of patients with cancer suffer from pain at the time of diagnosis, with about 80% of patients with advanced cancer experiencing moderate to severe pain [86]. In the older adult population, it is estimated that more than 50% have a chronic pain disorder, with the rate of prevalence

substantially higher in the long-term care setting (49%–89%) [87].

Pain in the patient with cancer is a problem that involves many people, including the patient and family, doctors, nurses, health authorities and medical education bodies, because to some extent we are all affected by the patient's cancer pain if it is not treated properly. Related to this, it is estimated that this pain is not well treated in as much as 50% to 80% of these patients, who have indicated not having received satisfactory relief [88]. Opioids are the most effective analgesics for severe pain and are a first-line treatment option to acute and terminal cancer pain treatments [89]. In addition, in recent years, an increasing trend in the prescription of opioids for non-cancer patients has been observed [90,91], which may be appropriate for the treatment of chronicnon-cancer pain such as low back pain [92] and for neuropathic pain [93], when the pain is intense, continuous and unresponsive to other analgesic standards.

Morphine causes a wide range of adverse effects, with early symptoms usually including somnolence and nausea, and constipation being the most important problem in long-term treatment. Further potential side-effects are euphoria, dysphoria, anxiety, pruritus, urticaria, weight loss bronchospasms, headaches and miosis. However, severe reactions such as respiratory depressions and pronounced hypotension are uncommon when the drug is only used in therapeutic doses. The adverse effects of morphine often constitute significant problems in clinical practice, with most patients (up to 80%) with chronic pain having reported having at least one adverse effect [94]. Tolerance refers a phenomenon in which exposure to a drug results in the diminution of an effect or the need for higher dose to maintain the effect [95]. Unfortunately, both acute and chronic administration of morphine may produce a rapid onset of analgesic tolerance, which is manifested over time in a reduction in the analgesic effect at the same dose, which then necessitates large daily doses to obtain the same efficacy [96]. Similarly, although opioid medications can provide essential pain relief for many patients, the development of some adverse effects and analgesic tolerance can have a significant impact on the quality of life and result in patients abandoning their treatment altogether.

Omega-3 PUFAs combined with morphine

Recently, some new strategies have been described for older adults to manage opioid-induced adverse effects, which can be implemented both before and during opioid treatment: dose reduction, opioid rotation, altering the route of opioid administration, and symptomatic management of adverse effects [97]. In addition, other strategies have been proposed in clinical practice to manage morphine-induced adverse effects, such as the use of adjuvants to opioids for the treatment of pain. This combination seeks alternatives to opioids for greater analgesia and the attenuation of opioid-induced adverse

reactions, such as nausea and vomiting, constipation, sedation, and respiratory depression. Many different classes of drugs can serve as effective adjunctsto opioids for pain treatment, such as nonopioid analgesics (nonsteroidal anti-inflammatory drugs such as aspirin, acetaminophen, ibuprofen and ketoprofen), antidepressants (eg, tricyclics, SSRIs), anticonvulsants (eg, carbamazepine, gabapentin), antiarrhythmics (eg., mexiletine) and sedatives, anxiolytics, tranquilizers (benzodiazepines such as alprazolam) [98]. However, these combined treatments canalso increase the risk for adverse treatment outcomes [87].

Beneficial effects have been observed after a combined treatment with morphine and omega-3 PUFA in an animal model of pain. For example; chronic morphine treatment displayed additive effects when combined with omega-3 PUFAs [65]. Surprisingly, even sub effective doses of morphine have been shown to potentiate omega-3 PUFAs antinociceptive effects [99]. Also, it has been observed that chroniccoadministration of morphine with omega-3 PUFAs attenuated or blocked the development of time-dependent tolerance with some adverse effects also have been diminished [65]

Conclusion

The findings discussed in this review suggest that omega-3 PUFAs is a viable alternative to pain treatment in various clinical situations and can provide clear benefits when used as adjuncts to morphine in chronic and acute pain treatment, with one of the most significant advantages of a combination treatment being the possible reduction of morphine side effects, which often acts as a major obstacle in pain treatment. Moreover, the use of a pharmaceutical formulation with a sub effective dose of morphine in combination with omega-3 PUFAs has been shown to improve the quality of pain relief and to reduce adverse events.

Acknowledgment

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