

## **Omega-3 fatty acids and neurological injury**

### **Prostaglandins, Leukotrienes and Essential Fatty Acids Nov-Dec 2007;77(5-6):295-300**

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FROM ABSTRACT

Studies with omega-3 polyunsaturated fatty acids (PUFA) have shown that these compounds have therapeutic potential in several indications in neurology and psychiatry.

Acute spinal cord injury (SCI) is an event with devastating consequences, and no satisfactory treatment is available at present.

The pathogenetic mechanisms associated with SCI include excitotoxicity, increased oxidation and inflammation.

We review here our recent studies, which suggest that omega-3 PUFA have significant neuroprotective potential in spinal cord trauma.

In a first study, we administered an intravenous bolus of alpha-linolenic acid (LNA) [an 18 carbon long plant omega-3] or docosahexaenoic acid (DHA) [a 22 carbon long fish omega-3] 30 min after spinal cord hemisection injury in adult rats.

The omega-3 PUFA led to increased neuronal and glial survival, and a significantly improved neurological outcome.

In subsequent studies, we tested DHA in a more severe compression model of SCI. We also explored a combined acute and chronic treatment regime using DHA.

Saline or DHA was administered intravenously 30 min after compression of the spinal cord. After injury, the saline group received a standard control diet, whereas DHA-injected animals received either a control or a DHA-enriched diet for 6 weeks following injury. We assessed locomotor recovery and analysed markers for cell survival and axonal damage, and we also investigated the effects of the treatment on the inflammatory reaction and the oxidative stress that follow SCI.

We showed that the acute DHA treatment is neuroprotective after compression SCI, even if the treatment is delayed up to an hour after injury.

The DHA injection led to an increased neuronal and glial cell survival, and the effect of the DHA injection was amplified by addition of DHA to the diet.

Rats treated with a DHA injection and a DHA-enriched diet performed significantly better at 6 weeks in terms of neurological outcome.

The analysis of the tissue after DHA administration showed that the fatty acid significantly reduced lipid peroxidation, protein oxidation and RNA/DNA oxidation, and the induction of COX-2.

Parallel studies in a facial nerve injury model in mice also showed pro-regenerative effects of chronic dietary administration of DHA after nerve lesion.

These observations suggest that treatment with omega-3 PUFA could represent a promising therapeutic approach in the management of neurological injury.

#### THIS AUTHOR ALSO NOTES:

“The beneficial effects of omega-3 polyunsaturated fatty acids (PUFA) have been documented in a variety of central nervous system disorders, including Zellweger's syndrome, schizophrenia, depression and Alzheimer's disease, which is both somewhat surprising, considering some of the fundamental differences between these conditions, but also promising, in particular in areas in which therapeutic options are limited.”

This research suggests that “omega-3 PUFA may have significant potential in acute neurological trauma, using as an example spinal cord injury (SCI).”

The pathogenesis of spinal cord injury “includes excitotoxicity associated with increased glutamate release, increased inflammation and oxidative stress.”

Secondary components of spinal cord injury include the formation of a glial scar, “which acts as a powerful barrier against axonal regrowth and reconnection.”

Studies show that the administration of an omega-3 fatty acids after spinal cord injury decreased neuronal loss and improved functional outcome.

Omega-3 fatty acids are also neuroprotective against excitotoxicity.

**[Excitotoxicity is the death of neurons caused by over excitation. Since the primary excitatory neurotransmitter in the central nervous system is the amino acid glutamate, excessive glutamate is considered the primary excitotoxin. The second most prevalent excitotoxin is aspartate (half of the aspartame artificial sweetener molecule). Both glutamate and aspartate use the N-methyl-d-aspartate (NMDA) receptor to excite central neurons.]**

“Omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid, have anti-inflammatory effects.”

“It had been shown that DHA can counteract glutamate-induced excitotoxicity.”  
**[Very Important]**

"As excitotoxicity, inflammation and oxidative stress are part of the pathogenetic mechanisms involved in the secondary injury associated with SCI, this led us to explore the potential of using omega-3 fatty acids as neuroprotective agents after SCI."

In this study, both the omega-3 fatty acids LNA or DHA induced significant neuroprotection: they reduced neuronal cell loss, oligodendrocyte loss, decreased the apoptosis, improved functional outcome including motor coordination, and protected the myelin after injury.

"In contrast, the omega-6 fatty acid arachidonic acid (AA) administered after injury, induced a totally opposite pattern of effects: it exacerbated injury, increased the size of the spinal cord lesion, decreased neuronal and glial cell survival and worsened the functional outcome." **[Very Important]**

DHA injected intravenously 30 min after trauma reduced significantly neuronal loss, and also led to an increased number of surviving oligodendrocytes, in various areas of the damaged cord.

Neurons average 80% survival after DHA treatment vs. 23% in controls.

"Our data showed that the fatty acid [DHA] decreases the oxidative stress associated with injury." **[Very Important]**

Oxidation was "significantly decreased by the administration of DHA after injury, either as the acute injection, or the acute injection combined with the enriched diet." **[Very Important]**

"All these observations, in two models of SCI, suggest that the acute administration of PUFA such as DHA at an early time after SCI, could confer significant neuroprotection."

"The time window is compatible with intervention by emergency services, and could become a first line of intervention in injured patients."

"Another dimension of the management of SCI is the chronic dimension, i.e. the treatment offered to patients during the recovery period. Our observations suggest that the maintenance of a high level of DHA intake is beneficial, and this is a measure, which could be easily implemented in a clinical setting."

Omega-3 fatty acids have beneficial effects in critically ill patients.

"Interestingly, a rather common practice is to infuse preparations enriched in soybean lipids, which therefore would contain an increased amount of omega-6 fatty acids. Our observations with arachidonic acid after spinal cord hemisection suggest that this practice could have detrimental consequences for the neurological outcome after SCI." **[Extremely Important]**

“In contrast, our results in animals maintained on a DHA-enriched diet, suggest that omega-3 PUFA could exert a positive influence on the recovery after injury.”

“The combination of an acute bolus of DHA with chronic maintenance of a preparation enriched in DHA, has a very promising therapeutic potential in the management of SCI and affects a multitude of pathogenetic mechanisms which are involved in trauma-induced damage.”

Omega-3 fatty acids have potential as a neuron pro-regenerative compound.

DHA can increase both maximum neurite length and the total number of neurites.

“The neurite-enhancing effects of DHA are apparent not only in tissue from an early postnatal stage, but also in tissue from adult or aged animals.”

Studies show that DHA has a neuroprotective potential in the treatment of peripheral nerve injury, and may also be important in the context of regeneration at the central level.

## CONCLUSIONS

Omega-3 PUFAs have a significant neuroprotective effect and a pro-regenerative potential.

With omega-3 supplementation, the “increased oxidation and inflammation associated with central injury are markedly decreased,” which confirms their anti-inflammatory and anti-oxidant potential.

DHA omega-3 fatty acid has a multitude of targets, ranging from ion channels to nuclear receptors.

DHA can “block depolarisation-induced increased glutamate efflux and the activation of glutamate receptors leading to excitotoxicity, partly through inhibition of voltage-sensitive Na<sup>+</sup> and Ca<sup>2+</sup> channels.”

DHA also modulates the expression of genes involved in neuroprotection.

“Chronic exposure to DHA also affects the composition of membranes, and in particular leads to an increased accumulation of phosphatidylserine in membranes, which has profound consequences for cell survival mechanisms.”

DHA omega-3 fatty acids give rise to the docosanoid neuroprotectin D1, which “may be a key mediator of the antioxidant and anti-inflammatory effect of DHA.”

“In the case of spinal cord injury, it is possible that the combination of an acute administration of DHA immediately after injury, and a chronic high intake of DHA has a significant therapeutic potential because of the harnessing of these various targets and mechanisms, which are synergistic and beneficial.”

**[Very Important]**

“The evidence of neuroprotection both at spinal cord level and at supraspinal level and after treatment with omega-3 PUFA holds great promise in the field of neurological trauma.” **[Very Important]**

KEY POINTS FROM DAN MURPHY

**[Excitotoxicity is the death of neurons caused by over excitation. Since the primary excitatory neurotransmitter in the central nervous system is the amino acid glutamate, excessive glutamate is considered the primary excitotoxin. The second most prevalent excitotoxin is aspartate (half of the aspartame artificial sweetener molecule). Both glutamate and aspartate use the N-methyl-d-aspartate (NMDA) receptor to excite central neurons.]**

- 1) Omega-3 polyunsaturated fatty acids have therapeutic potential in several indications in neurology and psychiatry.
- 2) The pathogenesis of spinal cord injury “includes excitotoxicity associated with increased glutamate release, increased inflammation and oxidative stress.”
- 3) This study shows that omega-3s have significant neuroprotective potential in spinal cord trauma.
- 4) Treatment with omega-3 PUFA could represent a promising therapeutic approach in the management of neurological injury.
- 5) “The beneficial effects of omega-3 polyunsaturated fatty acids have been documented in a variety of central nervous system disorders, including Zellweger's syndrome, schizophrenia, depression and Alzheimer's disease.”
- 6) The administration of omega-3 fatty acids after spinal cord injury decreased neuronal loss and improved functional outcome.
- 7) Omega-3 fatty acids are neuroprotective against excitotoxicity. DHA can block glutamate neurotoxicity. **[Very Important]**
- 8) “Omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid, have anti-inflammatory effects.”
- 9) Excitotoxicity, inflammation and oxidative stress are part of the pathogenetic mechanisms following spinal cord injury, and therefore omega-3 fatty acids act as neuroprotective agents.

- 10) The omega-6 fatty acid, arachidonic acid, administered after injury, exacerbated injury, increased the size of the spinal cord lesion, decreased neuronal and glial cell survival and worsened the functional outcome. **[Very Important]**
- 11) "Our data showed that the fatty acid [DHA] decreases the oxidative stress associated with [spinal cord] injury." **[Very Important]**
- 12) Oxidation is significantly decreased by the administration of DHA after injury.
- 13) The acute administration of DHA after spinal cord injury offers significant neuroprotection.
- 14) "Another dimension of the management of SCI is the chronic dimension, i.e. the treatment offered to patients during the recovery period. Our observations suggest that the maintenance of a high level of DHA intake is beneficial, and this is a measure, which could be easily implemented in a clinical setting."
- 15) Omega-3 fatty acids are beneficial in critically ill patients.
- 16) "A rather common practice is to infuse preparations enriched in soybean lipids, which therefore would contain an increased amount of omega-6 fatty acids. Our observations with AA after spinal cord hemisection suggest that this practice could have detrimental consequences for the neurological outcome after SCI." **[Important]**
- 17) Omega-3 fatty acids have potential as a neuron pro-regenerative compound.
- 18) DHA has a neuroprotective potential in the treatment of peripheral nerve injury, and may also be important in the context of regeneration at central level.
- 19) Omega-3 PUFAs have a significant neuroprotective effect and a pro-regenerative potential.
- 20) With omega-3 supplementation, the "increased oxidation and inflammation associated with central injury are markedly decreased," which confirms their anti-inflammatory and anti-oxidant potential.
- 21) "Chronic exposure to DHA also affects the composition of membranes, and in particular leads to an increased accumulation of phosphatidylserine in membranes, which has profound consequences for cell survival mechanisms."
- 22) "In the case of spinal cord injury, it is possible that the combination of an acute administration of DHA immediately after injury, and a chronic high intake of DHA has a significant therapeutic potential." **[Very Important]**
- 23) "The evidence of neuroprotection both at spinal cord level and at supraspinal level and after treatment with omega-3 PUFA holds great promise in the field of neurological trauma." **[Very Important]**