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Oxidative stress and antioxidant therapy in traumatic spinal cord injuries

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Abstract

Spinal cord injury (SCI) is often accompanied by motor, vegetative and sensitive dysfunctions that can significantly decrease the chance of the complete recovery of the patients. The pathophysiological implication of these dysfunctions is represented by the increased production of the reactive species that are extremely aggressive to the surrounding tissue. The combination of massive production of free radicals, low concentration of antioxidants and the hypermetabolism present in patients with SCI leads to enhancement of the oxidative stress.

Current studies are focused on several biological active compounds that are able to reduce the effects of free radicals – tissue necrosis, inflammation, infection, apoptosis. In this paper, the mechanism of the action of several biological active compounds that are able to significantly reduce oxidative stress in critical patients with spinal cord injury is presented.

Keywords: oxidative stress, spinal cord injury, antioxidants, free radicals, critically ill patient

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Introduction

Spinal cord injury (SCI) represents an aggression to the spinal cord resulting in a change, either temporary or permanent, of the cord's normal motor, sensory, or autonomic function. Patients with spinal cord injury usually have permanent and often devastating neurologic deficits and disability [1]. The early management of a patient with an acute spinal cord injury is one of the most difficult tasks in trauma cases and the outcome depends upon the accuracy, adequacy, and speed of first aid management, diagnosis, and treatment within the first few hours.

Secondary lesions in severe spinal cord injuries are mainly due to the inflammatory cascade activation and overproduction of free radicals [2]. A complex cascade of pathophysiologic events related to free radicals, vasogenic edema, and altered blood flow accounts for clinical deterioration and poor overall outcome [3-5].

Although the etiology and pathogenesis of spinal cord injury remain to be fully understood, it has been suggested that reactive oxygen species and oxidative stress have a significant role in the pathophysiology of spinal cord injury. Hypermetabolism, physiological and metabolic imbalances, multiple organ dysfunction or generalized infection and inflammation lead to the increased synthesis of reactive species. Subsequently an aggressive oxidative stress follows which, combined with spinal cord injury, reduces the chance of survival considerably.

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Biochemical and physiological aspects of oxidative stress in spinal cord injury

Reactive species significantly aggravate the clinical status of patients with SCI. These are represented by superoxide anion, hydrogen peroxide, hydroxyl radical, peroxynitrite, nitric oxide, lipid peroxyl and lipid alkoxyl

radicals (Table 1) [6-9]. The most important modulator of oxidative stress is tripeptide glutathione (Glu-Cys-Gly) [10].

The pathophysiological consequence of oxidative stress is due to the interaction of the reactive species with lipids, proteins, DNA and other vital macromolecules (Figure 1).

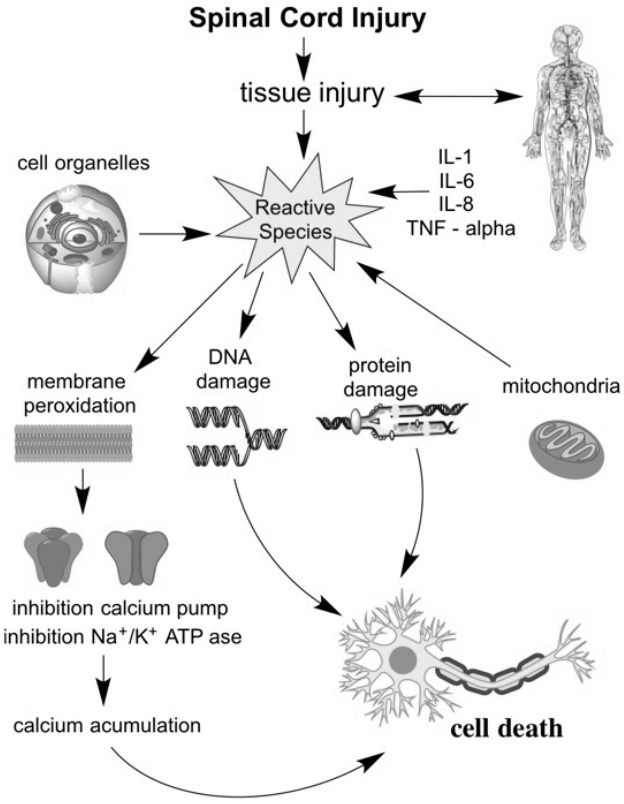

Fig. 1. Oxidative stress action in spinal cord injury

Reactive species have the ability to alter cell functions by blocking ion channels - calcium pump and Na^+ / K^+ ATPase [11], followed by an excessive accumulation of intracellular calcium ions and apoptosis [6, 12]. Neutrophils produce extremely potent modulators of inflammation. Proteases, elastases, pro inflammatory cytokines or myeloperoxidases are just some of the factors responsible for severe tissue inflammation [13, 14].

An increasing number of studies have concluded that mitochondria is responsible for the accelerated production of a significant number of reactive species, probably due to alterations in redox potential. The impaired electron transport chain leads to mitochondrial dysfunction, which furthermore blocks specific ion channels and inhibits specialized components in electron transport. Thus, highly reactive free radicals are produced. The most important step responsible for producing major quantities of superoxide radicals is represented by the transfer of electrons between channels I and III [8, 15-18] (Figure 2).

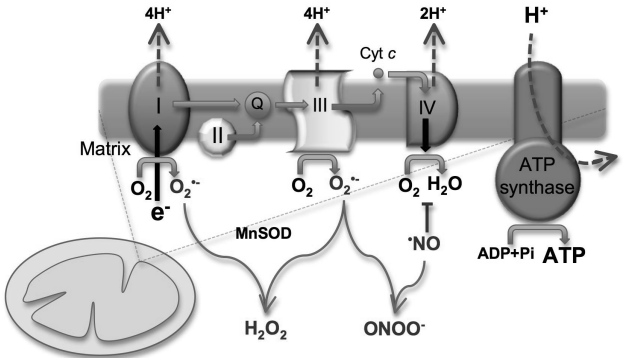

Fig. 2. Biochemical pathway for the production of free radicals in the respiratory chain ([16] with Elsevier Agreement)

Table 1. The characteristics of the free radicals

Reactive species	Chemical structure	Synthesis / pathways
Hydroxyl Radical	HO	Fentan reaction The transformation of hydrogen peroxide by the action of iron ions Mitochondrial damage – leakage of electrons
Superoxide Anion	O_2^-	Xanthine activity Mitochondrial dysfunction Endoplasmic reticulum dysfunction Activation of lipoxygenase Activation of cyclooxygenase
Oxide Anion	O^{2-}	Mitochondrial dysfunction Respiratory chain Denaturation of myoglobin, haemoglobin and cytochrome
Hydrogen Peroxide	H_2O_2	Biochemical reactions catalyzed by superoxide dismutase
Nitric Oxide	NO	Biological and biochemical activity of endothelial cells Inhibition of cell surface receptors
Peroxynitrite	ONOO	The reaction between nitric oxide and superoxide anion
Lipid Peroxyl	LOO	The action of iron ions on lipid hydroperoxide The action of superoxide anion on cell membranes
Lipid Alkoxyl	LO	The action of iron ion on lipid peroxyl

The imbalanced ratio of oxidant compounds and antioxidants leads to a severe tissue aggression, with severe consequences. Tissue destruction is produced by cell membrane injury, edema, axonal destructions, inflammation, hyperbiosynthesis of highly reactive free radicals, accumulation of calcium in cells, injury caused by ischemia – reperfusion, endothelial injury or poor vascularization caused by blood vessel damage and hypothension. It has been demonstrated that the level of reactive species increases sharply in about an hour after the spinal cord injury [6].

Reperfusion of ischemic tissue is often associated with microvascular dysfunction, enhanced fluid filtration and leukocyte plugging in capillaries. Activated endothelial cells in all segments of the microcirculation produce more oxygen radicals, but less nitric oxide, in the initial period following reperfusion. The resulting imbalance between superoxide and nitric oxide in endothelial cells leads to the production and release of inflammatory mediators and enhances the biosynthesis of adhesion molecules that mediate leukocyte-endothelial cell adhesion [19-23]. Moreover, reactive species induce mitochondrial dysfunctions [21], activate neuronal cell cyclooxygenase [24] and produce electrolyte imbalances at the cellular level [25].

Only cerebral endothelial cells are able to fight oxidative stress at a higher capacity than other tissues due to their higher concentrations of antioxidant enzymes [26-29].

A series of methods for monitoring and assessing the level of oxidative stress in the body have been proposed. Biochemical markers identified in this regard are: glutathione-S-transferase (GST), glutathione-peroxidase (GPx), glutathione level (GSH), catalase (CAT), superoxide dismutase-(SOD), malonildialdehyde (MDA) and total reactive antioxidant potential [30-32].

In addition, other conditions in the Intensive Care Unit (ICU) also increase the level of oxidative stress [33, 34]. Petronilho et al. have shown that sepsis is an extremely important factor in emphasizing side effects of oxidative stress [35]. Traumatic injuries resulting with complex surgery, general anaesthesia or long term / excessively administration of certain drugs in intensive therapy also produce high quantities of free radicals [9, 36, 37].

Methods of reducing oxidative stress

At the moment there are a lot of alternative treatments investigated in this respect - stem cell therapy, regulation of inflammatory response, Swann cell transplantation or administration of biologically active compounds that seem to be able to reduce oxidative stress [38, 39].

Antioxidants are reducing agents, participating in the redox reactions. Thus, they have the ability to protect cells from lesions induced by free radicals. Glutathione peroxidase, catalase, thioredoxin reductase and superoxide dismutase [40] represent endogenous antioxidants which in case of severe trauma are outnumbered by free radicals [41-43].

There are many studies that recommend administration of *methylprednisolone* in spine injuries [44]. Laboratory studies indicate that methylprednisolone inhibits lipid peroxidation chain reactions by blocking the production of lipid peroxyl radicals, the antioxidant action of methylprednisolone being enhanced by the inhibition of nuclear factor kappa B (NFκB) [45, 46].

Kamence et al. [44] demonstrated that administration of cysteine prodrug *L-2-4-carboxylate oxothiozolidine* has remarkable effects in reducing the level of free radicals in patients with spinal cord injury.

Vitamin E (α-tocopherol), a lipid-soluble antioxidant is also important for neural tissue integrity. Increased plasma concentrations of α-tocopherol leads to suppression of prostaglandin E2 production, which is responsible for severe inflammation. Morsy et al. showed that administration of 600 mg α-tocopherol, twice a week for 6 weeks, to laboratory mice with spinal cord injury significantly reduced plasma levels of free radicals [23].

Biochemically, *guanosine* is a nucleotide and is composed of a guanine attached to a ribose [47]. Recent studies suggest that guanosine is responsible for stopping the action of oxidative stress and stimulating cell proliferation. Moreover, it participates in the biosynthesis of a number of factors with neuroprotective effect – neuron growth factor, fibroblast growth factor and transforming growth factor. Jiang et al. confirmed the beneficial action of guanosine, reporting that administration of this compound stimulates oligodendrocytes, which significantly contributes to remyelination [48]. Dal-Cim et al. and also Pesch et al. confirmed the beneficial effects of guanosine [49, 50] reporting a significant decrease in oxidative stress induced by inflammation, destruction of mitochondria or endoplasmic reticulum [51].

Another compound used in order to reduce oxidative stress is *montelukast*. Biochemically and pharmacologically, this active compound is an antagonist of cysteinyl leukotriene receptors (CysLT) [52]. Currently in clinical practice it is used for its anti-inflammatory and bronchodilator effects. Cavus et al. demonstrated that the administration of montelukast in severe spinal cord injury significantly decreased the level of tissue injury produced by free radicals. Histopathological and biochemical studies have shown that tissues presented less inflammation markers and the pro-inflammatory mediators were found in lower concentrations as

compared to the control groups when montelukast was administered [53]. Gokhan et al. also pointed out that the administration of montelukast significantly reduced the injuries produced by free radicals, tissue inflammation and ischemia-reperfusion on spinal cord injury in rats [54].

Other important antioxidant compounds are *selegiline* ((R) N-methyl-N-(1-phenylpropan-2yl) prop-1-yn-3-amine) [55] and *edavarone* (2-methyl 1-phenyl-2-one pyrazolin) [56]. Both compounds have significant neuroprotective effects by stimulating the activity of antioxidant enzymes – superoxide dismutase and catalase.

Chronidou et al. studied the effect of *amifostine* (S-2.3 aminopropylaminoethylphosphorothioic acid) on oxidative stress and production of free radicals [40]. The compound has remarkable protective effects on neuronal cells. Amifostine is used in clinical practice to reduce the oxidative effects produced by aggressive treatments such as chemotherapy or radiotherapy. Experimental studies have shown its neuroprotective effects in laboratory mice with spinal cord injury [40].

Docosahexaenoic acid, together with α-linolenic acid and eicosapentaenoic acid, is part of the physiological composition of cell membranes, constituting the structural composition of phospholipids. It has been reported that exogenous administration of *docosahexaenoic acid* increases axonal and neuronal regeneration capacity after spinal cord injury. Paterniti et al. have demonstrated its ability to modulate pro-inflammatory response and to decrease the oxidative stress in laboratory animals [57].

An important factor in regulating physiological neuronal tissue response is the *nerve growth factor* with remarkable antioxidant effects. Its mechanisms of action are based on the activation of specific receptors involved mainly in intracellular kinases pathways. Zhang et al. measured and quantified these effects on spinal cord, in rats, by the administration of exogenous nerve growth factor and showed that recovery from acute spinal cord injury was improved. They also observed an increased level of neural cells that have survived the trauma [58].

Tetramethylpyrazine is extracted from Chinese plants and possesses antioxidant properties. It blocks the accumulation of intracellular calcium and reduces the oxidative capacity of reactive species. Chen et al. showed that when administered intravenously tetramehylpyrazine alters oxidative stress [59]. Fan et al. also demonstrated the antioxidant effects of this compound in rabbits with SCI [60].

Numerous studies have shown that *N-acetylcysteine* has protective effects against free radicals [61] by increasing the production of glutathione peroxidase [62].

Biomacromolecules complexes that contain metal ions are also studied for their remarkable antioxidant properties [28]. M*etalloporphyrin*, a biologically active compound containing the manganese (III) ion, is able to block the transformation of superoxide anion to hydrogen peroxide and further to water. Liu et al. studied such a compound - Mn (III) -tetrakis- (4-benzoic acid) -porphyrin (MnTBAP), confirming its inhibitory effect on oxidative stress, in laboratory rats with spinal cord injury [18].

The extract from milk thistle Silybum Marianum, a European plant, *silybin* (CA No. 22888-79-6), is known for its anti-inflammatory effects [63]. Silybin has been used for a long time in liver disease management. Recent studies demonstrated its antioxidant activity in neuronal tissue damages from spinal cord injuries [64] while Perumal Vijayaraman et al. confirmed its beneficial effect in laboratory mice with spinal cord injury [65]. Cho et al. showed that it inhibited the oxidation of fatty acids and that it has anti-apoptotic and anti-inflammatory effects [66]. Kumar et al. studied the effects of liposomal silymarin and concluded that this form has several advantages in fighting oxidative stress. Controlled release of the compound and the bioavailability provided by the liposomal matrix greatly increased the neuroprotective effects of the compound [63].

α-lipoic acid is known as a powerful antioxidant by blocking the activity of free radicals and studies conducted by Emmez et al. revealed its neuroprotective effects [67]. This drug also proved to be beneficial in multiple sclerosis, ischemia-reperfusion injury and peripheral nerve injury [68].

Administration of *β-glucan* significantly reduces oxidative aggression of free radicals and secondary lesions in SCI. Kayali et al. have demonstrated in a study on laboratory mice with spinal cord injury that its administration (250 mg/kg for 5 days) significantly decreased the level of biochemical markers specific for oxidative stress [69]. The action was confirmed by the measurement of plasma levels of malonyldialdehyde, superoxide dismutase and gluthatione peroxidase which were found significantly lower when tested in laboratory mice with spinal cord injury.

Salvianolic acid B as a biological active antioxidant extracted from Radix Salviae Miltiorrhizae showed its neuroprotective effects and confirmed the antioxidant and anti-inflammatory activity upon tissue affected by spinal cord injury [70].

Conclusion

Polytrauma often leads to damage of the spine and medulla and the repercussions arising from these lesions are devastating for patients in a critical condition. Cell physiological imbalances lead to accele-

rated biosynthesis of highly reactive chemical species. Current research pays more attention to this phenomenon, due to the complex pathophysiology involved. Critically ill patients with spinal cord injury are more prone to oxidative stress due to the multitude of the biological dysfunctions. There are many biologically active substances with antioxidant properties that have been studied in experimental models and have proved to be able to reduce oxidative stress, but further clinical trials are required. In conclusion, inhibition of oxidative aggression can significantly reduce the occurrence of inflammation, infection, apoptosis and thus severe organ dysfunction. Therefore, supplementation therapy with strong antioxidants may improve the outcome of these patients. Monitoring specific biomarkers for oxidative stress can guide antioxidant supplementation in patients with spinal cord injury.

Conflict of interest

Nothing to declare

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Stresul oxidativ şi terapia antioxidantă în leziunile medulare traumatice

Rezumat

Leziunile măduvei spinării sunt adesea acompaniate de disfuncţii motorii, vegetative şi senzitive care conduc la scăderea semnificativă a şanselor de recuperare a pacienţilor cu traume severe. Implicaţiile fiziopatologice sunt reprezentate de biosinteza speciilor reactive cu efect extrem de agresiv asupra ţesutului din jur. Coroborarea producţiei masive de radicali liberi cu scăderea concentraţiei de antioxidanţi şi hipermetabolismul prezent la pacienţii critici conduce la instalarea stresului oxidativ.

Cercetarea actuală se concentrează asupra acţiunii unei serii de compuşi biologic activi capabili să reducă efectele radicalilor liberi asupra necrozei tisulare, inflamaţiilor sau apoptozei celulare. În această lucrare de actualizare este prezentat mecanismul de acţiune a compuşilor biologic activi capabili să reducă semnificativ stresul oxidativ la pacienţii critici cu leziuni medulare.

Cuvinte cheie: stres oxidativ, leziuni spinale, antioxidanţi, radicali liberi, pacient critic