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Excitotoxicity, Ionic Imbalance and Oxidative Damage

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Introduction

The combination of direct cellular injury and ischemia/hypoxia causes a large spike in extracellular glutamate, the principal excitatory neurotransmitter in the CNS, within minutes of primary SCI. Calcium influx occurs when glutamate binds to both ionotropic (NMDA, AMPA, and Kainate receptors) and metabotropic receptors. Because glutamate receptors are widely expressed on the surface of all glia and endothelial cells, its function is not limited to neurons. Excess glutamate can also be released extracellularly by astrocytes when their intracellular Ca^{2+} levels rise. Due to lipid peroxidation, activated astrocytes' ability to re-uptake glutamate from the interstitial space is reduced, resulting in further glutamate buildup in the SCI environment. In the acute stage of damage, increased glutamate levels in the white matter were identified using microdialysis. According to Panter and colleagues' research, glutamate levels rise for the first 20–30 minutes after SCI and then recover to baseline after 60 minutes.

Description

The concentration of free Ca^{2+} in different sections of the cell can vary significantly under normal conditions. Ca^{2+} levels in the cytosol range from 50-100 nM, while they reach 0.5–1.0 mM in the endoplasmic reticulum lumen. The cell suffers from a long-term aberrant rise in Ca^{2+} concentration in the cytosol, mitochondria, or endoplasmic reticulum. Mitochondria are important players in calcium-dependent neuronal death. NMDA receptor overactivity causes mitochondrial calcium excess in neurons during glutamate-induced excitotoxicity, which can lead to apoptotic or necrotic cell death. Ca^{2+} enters mitochondria via the mitochondrial calcium uniporter shortly after SCI (MCU). While mitochondrial calcium stores are limited during a neuron's resting state, they can store a large amount of Ca^{2+} after activation. Calcium excess also activates a slew of protein kinases and phospholipases, leading to calpain-mediated protein degradation and oxidative damage as a result of mitochondrial dysfunction.

Increased glutamate release and Ca^{2+}-dependent excitotoxicity damage astrocytes, oligodendrocytes, and myelin in the wounded white matter. Oligodendrocytes display evidence of caspase-3 activation and other apoptotic features during the first few hours after injury, and their density decreases. While ionic imbalance causes glutamate excitotoxicity in the white matter, it is mostly connected with the activity of neuronal NMDA receptors in the grey matter. In the first week of SCI in the rat, activation of NMDA receptors and subsequent Ca^{2+} excess appears to promote intrinsic apoptotic pathways in neurons and oligodendrocytes, resulting in cell death. The use of an NMDA receptor antagonist (MK-801) soon after a SCI has been linked to enhanced functional recovery and decreased edoema.

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Mitochondrial calcium excess also slows mitochondrial respiration and causes ATP depletion, which disables the Na^+/K^+ ATPase and raises intracellular Na+ levels. The Na^+ dependent glutamate transporter, which normally uses the Na^+ gradient to transmit glutamate into cells, now functions in the other direction. Furthermore, an excess of intracellular Na^+ causes the activity of the Na+/Ca^{2+} exchanger to reverse, enabling more Ca^+ to enter the cell. Depolarization of the cells activates voltage-gated Na^+ channels, allowing Cl and water to enter the cells alongside Na^+, causing swelling and edoema. Increased Na^+ concentration causes the Na^+/H^+ exchanger to become overactive, resulting in an increase in intracellular H^+. Intracellular acidosis exacerbates the injury-induced ionic imbalance by increasing membrane permeability to Ca^{2+}. Because of the large concentration of voltage gated Na^+ channels in the nodes of Ranvier, axons are more vulnerable to ionic imbalance injury. Evidence is mounting that administering Na^+ channel blockers like Riluzole reduces tissue damage and improves functional recovery in SCI patients, highlighting sodium as a major participant in secondary injury pathways [1-5].

Conclusion

Free radicals and nitric oxide are produced as a result of SCI (NO). Mitochondrial Ca^{2+} overload activates NADPH oxidase (NOX) and causes the electron transport chain to produce superoxide (ETC). The activities of NOX and ETC produces reactive oxygen and nitrogen species (ROS and RNS), which activate cytosolic poly (ADP ribose) polymerase (PARP). PARP depletes and consumes NAD^+, resulting in glycolysis failure, ATP depletion, and cell death. Furthermore, PAR polymers generated by PARP activity cause mitochondrial apoptosis inducing factor (AIF) release and cell death. Acidosis produced by SCI, on the other hand, causes the release of intracellular iron from ferritin and transferrin. More superoxide radicals are produced when Fe^{2+} is spontaneously oxidised to Fe^{3+}.The Fenton reaction creates extremely reactive hydroxyl radicals as a result of the Fenton reaction between Fe^{3+} and hydrogen peroxide. The resulting ROS and RNS react with a variety of targets, the most harmful of which are lipids in the cell membrane. Measurements of free radical activity and end products, such as Malondialdehyde (MDA), are more trustworthy following SCI because free radicals are short-lived and difficult to assess. MDA levels are raised as early as 1 hour and up to 1 week after SCI, according to current findings.

Acknowledgement

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Conflict of Interests

None.

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