JCEI /
Journal of Clinical and Experimental Investigations
2014; 5 (1): 131-136
doi: 10.5799/ahinjs.01.2014.01.0378

REVIEW ARTICLE / DERLEME

Pathophysiology of the spinal cord injury

Omurilik yaralanmaların patofizyolojisi

Tevfik Yılmaz[1], Yahya Turan[1], Ayşenur Keleş[2]

ABSTRACT

Spinal cord injury (SCI) causes significant morbidity and mortality leading to serious social problems. Although many studies conducted on it, any universal treatment protocol has not been accepted to date. Studies about treatment of SCI focused on two mechanisms. First is usage of neuroprotective agents and second are regeneration studies to improve axonal functions of injured spinal cord. Pathophysiological changes occurring after SCI has to be well understood in order to develop ideal treatment.
J Clin Exp Invest 2014; 5 (1): 131-136

Ker words: Spinal cord injury, pathophysiology

ÖZET

Omurilik yaralanması toplumsal düzeyde problemlere yol açan morbidite ve mortalitenin önemli nedenlerindendir. Günümüze kadar pek çok çalışma yapılmasına rağmen evresel tedavi protokolü geliştirilememiştir. Omurilik yaralanmalarının tedavisinde çalışmalar iki mekanizma üzerine yoğunlaşmıştır. Birincisi hasar görmüş omuriliği koruyucu nöroprotektif ajanların kullanılması diğeri hasarlanmış omurilikte aksonların fonksiyonlarını kazanabilecekleri rejenerasyon çalışmalarıdır. Etkin tedavinin bulunabilmesi için omurilik yaralanması sonrası patofizyolojik değişiklikler iyi bilinmelidir.

Anahtar kelimeler: Omurilik yaralanması, patofizyoloji

INTRODUCTION

The spinal cord injury (SCI) is characterized by the loss or degradation of motor, sensory and autonomic functions as a result of the wholly or partly damage in the spinal cord for reasons such as trauma. This injury is a very important public health problem which necessitates a life-long treatment and care costs besides labor and loss of income and which negatively affect patients, their family and the country's economy with social and psychological problems [1,2]. More than half of the survivors from injury cannot return back to normal life [3]. On the other hand, the fact that the vast majority of spinal cord injuries are seen in healthy young adults who are between the ages of 15-25 is a serious social problem. Intensive efforts spent for treatment so far, although it contributes to the modern approach positively, a treatment protocol which is an effective and permanent as well as a universal one has not been developed yet [4-6]. That the adult central nervous system after injury is not regenerated is a major problem. For many years, many researchers have tried to find different methods on the pathophysiological mechanisms of acute SCI in order to improve neurological function [7]. Experimental studies on this subject showed that SCI that occurs after injury could worsen further after the trauma. Modern pharmacological treatment protocols being developed aims to reduce neuronal damage and aims to minimize the neurologic sequelae.

Epidemiology

The incidence of spinal cord injury in epidemiological studies in the United States has been reported to be 30 to 50 cases per year in a million, its prevalence has been reported to be 12,000 new cases per year [8]. The most common causes of SCI include motor vehicle accidents, sports and leisure injuries, work-related accidents, injuries from being beaten and falls at home [1]. These are more common in men especially in adults and in young adults. The causes of SCI vary by geographic regions.

A complete SCI occurred in 45% of the clinical picture after spinal cord trauma. 63% of spinal trau-

[1] *Dicle Universty Faculty of Medicine, Department of Neourosurgery, Diyarbakır, Turkey*
[2] *Dicle Universty Faculty of Medicine, Department of Pathology, Diyarbakır, Turkey*

Correspondence: Tevfik Yılmaz,
Department of Neurosurgery, Faculty of Medicine, Dicle University, Diyarbakır, TURKEY Email: kartaltevfik@hotmail.com

Received: 27.08.2013, Accepted: 01.12.2013

ma is cervical, 16% of it is thoracic and 20% of it is at the level of thoracolumbar vertebrates. While high cervical trauma caused tetraplegia, the traumas far below cause paraplegia. Tetraplegia and paraplegia are present at almost half of traumas [5.9-11].

In a study conducted in Turkey in 1992, the incidence of traumatic SCI has been reported to be 12.7 new cases in a million and totally 581 spinal cord injuries have been reported. Among these, the most common causes of spinal cord injuries are the motor vehicle accidents (48.8%), falls (36.5%), cutting injuries (3.3%), gunshot wounds (1.9%), and jumping into the water (1.2%). Male / female ratio is found to be 2.5 / 1, respectively [12].

SCI associated with underlying degenerative and pathological process such as osteoporosis are more common in women due to fall in future years, and ranks first among the reasons. Spinal cord injuries other than trauma widely include tumors (25%), spinal vascular diseases (25%), inflammatory diseases (20%), spinal stenosis (19%), and the less seen ones include surgical intervention, radiation myelopathy, neural tube defects and other causes [13].

Pathophysiology

The concept of two-step mechanism in SCI was introduced when, in the early 1900s, Allen showed that progressive damage occurred in animals with spinal cord injured [14,15]. It has been reported that the first one was primer-mechanical damage and the latter was secondary injury in which many factors triggered by these play a role.

1. Primer mechanical damage

The most common mechanism of human SCI is spinal cord compression which continue post beat [16]. Flexion, extension, dislocation or distraction forces related to rotation cause penetrating injuries, strains or tears in neural tissues and vascular structures. Other possible mechanical effects of bone structures are ligaments or the effects related to the compression which results from the hematomas in the spinal canal [15,17,18].

While bleeding in spinal cord trauma starts in early period, the interruption of blood flow occurs in a later period. Interruption of blood flow leads to hypoxia and ischemia local infarction. This, particularly, causes damage to the gray matter whose metabolic requirement is more. Neurons located in the damaged area are interrupted physically and myelin thickness is reduced. Also, edema and macrophages in the damaged area are other factors leading to deterioration of nerve transmission [19].

2. Secondary mechanical damage

It is a damage which is started by primary injury and in which many pathophysiological mechanisms are defined when it develops in the hours and days after injury [7]. The main pathological process underlying all of these mechanisms is lack of energy due to impaired perfusion at the cellular level and ischemia [20-23]. It has been reported that ischemia begins immediately after traumatic SCI and if not treated, it deteriorates in the first 3 hours and continues for at least 24 hours [7]. After SCI, in spinal cord, there are many changes including hemorrhage, edema, demyelination, the formation of cavities with axonal and neuronal necrosis and a series of pathological changes which ended with infarction. Increased levels of glutamate, excitotoxicity, oxidative damage, ischemia, Ca++ dependent nitric oxide production, and free radical damage and lipid peroxidation in cell membranes are the contents of the secondary injury cascade [18,24,25]. However, many studies indicate that the spinal cord has a remarkable capable of healing capacity. In order that progressive tissue can pass in front of necrosis in this healing, the most important factor is to ensure proper blood flow. SCI is not only a pathology remaining in the injury in area the spinal cord. By being affected by local injuries in spinal cord, neurons in descending pathways in the brain exhibit pathological chain of events from atrophy to apoptosis or necrosis [23]. Well vascularized astrocytic environment allow the axons to regenerate in the regions if the spinal cord injuries [26]. Therefore, understanding the mechanisms of the secondary injury, which can cause neuronal death after injury, stands as the most important issue in implementing advanced therapies [27]. Mechanisms that cause secondary damage to occur are held in two parts as systemically and local effects [2,7].

Systemic factors

Systemic factors that play roles in acute SCI are hypotension due to neurogenic shock, decreased cardiac output and respiratory failure [18,28]. In this case, metabolites and oxygen are prohibited to reach the tissues they need [18,23,28,29]. Drop in systemic blood pressure must absolutely be brought under control in a patient in spinal shock. Because the perfusion pressure is directly connected to the systemic blood pressure, the damage to the spinal cord is exacerbated. Therefore, a problem which may arise in the cardiopulmonary system may increase the severity of SCI by corrupting spinal cord perfusion. On the other hand, in order to avoid intramedullary hyperemia and hemorrhage, it has been

said that blood pressure should be kept only in normotensive levels [18]. Post-traumatic hypotension occurring immediately after the injury may take days or even months. In animal models with spinal cord trauma, normotension has been provided with blood transfusion and dopamine, thus, blood flow to the spinal cord has been able to be increased but because local microcirculation is damaged, spinal cord functions haven't been improved [18,30].

Local vascular effects

It is known that severe SCI causes substantial decrease in blood supply and ischemia begins right after the trauma [7]. Systemic hemodynamic changes are reflected to blood flow in the spinal cord which's otoregulation was disrupted. For this reason systemic hypotension and hypoxia further detoriates the ischemia formed by spinal injury [31]. Ischemia, causes lack of energy by unsatisfactory transport of glucose and oxygen to the tissues resulting in decrease in ATP stores [32]. The exact causes of post-traumatic ischemia has not been fully understood. Focal narrowing of sulcal arterioles and intramedullary capillaries, fragmentation, aneurysmal dilatation or occlusion have been exhibited in experimental studies [20,22]. Kaptanoğlu et al demonstrated progressive vascular damage in spinal cord contusion injury model for the first time by using Evans blue technique. In this study there was 76% increase in uptake of Evans blue in the injury area at 24th hour compared to those at 2nd hour [33]. Decreased pH of the tissue due to lactic acidosis, congestion and venous stasis due to accumulation of fibrin and platelets, capillary endothelial damage, edema, petechial hemorrhages, vasoactive cytokines are some of the causes of ischemia. As a result, the system shifts to anaerobic respiration. Ischemia and subsequent triggering of anaerobic respiration leads to many of the pathological processes [18,34]. The proteinaceous leak through the intrinsic spinal cord veins, leads to edema at the site of injury and peripheral tissues [31]. Edema, causes relatively increased spinal cord pressure and this leads to disruption of local blood flow of the spinal cord [35]. In a study conducted by Kaptanoğlu et al. magnesium was found to reduce edema and vascular permeability ultrastructurally in spinal cord injuries [36].

Ionic mechanisms

After spinal cord trauma, abnormalities in the concentration of the electrolyte and gradient changes were observed [37]. In humans with 4-aminopyridine chronic SCI has increased axonal message and showed a recovery sign in moderate levels. This effect of 4-aminopridinin has been shown in cats with SCI by blocking the fast K+ channels [38]. On the other hand, ischemia-reperfusion injury leads to a significant increase in formation of glutamate and free radical. The destruction of the blood-spinal cord barrier can be prevented by antagonism of glutamate in endothelium. It has been shown that Glutamate receptor blockers improve neurological outcomes in an experimental SCI [7,39,40]. Mg+ is believed to decrease its by-products of lipid peroxidation with the indirect effect resulting from antagonism of glutamate [33]. The role of Ca ++ ion in the cell death is thought to be the most.Ca++ ions leads to promote the cell damage by activating phospholipases, proteases and phosphorylases in the cell. On the other hand, in the experimental spinal cord studies, calcium channel blockers were also tested in order to prevent secondary injury. There are many studies showing that these agents improve blood flow to the spinal cord and have a positive effect on healing [18,41-43]. It has been shown that, after SCI, dopamine, adrenaline, nimodipine, and dextran increase blood flow and promote neurological recovery [18,44].

Free radicals

To maintain cell viability, it is important to prevent the generation of intense free radicals [45]. The effectiveness of anti-oxidative defense mechanisms was reduced by aging and it was shown to be have a significant effect on the pathophysiology of SCI. In studies of experimental SCI carried on old and young rats two week mortality was 20% and 50% in young and old rats, respectively [46]. Free radical scavenger agents such as, Cyclosporin A[15], EPC-K1 [47], vitamin E and selenium [16] are shown to be useful for SCI. Kaptanoğlu et al. showed that melatonin, Mexiletine, erythropoietin, thiopental and propofol inhibit the lipid peroxidation after SCI [48-50].

Opiate receptors

An experimental study showed a marked release of endogenous opioid peptides locally in spinal cord injuries [23]. Preventing progressive tissue damage by opiate receptor blockage suggested that endogenous opioids might have a role in the pathophysiology of secondary injury. Faden et. al reported that post traumatic hypotension, spinal cord blood flow and the patient's clinic was improved by a non-selective opioid antagonist, naloxone, after acute SCI [51]. The most affected opioid is dynorphin in human spinal cord injuries and the severity of the

trauma and dynorphin levels has been reported to be correlated [52].

Inflammatory response

Inflammatory response is initiated within hours by peripheral immune cells such as macrophages, neutrophils, and T cells after SCI and reaches maximum level in a few days [53,54]. This response is observed as the endothelial damage, the release of mediators of inflammation, vascular permeability, edema formation, migration of peripheral inflammatory cells and activation of microglia. Macrophages, and neutrophils play a role in the growth of the lesion and tissue damage. Macrophages and microglia play a role in inflammatory reactions and secondary pathological changes by the release of cytokines (TNF, IL-1, IL-6, IL-10). Inflammatory mediators such as bradykinin, prostaglandins, leukotrienes, platelet activating factor and serotonin accumulate at the lesion site in injured spinal cord. Additional cytokines, chemokines, nitric oxide, oxygen and expression of nitrogen species in response to inflammatory cytokines accelerate the central nervous system inflammatory response [54]. In two independent SCI model, 30 minutes after traumatic injury iv administration of systemic IL-10 resulted in systemic decreased inflammation. IL-10 is neuroprotective, and improves motor function [54].

Excitatory amino acids

NMDA receptors is thought to be have a directory role in excitatory neurotransmission of the spinal cord [55]. In connection with this the NMDA receptor blockade has been shown to have a protective effect against secondary damage to traumatic and ischemic models [2]. With the administration of NMDA antagonists significant neurological improvement and significant decrease in edema occur [56]. This group receptors can be blocked by Mg++ [57]. Likewise, administration of AMPA antagonists have been reported to reduce injured area and cause functional improvement [58].

Glutamate is the major excitatory neurotransmitter in the central nervous system. Neuronal damage caused by excessive activation of glutamate receptors was detected by Olney et al. and defined as excitotoxicity [28]. Excitatory amino acids, glutamate and aspartate, rise within minutes after SCI [59]. After experimental SCI, concentration of extracellular excitatory amino acid in the spinal cord reach to the toxic levels within 15 minutes and maintain its toxcicity as well as 120 minutes [23]. Extracellular excitatory amino acids are quite toxic for the neurons in spinal cord.

Apoptosis

Presence apoptosis is shown after traumatic SCI of human being which is triggered by release of cytokines, inflammatory injury, free radical injury and excitotoxicity [28,60,61]. Apoptotic cell death is observed after 3 hours to 8 weeks after traumatic SCI. Apoptosis occurs around lesion center as well as Wallerian degeneration area of descending and ascending white matter tracts [60]. Experimental studies have shown that apoptosis in oligodentrocytes aggravates demyelinization occurring after a few weeks of injury. Crowe te al. have defined the oligodentrocytic changes in SCI for the first time [62]. In addition it's thought that apoptosis adversely effects the outcome by increasing neuronal loss [28]. Some authors advocate that apoptosis in microglia worsens secondary inflammatory injury [61]. Experimental studies support that SCI exaggerates caspase activation [28]. Caspases are triggered by signals activating apoptosis and play an active role in all three pathways of apoptosis [63].

Apoptotic cell death occurs in all cellular components of the spinal cord (neurons, astrocytes, oligodentrocytes, and microglia). Neuronal protection is essential since neurons of the spinal cord have no reproduction capability [3]. Although glias has regeneration potential, inhibiting the glial death support the neuronal protection by two similar mechanisms. First, glia provides neurotrophic and metabolic support to injured neurons, which needs this support for recovery. Second, glia removes apoptotic mediators such as cytokines, free radicals released from dying cells, which are toxic to adjacent cells [3].

CONCLUSION

There are many experimental studies have been conducted and also still ongoing to understand pathophysiology of SCI. However, as a result of these studies an ideal treatment model to apply on human beings has not been developed yet. Clarifying the pathophysiology of SCI will contribute significantly to determine the optimal treatment.

REFERENCES

1. Tator CH. Biology of neurological recovery and functional restoration after spinal cord injury. Neurosurgery 1998;42:696-707.
2. Dumont RJ, Verma S, Okonkwo DO, et al. Acute spinal cord injury, part II: contemporary pharmacotherapy. Clin Neuropharmacol 2001;24:265-279.
3. Li M, Ona VO, Chen M, et al. Friedlander RM. Functional role and therapeutic implications of neuronal

caspase-1 and -3 in a mouse model of traumatic spinal cord injury. Neuroscience 2000;99:333-342.

4. Dumont AS, Dumont RJ, Oskouian RJ. Will improved understanding of the pathophysiological mechanisms involved in acute spinal cord injury improve the potential for therapeutic intervention? Curr Opin Neurol 2002;15:713-720.
5. Fehlings MG. Summary statement: the use of methylprednisolone in acute spinal cord injury. Spine 2001;26:S55.
6. Schwab ME. Repairing the injured spinal cord. Science (New York, N.Y.) 2002;295:1029-1031.
7. Tator CH. Review of experimental spinal cord injury with emphasis on the local and systemic circulatory effects. Neurochirurgie 1991;37:291-302.
8. Lasfargues JE, Custis D, Morrone F, et al. A model for estimating spinal cord injury prevalence in the United States. Paraplegia 1995;33:62-68.
9. Dryden DM, Saunders LD, Rowe BH, et al. The epidemiology of traumatic spinal cord injury in Alberta, Canada. Can J Neurol Sci 2003;30:113-121.
10. Griffin MR, Opitz JL, Kurland LT, et al. Traumatic spinal cord injury in Olmsted County, Minnesota, 1935-1981. Am J Epidemiol 1985;121:884-895.
11. Pagliacci MC, Celani MG, Zampolini M, et al. An Italian survey of traumatic spinal cord injury. The Gruppo Italiano Studio Epidemiologico Mielolesioni study. Arch Phys Med Rehabil 2003;84:1266-1275.
12. Karacan I, Koyuncu H, Pekel O, et al. Traumatic spinal cord injuries in Turkey: a nation-wide epidemiological study. Spinal cord 2000;38:697-701.
13. Citterio A, Franceschini M, Spizzichino L, et al. Nontraumatic spinal cord injury: an Italian survey. Arch Phys Med Rehabil 2004;85:1483-1487.
14. Allen AR: Surgery of experimental lesion of spinal cord equivalent to crush injury of fracture dislocation of spinal column. A preliminary report :. J.A.M.A. 1911.;57:878-880.
15. Kaptanoğlu E. Omurilik yaralanmasının patofizyolojisi,, Vol. cilt 2 Ankara: Temel Nöroşirürji 2010:, 1623-1635 , pp.
16. Anderson DK, Means ED, Waters TR, Green ES. Microvascular perfusion and metabolism in injured spinal cord after methylprednisolone treatment. J Neurosurg 1982;56:106-113.
17. Fehlings MG, Sekhon LH, Tator C. The role and timing of decompression in acute spinal cord injury: what do we know? What should we do? Spine 2001;26:S101-110.
18. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg 1991;75:15-26.
19. Young W. Secondary injury mechanisms in acute spinal cord injury. J Emerg Med 1993;11 Suppl 1:13-22.
20. Anthes DL, Theriault E, Tator CH. Ultrastructural evidence for arteriolar vasospasm after spinal cord trauma. Neurosurgery 1996;39:804-814.
21. Holtz A, Nystrom B, Gerdin B. Relation between spinal cord blood flow and functional recovery after blocking weight-induced spinal cord injury in rats. Neurosurgery 1990;26:952-957.
22. Koyanagi I, Tator CH, Lea PJ. Three-dimensional analysis of the vascular system in the rat spinal cord with scanning electron microscopy of vascular corrosion casts. Part 2: Acute spinal cord injury. Neurosurgery 1993;33:285-291; discussion 292.
23. Amar AP, Levy ML. Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. Neurosurgery 1999;44:1027-1039; discussion 1039-1040.
24. Choi WS, Lee EH, Chung CW, et al. Cleavage of Bax is mediated by caspase-dependent or -independent calpain activation in dopaminergic neuronal cells: protective role of Bcl-2. J Neurochem 2001;77:1531-1541.
25. Eaton MJ. Cell and molecular approaches to the attenuation of pain after spinal cord injury. J Neurotrauma 2006;23:549-559.
26. Zhang Z, Guth L. Experimental spinal cord injury: Wallerian degeneration in the dorsal column is followed by revascularization, glial proliferation, and nerve regeneration. Exp Neurol 1997;147:159-171.
27. Lou J, Lenke LG, Ludwig FJ, O'Brien MF. Apoptosis as a mechanism of neuronal cell death following acute experimental spinal cord injury. Spinal cord 1998;36:683-690.
28. Dumont RJ, Okonkwo DO, Verma S, et al. Acute spinal cord injury, part I: pathophysiologic mechanisms. Clin Neuropharmacol 2001;24:254-264.
29. Guha A, Tator CH, Rochon J. Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. Stroke 1989;20:372-377.
30. Dolan EJ, Tator CH. The effect of blood transfusion, dopamine, and gamma hydroxybutyrate on posttraumatic ischemia of the spinal cord. J Neurosurg 1982;56:350-358.
31. Sandler AN, Tator CH. Review of the effect of spinal cord trama on the vessels and blood flow in the spinal cord. J Neurosurg 1976;45:638-646.
32. Kirshblum SC, Groah SL, McKinley WO, et al. Spinal cord injury medicine. 1. Etiology, classification, and acute medical management. Arch Phys Med Rehabil 2002;83:S50-57, s90-58.
33. Kaptanoglu E, Beskonakli E, Solaroglu I, et al. Magnesium sulfate treatment in experimental spinal cord injury: emphasis on vascular changes and early clinical results. Neurosurg Rev 2003;26:283-287.
34. Agrawal SK, Nashmi R, Fehlings MG. Role of L- and N-type calcium channels in the pathophysiology of traumatic spinal cord white matter injury. Neuroscience 2000;99:179-188.
35. Schwab ME, Bartholdi D. Degeneration and regeneration of axons in the lesioned spinal cord. Physiol Rev 1996;76:319-370.

36. Kaptanoglu E, Beskonakli E, Okutan O, et al. Effect of magnesium sulphate in experimental spinal cord injury: evaluation with ultrastructural findings and early clinical results. J Clin Neurosci 2003;10:329-334.
37. Bracken MB, Holford TR. Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function in NASCIS 2. J Neurosurg 1993;79:500-507.
38. Nashmi R, Fehlings MG. Mechanisms of axonal dysfunction after spinal cord injury: with an emphasis on the role of voltage-gated potassium channels. Brain Res Brain Res Rev 2001;38:165-191.
39. Guha A, Tator CH, Piper I. Effect of a calcium channel blocker on posttraumatic spinal cord blood flow. J Neurosurg 1987;66:423-430.
40. Lucas JH, Wang GF, Gross GW. NMDA antagonists prevent hypothermic injury and death of mammalian spinal neurons. J Neurotrauma 1990;7:229-236.
41. Faden AI. Pharmacotherapy in spinal cord injury: a critical review of recent developments. Clin Neuropharmacol 1987;10:193-204.
42. Hall ED, Wolf DL. A pharmacological analysis of the pathophysiological mechanisms of posttraumatic spinal cord ischemia. J Neurosurg 1986;64:951-961.
43. Ross IB, Tator CH, Theriault E. Effect of nimodipine or methylprednisolone on recovery from acute experimental spinal cord injury in rats. Surg Neurol 1993;40:461-470.
44. Fehlings MG, Tator CH, Linden RD. The effect of nimodipine and dextran on axonal function and blood flow following experimental spinal cord injury. J Neurosurg 1989;71:403-416.
45. Heffner JE, Repine JE. Pulmonary strategies of antioxidant defense. Am Rev Respir Dis 1989;140:531-554.
46. Genovese T, Mazzon E, Di Paola R, et al. Increased oxidative-related mechanisms in the spinal cord injury in old rats. Neurosci Lett 2006;393:141-146.
47. Fujimoto T, Nakamura T, Ikeda T, et al. Effects of EPC-K1 on lipid peroxidation in experimental spinal cord injury. Spine 2000;25:24-29.
48. Kaptanoglu E, Sen S, Beskonakli E, et al. Antioxidant actions and early ultrastructural findings of thiopental and propofol in experimental spinal cord injury. J Neurosurg Anesthesiol 2002;14:114-122.
49. Kaptanoglu E, Solaroglu I, Okutan O, et al. Erythropoietin exerts neuroprotection after acute spinal cord injury in rats: effect on lipid peroxidation and early ultrastructural findings. Neurosurg Rev 2004;27:113-120.
50. Kaptanoglu E, Tuncel M, Palaoglu S, et al. Comparison of the effects of melatonin and methylprednisolone in experimental spinal cord injury. J Neurosurg 2000;93:77-84.
51. Faden AI, Jacobs TP, Smith MT, Zivin JA. Naloxone in experimental spinal cord ischemia: dose-response studies. Eur J Pharmacol 1984;103:115-120.
52. Faden AI, Jacobs TP, Holaday JW. Comparison of early and late naloxone treatment in experimental spinal injury. Neurology 1982;32:677-681.
53. Balentine JD. Pathology of experimental spinal cord trauma. I. The necrotic lesion as a function of vascular injury. Lab Invest 1978;39:236-253.
54. Bethea JR, Dietrich WD. Targeting the host inflammatory response in traumatic spinal cord injury. Curr Opin Neurol 2002;15:355-360.
55. Faden AI, Simon RP. A potential role for excitotoxins in the pathophysiology of spinal cord injury. Ann Neurol 1988;23:623-626.
56. Yanase M, Sakou T, Fukuda T. Role of N-methyl-D-aspartate receptor in acute spinal cord injury. J Neurosurg 1995;83:884-888.
57. Agrawal SK, Fehlings MG. Role of NMDA and non-NMDA ionotropic glutamate receptors in traumatic spinal cord axonal injury. J Neurosci 1997;17:1055-1063.
58. Wrathall JR, Choiniere D, Teng YD. Dose-dependent reduction of tissue loss and functional impairment after spinal cord trauma with the AMPA/kainate antagonist NBQX. J Neurosci 1994;14:6598-6607.
59. Liu D, Thangnipon W, McAdoo DJ. Excitatory amino acids rise to toxic levels upon impact injury to the rat spinal cord. Brain Res 1991;547:344-348.
60. Emery E, Aldana P, Bunge MB, et al. Apoptosis after traumatic human spinal cord injury. J Neurosurg 1998;89:911-920.
61. Shuman SL, Bresnahan JC, Beattie MS. Apoptosis of microglia and oligodendrocytes after spinal cord contusion in rats. J Neurosci Res 1997;50:798-808.
62. Crowe MJ, Bresnahan JC, Shuman SL, et al. Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. Nat Med 1997;3:73-76.
63. Ozawa H, Keane RW, Marcillo AE, et al. Therapeutic strategies targeting caspase inhibition following spinal cord injury in rats. Exp Neurol 2002;177:306-313.