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The role of Omega-3 and Omega-9 fatty acids for the treatment of neuropathic pain after neurotrauma☆

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ABSTRACT

Omega-3 polyunsaturated fatty acids (PUFAs), such as docosaexaenoic acid (DHA) and eicosapentaenoic acid (EPA), mediate neuroactive effects in experimental models of traumatic peripheral nerve and spinal cord injury. Cellular mechanisms of PUFAs include reduced neuroinflammation and oxidative stress, enhanced neurotrophic support, and activation of cell survival pathways. Bioactive Omega-9 monounsaturated fatty acids, such as oleic acid (OA) and 2-hydroxy oleic acid (2-OHOA), also show therapeutic effects in neurotrauma models. These FAs reduces noxious hyperreflexia and pain-related anxiety behavior following peripheral nerve injury and improves sensorimotor function following spinal cord injury (SCI), including facilitation of descending inhibitory antinociception. The relative safe profile of neuroactive fatty acids (FAs) holds promise for the future clinical development of these molecules as analgesic agents. This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo V. Escribá.

Contents

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1. Introduction

Fatty acids (FAs) are an important component of the diet and play a major role in the lipid composition of cell membranes [1]. Some fatty acid metabolites, such as prostaglandins, thromboxanes and leukotrienes, also play a crucial role as cell signaling molecules [2]. Docosaexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) are the most important long chain Omega-3 fatty acids involved in physiological functions. As the total production of endogenous EPA and DHA is not enough to mediate all required physiological requirements under normal conditions, these polyunsaturated fatty acids (PUFAs) must be supplemented in the diet from fish, eggs and nuts and, their supply is especially important in the adequate development of the nervous system during embryonic development of the fetus [3].

Change in the lipid membrane composition may affect cell signaling pathways leading to disease development. Therefore, membrane-lipid therapy can also be used to prevent or reverse several pathophysiological processes [4]. Although vascular diseases and tumor pathologies have been linked with the intake of saturated and trans-monounsaturated lipids [5], intake of PUFAs prevent or reverse systemic pathological conditions such as obesity [6].

More recently major advances have been made in our understanding of how FAs can be used as potential therapeutic agents to ameliorate high impact symptoms of neurotrauma associated with spinal cord injury (SCI) [7] and peripheral nerve injury [8]. In this mini-review we present recent findings demonstrating neuromodulatory effects of FAs and their recent application for the treatment of chronic complications, such as neuropathic pain, in addition to recovery of motor function after SCI [7].

2. Omega-3, -6 and -9 fatty acids as neuroactive molecules

The physiological functions of Omega-3 fatty acids in the nervous system involve the maintenance of membrane fluidity which is crucial for cell adhesion, axonal guidance, dendritic formation, synapse integrity and neurotransmission [9]. At the mechanistic level PUFAs are known to mediate antioxidant [10], anti-inflammatory [11], and neuroprotective effects [12]. Furthermore, endogenous derivatives of Omega-3 FAs, specifically Resolvin D and E derived from DHA and EPA respectively, and act as endogenous anti-inflammatory mediators in a peripheral inflammation model [13].

Administration of Omega-3 PUFAs have been assessed for the treatment of hyperactive disorder attention deficit [14], Alzheimers [15], depression [16], neurodegenerative diseases [17] and spinal cord injury [18]. Although only partial therapeutic effects with Omega-3 PUFAs were identified, these studies reveal that these fatty acids can mediate a variety of physiological functions and, with further characterisation may show therapeutic promise for neurotraumatic conditions.

With regards to Omega-6 fatty acids, Arachidonic Acid (AA) mediates pro-inflammation and through the biosynthesis of eicosanoids by cyclooxygenase enzymes (COX-1 and COX-2). Derivatives of AA include the leukotrienes, thromboxanes and prostaglandins, molecules which lead to inflammation, free radical production, vasoconstriction and platelet aggregation, and neurological deterioration [19]. In contrast, other AA derivatives, such as the Lipoxins play a beneficial role in the nervous system. Specifically, Lipoxin A4 (LXA4) through the activation of its receptor ALXR in astrocytes, reduces brain damage after a traumatic brain injury, and decreases the release of proinflammatory cytokines, including TNFα, IL-1β and IL-6 [20]. Furthermore, LXA4 potentiates the endocannabinoid modulatory system, acting as an allosteric modulator of the cannabinoid receptor 1 [21].

Oleic acid (OA) is one of the most representative monounsaturated Omega-9 fatty acids. Enriched monounsaturated Omega-9 fatty acids intake in the diet is associated with reduction in anger and irritability [22]. In addition adherence to a Mediterranean diet rich in oleic acid has been shown to reduce pain in patients with inflammatory arthritis [23], while ingestion of a mixture of fatty acids including oleic acid improves somatosensory evoked potentials in female carriers of X-linked adrenoleukodystrophy (ADL) (rare inherited demyelinating disorder) while reducing inflammation [24]. Indeed, during development upregulation of the enzyme stearyl coenzyme A desaturase-I (SCD-1), responsible for OA synthesis within the central nervous system (CNS), has been shown to increase myelin basic protein levels [25], suggesting a central role for this FA in neuronal function.

Fatty acids are also endogenous ligands for the peroxisome proliferator-activated receptor (PPAR) family, with unsaturated fatty acids such as OA having a greater affinity for the receptor than saturated FAs [26]. OA activation of the PPARα receptor is essential for neuronal differentiation and upregulation of GAP-43 and MAP-2 [27]. With respect to the modulation of glia, OA inhibits the permeability of gap junctions in astrocytes [28], in contrast to Omega-3 fatty acids which increase their permeability [29]. OA mediates anti-inflammatory effects through the inhibition of reactive oxygen species (ROS), p38 MAPK and Akt signaling pathways/IKK/NF-kappaB as characterized in BV2 cells microglia line culture [30]. Furthermore, OA derivatives, such as oleamide and nitro-OA, modulate COX-2 expression in cultured microglia [31]. In this respect, our group has shown that the modified OA molecule, 2-OHOA, reduces the COX-2/COX-1 ratio in lipopolysaccharide-activated macrophage cells [8]. At the neuronal level, OA blocks reuptake of gamma-aminobutyric acid (GABA) [32], and acts as an allosteric factor for the 5-HT7A serotonin receptor [33]. In addition the condensation product made between OA and dopamine, N-oleoyl-dopamine, has been proposed as a dopamine receptor agonist with a central action for facilitating locomotion [34].

Additional neuroactive properties of OA have been characterised in relation to its synthesis from Albumin (A), which is naturally present in the CNS during development [35]. Albumin induces synthesis of OA by astrocytes an activates the SREBP-1 and SCD-1 enzymes [36]. The A-OA complex present in the extracellular space is then incorporated into neurons and promotes dendritic growth through the upregulation of GAP-43 and microtubule associated protein (MAP-2) [37]. Furthermore, the neurotrophic effect of OA is synergistic with the effect of NT3 and NT4/5 [38] (Fig. 1).

To date only a few clinical studies have identified a therapeutic effect of fatty acids for CNS disorders or neurotrauma. Clinical trials earlier demonstrated the efficacy of Fortasyn® Connect, a nutritional supplement that contains a mixture of DHA and EPA for cognitive deficits associated with Alzheimer's disease [39], although this therapeutic effect has not been replicated. In a trial for attention deficit hyperactivity disorder in children no benefit of DHA was found for the primary outcome measures studied, but an intriguing beneficial effect was found for cognitive score in ApoE4 negative allele patients [14]. Although no positive clinical trial has been performed, there is a growing body of strong preclinical evidence which suggests that Omega-3 fatty acids administered as a nutritional supplement could be effective for the treatment of traumatic brain injury and post-concussion syndrome patients [40]. A double-blind crossover study for the treatment of adrenoleukodystrophy, a demyelinating brain disorder, with chronic oleic acid (OA) in addition to erucic acid as a nutritional supplement, showed an increase in white matter following treatment [41].

3. Omega-3 and Omega-9 fatty acid characterisation in peripheral and central nervous system injury models

3.1. Peripheral neurotrauma models

Systemic administration of Omega-3 PUFAs prevents myelin and peripheral nerve degeneration following low-dose radiation exposure in rat fetuses [42]. This observation was previously supported by the examination of peripheral nerve injury in mice where endogenous Omega-3 PUFA levels are elevated due to the Fat-1 gene which encodes for Omega-3 FA desaturase [43]. In this study when compared to wild

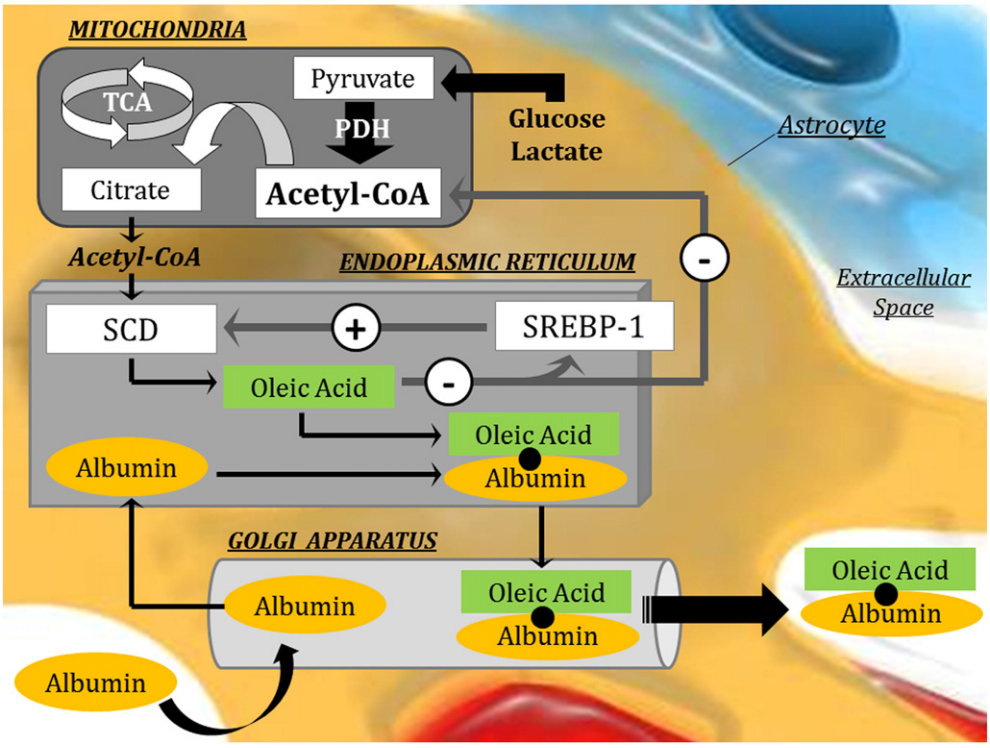

Fig. 1. Regulation of oleic acid synthesis by receptor-mediated endocytosis of albumin in astrocytes. Transcytosis of albumin and its passage through the endoplasmic reticulum (ER), the sterol regulatory element-binding protein-1 (SREBP-1) which is regulated by internal levels of oleic acid, induces stearoyl-CoA 9-desaturase (SCD), which is responsible for oleic acid synthesis. In parallel pyruvate deshydrogenase (PDH), with the synthesis of acetyl-CoA, is used as a precursor for oleic acid synthesis. The complex formed by oleic acid-albumin is then released to the extracellular medium by active exocytosis. ABP, albumin-binding protein [36].

type mice, the Fat-1 strain showed evidence of enhanced neuroprotection and functional recovery following peripheral nerve injury [43], including protection against muscle atrophy [43]. At the neuronal level, activation of ATF-3 as a marker of damage in the dorsal root ganglia of Fat-1 mice was lower following nerve injury compared to the wild type group [43]. These studies support the idea that a higher endogenous Omega-3 PUFAs promote beneficial effects after peripheral nerve injuries.

OA as a Omega-9 FA, is known to modulate arthritic pain in patients [44] in addition to orofacial pain in one experimental animal model [45]. Recently mechanistic evidence for the action of OA, and derivatives such as Oleamide or Nitro-OA, within the injured peripheral nervous system has been shown by the desensitisation of the transient receptor potential channels within the dorsal root ganglia [31]. Furthermore eicosatrienoic acid (ETA), a metabolite of OA, is known to be a potent inhibitor of leukotriene B4 synthesis [46], which in turn is known to mediate central sensitization to noxious stimuli [47] and to modulate mechanical and thermal nociception [48].

3.2. Central neurotrauma models

With regards to traumatic brain injury, the Omega-3 PUFA DHA, exhibits neuroprotective and anti-inflammatory effects when assessed in an ischemic brain injury model, accompanied by a decrease in oxidative stress [49]. Administration of Omega-3 PUFAs derivatives such as Resolvin E1, has also been shown to improve motor and post-traumatic sleep function, in addition to reduced microglia reactivity following traumatic brain injury [50]. Moreover increased levels of endogenous Omega-3 PUFA, mediated by the Fat-1 gene that encodes Omega-3 fatty acid desaturase (see above) mediates hippocampal cornu Ammonis 1 (CA1) neuroprotection and improved cognitive function following global ischemia in an experimental injury model [51].

After SCI, DHA administration has been shown to mediate neuroprotection and improvement in motor function [52]. Furthermore, the combination of an intravenous bolus dose of DHA with a DHA-enriched diet also leads to greater spinal white matter neuroprotection and locomotor activity following SCI [53], with reduced neuronal and oligodendrocyte loss and microglia/macrophage activation [54]. DHA treatment reduces pro-inflammatory cytokine expression, glial fibrillary acidic protein and apoptosis induced by spinal cord trauma [55]. Functional improvement and neuroplasticity reflects sprouting of corticospinal and serotoninergic fibres to make synaptic contact onto interneurones and motoneurones [56]. More recently the fatty acid binding protein 5 (FABP5) has been identified as a molecule responsible for cellular uptake and metabolism of DHA following SCI, which mediates the neurorestorative effects of DHA [57].

4. Neuropathic pain after neurotrauma

4.1. Peripheral nerve injury

Peripheral nerve injury often leads to neuropathic pain and chronic pain comorbidities such as anxiety [58]. Standardised experimental pain models, such as the spared nerve injury (SNI) model, can be used to assess new analgesics by measuring clinically-relevant symptoms [59]. Reflex hypersensitivity to both mechanical and thermal stimuli develop soon after SNI [59], with the additional development of anxiety-like behavior [60]. SNI elicits microglia cell activation within the spinal dorsal horn which in turn mediates change in sensory function [61]. Activation of microglia require cyclooxygenase COX-1 and COX-2 enzymes to release prostaglandin E2 [62]. Furthermore following SNI constitutive expression of COX-1 enzyme within spinal dorsal horn microglia is increased [63], and COX-2 upregulation has been identified in both human and rat tissue following peripheral nerve injury [64].

4.2. Spinal cord injury

SCI involves several changes in sensorimotor function below the spinal injury level, including paralysis and the development of chronic

symptoms, including pain and spasticity [7]. Development of neuropathic pain after SCI is mediated by spinal and supraspinal pathophysiological mechanisms [65], which leads to reduced quality of life [66]. Microglial cell reactivity exacerbates secondary damage following SCI and promotes sensory dysfunction related to pain [67]. During acute SCI the release of neuroinflammatory mediators such as cytokines promote morphological and functional changes in resident microglia cells [68]. Microglia activation is related to sensory dysfunction at [69] and above the SCI [67]. As multiple pathophysiological mechanisms related to the development of neuropathic pain are triggered following SCI, novel pharmacological treatments should be designed to control neuroinflammation, spinal excitability mediated by NMDA receptors and restoration of descending antinociception [7].

4.3. Omega-3 and Omega-9 fatty acids for the treatment of pain

Clinical studies have shown that Omega-3 FAs provide some relief of neuropathic pain conditions, especially after diabetic peripheral neuropathy. A systematic review of the effect of alpha lipoic acid (ALA) administration to treat diabetic peripheral neuropathy symptoms, including pain, suggests some effect following a 3 weeks administration protocol [70]. More specifically oral administration of ALA significantly reduced symptoms of diabetic neuropathy (dysesthesia and burning pain) and neuropathic deficits (paresthesia) when compared to placebo [71]. In a series of case studies of people with neuropathic pain, reduction of symptoms was observed with high oral doses of Omega-3 FAs for pathologies including cervical radiculopathy and thoracic outlet syndrome. These patients reported clinically significant pain reduction up to 19 months following treatment initiation. No serious adverse effects were reported [72]. Analgesic properties of Omega-3 FAs have also been identified in pain symptoms unrelated to neurotrauma, such as headache [73] and rheumatoid arthritis [74].

In experimental animal models with pre-emptive administration of Omega-3 FAs, modulation of thermal noxious reflex responses following partial sciatic nerve ligation has been observed [75], corroborated with an enriched diet of Omega-3 fatty acids administered nerve injury [76]. The same group showed that a diet containing a greater amount of linolenic acid, a Omega-3 PUFA, administered before nerve injury was more effective in reducing thermal hyperalgesia when compared to animals treated with a diet containing a high amount of linoleic acid, a Omega-6 PUFA [77]. Using an experimental model of SCI an 8 weeks pre-emptive enriched diet of DHA reduced heat thermal hyperalgesia, in addition to reduced sprouting of CGRP nociceptive afferents and p38-MAPK dorsal horn neurons and spinal levels of inositol [78]. Finally, Resolvin E1, a metabolite of DHA, administered via the intrathecal route 3 weeks after nerve injury temporarily reduced mechanical and heat noxious reflex activity, in addition to lipopolysaccharide-induced microgliosis and TNF-α release in primary micoglial cultures [79].

With regard to Omega-9 FAs, derivatives of OA such as oleamide and nitro-OA have been shown to modulate nociception and anxiety in uninjured rats [80]. The bioactive OA form, 2-hydroxyoleic acid (2-OHOA), is a FA which has demonstrated effect as a hypotensive agent and for anti-cancer properties [81]. Recently we have shown that the oral administration of 2-OHOA significantly reduced ipsilateral mechanical and thermal noxious reflex responses, decreased the COX-2/COX-1 ratio in lipopolysaccharide-activated macrophage cells and OX-42 expression within the ipsilateral lumbar spinal dorsal horn 7 days after spared nerve injury. Moreover, 2-OHOA significantly restored inner-zone exploration in the open-field test compared with the vehicle-treated sham group at 21 days after SNI suggesting a reduction in anxiety as a pain comorbidity [8] (Fig. 2).

Lastly our group has shown that the combination of albumin and oleic acid (A-OA) via the intrathecal route, synergistically promoted early recovery of locomotor activity and promoted *de novo* descending antinociception of Tibialis Anterior noxious reflex activity. In addition, spinal L4–L5 immunohistochemistry demonstrated a unique increase in serotonin innervation within the dorsal and ventral horn with A-OA treatment when compared to uninjured tissue, in addition to a reduction in NR1 NMDA receptor phosphorylation and microglia, one month after SCI. These mechanisms of action suggest that A-OA as a potential analgesic and neurotrophic factor [7]. Furthermore, intrathecal injection of A-OA has also been shown to reduce PPARα immunoreactivity within glia cells following SCI, indicating a possible interaction with nuclear hormone receptor regulation in the injured CNS [82] (Fig. 3).

Several studies indicate that fatty acids modulate membrane proteins related to ion channels including the transient receptor potential family, that could mediate the observed analgesic effect in preclinical models. The lipid composition in the immediate microenvironment influences the physiological function of membrane proteins related to cellular signaling processes [83] especially involving G-proteins [84]. Recent studies have concluded that the lipid composition within the plasma membrane can modulate the activity of ion channels [85]. Specifically, potassium channels can be directly modulated by lipids, such as the KCNQ/Kv7 family voltage-gated K^+ channels [86]. Moreover, it has been demonstrated that the inwardly rectifying potassium channel (Kir2.2) interacts with phosphatidyl inositol diphosphate, promoting conformational changes to an open state [87]. With regards to other ion channels that are influenced by change in membrane lipid composition, the Transient receptor potential (TRP) channels may play an important role in the potential analgesic effect of fatty acids. PUFAs administered as DHA or EPA are known to modulate the TRPA1, TRPV1 and TRPM8 channels in sensory neurons [88]. TRP ion channels receptors are known to be important modulators of pain processing, and membrane lipid therapy may represent a promising new approach through the exogenous intake of fatty acids [89].

5. Further characterisation of Omega-3 and Omega-9 fatty acids for the treatment of neurotrauma

Several important issues remain to be addressed before Omega-3 and Omega-9 FAs are applied for the clinical treatment of peripheral or central nervous system injury.

Better pharmacological characterization of the application of Omega-3 and Omega-9 FAs and their neuroactive metabolites is required to define the optimal route, timing, therapeutic window and systemic distribution following their administration for the treatment of nerve injury and associated symptoms. Furthermore more safety studies are required to demonstrate the innocuous effect of FA treatment for the promotion of neuroprotection and neuroplasticity in appropriate patient groups for future clinical trials [90]. This includes further characterisation of FA modulation of adaptive and maladaptive neuroplasticity and the development of high impact symptoms such as pain and spasticity [7].

6. Conclusions

Experimental studies support the use of polyunsaturated fatty acids as a promising pharmacological therapeutic approach for the treatment of central and peripheral traumatic injuries. Polyunsaturated FAs such as DHA and EPA, mediate their effects in experimental neurotrauma models by mediating neuroprotective and neurotrophic effects in combination with a reduction in neuroinflammation.

In contrast, treatment with the CIS-monounsaturated Omega-9 FA oleic acid, administered in combination with albumin or as 2-hydroxyoleic acid, promotes recovery of hindlimb motor function and reduces spasticity following SCI, in addition to promoting antinociception and anxiolytic effects following both central and peripheral nerve injury. Several mechanisms of action associated with FA treatment effects following neurotrauma have been demonstrated, including the modulation of activated peroxisome proliferation alpha nuclear receptors.

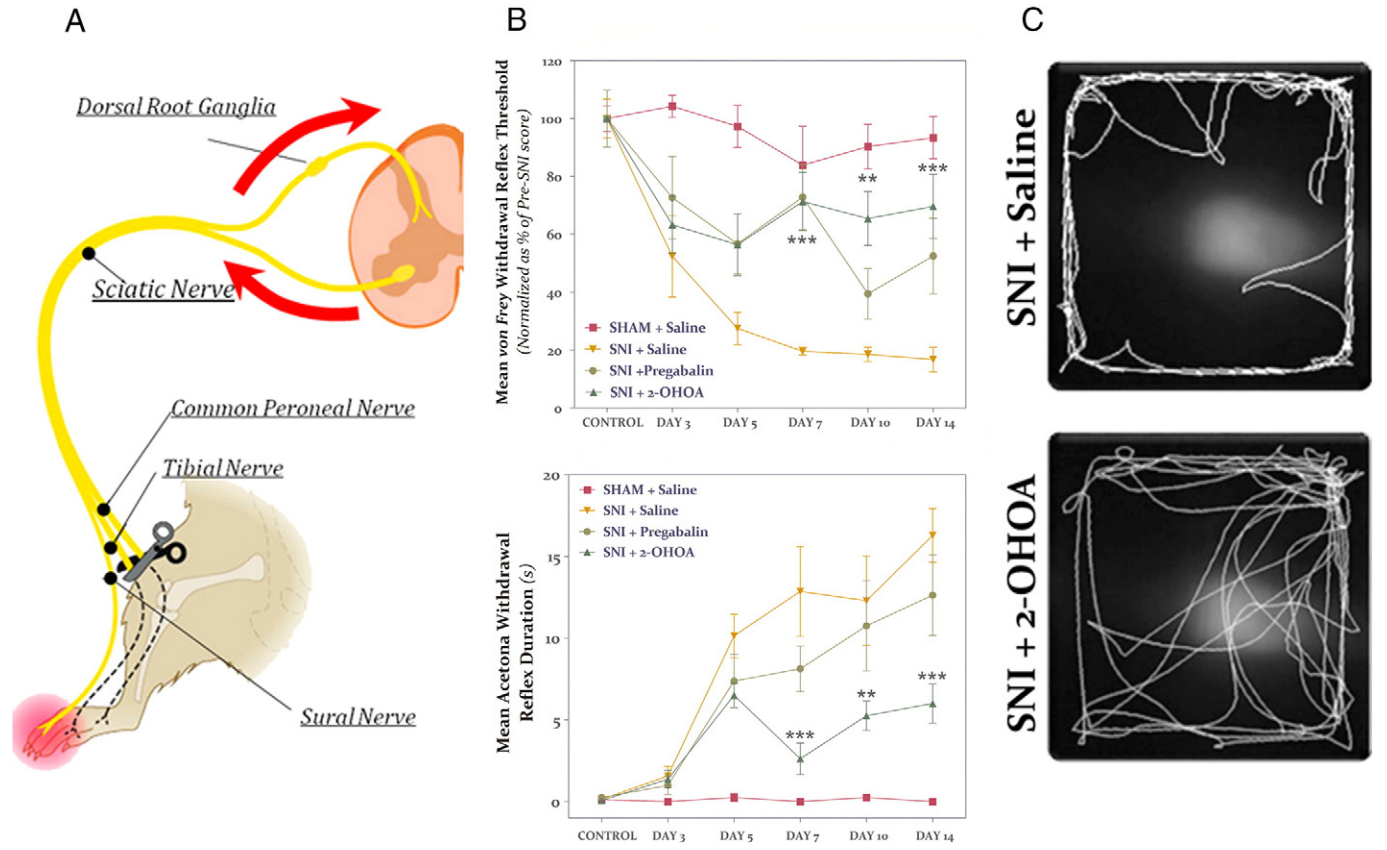

Fig. 2. Analgesic effects of systemic administration of 2-hydroxyoleic acid (2-OHOA) following peripheral nerve injury. (A) The Spared Nerve Injury Model was used to screen for potential analgesic effects of 2-OHOA. (B) Reflex hypersensitivity to both mechanical (top graph) and cold (bottom graph) test stimuli was significantly reduced following oral administration of 2-OHOA, compared to administration of Pregabalin (**p<0.05, ***p<0.001) (C) Oral administration of 2-OHOA reversed pain-associated comorbidities, such as open-field induced anxiety (upper panel), measured as the time spent by the animal entering the inner area of the 1 m^2 arena (lower panel) [8].

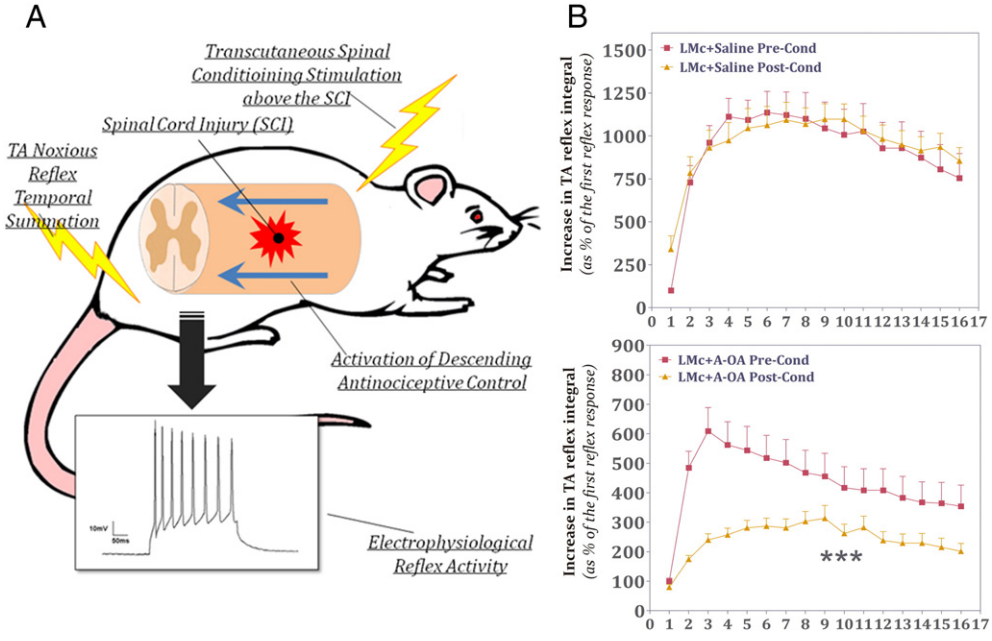

Fig. 3. Descending antinociception of noxious reflex activity below spinal cord injury following treatment with intrathecal oleic acid and albumin. (A) The thoracic contusion spinal cord injury experimental model was used to identify modulation of Tibialis Anterior noxious reflex temporal summation following transcutaneous spinal conditioning stimulation above the injury site. (B) Intrathecal administration of albumin-oleic acid (A-OA), administered up to one month after spinal cord injury promoted *de novo* descending antinociception of noxious reflex activity (lower graph), when compared to no effect in the control group in animals treated with saline (***p<0.001) [7].

This review has shown that both polyunsaturated Omega-3 fatty acids and CIS-monounsaturated Omega-9 fatty acids may constitute novel treatment effects that could be translated to the clinic for a range of central and peripheral nervous system pathologies, to restore sensorimotor function.

Transparency document

The Transparency document associated with this article can be found, in online version.

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