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PATHOPHYSIOLOGY OF SPINAL CORD INJURY AND EFFECT OF POLYUNSATURATED FATTY ACIDS

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ABSTRACT:
The purpose of this paper is to review the current literature regarding the pathophysiology of spinal cord injury and effects of polyunsaturated fatty acids in that injury. Different types of polyunsaturated fatty acids affect differently in spinal cord injury. ω-3 fatty acids decrease the injury and improve the functional outcome. In contrast ω-6 fatty acids aggravate the injury and worsen the outcome. Although research regarding spinal cord injury remains limited, pathophysiology of spinal cord injury and effects of ω-3 and ω-6 fatty acids including mechanism of action through which they produce these effects in that injury were reviewed in this paper with available current literature. Most of the studies regarding spinal cord injury were done in animals. So, further studies should be conducted to know and prove these effects of the polyunsaturated fatty acids in spinal cord injury in human trials in future.

INTRODUCTION

The Spinal Cord (SC) is part of the central nervous system (CNS) and extends from the brain passing through vertebral column from foramen magnum to the space between first and second lumbar vertebrae. It has motor and sensory functions, neural circuits and can coordinate certain reflexes. Spinal Cord Injury (SCI) is damage to the spinal cord that results in a loss of function (motor or sensory). Functional impairment (disability) like weakness, loss of sensation and devastating psychological problems can be produced by SCI. There is no treatment for SCI at present (Beattie et al 2002b).

Pathophysiology of Spinal Cord Injury

Events that occur during SCI have been studied in experimental animal models (Beattie et al., 2002b). Common models used in SCI research are contusion injury (Tator, 1995; Young, 2002), concussion (Wrathall JR et al., 1985), compression of the cord (Rivlin AS et al., 1977) and spinal cord ischemia (Watson BD et al., 1986). Contusion injury model is most commonly studied. One disadvantage of these experimental models is they are not reproducible (Khan M et al., 1983). Pathological sequences that occur during SCI are divided in to two phases,

1. Primary injury
2. Secondary injury (Tator and Fehlings, 1991)

Primary Injury

Primary Injury occurs immediately at the site of impact called epicenter. Mechanical forces at the site of impact produce neuronal cell rupture and a hemorrhagic zone of necrosis (due to rupture of endothelial cell membranes). No gross damage is visible at site of lesion immediately after injury except hemorrhage of gray matter in SC. Direct cell death occurs at the site of injury. Hemorrhage mainly localizes to gray matter as it is highly vascular and soft in consistency (Tator, 1995). Tissue disruption due to primary injury is proportional to amount of force transferred to the spinal cord during impact (Blight AR et al., 1986).

Secondary Injury

Primary injury instigates a series of biochemical, vascular and inflammatory events that cause secondary injury which further exacerbates neuronal damage in SCI. Inflammatory events can continue up to 4 days post trauma (Natasha Olby, 1999). Secondary injury is an auto destructive process mediated by a variety of active lipid metabolites and reactive oxygen species produced in response to tissue injury (Faden 1983). Within a few hours (2-8h) after injury, gray matter hemorrhage expands, numerous petechial hemorrhages and edema occurs in the white matter (Guth et al., 1999). Grossly, hemorrhage with cellular debris is visible up to 1 week at the site of injury. Later small cavities and finally cystic regions surrounded by glial scar tissue appear at site of injury (Beattie et al., 2002b). In chronic cases, atrophy of the cord occurs.

Figure below shows the gross events that occur during SCI.

Secondary Injury is mediated by:

1. Damage caused by free radicals and vascular abnormalities
2. Biochemical events
3. Apoptosis and necrosis

1. Damage caused by vascular abnormalities and lipid peroxidation: After acute injury, local and systemic vascular abnormalities which develop over several hours cause ischemia and necrosis of the injured section of the spinal cord (Janssen LAA, 1991; Coughlan AR 1993). Grey matter neurons are more vulnerable to ischemic injury than white matter neurons due to their high metabolic requirements (Senter HJ et al., 1979).

Surprisingly after a period of hypoperfusion, blood supply to spinal

cord drastically increases for some time which leads to exacerbation of secondary injury due to production of oxygen free radicals (Lukacova et al., 1996).

2. Biochemical events:

Biochemical events that cause secondary SCI involve activation of an excitatotoxic cascade, cellular inflammatory response and uncontrolled glutamate release. Activation of excitatotoxic cascade leads to activation of Phospholipase-A2 (PLA-2) (Fleming et al., 2006). Immediately after SCI PLA-2 activity was increased and remained elevated even up to 7 days postinjury (Lin NK et al., 2006). The mechanism by which the PLA-2 activity increases is unclear. It may be due to intracellular calcium influx subsequent to injury, which activates PLA-2 causing hydrolysis of membrane phospholipids to produce arachidonic acid (AA) (Stokes et al., 1983; Young et al., 1986).

3. Cell death

Ischemia, lipid peroxidation by oxygen free radicals (reactive oxygen species) and glutamate excitotoxicity cause cell death through different mechanisms such as necrosis or apoptosis after SCI in human beings (Emery et al., 1998). Cells at the site of impact (epicenter) undergo necrosis due to severe trauma.

Effect of Polyunsaturated Fatty Acids (PUFA) in SCI

Polyunsaturated fatty acids are lipids that contain more than one double bond in their structure. PUFAs are structural components of phospholipids, which are the main constituents of cell membranes. There are different types of PUFAs like omega (ω)-3 PUFA, omega-6 PUFA and omega-9 PUFAs. ω-3 PUFAs include the essential fatty acids alpha-linolenic acid (ALA). ω-3 PUFAs also include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alpha-linolenic acid is the biosynthetic precursor of DHA and EPA. The ω-6 PUFA studied primarily is Arachidonic acid (AA). Oleic acid is a ω-9 PUFA. This paper will review the effects of ω-3 PUFAs and AA in SCI.

Effect of ω-3 PUFAs in SCI:

ω-3 PUFAs have a neuroprotective effect (Laurite et al., 2000; Blondeau et al., 2002). ALA, DHA and EPA (ω-3 PUFAs) have anti-inflammatory and neuroprotective effects (Mori et al., 2004). Most of these effects were studied using DHA. ALA is biosynthetic precursor of DHA, EPA. ALA or DHA treatment 30 min after hemisection of spinal cord resulted in decreased lesion size, increased neuronal and oligodendrocyte survival and improved locomotor function. Neuroprotective effects of ALA may be mediated, at least in part, by different mechanisms other than converting to DHA (Demar et al., 2005). ALA has affinity for potassium channels (such as TREK and TRAAK) and activates those channels (Lauritzen et al., 2000).

Beneficial effects of eicosapentaenoic acid (EPA)

Eicosapentaenoic acid (EPA) is a biosynthetic precursor of DHA and has anti-inflammatory and neuroprotective properties in animal models of neuroinflammation (Taepavarapruk et al., 2010). Administration of EPA intravenously 30 min after compression injury of spinal cord in rats resulted in decreased axonal injury; improved neuronal outcome and reduced extent of secondary SCI. Bolus i.v administration of 250 nmol/kg DHA have produced similar effects in rat SCI (Siew-Na Lim et al., 2010). Neuroprotective effects of DHA and EPA are mediated partly by their metabolites.

CONCLUSION

Pathophysiology of SCI involves mainly primary and secondary injury. Primary injury is irreversible and is due to traumatic insult or shear forces which leads to tissue disruption, vascular abnormalities and necrotic cell death. Secondary injury is mediated through excitotoxicity of glutamate, lipid peroxidation and damage caused by free radicals and inflammatory mediators like eicosanoids. All these finally cause apoptotic cell death. Secondary injury can be reduced by ω-3 PUFA supplementation both in the form of bolus and chronic maintenance of a preparation enriched in ω-3 fatty acids. Duration and the dose of supplementation have to be investigated in future. Beneficial effects in the management of SCI by reducing inflammation, lipid peroxidation and oxidative stress have been observed using ω-3 fatty acids (ALA, DHA and EPA). ω -3 PUFAs have significant neuroprotective effect and a pro-regenerative potential. Eggs, fish, oils and algae contain high quantities of DHA. Maternal diets rich in fish are associated with reduced risk for CP in offspring (Petridou et al., 1998).

REFERENCES

1. Bunge RP, Pucket WR, Becena JL, Mareillo A, Quencer RM, observations on the pathology of human spinal cord injury. Adv Neurol 1993; 59:75-89.
2. Kakulas BA, The applied neuropathology of human spinal cord injury. Spinal Cord 1999; 37 (2): 79-88.
3. Blight AR. Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line sampling. Neuroscience 1983; 10(2):521-43.
4. Eidelberg E, Strahley D, Erspamer R, Watkins CJ. Relationship between residual hind limb-assisted locomotion and surviving axons after incomplete spinal cord injuries. Exp neurol 1977; 56(2): 312-22.
5. Fehlings MG, Tator CH. Relationships among the severity of spinal cord injury, residual function axon counts and counts of retrogradely labeled neurons after experimental spinal cord injury. Exp Neuol 1995; 132(2):220-28
6. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal trauma with emphasis on vascular mechanisms. J Neurosurg 1991; 75(1): 15-26)
7. Sentor HJ, Venes JL. Loss of autoregulation and post traumatic ischemia following experimental spinal cord trauma. J Neurosurg 1979; 50(2): 198-206.
8. Lukacova N, Halat G, Chavko M, Marsala J. Ischemia- reperfusion injury in spinal cord of rabbits strongly enhances lipid peroxidation and modifies phospholipid profiles. Neurochem Res 1996; 21(8):869-73.
9. Hall E, Free radicals in central nervous system injury. In: Rice –Evans CA, Burdon R, editors. Free radical damage and its control. New York: Elsvier Science, 1994:217-38.
10. Cuzzocera S, Riley DP, Caputi AP, Salvemini D. Antioxidant therapy: a new pharmacological approach in shock, inflammation and ischemia-reperfusion injury. Pharmacol rev 2001; 53(1):135-59.
11. Sakamoto A, Ohnishi ST, Ohnishi T, Ogawa R. Relation between free radical production and lipid peroxidation during ischemia-reperfusion injury in the rat brain. Brain Res 1991;
12. Kurihara M. Role of monoamines in experimental spinal cord injury in rats. Relationship between Na+K+ATPase and lipid peroxidation. J Neurosurg 1985; 62(5):743-9.
13. Wrathall JR, Teng YD, Choiniere D. Amelioration of functional deficits from spinal cord trauma with systematically administered NBQX, an antagonist of non-N-Methyl d-aspartate receptors. EXP Neurology 1996; 137(1):119-26.
14. Emery E, Aldana P, Bunge MB, et al Apoptosis after traumatic spinal cord injury. J Neurosurg 1998; 89(6):911-20.
15. Casha S, Yu WR, Fehlings MG. Oligodendroglial apoptosis occurs along degenerating axons and is associated with FAS and p75 expression following spinal cord injury.
16. Popovich PG, Wei P, stokes BT. Cellular inflammatory response after spinal cord injury in Sprague Dawley and Lewis rats. J Comp Neurol 1997; 377 (3): 443-64.
17. Tonai T, Taketani Y, Ueda N et al. Possible involvement of interleukin-1 in cyclooxygenase-2 induction after spinal cord injury in rats. J Neurochem 1999; 72(1):302-9
18. Li GL, Bordin G, Farooque M et al: apoptosis and expression of Bcl-2 after compression trauma to rat spinal cord. J. Neuropathol. Exp. Neurol. 55, 280-289 (1996).
19. Baptiste DC, Fehlings MG: Pharmacological approaches to repair the injured spinal cord. J Neurotrauma 23, 318-334 (2006)
20. Fleming JC, Norenberg AD, Ramsay DA et al: The cellular inflammatory response in human spinal cords after injury. Brain 129, 3249-3269 (2006). Detailed account of the types of inflammatory cells found in human spinal cord after various types of spinal cord injury.
21. Gris D, Hamilton EF, Weaver LC: the systemic inflammatory response after spinal cord injury damages lung and kidneys Exp. Neurol. 211, 259-270 (2008).
22. Blesch A, Tuszynski M: spinal cord injury: plasticity, regeneration and the challenge of translational drug development. Trends Neurosci.3291), 41-47(2009).
23. Sahuquillo J., Pocca MA., Amoros S: current aspects of pathophysiology and cell dysfunction after severe head injury. Curr. Pharm. Design 7, 1475-1503 (2001).
24. Katsuki, H., Okuda, S., 1995 Arachidonic acid as a neurotoxin and neurotrophic substance. Prog. Neurobiol. 46, 607-636.
25. Wrathall JR, Pettegrew RK, Harvey F. Spinal cord contusion in the rat: Production of graded reproducible, injury groups. Exp neurol 1985; 88:108-122.