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PERSPECTIVE

Provision of nutrients after acute spinal cord injury: the implications of feast and famine

Traumatic spinal cord injury (SCI) often leaves patients with devastating neurological deficits. The traumatic event – or primary injury – can be due to mechanisms such as compression, distraction, shear, laceration or (rarely) even transection. Thereafter SCI patients are vulnerable to progressive, delayed damage as a result of secondary insults and secondary injury. Secondary insults such as hypoxia and hypotension occur at the level of the organism from a myriad of causes. Secondary injury occurs at the molecular level and includes processes such as ischemia, excitotoxicity, ionic dysregulation, free radical formation, inflammation, oxidative damage, and activation of necrotic and apoptotic cell death signaling events. Despite the great progress we have made in understanding delayed insults that follow SCI, physicians have little to offer save for supportive care, especially now that methylprednisolone administration has become controversial. This supportive care is largely focused upon optimizing nutrient delivery to the injured spinal cord.

Unfortunately, the delivery of nutrients to the injured spinal cord is well known to be problematic following injury. Patients with SCI frequently exhibit autonomic and hemodynamic instability in the first week after their injury and secondary insults commonly result from neurogenic shock, hemorrhagic shock or concomitant injuries (Inoue et al., 2014). There is thus a strong rationale for ICU monitoring and blood pressure support early after SCI. Conceptually this blood pressure support can be thought of as avoiding hypotension and a deficiency of nutrients or as providing nutrient excess by achieving supranormal blood pressures.

A handful of studies have correlated blood pressure augmentation with improved neurological outcomes following SCI however all provide only Class III evidence. None of these studies investigated the role of blood pressure elevation independent of other confounds inherent to an aggressive care strategy making a causal relationship impossible to establish. Nonetheless, the first guidelines for the management of acute SCI published in 2002 recommended at the option level that hypotension – defined as a systolic blood pressure < 90 mmHg – should be avoided and that a mean arterial blood pressure (MAP) of 85–90 mmHg should be targeted in the first 7 days following SCI (Hadley et al., 2002). These recommendations were essentially unchanged in the 2013 update of the guidelines.

The benefit inherent to this practice is thus uncertain, especially when one considers that impaired mitochondrial function is known to cause cellular energy failure even when sufficient nutrients are provided to the injured spinal cord. ATP is the fuel for most energy-dependent cellular functions (McEwen et al., 2007, 2011), along with NADH generated by the citric acid cycle. In most higher-order animals, nearly 95% of all adenosine triphosphate (ATP) is synthesized in mitochondria (McEwen et al., 2011). Following central nervous system (CNS) injury, numerous secondary injury pathways act to increase intracellular calcium levels. When calcium levels rise to a critical level in the intracellular matrix of the mitochondria, a channel known as the mitochondrial permeability transition pore (mPTP) opens. This channel, first described by Haworth and Hunter, allows free passage of molecules less than 1,500 kDa between the mitochondrial matrix and inner membrane space when open, disrupting the transmembrane electrochemical gradient necessary for the electron transport chain to generate ATP (McEwen et al., 2011). mPTP opening has been shown to occur within 15–60 minutes of SCI (McEwen et al., 2011) and in addition to restricting the production of ATP, mPTP opening leads to further insult from free radical production and oxidative damage to cellular contents. The result can be cellular necrosis or apoptosis.

In this context, it is interesting that hospitals commit extensive resources to monitoring and treating blood pressure in SCI patients despite little evidence of benefit. Meeting the mean arterial pressure targets recommended in the guidelines requires the administration of vasoactive agents in almost all cases (Hawryluk et al., 2014; Inoue et al., 2014). When one considers that there are approximately 12,500 spinal cord injuries in the United States annually and that a day of ICU care costs $2,500–4,000 the costs inherent to following these guidelines is substantial. Using the conservative estimate of $2,500 per day, this means that the cost of 7 days of ICU care for MAP augmentation in these patients would be $218,750,000. The cost for one additional ICU day for all of these patients is $31,250,000. A guideline mandating 7 days of ICU care thus has substantial economic consequences and further data which better delineates the putative benefits of MAP augmentation is badly needed.

This served as impetus for a recent paper in which Hawryluk et al. (2014) explored the relationship between MAP values and neurological recovery in patients with acute SCI. Data for 100 such patients admitted to the University of California San Francisco over a 6-year period was collected. These patients were managed with a MAP goal of > 85 mmHg for 5 days similar to published guidelines. A data collection system stored physiologic data from the bedside monitor used in the ICU care of these patients every minute. Matlab software was used to compute how time spent below 80 different MAP thresholds (40–120 mmHg in 1 mmHg increments) correlated with outcome over various epochs up to 30 days from the time of injury.

This study made a number of important observations. First, a large number of measurements were below 85 mmHg despite overall acceptable average MAP values. This speaks to the difficulty inherent to consistently achieving a MAP > 85 mmHg in SCI patients who may have neurogenic and/or hemorrhagic shock and perhaps difficulty overcoming homeostatic mechanisms. MAP values of 70–75 mmHg appeared to be the lowest associated with neurological benefit consistent with a previous report (Cohn et al., 2010). MAP values of 85–90 mmHg most robustly distinguished neurological outcome. Higher average MAP values correlated with improved recovery for only 2–3 days following SCI. By contrast, MAP values below 85 mmHg (referred to hence forth as relative hypotension) correlated with outcome for 5–7 days after injury. These data suggest that both MAP augmentation and the avoidance of relative hypotension have neuroprotective effects which diminish with time following a SCI. Relative hypotension seems to be more detrimental.

Although the results of the Hawryluk study reflect a correlation rather than causation, they provide support for the current guidelines suggesting that MAP thresholds > 85 mmHg may be beneficial for 5–7 days following acute SCI. Moreover, this study suggests that avoiding relative hypotension is more important than efforts to achieve supranormal spinal cord blood flow. Given the decline in benefit over time, a shorter period might be considered if MAP augmentation leads to adverse effects such as cardiac dysrhythmia and ischemia, deep vein thrombosis, pressure sores, nosocomial infections and deconditioning (Inoue et al., 2014).

The Achilles heel of efforts to ameliorate CNS injury would seem to be mitochondrial dysfunction. Even when clinicians achieve an adequate or surplus supply of nutrients, cellular energy failure may render those efforts futile. The study from Hawryluk

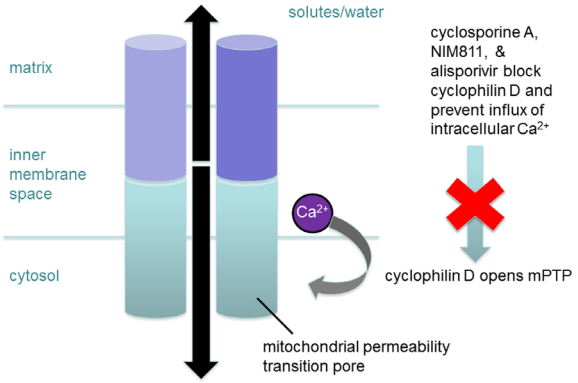

Figure 1 The mitochondrial permeability transition pore (mPTP).
In the injured spinal cord, mPTP opening is triggered by supranormal calcium levels, a sequelae of multiple mechanisms of secondary injury. Calcium interacts with cyclophilin D to achieve mPTP opening which eliminates the electrochemical gradient necessary for ATP production by the electron transport chain. This can lead to cellular energy failure and cell death. Several experimental therapeutics prevent the opening of the mPTP by inhibiting cyclophilin D. This may protect CNS tissue following injury and enhance the benefit associated with augmenting nutrient supply to injured spinal cord tissue.

et al. (2014) importantly suggests that SCI patients have sufficient mitochondrial function remaining to utilize nutrients when provided in excess. It would be very interesting to determine if greater neurological benefit is seen when MAP augmentation is paired with a therapeutic agent that preserves mitochondrial function. Several such therapeutics are currently being investigated, including mPTP blockers such as cyclosporine A, NIM811, bongkrekic acid, and alisporivir. Cyclosporine A and NIM811 are an immunosuppressant and non-immunosuppressant, respectively, that are discussed below. Alisporivir inhibits mPTP by binding to cyclophilin D and is currently used in the treatment of hepatitis C (Naoumov, 2014). Bongkrekik acid is produced in fermented coconuts by bacteria and prevents ATP from leaving the cell by blocking the adenine nucleotide translocator, which is responsible for exporting ATP from the mitochondrial matrix.

The notion that the mPTP could be pharmacologically inhibited ultimately results from a case report (Gogarten et al., 1998) describing a much better than expected outcome in a human TBI patient on cyclosporine A for a liver transplant. Subsequent laboratory investigations determined that cyclosporine A inhibits the mPTP by binding to and sequestering cyclophilin D. The additional discovery that cyclosporine A's immunosuppressive moiety is distinct from its neuroprotective moiety has raised the interesting possibility that mitochondria may be targeted without potential adverse side effects from immunosuppression.

NIM811 is a cyclosporine derivative - comprised of its neuroprotective but not its immunosuppressive moiety - which has demonstrated the ability to inhibit the mPTP channel at smaller concentrations than are required with cyclosporine A (**Figure 1**). In a laboratory investigation, rats that received a spinal cord contusion after pretreatment with NIM811 demonstrated significantly greater ATP production and oxygen carrying capacity (McEwen et al., 2007). Additionally, levels of free radicals and cytochrome c were significantly reduced (McEwen et al., 2007). Cytochrome c is an important signaling molecule which can trigger cell death following its release by injured mitochondria. In a similar study, rats that received a spinal cord contusion were given NIM811 following their injury, as opposed to pretreatment. Tissue analysis 7 days post-injury demonstrated enhanced volumes of spared grey and white matter, likely through inhibition of apoptotic mechanisms (Ravikumar et al., 2007). Although further study of NIM811and similar agents is needed, there is great hope that such a pharmacologic agent might be translated to humans in the future. Inhibition of calcium-induced mitochondrial dysfunction has the potential to substantially impact outcomes following CNS injury.

Many believe that a combination of therapies will be required to meaningfully improve outcome from CNS injuries (Rowland et al., 2008; Hawryluk et al., 2014). The paper by Hawryluk et al. (2014) suggests that efforts to avoid relative hypotension and to augment blood flow to the injured spinal cord is associated with improved outcome and will be an important component of future combinatorial strategies to improve outcome from SCI. Ultimately, however, a prospective study randomizing patients to different MAP targets will be required to prove that MAP augmentation plays a causative role in improving neurological outcomes in SCI patients. Hopefully more substantial benefit will come when this approach is combined with other therapeutics such as those that target mitochondrial dysfunction or other secondary injury mediators.

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References

Cohn JA, Wright S, McKenna S, Bushnik T (2010) Impact of mean arterial blood pressure during the first seven days post spinal cord injury. Top Spinal Cord Inj Rehabil 15:96-106.
Gogarten W, Van Aken H, Moskopp D, Roos N, Schleef J, Marcus M, Meyer J (1998) A case of severe cerebral trauma in a patient under chronic treatment with cyclosporine A. J Neurosurg Anesthesiol 10:101-105.
Hadley MN, Walters BC, Grabb PA, Oyesiku NM, Przybylski GJ, Resnick DK, Ryken TC, Mielke DH (2002) Guidelines for the management of acute cervical spine and spinal cord injuries. Clin Neurosurg 49:407-498.
Hawryluk GWJ, Whetstone W, Saigal R, Ferguson A, Talbott J, Bresnahan J, Dhall S, Pan J, Beatti M, Manley G (2014) Mean arterial blood pressure correlates with neurological recovery following human spinal cord injury: analysis of high frequency data. J Neurotrauma doi:10.1089/neu.2014.3778.
Inoue T, Manley GT, Patel N, Whetstone WD (2014) Medical and surgical management after spinal cord injury: vasopressor usage, early surgerys, and complications. J Neurotrauma 31:284-291.
McEwen M, Sullivan G, Rabchevsky A, Springer J (2011) Targeting mitochondrial function for the treatment of acute spinal cord injury. Neurotherapeutics 2:168-179.
McEwen ML, Sullivan PG, Springer JE (2007) Pretreatment with the cyclosporin derivative, NIM811, improves the function of synaptic mitochondria following spinal cord contusion in rats. J Neurotrauma 24:613-624.
Naoumov NV (2014) Cyclophilin inhibition as potential therapy for liver diseases. J Hepatol 61:1166-1174.
Ravikumar R, McEwen ML, Springer JE (2007) Post-treatment with the cyclosporine derivative, NIM811, reduced indices of cell death and increased the volume of spared tissue in the acute period following spinal cord contusion. J Neurotrauma 24:1618-1630.
Rowland JW, Hawryluk GW, Kwon B, Fehlings MG (2008) Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. Neurosurg Focus 25:E2.