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Use of Omega-3 Fatty Acids in the Treatment of Neuropathic Pain

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Abstract

Neuropathic pain may be the consequence of an injury or dysfunction of the nerves, spinal cord, or brain, resulting in the nociceptive system behaving abnormally with there being a total lack of a causal relationship between tissue injury and pain. Epidemiological research has shown that the prevalence of neuropathic pain is probably between 6.9% and 10% worldwide. This painful condition is a major clinical problem, as it represents a debilitating condition that seriously compromises the quality of life. In addition, neuropathic pain and its associated syndromes share an important pharmacological feature in that they respond poorly, or only partially, to the available therapies, which often have significant adverse effects. Therefore, there is still a need to explore new therapeutic strategies in order to identify effective and safer drugs with minimal or at least reduced, adverse effects. This review examines a number of preclinical and clinical studies using omega-3 PUFAs in the treatment of neuropathic pain. However, further studies are still needed to determine the potential use of chronic omega-3 fatty acids in peripheral neuropathic pain.

Keywords: Omega-3 polyunsaturated fatty acid; Neuropathic pain; Nutraceuticals

Abbreviations: CCI: Chronic Constriction Injury; JNK: C-Jun N-Terminal Kinase; MPO: Myeloperoxidase ATF: Activating Transcription Factor; SCDH: Spinal Cord Dorsal Horn; ALA: Alpha-Linolenic Acid Fatty Acid; DPA: Docosapentaenoic Acid; DHA: Docosahexaenoic Acid.

Introduction

Even after recent advances in the understanding of pain physiology and in the development of new analgesics, several studies have clearly demonstrated that these new drugs fail to solve the two major problems in the pharmacological treatment of chronic conditions such as neuropathic pain, namely, optimal efficacy and adverse effects [1-6]. As a result, the treatment can fail and lead to disappointment, anguish and economic loss of the patient.

In fact, chronic pain of a neuropathic origin is one of the most complex and difficult types to treat, which can have a negative impact on a patient's quality of life [7-10]. Sufferers of chronic neuropathic pain have been reported to have higher degrees of anxiety and depression scores, as well as increased sleep disturbance [7,11]. Successful treatment is difficult due to several factors, including the complex pathophysiology of neuropathic pain, variations between different types of neuropathic syndrome among patients, and the difficulty of providing an accurate diagnosis [12]. Often, after treatment, patients with neuropathic pain do not achieve a satisfactory pain relief,

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or cannot tolerate effective doses because of the adverse effects [13,14]. Related to this, it has been estimated that only about 40-60% of patients achieve pain relief through monotherapy [1,15].

Over the last decade, new targets for possible treatment options are emerging such as novel chemical molecules, formulations, and routes of administration, as well as combinations of known analgesics [6]. In addition, for many years, traditional medicine, chemical plant compounds and derivatives of plant and animal origin have been utilized to try to alleviate and/or cure many pathological states.

At present, there are several chemical substances known to be able to perform the functions of food and drugs, which are referred to as nutraceuticals. These include food of an animal or vegetable origin, with omega-3 polyunsaturated fatty acids (ω-3 PUFAs) being an example of these, and in recent years, many studies have shown their benefits to human health [16]. In particular, they have achieved positive results in situations related to inflammatory pain, such as inflammatory bowel disease [17], inflammatory joint pain [18], knee osteoarthritis [19,20], keen pain [21], rheumatoid arthritis [22-30], neck, back or shoulder pain [31,32], neuropathic pain [33,34], musculoskeletal injury [35], dysmenorrhea [35] and chronic headaches [36], with fish oil being a principal source of ω-3 PUFAs.

The purpose of this review is to summarize the preclinical and clinical characteristics of omega-3 fatty acids for the treatment of neuropathic pain.

Omega-3 polyunsaturated fatty acids

Humans can synthesize long omega-3 fatty acids from alpha-linolenic acid fatty acid (ALA; 18:3 ω-3) through a series of desaturation (addition of a double bond) and elongation (addition of two carbon atoms) reactions. In this metabolic pathway, delta-6 desatuarse is considered to be the rate-limiting enzyme.

Figure 1 depicts the metabolic pathways of omega-3. The ω-3 PUFA series begins with alpha-linolenic acid (ALA; 18:3 ω-3), with the other omega-3 PUFAs being derived from ALA, as well as from docosapentaenoic acid (DPA; 22:5 ω-3) and docosahexaenoic acid (DHA; 22:6 ω-3), via a series of desaturation, elongation and ultimately β-oxidation reactions [36]. The primary source of ALA is plants, which is concentrated mainly in some seeds, nuts and vegetable oils [37,38], whereas the principal ω-3 PUFAs from marine sources are EPA and DHA, with DPA being present at fairly low levels in most fish oils [39].

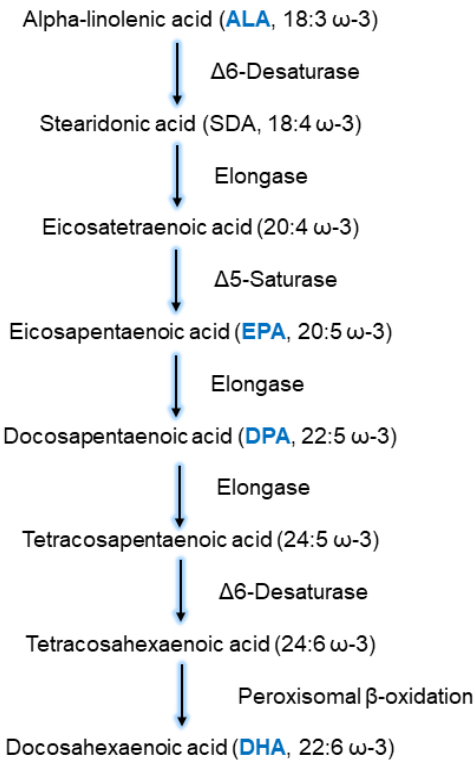

Figure 1: Diagram illustrating the biosynthetic pathway of Omega-3 polyunsaturated fatty acids.

The nervous system is a tissue with a high content of polyunsaturated fatty acids, especially DHA. Several effects have demonstrated DHA to be present in the CNS, with it playing a crucial role in the brain, such as in the alteration of membrane biophysical properties, the regulation of dopaminergic, serotonergic, cholinergic and glutamatergic neurotransmissions, and affecting the activity of membrane bound enzymes, ion channels, cell signaling pathways and neurite growth, as well as producing lipid raft, antiapoptotic and gene activity effects [40].

Compared with the 10-20% representation of DHA, EPA comprises only 0.1 % of total brain fatty acids [41]. At the CNS level, EPA has been demonstrated to have effects on the membrane biophysical properties, the ion channel modulation, lipid rafts, neuronal membrane excitability, cell signaling pathways, and the production of

proinflammatory eicosanoids, as well as producing antioxidant and anti-inflammatory responses [40].

Preclinical Studies: Peripheral nerve injury and chronic constriction injury (CCI) of the sciatic nerve [42] are driven by degeneration, neuroinflammation, and neuronal plasticity, which results in neuropathic pain symptoms such as allodynia and hyperalgesia.

Studies on mice expressing the fat-1 gene encoding for ω-3 fatty acid desaturase have shown an increase in endogenous ω-3 PUFAs and a concomitant decrease in ω-6 PUFAs. Related to this, Gladman et al. [43] reported that both *in vitro* and *in vivo* experiments have indicated neuroprotective and neurotrophic effects of endogenous ω-3 PUFAs, which could lead to a secondary effect on regeneration after a sciatic nerve, crush injury.

At the peripheral nerve level, the administration of DHA for 2 weeks after chronic constriction injury (CCI) of the sciatic nerve produced a reduction in the activity and duration of neuropathic pain syndrome, and also prevented the development of degenerative changes in the foot tissues [44].
In addition, at the level of dorsal root ganglia, the chronic administration of DHA produced changes in microglia/macrophage activity, suggesting its involvement in the development of the pathological changes associated with neuropathic pain [45].

Manzhulo et al. [46] studied the DHA analgesic effect on neuron-astrocyte interactions in the spinal cord dorsal horn superficial lamina after CCI, with the results indicating that DHA analgesic activity in neuropathic pain is related to suppression of reactive astrocyte and the inhibition of the signaling pathways of nitric oxide and Substance P.

The c-Jun N-terminal kinase (JNK) in the central nervous system plays a critical role in the processing of neuropathic pain. Phosphorylated JNK (p-JNK), the active form of JNK, is selectively expressed in the hyperactive glia of the spinal dorsal horn after peripheral nerve injury, and is essential for the activation of glia. Recent studies have revealed that the DHA analgesic effects on neuropathic pain, at least in part, are produced by suppression of the microglia-mediated inflammatory response through inhibition of the JNK signaling pathway [47].

In another investigation, Silva et al. [48] studied the effects in mice of concentrated fish oil (DHA/EPA) on nerve regeneration and the prevention of neuropathic pain after partial sciatic nerve ligation. These studies showed that ω-3 PUFAs have regenerative and possibly protective properties, as well as anti-neuro inflammatory activity. However, no data are available about EPA used alone in neuropathic pain treatment in preclinical studies.

Despite early reports indicating the beneficial effects of ω-3 PUFAs on peripheral nerve injury, the underlying mechanisms involved are not yet fully understood, but a combination of multiple targets has been suggested, including:

- At the peripheral nerve level (sciatic nerve), an increased neuronal expression of growth-associated protein 43(GAP-43; a marker of axonal growth and regeneration) and of the total number of myelinated fibers in the sciatic nerve, with reduced myeloperoxidase (MPO) activity (indirect measure of neutrophil migration) [48];
- At the level of the dorsal root ganglion (DRG), neurons reduce the expression of activating transcription factor 3 (ATF-3; a marker of neuronal injury) [48] microglia/macrophage activation, satellite formation and apoptosis [45];
- At the level of the spinal cord dorsal horn (SCDH), neurons reduce the reactive astrocyte number, neurotransmission of nitric oxide (NO), substance P [46] and the level of TNF [48].
- At the level of the cuneate nucleus in the medulla oblongata, neurons reduce the microglia-mediated inflammatory response (with a diminished release of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6) and also the metabolic derivative of DHA (resolvin D, RvD) through the inhibition of the JNK signaling pathway (Figure 2).

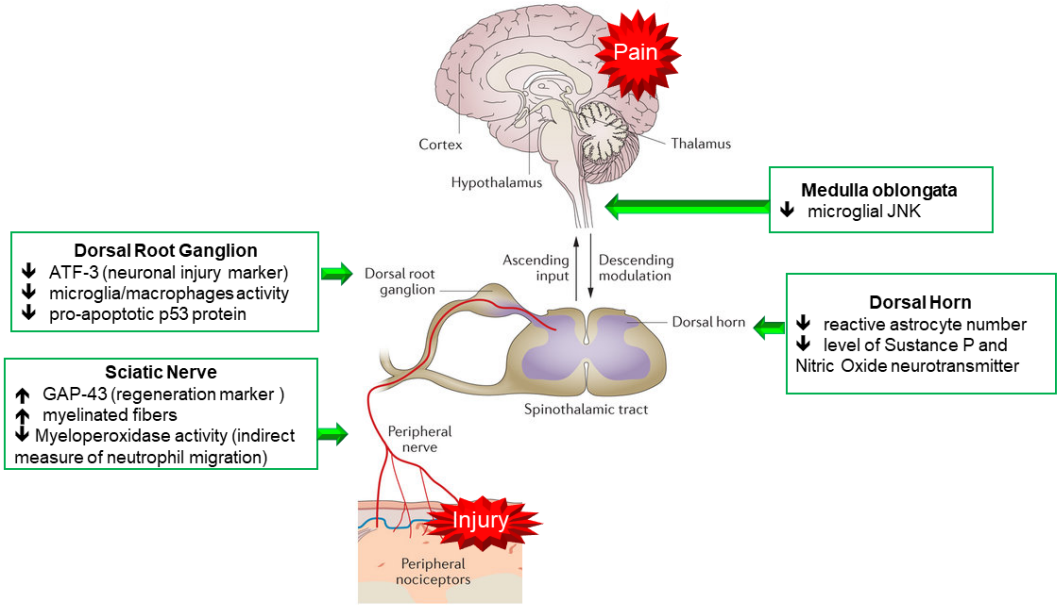

Figure 2: Signaling mechanisms of ω-3 PUFA effects on neuropathic pain pathways.

Clinical Studies: A few studies have demonstrated the beneficial effects of ω-3 PUFAs on peripheral nerve damage, with it having been suggested that ω-3 PUFAs may be an aid in the management of patients suffering from neuropathic pain [34]. Related to this, a systematic review of Zhang et al. [49] evaluated the effects of oral ω-3 PUFA supplementation on peripheral nerve integrity, by including both subjective and objective measures of peripheral nerve structure and/or function. This review demonstrated that ω-3 PUFA supplements can improve the peripheral nerve function and/or the quality of life.

Conclusions

The underlying mechanisms involved in the reported beneficial effects of ω-3 PUFAs on peripheral nerve injury are not yet fully understood, but a combination of multiple targets has been suggested, involving both neuronal and immune components, and leading to subsequent anti-neuroinflammatory, anti-nociceptive and neurodegenerative responses.

The findings discussed in this review suggest that ω-3 PUFAs are a viable alternative for treating peripheral nerve injury, and may be a safe, cost-effective adjunct for the prevention or treatment of post-injury neuropathic pain in humans.

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