Mitochondrial Dysfunction in Nervous System Injury

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Mitochondria Structure

Mitochondria are organelles that evolved from a symbiotic relationship between aerobic bacteria and primordial eukaryotic cells. Despite being in eukaryotic organisms, mitochondria still carry a functional relic of their original genome. They are intracellular tubular organelles delimited by two membranes. The outer mitochondrial membrane is permeable to ions and small proteins of molecular weights <10 kDa, whereas the inner mitochondrial membrane houses the multimeric enzyme complexes of the electron transport chain (ETC). Human mitochondria DNA is a circular double-stranded molecule of approximately 16.6 kb in length with the genome containing 37 genes. Of these, 13 genes encode protein subunits of respiratory chain complexes, with a significant amount of mitochondrial proteins being encoded by the nuclear genome and transported into the mitochondria. For example, complex II is solely composed of proteins encoded by nuclear genes. The varying mitochondrial density in various tissues is usually dictated by the need for oxidative phosphorylation and energy production. Cardiac and skeletal muscles and neurons have the highest density of mitochondria, hence their sensitivity to energy-dependent defects resulting from mitochondrial dysfunctions following injury.

Mitochondria Electron Transport Chain, Membrane Potential, and Energy Metabolism

Central to the role of mitochondria is energy metabolism through the production of ATP. This energy production is usually carried out at the level of the inner mitochondrial membrane through oxidative phosphorylation involving the reduction of oxygen to water by multimeric enzyme complexes. The ETC is composed of NADH–ubiquinone oxidoreductase (complex I), succinate dehydrogenase–CoQ oxidoreductase (complex II), cytochrome reductase (complex III), cytochrome oxidase (complex IV), and ATP synthase, which is sometimes referred to as complex V. These multimeric complexes are arranged in the inner mitochondrial membrane according to their reduction potentials. During oxidative phosphorylation, ETC complexes are usually involved in the reduction and oxidation reactions through reducing equivalents such as NADH or succinate, which are transported into the mitochondria from the cytosol. In the process, protons are pumped from the matrix into the intermembrane space, terminating with the reduction of $O_2$ to $H_2O$. The transfer of protons from the matrix to the inner mitochondrial membrane leads to the generation of a mitochondrial membrane potential ($\Delta\Psi_m$) of 150–180 mV, which usually determines the energetic status of the mitochondria. This reserve of potential energy through the electrochemical gradient is then coupled to the generation of ATP from ADP and inorganic phosphate $P_i$ through the ATP synthase complex (complex V).

Ca$^{2+}$ Regulation and Excitotoxicity

Mitochondria under normal conditions usually act as high-capacity Ca$^{2+}$ sinks through a highly complex system for the regulation and the transportation of Ca$^{2+}$. Through these processes, mitochondria sense and respond to changes in cytosolic Ca$^{2+}$ loads to maintain cellular Ca$^{2+}$ homeostasis that is required for normal neuronal function. Disruptions in Ca$^{2+}$ homeostasis are one of the major factors that contribute to the neuropathology following central nervous system (CNS) injury. It has been shown that following CNS injury, mitochondrial dysfunction is primarily involved in glutamate neurotoxicity. Glutamate excitotoxicity is usually triggered by the excessive influx of calcium following activation and overstimulation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. The resulting increase in intracellular calcium has been shown to lead to impaired function of the mitochondrial ETC and formation of reactive oxygen species/reactive nitrogen species (ROS/RNS), particularly superoxide anion and hydrogen peroxide. In addition, as mentioned previously, extreme loads of Ca$^{2+}$ have been shown to lead to the opening of the mitochondrial permeability transition pore (mPTP) and induction of the apoptotic pathways, eventually leading to neuronal cell death following CNS trauma.

Mitochondria and Oxidative Stress

Oxidative stress can be defined as an imbalance in the antioxidant defense mechanisms and the amount of ROS/RNS produced. The mitochondria are a key source of ROS. Through the generation of ATP via the oxidative phosphorylation by the ETC components, there is always some leakage of electrons (1% or 2%) from the mitochondria resulting in the partial reduction of $O_2$ to form superoxide anion $O_2^-$, a majority of which is generated from complex I.
and complex III of the ETC. The production of superoxide anion can occur when the ETC is impeded following mitochondrial injury. Note that the production of ROS by the mitochondria is tightly linked to the mitochondrial membrane potential since hyperpolarization or high mitochondrial membrane potential promotes the production of ROS. With a high mitochondrial membrane potential, the ETC cannot transfer protons against the electrochemical proton gradient from the matrix. This, in essence, leads to a reduced state of electron carriers and an increase in the half-life of semiquinone. The intermediates thus remain in a prolonged reduced state, thereby increasing the chances of electron leakage and partial reduction of O$_2$ to superoxide anion O$_2^-$. As discussed later, it is on this basis that mitochondrial protein uncouplers are gaining importance as possible therapeutics for CNS injuries.

As noted previously, one major pathway predominantly involved in the production of ROS/RNS is the secondary activation of glutamate receptors and excitotoxicity following injury to the nervous system. Following CNS injury, the cytosolic levels of Ca$^{2+}$ increase and are sequestered into the mitochondrial matrix through various transporters, as stated previously. However, excessive calcium loads result in the dysregulation of mitochondrial Ca$^{2+}$ homeostasis, leading to the activation of nitric oxide synthase (iNOS) and the production of nitric oxide radical (NO$^-$). The presence of nitric oxide NO and superoxide anion O$_2^-$, as seen in Figure 1(g), leads to the formation of peroxynitrite ONOO$^-$, another significant RNS, which can lead to the oxidative modification of proteins through nitration. Elevated intracellular Ca$^{2+}$ levels also activate phospholipase A$_2$; this enzyme liberates the unsaturated fatty acid arachidonic acid, initiating the formation of free radicals via the cyclooxygenase-2 and lipoxygenase pathways. Arachidonic acid can also be oxidized, leading to the formation of lipid peroxidation products such as 4-hydroxynonenal (HNE), malodialdehyde (MDA), and acrolein. The activation of inflammatory response following CNS injury also leads to the production of substances such as cytokines, tumor necrosis factor-$\alpha$, and interleukin-1$\beta$ that can damage neurons. In addition, activation of microglia and astrocytes can also lead to the generation of more ROS. For example, NADPH and xanthine oxidase significantly contribute to O$_2^-$ production upon activation of microglia. If the significant increase in ROS and RNS following CNS injury is not controlled, damage to DNA, proteins, or lipids would result, eventually leading to loss of function and possibly neuronal cell death.

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**Figure 1** A summary of the production of reactive oxygen and nitrogen species (ROS/RNS) following CNS injury. In addition, the figure displays the antioxidant systems that provide protection against increased oxidative stress as seen in nervous system injury.
Mitochondria Permeability Transition Pore

The mitochondrial permeability transition (mPT) is defined as an increase in the permeability of the inner mitochondrial membrane to solutes that have molecular masses lower than 1.5 kDa. The induction of this transition has since been demonstrated to involve the opening of a 2- or 3-mm inner membrane megachannel referred to as the mPTP. This pore is a voltage-dependent channel that is activated by the elevation of Ca\(^{2+}\) levels, oxidative stress, and low inner mitochondrial membrane potentials as observed in most nervous system injuries. The exact identity of this megachannel is still under investigation. However, progress has been made in trying to provide a logical model for its composition. The minimum configuration of the mPTP requires the adenine nucleotide translocator (ANT), which is located in the inner mitochondrial membrane, in association with outer mitochondrial membrane proteins such as the voltagedependent anion channel and cyclophilin D (a peptidyl–prolyl cis–trans isomerase whose activity is usually inhibited by immunosuppressant cyclosporine A (CsA)). In addition, other proteins, such as Bcl-2 and Bax, have been shown to interact with ANT, providing a regulatory role for mPTP. The exact physiological function of mPTP has not yet been established; however, there seems to be a clear consensus on its involvement in the induction of permeability transition in the neuropathology of various CNS injuries, such as traumatic brain injury (TBI) and spinal cord injury (SCI). This is particularly evident since it has been established that CNS injury triggers the opening of mPTP, resulting in a collapse of the electrochemical gradient, the swelling of mitochondria, the inhibition of ATP synthesis, the release of apoptotic factors, and the eventual initiation of cell death pathways that are blocked by the use of the cyclophilin D binding immunosuppressant drug CsA.

Mitochondria Apoptosis and Necrosis

Mitochondria also play a central role in the regulation of both programmed cell death (also known as apoptosis) and uncontrolled cell death (i.e., necrosis). Evidence of apoptosis following CNS trauma (discussed later) has been well established. As mentioned previously, events leading toward CNS injury usually occur in a biphasic manner – that is, through a primary necrotic process that results in rapid and significant decline in the levels of ATP and in the ensuing hours, days, and weeks, a secondary injury that exacerbates the primary insult occurs through apoptosis. These two mechanisms of neurodegeneration differ in their morphological features of general cell structure. Apoptosis is marked by cell shrinkage and DNA fragmentation, whereas necrosis is marked by cellular swelling and uncontrolled cell lysis.

As noted previously, following CNS injury, there is an increase in oxidative stress and excitotoxicity leading to Ca\(^{2+}\) overload, which in turn triggers the induction of the permeability transition. This usually leads to excessive mitochondrial swelling and depolarization of the mitochondria and uncoupling of the oxidative phosphorylation, eventually leading to a rapid decline in ATP reserves which if not restrained, as seen in severe CNS injuries, would more often than not lead to necrotic cell death. However, it has been shown that transient opening of the mPTP is associated with the induction of apoptosis through the release of cytochrome c and other pro-apoptotic proteins. Released cytochrome c usually complexes with apoptosis protease-activating factor 1 (Apaf-1), dATP, and procaspase-9 to form the high-molecular-weight complex, the apoptosisome. The apoptosisome then activates downstream effector caspases, which then initiate the apoptotic cascade. However, apoptotic events can still occur without the opening of the permeability transition pore. Pro-apoptotic proteins, such as Bax and Bad, also have been thought to be capable of forming pores in the outer mitochondrial membrane, thereby influencing the release of other pro-apoptotic proteins such as cytochrome c, apoptosis inducing factor, endonuclease G, and Smac/Diablo, thereby activating the apoptotic cascade. However, their role in CNS injury is still not well established. These various pathways have been summarized in Figure 2.

Mitochondria and Antioxidant Defense System

Cells are equipped with efficient strategies to control and maintain the intracellular levels of ROS/RNS and antioxidants. As mentioned previously, following CNS injury there is extensive production of ROS/RNS through a wide range of mechanisms. If these levels are not controlled, these ROS/RNS could lead to oxidative damage to key mitochondrial proteins or enzymes, DNA, and lipids, leading to a loss in function of the mitochondria, decline in ATP production, and possibly eventual cell death as observed in most events following CNS injuries. As a result, mitochondria have developed a defense system to protect themselves and the cell from the possible deleterious effects of these ROS/RNS through the use of key enzymes and proteins (discussed later). The key antioxidant found in the mitochondria is manganese superoxide dismutase (MnSOD), with the glutathione and thioredoxin antioxidant systems playing key roles in the
regulation of ROS/RNS. Figure 1 provides a summary of the key pathways of antioxidant systems which are discussed here with emphasis on CNS injury.

As a first line of defense following CNS injury and against production of ROS, the mitochondria use the MnSOD (Figure 1(a)). There are two classes of SOD; manganese SOD (Mn-SOD), which is predominately located in the mitochondrial matrix, and copper/zinc SOD (Cu/Zn SOD), which is predominately found in the cytosol, although studies have shown that Cu/Zn SOD can also be located in the intermembrane space of the mitochondria. The SOD enzymes catalyze the disproportionation of O$_2^-$ to H$_2$O$_2$ and H$_2$O, thus eliminating the cytotoxic superoxide anions from the cell. However, the disproportionation of O$_2$ generates H$_2$O$_2$, another ROS. H$_2$O$_2$ also can lead to oxidative damage through various mechanisms. In the presence of transition metal ions such as Fe$^{2+}$ or Cu$^+$, H$_2$O$_2$ can undergo a Fenton reaction resulting in the generation of hydroxyl radicals OH$_3$, a much more toxic ROS that can exact excessive damage at distant sites from where H$_2$O$_2$ was generated. As a result, there is need for the cell to regulate intracellular levels of H$_2$O$_2$. One immediate mechanism through which the intracellular levels of H$_2$O$_2$ are regulated is via the enzyme catalase (Figure 1(b)), which catalyzes the conversion of H$_2$O$_2$ to H$_2$O and dioxygen. However, catalase is not found in brain mitochondria; as a result, CNS mitochondria predominantly depend on other peroxidases to regulate the levels of H$_2$O$_2$. One mechanism involves the glutathione (GSH) system in conjunction with glutathione peroxidase (GPx) and glutathione reductase (GR), as shown in Figures 1(c) and 1(d). GSH is usually synthesized in the cytosol but is then transported into the mitochondria through various mechanisms. H$_2$O$_2$ can be converted to water by GPx (Figure 1(c)) using GSH as the hydrogen donor. The oxidized glutathione (GSSG) is then recycled back to GSH by the enzyme GR (Figure 1(d)), which uses NADPH as a cofactor. Another antioxidant system associated with glutathione is through the enzyme glutathione-S-transferase (GST). As mentioned previously, following CNS injury, there is a significant production of reactive aldehydes such as HNE or MDA which, if not eliminated from the cell, could lead to additional damage. The levels of these reactive aldehydes are usually regulated by the enzyme GST, which catalyzes their conjugation to GSH as shown in Figure 1(e). With the aid of multidrug-resistant protein-1 (MRP1), this GS-alkenal conjugate is exported out of the cell, removing toxic reactive aldehydes (Figure 1(f)). Peroxiredoxins are another important H$_2$O$_2$-removal antioxidant system. Peroxiredoxins belong to a family of enzymes that are homodimers and require no prosthetic groups. They use thioredoxin-2 to reduce H$_2$O$_2$.
Mitochondria and Traumatic Brain Injury

TBI is a serious health care problem in the United States, with more than 400,000 individuals hospitalized each year and an estimated annual cost of $25 billion. As noted previously, for most CNS injuries the pathophysiological events in TBI occur in a biphasic manner. Following TBI, the primary insult results in a rapid and significant necrosis of cortical tissue at the site of injury, and in the ensuing period (days and weeks) a secondary injury occurs that exacerbates the primary damage. One underlying feature of this secondary injury in both experimental and clinical TBI is the loss in mitochondrial bioenergetics. This loss is usually characterized by mitochondrial dysfunction that includes exposure of neurons to excitotoxic levels of excitatory neurotransmitters with excessive uptake of Ca\textsuperscript{2+} and eventual overload, generation of reactive oxygen species, induction of the opening of mPTP, release of cytochrome c, inhibition of ATP production, and ultimately neuronal cell death. Following TBI, ROS/RNS can also be generated through other cellular pathways, such as calcium activation of phospholipases, iNOS xanthine oxidase, the Fenton and Haber–Weiss reactions, and by inflammatory cells, as previously discussed. It has been shown that following TBI there is a significant loss in mitochondrial bioenergetics, possibly through the loss of activity of key enzymes. It has also been shown that following experimental TBI, there is increased oxidative damage in mitochondria. Using proteomics, it has since been shown that key mitochondrial-related proteins are oxidatively modified, contributing to the loss in mitochondrial-related bioenergetics. There is currently no particularly effective therapeutic intervention for TBI; thus, TBI still presents clinicians and researchers with a major challenge.

Mitochondria and Spinal Cord Injury

Spinal cord injuries are the leading causes of disability and mortality in the United States, with the estimated incidence rate of 43–55 per million annually. The primary cause of SCI is automobile collisions, followed by violence, falls, and injuries in sporting events. Like TBI, SCI also undergoes multiple secondary injuries following the initial or primary impact. SCI results in hemorrhage, edema, axonal demyelination, increased glial activity, and the eventual compromise and loss of neurological function. The pathophysiology of SCI is characterized by an immediate and irreversible primary insult that is composed of physical and mechanical trauma. The generation of sharp bone fragments, contusions, compression, and eventual concussion are often observed. This damage is more manifested as ischemia through continuous compression after injury. The secondary injury, which is also considered as the more severe, involves a highly complex cascade of molecular downstream events that range from early neuronal apoptosis at the site of injury to the degeneration of white matter tracts weeks after injury among many other pathologies. Although there are a significant number of factors that contribute to the events seen in the secondary injury during SCI, such as ischemia, edema, ionic imbalances, compromised energy metabolism, and biochemical changes, mitochondria play a significant role in the neuropathology of SCI. Following SCI, there is a sustained activation of glutamate receptors, which leads to the intracellular accumulation of high levels of Ca\textsuperscript{2+} and a rapid impairment of mitochondrial function. This glutamate-mediated excitotoxicity, the formation of ROS, and lipid peroxidation are prominent events thought to contribute to neuronal dysfunction and cell loss following traumatic damage and ischemic injury to the CNS. Evidence for the involvement of mitochondria in these mechanisms stems from the fact that there is impaired mitochondrial function and lipid peroxidation within 1 h following experimental SCI, with an increase in ROS or evidence of oxidative damage occurring at 4 h and 24 h and as long as 4 weeks following injury. In addition, there were changes in the levels of ROS scavenger molecules 24 h following injury, as characterized by an increase in catalase activity and GSH levels. There is no known highly effective therapeutic remedy for SCI; however, there is a time window through which therapeutic interventions would be protective, as discussed in the next section. A summary of the pathophysiology of the secondary injury following SCI is given in Figure 3.

Stroke (Cerebral Ischemia)

Stroke (cerebral ischemia) is a major cause of death and the primary cause of adult disability in most
industrialized countries, accounting for the largest number of hospitalizations among neurological disorders. Thrombolytic stroke occurs as a consequence of irreversible brain injury resulting from cerebral ischemia provoked by interruption of cerebral blood flow through the occlusion of cerebral arteries. As in SCI and TBI, the mitochondria also play a critical role in the pathological mechanisms leading to tissue damage and infarction following stroke. Reduction or interruption of regional blood flow in the brain produces ischemic injury when delivery of metabolic substrates (i.e., glucose and oxygen) fails to meet the energy demand of the affected tissue. As in SCI and TBI, glutamate also plays a significant role in the pathogenesis of ischemic brain injury through mechanisms already discussed. Briefly, glutamate is released at high concentrations within the core of the cerebral infarction and in the penumbral tissue, over-activating its receptors and leading to excessive influx of calcium that activates a myriad of pathways, leading to mitochondrial dysfunction and to neuronal cell death (excitotoxicity), as previously discussed.

**Therapeutic Interventions for Mitochondrial Involvement in CNS Disorders**

The mechanisms that follow TBI, SCI, and stroke, among other CNS injuries, are similar, consisting of a primary injury that is further compounded with a secondary injury. Since the secondary injury evolves over time, this has provided a possible window of opportunity through which therapeutic interventions can be developed. Most therapeutic strategies have successfully concentrated on facilitating the actions of antioxidant enzymes, maintaining mitochondrial function, or inhibiting the formation of ROS/RNS following CNS injury. One key therapeutic strategy following

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**Figure 3** A summary of the pathophysiological events in SCI following the initiation of the secondary injury pathways. Following SCI, there is neuronal depolarization that leads to glutamate release and activation of NMDA and AMPA receptors. This then leads to excessive influx of calcium, resulting in an overload. Ca$^{2+}$ as a second messenger leads to mitochondrial dysfunction and activation of iNOS, arachidonic acid (AA), and calpain. These calcium-activated events lead to production of ROS/RNS, cytoskeleton degradation, axonal and myelin damage, activation of apoptosis, and eventual neuronal cell death. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazol propionic acid. Adapted from Hall ED and Springer JE (2004) Neuroprotection and acute spinal cord injury: A reappraisal. *NeuroRx* 1(1): 80–100. Halestrap AP, McStay GP, and Clarke SJ (2002) The permeability transition pore complex: Another view *Biochimie* 84: 153–166.
CNS injury has been the use of CsA. As noted previously, CsA is a potent immunosuppressive drug that transiently inhibits the opening of mPTP by unbinding mitochondrial matrix cyclophilin D from the pore. In experimental TBI, CsA dramatically reduces Ca\(^{2+}\)-induced cytoskeleton changes, improves mitochondrial function, and significantly ameliorates the volume of cortical damage in rodents. However, CsA does not offer the same neuroprotective effects in SCI as seen in TBI due to the intrinsic differences. These intrinsic differences have further complicated the search for therapeutic interventions for SCI. Moreover, CsA may have its own damaging effects with regard to ROS generation under certain conditions. However, there are ongoing studies that show that NIM811, a nonimmunosuppressive CsA derivative, is able to provide neuroprotective effects in both TBI and SCI models. Preliminary results indicate that NIM811 increases cortical tissue sparing, improves mitochondrial function, and reduces mitochondrial oxidative stress after TBI in adult rats. This agent could provide a promising approach in the development of a therapeutic intervention for both SCI and TBI.

Since there is an increase in oxidative stress following CNS injury, the use of antioxidants and antioxidant-related compounds has also been shown to provide neuroprotective effects following CNS injury. For example, it has been demonstrated that posttraumatic administration of the N-type calcium channel blocker SNX-111 (S) and a novel blood–brain barrier penetrating antioxidant U-101033E (U) significantly ameliorates mitochondrial dysfunction induced by TBI in rats. However, caution should be exercised since U-101033E was shown to induce protein oxidation even though it is an inhibitor of lipid peroxidation. In addition, the use of N-acetylcysteine (NAC) has also resulted in improvement of mitochondrial function following TBI. Moreover, NAC protected striatum in injury from the lesions modulated by the complex II inhibitor 3-nitopropionic acid. A creatine-supplemented diet significantly attenuates cortical damage after TBI in rodents and induces tissue sparing and possibly provides neuroprotection following SCI.

Mitochondrial uncoupling has also been used as an effective neuroprotective strategy following CNS injury. As noted previously, the production of ROS by the mitochondria is tightly dependent on the mitochondrial membrane potential. As a result, it has been suggested that a reduction in the membrane potential through transient uncoupling would decrease the membrane potential and reduce ROS production and Ca\(^{2+}\) uptake. Mitochondrial uncoupling in vitro reportedly reduces neuronal mitochondrial Ca\(^{2+}\) loading and can inhibit excitotoxic cell death. The use of the uncoupler 2,4-dinitrophenol (2,4-DNP) following stroke/cerebral ischemia has been shown to result in early stabilization of mitochondrial homeostasis and a reduction in the release of cytochrome c into the cytoplasm. Also, administration of uncouplers DNP and carbonylcyanide-p-trifluoromethoxyphenylhydrazone following TBI and SCI has been shown to lead to less tissue loss, improved behavioral outcomes, a reduction in mitochondrial oxidative damage, Ca\(^{2+}\) loading, and dysfunction, and significantly reduces mitochondrial dysfunction associated with injury. As a result, mitochondria uncoupling could potentially be another therapeutic intervention strategy for TBI.

Since glutamate-related excitotoxicity is one of the mechanisms involved in the secondary mechanism following SCI, it has been hypothesized that antagonists against non-NMDA receptors would provide protection following SCI. Fifteen-minute post-SCI treatment with one non-NMDA receptor antagonist, 2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzol[f] quinoxaline-7-sulfonamid disodium (NBQX), resulted in improvements in mitochondrial function and a reduction in the levels of ROS and lipid peroxidation products. The therapeutic interventions are not limited to those discussed in this article. There is much ongoing promising research for the development of therapeutic interventions against nervous system injuries.

Conclusions

CNS injuries such as TBI, SCI, and stroke are among the leading causes of disabilities in the population. An urgent program for the development of therapeutic interventions is needed. There are several pathological events that occur following CNS injury/trauma that lead to neuronal cell death. These events occur in a biphasic manner, consisting of an initial or primary insult followed by a prolonged and more deleterious secondary injury. Central to these pathologies are the mitochondria involving postinjury pathological events, such as glutamate-induced excitotoxicity, Ca\(^{2+}\) dysregulation, production of ROS/RNS, increased oxidative stress, loss of mitochondrial membrane potential, induction of mPTP, release of pro-apoptotic bodies, and activation of downstream caspases leading to eventual cell death. The increased Ca\(^{2+}\) levels also lead to reduced mitochondrial bioenergetics and compromised ETC capacity demonstrated by altered oxygen consumption in TBI and SCI. Promising therapeutic strategies are being developed to provide neuroprotection against nervous system injuries. The use of antioxidants and antioxidant-related compounds, dietary intervention using creatine supplementation, the use of mPTP blockers such as cyclosporin...
A, mitochondria uncouplers, the use of NMDA antagonists, among many others, are potential approaches to therapeutic treatment of TBI and SCI. ‘Omic’ methods, such as genomics, proteomics, lipidomics, and metabolomics, may offer means of better understanding the molecular mechanisms of TBI, SCI, and stroke, as well as monitoring the efficacy of therapeutic interventions.

See also: Apoptosis in Nervous System Injury; Brain Trauma; Exocytosis: Ca2+-Sensitivity; Mitochondrial Organization and Transport in Neurons; Oxidative Damage in Neurodegeneration and Injury; Programmed Cell Death; Spinal Cord Injuries; Stroke; Stroke: Injury Mechanisms.

Further Reading
