

## NEUROBIOLOGY

# Neuroprotection of Spinal Neurons Against Blunt Trauma and Ischemia

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Each year in the United States there are over 10,000 new cases of para- and quadriplegia, and more than 100,000 cases of limited, but permanent, neurological losses. Many of these losses result from blunt trauma and ischemia to the spinal cord which leads to neuron death. Although blunt trauma directly kills neurons due to the physical trauma, over the subsequent 48 hours an even larger population of neurons dies due to secondary causes. One of leading triggers of this neuron death is ischemia due to the disruption of the blood circulation. Selective, but unavoidable, spinal cord ischemia occurs during thoracoabdominal surgery to repair aortic aneurysms. This ischemia leads to neuron death, functional neurological loss, and paraplegia in up to 33% of the cases. Thus, both blunt trauma and induced ischemia have similar triggers of neuron death. To reduce the

neurological losses resulting from ischemia mechanisms must be found to make spinal neurons more tolerant to ischemic insult and other secondary causes of neuron death. In this review we discuss mechanisms being developed, predominantly using animal models, to provide neuroprotection to prevent neurological losses following blunt trauma and during induced spinal cord ischemia. In parallel, our own experiments are looking at neuroprotective techniques using adult human neurons. We believe the optimal neuroprotective approach will involve the perfusion of the ischemic region of the spinal cord with a hypothermia solution containing a combination of pharmacological agents.

*Key words: DRG neurons, Adult human neurons, Spinal cord injury*

**B**lunt trauma to the spinal cord leads to a cascade of secondary events that cause neuron death. In the usual blunt-trauma model of spinal cord injury, damage secondary to the mechanical injury can not be easily separated from damage secondary to the delayed ischemic injury and reperfusion injury. Therefore, many experimental models have focused on developing neuroprotective mechanisms that are effective during induced spinal cord ischemia in animal models rather than following blunt trauma. Blunt trauma (mechanical injury) to the spinal cord usually does not result in complete anatomical transection. Further, spinal cord function frequently decreases with time after the injury. Thus, immediately following a spinal cord trauma an individual might exhibit some neurological loss but still retain sensory input and motor function. However, subsequently a complete loss of neurological function is seen. Such observations have led to the concept that secondary neuron injury, including ischemia, are responsible for this phenomenon (24, 138, 31, 121, 153).

Ischemia is related to a major systemic reduction of blood flow (3,33,153,139,46,50,110) and a loss of microcirculatory flow in both gray and white matter of the spinal cord (4, 8, 19, 15, 46, 77, 97, 107, 110, 116). Following delayed ischemic reperfusion there is frequently even more nerve injury and enhanced functional neurological loss.

Paraplegia due to thoracoabdominal aneurysm repair remains an unpredictable and unpreventable complication due to the required surgical interventions. The paraplegia is because thoracoabdominal aneurysm repair frequently leads to ischemia of the spinal cord resulting brief to prolonged aortic occlusion leading to devastating neurological injury to the spinal cord and irreversible injury (29, 68, 137). These surgeries are associated with postoperative paraplegia rates from 1.5–33% of the cases (43% in high-risk patients) (80, 135, 18, 26, 27, 39, 15, 120, 103). The extent of the neurological loss depends on the amount of the disease, the type of aortic disease, and the duration of the aortic occlusion. To minimize the immediate and long-term ischemia-induced neurological losses it is essential to minimize the number of neurons killed during ischemia and reperfusion. Clinical attempts to reduce neuron death have focused on preservation of blood flow, decreasing the energy requirements of spinal neurons using protective agents such as hypothermia, barbiturates, and antioxidants. In animal models alkalization, calcium channel blockers and NMDA receptor antagonists have

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also been used. However, no reliable technique has been developed for clinical application that reduces neuron death due to trauma and the secondary causes of neuron death.

Little is known about how the various causes of ischemia-induced death of adult human neurons may be prevented and how to minimize neuron death. This review is aimed at studying various methods that might be applied clinically to enhance neuroprotection of adult human neurons against ischemia-induced death.

### Mechanisms of neurotoxicity

**Systemic hypothermia.** Has been shown to be neuroprotective but it carries the risk of inducing cardiac disorders. Therefore, systemic hypothermia is precluded from routine clinical application. Further, ventricular fibrillation and cardiac standstill may occur when body temperature is reduced to about 32°C. Due to the complication of systemic hypothermia many tests have been carried out to determine whether regional hypothermia of the spinal cord is effective in providing neuroprotection. The central nervous system (CNS) tissue tolerates a reduction in temperature to 5°C without permanent neurological complications (96). However, the optimal temperature for neuroprotection of adult human spinal cord neurons has not been determined. Hypothermia during ischemia reduces the decline in the concentration of ATP and glucose when compared to neurons undergoing normothermic ischemia (1). Hypothermia does not influence lactate concentrations (1). Within 24 hours of reperfusion high-energy phosphates increase to above control levels and both glucose and lactate levels are normalized in animals receiving hypothermia (1). These observations support the hypothesis that hypothermia slows the consumption of energy substrate but does not prevent anaerobic metabolism.

Strategies for providing neuroprotection due to induced ischemia include providing distal aortic perfusion during crossclamping (27,108,109,4,118), CSF drainage to maintain a spinal cord perfusion gradient (30,73), reimplantation of critical intercostal arteries (136), and pharmacologic neuroprotection (105,112). However, none of these approaches provides sufficient and reliable protection from neurological loss, especially following prolonged periods of ischemia.

### Triggers of Neuron Death

**Ischemia.** The fundamental cause of spinal cord damage due to blunt trauma and induced ischemia is a reduced

blood flow to the spinal cord segment subject to the occlusion. However, there are also interdependent events, including proximal hypertension, increased cerebrospinal fluid (CSF) pressure, distal hypotension, interruption to blood flow to critical intercostal or lumbar arteries, duration of aortic clamping, extent to aortic disease, and the presence of aortic dissection, that contribute to hypoxia and irreversible neurologic damage (108, 109).

Ischemic neuron injury also results from the loss of the substrate necessary for aerobic metabolism, leading to the accumulation of lactic acid and ultimately the loss of intracellular energy stores necessary for cellular viability. This neurological challenge is enhanced by the reperfusion of ischemic tissue which frequently induces a second wave of injury due to the liberation of free radicals and other toxic compounds. Important mediators of ischemia-reperfusion injury in the CNS are the amino acids glutamate and aspartate released from interneurons (34, 114). These excitatory neurotransmitters are released in toxic amounts by ischemic cells and during reperfusion and promote additional immediate as well as delayed neuron death (126).

**Free radicals.** Much of the ischemic and reperfusion injury to CNS neurons is secondary to the production of free radicals that alter lipid membranes, inducing lipid peroxidation leading to further destruction of cells and ultimately cell death (4, 5, 10, 13, 14, 21, 38, 54, 155). Results indicate that both regional ischemia and acute spinal cord injury are mediated via the production of free radicals that attack the cell membrane lipids in the traumatized region. Normal spinal blood flow is approx. 15ml/100 gm/min with a lower limit of about 10ml/100gm/min. Severe blunt trauma causes spinal blood flow to decrease to levels that induce irreversible damage. This decrease in spinal cord blood flow can be reversed by the administration of Tiriazad (56).

Blunt trauma results in hemorrhage at the traumatized site and also in a significant influx of calcium into the traumatized cells. The calcium influx activates other mechanisms, including the activation of various phospholipases and the subsequent release of arachadonic acid as well as increased prostoglandin synthetase activity (11, 36, 49, 67, 132, 35, 154). The initial cascade of damage also induces the production of free radicals leading to lipid peroxidation products that activate phospholipases, resulting in the further release of arachadonic acid. The arachadonic acid is then metabolized via prostoglandin synthetase-catalyzed reaction, producing various arachadonic metabolites. Many of these metabolites, including thromboxane E<sub>2</sub> and prostaglandin F<sub>2a</sub> are potent mediators of ischemia. Iron released from hemoglobin present in damaged red blood cells at the site of trauma is a very potent catalyst for free radical

production and lipid peroxidation (12,13). The arachadonic acid metabolites promote further ischemia in the gray matter, and this gray matter ischemia produces fairly significant lactic acidosis intracellularly and free radical generation, which then produces further lipid peroxidation. The oxygen-containing free radicals and lipid peroxidation products appear to be central modulators of the ischemic damage to the traumatized tissues. Unfortunately, the lipid peroxidation products and free radicals promote further release of arachadonic acid and further production of the ischemia-promoting arachadonic acid metabolites. These metabolites also promote the spread of ischemia from gray matter into the white matter, producing demyelination and axonal damage that results in permanent neurological deficits.

**Acidification.** Numerous *in vivo* experiments (71;71, 74,84,101,122,142) have shown that intracellular brain acidosis, resulting from the accumulation of lactic acid during global and focal cerebral ischemia, is a significant factor in perpetuating the cycle of cellular dysfunction leading to neuronal injury. Ischemia, both *in vitro* and *in vivo*, induce transient acidosis (pH 7.3 to 6.5), and induces both necrotic and apoptotic neuron loss (32). The extent of necrosis depends on the extent and duration of the acidosis. Acidosis may trigger ischemic neuron death by nonselective denaturation of nucleic acids and proteins (95), stimulation of the  $\text{Na}^+/\text{H}^+$  and  $\text{Cl}^-/\text{HCO}_3^-$  exchanger to trigger cellular swelling (122,129,130), formation of lipid peroxidation as a result of iron-catalyzed free radical generation (106), inhibition of mitochondrial metabolism, impediment of postischemic recovery (61), and alterations in calcium homeostasis (72). Acidification of adult DRG neurons (from 7.4 to 6.0 or 5.8) increases glutamate-induced currents which can lead to neuron death (150,144,149).

**Ischemia-induced release of excessive excitatory amino acids (EAAs).** Mammalian spinal and DRG neurons possess glutamate receptors (117) and DRG both contain and release glutamate (48,133,115). Spinal cord ischemia and other forms of CNS insult result in a massive accumulation of EAAs (such as glutamate and aspartate) causing excessive stimulation of the NMDA subtype of glutamate receptors (134) leading to DRG and spinal neuron death (123,44,42,85,100,134,57,76,51,78,83,85,92). *In vivo* micro dialysis of the swine spinal cord showed that 60 minutes of ischemia induces the massive release of EAA neurotransmitters that accumulate to toxic concentrations (100 mM, a 3-fold increase) (111). Injection of this concentration of glutamate or aspartate into the spinal cord results in neuron death for several hundred micrometers around the injection site (82).

**NMDA activation and disruption of calcium homeostasis.** Ischemia induces DRG and spinal neuron

death by triggering a disruption of their  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, leading to a massive calcium influx and loss of neuron calcium homeostasis (2,69,115). NMDA-receptor-mediated toxicity is due to the influx of extracellular  $\text{Ca}^{2+}$  (143,104). The released glutamate stimulates its own release in a positive feedback loop by its interaction with non-NMDA receptor subtypes (134). Calcium-induced  $\text{Ca}^{2+}$  release and the further influx of  $\text{Ca}^{2+}$  through voltage-gated  $\text{Ca}^{2+}$  channels after glutamate-induced depolarization also contribute to glutamate toxicity. The massive increase in (2) that activates this self-destructive cellular cascade involves many calcium-dependent enzymes, such as phosphatases (e.g. calcineurin), proteases (the calpains), and lipases. Postsynaptic neuronal elements, as well as glial cells, contribute to the extracellular overflow of excitatory amino acids during ischemia due to the post-synaptic elements leaking or releasing glutamate and aspartate, and glial cells losing their ability to convert glutamate to glutamine effectively (143). NMDA-receptor activation induces apoptosis or necrosis depending on the severity of the insult (98,140). Selective NMDA receptor antagonists (99,124) and  $\text{Ca}^{2+}$  channel blockers can thus prevent glutamate-induced neurotoxicity (131) (see later section on Stabilization of Calcium Homeostasis).

## Mechanisms of Neuroprotection

**Hypothermia.** Hypothermia has been widely studied for its ability to provide neuroprotection and improve neuron tolerance to hypoxia and ischemia reperfusion neuron injury (6,7,16,81,89,110,145,25,112,22,17,58). Regional hypothermic perfusion of the spinal cord via retrograde venous perfusion with hypothermic saline solution significantly reduces neurological loss due to ischemia (23,25,58,103). Hypothermia may provide neuroprotection by reducing tissue metabolism (decreased oxygen demand) by spinal cord neurons and reducing the consumption of energy metabolites during ischemia. However, this role of hypothermia on spinal cord neurons is assumed to be secondary. More importantly hypothermia may act by stabilizing the neuron membrane, reducing the release of excitatory neurotransmitters, stabilizing intracellular calcium homeostasis, blocking NMDA receptors.

Hypothermia may also provide neuroprotection from ischemia-induced excitotoxicity by markedly reducing the excessive accumulation of extracellular EAAs (predominantly glutamate). The degree of hypothermia used to provide neuroprotection against ischemia on the same and different animals and in *in vitro* models varies extensively: from slight (33-35°C) (cats) (94); 33°C (rabbits/

rats) (66,141); 34°C (rat) (88,90) to extreme (2-5°C): 2°C (dogs) (152); 4°C (together with adenosine) (swine) (102, 103,102); 5°C (rabbits) (86, 89); 5°C (rabbits) (91).

**Preconditioning with hypothermia.** Perfusion with a hypothermic (27°C) solution for 5 minutes starting 10 minutes after CNS ischemia provides no neuroprotection. However, perfusion started immediately after ischemia (to 27°C but not 34°C for 2 h) provides neuroprotection (70). Thus, the timing of the hypothermic perfusion is critical to providing neuroprotection. Hypothermic preconditioning of adult rabbit spinal neurons increases their tolerance to ischemia from 26 to 41 minutes (110). Pre-hypothermia together with thiopental, that reduces neuronal metabolic requirements, further increases neuron tolerance to ischemia to 57 minutes (110).

**Stabilization of calcium homeostasis.** Neurotoxicity due to ischemia-induced increased  $(2)_i$  can be significantly reduced by nominally  $Ca^{2+}$ -free medium (69), extracellular alkalization, and the NMDA and non-NMDA receptor antagonists (D-AP5 and CNQX) in combination, which significantly reduce the increase in  $(2)_i$  (69). Calcium entry into peripheral and central neurons can also be prevented by the calcium channel blocker TA3090 (9).

**Blockade of NMDA receptors.** Activation of adult DRG neuron NMDA receptors can be blocked by competitive antagonists (151). Clinically the NMDA receptor antagonist memantine provides neuroprotection against cerebral ischemia (20) but not spinal cord ischemia (147). For spinal neurons gacyclidine (GK-11) (1.0 mg/kg), the non-competitive NMDA receptor antagonist, provides the best protection against ischemia (37,45). In animal models, blocking NMDA receptors with  $MgSO_4$  and MK-801 (1.0 mg/kg) provide neuroprotection against ischemia (39,40). Neuroprotection of spinal neurons against ischemia is also enhanced by perfusion with hypothermic saline plus adenosine (103,120);(102). Adenosine appears to provide neuroprotection by suppressing the neurotoxic GABA-activated current (IGADA) in a majority of the neurons (77%)(64).

**Adenosine.** Adenosine has been extensively used in a variety of solutions for the preservation of the heart, liver, kidney, and pancreas for transplantation and other surgical procedures (128). The addition of adenosine to the hypothermic perfusion solution further decreases neurological losses compared to the perfusion of hypothermic saline alone (58,87,102,103,128,148). Adenosine activation of both the A1- and A2-Adenosine receptors is most likely responsible for the beneficial effects of adenosine on ischemic neuronal tissue. A1-receptor activation decreases neuronal excitability and limits the damaging influx of calcium through voltage-gated channels. Adenosine inhibits the release of excitatory

neurotransmitters thus reducing the activation of NMDA receptors (119,125). In addition, stimulation of A2-receptors causes vasodilation and inhibits platelet aggregation, neutrophil activation and subsequent free radical production, thereby reducing reperfusion injury after an ischemic interval (87,119,125). The vasodilation might be beneficial because it might increase blood flow to the spinal cord.

**Alkalinization.** Neurotoxicity due to trauma-induced brain acidosis can be reduced by systemic alkalization (113). Although mouse neocortical neurons in primary culture die when exposed to azide-induced chemical anoxia (100 mM), they survive when maintained at pH 8.2 (69). Systemic alkalization improves neurological outcome after global and focal cerebral ischemia (65,79,79). Alkalinizing agents are effective in reducing infarct volume following focal cerebral ischemia (cat) (79).

**Reduction of free-radicals.** Ischemia-induced lipid peroxidation causes the production of free radicals which damage vital cellular proteins leading to neuron death. Neurotoxicity is also intricately linked to the activation of three distinct neuronal endonucleases which are exquisitely pH dependent suggesting that intracellular pH influences nitric oxide (NO)-induced toxicity. NO toxicity can be caused by the NO generators sodium nitroprusside (SNOP) (300 mM), 3-orpholinosydnonimine (300 mM), or 6-(2-hydroxy-1-methyl-2-nitrosohydrazino)-N-methyl-1-hex anamine (300 mM). NO generated neurotoxicity appears to be pH dependent because neurons exposed to NO generators under acidic conditions (pH 7.4 to 7.0) are killed, while alkaline conditions (pH 7.6) are neuroprotective (146). Mitochondria also assist in providing neuroprotection by controlling free radicals.

Tirilazad is a very potent scavenger of free radicals, antioxidant, and extremely potent inhibitor of lipid peroxidation (3,10,11,14,38,53-55). It is very effective in the reactions catalyzed by iron. Tirilazad also appears to decrease the amount of arachadonic acid released at the trauma site. This decrease may be secondary to its inhibition of the positive feedback pathway mentioned previously or may be due to a separate second mechanism. The antioxidant effect is not related to any glucocorticoid activity of this compound. Tirilazad does not have any effect on the hypothalamic-pituitary-adrenal axis and does not appear to act via the steroid receptor. In a cat model of acute subarachnoid hemorrhage, Tirilazad treatment causes a blunting of the rise in intracranial pressure suggesting that one mechanism providing CNS protection against spinal cord injury might be the effect of Tirilazad on CSF pressure (47). Tirilazad has also been shown to lower CSF pressure thereby improving perfusion pressure and thus to improved neurological outcome following aortic

occlusion (41).

**Neuroprotection by Neurotrophic Factors.** Application of multiple neurotrophins to neurons reduces EAA excitotoxicity-induced neuron death (52,75).

**Neuroprotection by stress-related (heat shock) proteins.** Heat shock protein (HSP) expression is increased by stress (59). Adult DRG neurons subjected to stress up-regulate HSP synthesis *in vivo* as well as in isolated DRG neurons and the HSPs improve neuron survival (28). Prolonged, but mild hypothermia (minimum of 33°C for 24 hours) induced 1 hour after resuscitation increases the levels of stress-related proteins and reduces neuron loss (60). Heat shock proteins may act by buffering neurons from free radicals. These results suggest that preconditioning spinal neurons with a hypothermic and alkaline solution prior to ischemic insult might induce enhanced ischemic neuroprotection.

**Lowering CSF pressure.** Lowering CSF pressure decreases intraspinal pressure significantly, which in turn reduces ischemic damage by improving the perfusion pressure in the neural and supporting tissue (47,62,63, 138). Similarly, CSF drainage induces an improvement in neurological outcome and in perfusion pressure in the injured spinal cord (41).

### Neuroprotection for Adult Human Neurons

Much of the work so far discussed had involved experiments on animal models. However, before applying these techniques in clinical trials it is important to determine whether they provide neuroprotection to adult human neurons. Work in our laboratory has assessed various mechanisms for providing neuroprotection to adult human dorsal root ganglion (DRG) neurons removed from organ donors within 1½ of clamping the aorta of the donor. Once the DRG are dissociated the neurons survive and remain electrically excitable for more than 2 months *in vitro* (127). Although once dissociated the neurons have long viability, the challenge is to obtain viable dissociated neurons. This is because the neurons in the intact DRG die due to ischemia and ischemia-related secondary causes. Thus it is essential to provide protect the neurons while they are in the intact DRG. This protection can be provided by methods similar to those used in models, i.e. hypothermia (4-20°C) and alkalization (pH 8.0- 9.3) which increase neuron viable compared to DRG maintained under physiological conditions (36.5°C at pH 7.4) by 41-fold and 14% respectively (unpublished results). However, subjecting the DRG to hypothermia and alkalization simultaneously increases neuron viability 104-fold.

Similar as has been found in animal models, antioxidants also provide neuroprotection and increase the number of

viable dissociated adult human DRG neurons by about 20% (unpublished results). These results suggest that when antioxidants are used simultaneously with hypothermic and alkaline conditions the degree of neuroprotection will be even further increased. Additional experiments are being carried out to test whether combining various pharmacological agents together with hypothermic and alkaline conditions and antioxidants further increase the extent of neuroprotection.

### Conclusions

Blunt trauma and ischemia lead to neuron death and functional neurological losses due to a variety of primary and secondary causes. Techniques are required that provide neuroprotection to spinal cord neurons following blunt trauma and during induced ischemia and reperfusion. Techniques developed using a number of animal models show promise for reducing neurological losses normally induced by spinal cord ischemia.

Localized hypothermia of the spinal cord segment subject to ischemia provides neuroprotection. However, the temperatures used to provide neuroprotection in these models varies extensively and no optimal temperature had been found, for either a specific animal model or between models. This suggests that there may be major differences in the requirements of neurons from different animal models, or the differences result from the techniques applied. Regardless of the differences, it is vital to determine the temperature that provides optimal neuroprotection to adult human neurons. The neuroprotection provided by hypothermia can be enhanced if is used in combination with various pharmacological agents, such as adenosine, free radical scavengers, and NMDA receptor blockers. Further experiments are required to determine whether combining these and other pharmacological agents, as well as applying them together with hypothermia and alkalization further enhance the degree of neuroprotection. Finally, before clinical trials can be carried out it will be crucial to test each of these approaches on adult human neurons to determine whether they provide effective neuroprotection. when used in clinical trials. We believe our the use of isolated adult human DRG provide an excellent model on which these techniques can be tested for their relevancy to the adult human nervous system.

### Resumen

Cada año en los Estados Unidos ocurren más 10,000 nuevos casos de paraplegia y cuádraplegia, y más de 100,000 casos de pérdida neurológica, limitada pero permanente. Muchas de estas pérdidas se deben a un

trauma cerrado e isquemia en la médula espinal lo que puede conducir a la muerte de neuronas. Aunque el trauma cerrado mata las neuronas directamente debido trauma físico, en las siguientes 48 horas muere una mayor población de neuronas por causas secundarias. Uno de los activadores principales en la muerte neuronal es la isquemia debido a la interrupción del flujo sanguíneo. Selectiva, pero evitable, la isquemia de la médula espinal ocurre durante los procedimientos quirúrgicos de la aorta torácica abdominal para reparar los aneurismas. Esta isquemia conduce a muerte neuronal, pérdida de la función neurológica y paraplegia en un 33% de los casos. Tanto el trauma cerrado como la isquemia inducida, tienen activadores similares en la muerte neuronal. Para reducir la pérdida neurológica como resultado de la isquemia deben buscarse mecanismos para lograr que las neuronas de la médula espinal sean más tolerantes al insulto vascular y otras causas secundarias de muerte neuronal. En esta revisión, discutimos los mecanismos que están en desarrollo, usando mayormente modelos animales, para proveer neuroprotección en la prevención de pérdida neurológica luego de un trauma cerrado y durante la isquemia inducida en la médula espinal. Paralelamente, nuestros propios experimentos examinan las técnicas de neuroprotección utilizando neuronas de humanos adultos. Creemos que el acercamiento más óptimo para la neuroprotección incluirá la perfusión de la región isquémica de la médula espinal con una solución hipotérmica compuesta por una combinación de agentes farmacológicos.

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