Submitted to the University of Adelaide for the degree of

Doctor of Science

Robert Vink, BSc (Hons), PhD

TABLE OF CONTENTS

DECLARATION

I, Robert Vink, declare that none of the work contained herein has formed part or all of an award for another degree.

July 11th, 2012

STATEMENT SUPPORTING THE SUBMISSION

The following statement will address my contributions to the study of secondary injury in neurotrauma, and more specifically the discovery and characterisation of magnesium's role in traumatic brain and spinal cord injury, as well as the subsequent work characterising the role of substance P in brain injury. The references cited refer to my list of publications following the statement.

Dot Point Summary

- First to apply phosphorus magnetic resonance spectroscopy to the study of traumatic brain injury (TBI) and spinal cord injury (SCI)
  - led to a complete description of high energy phosphate metabolism after CNS trauma
  - led to the co-development of the lateral fluid percussion model of rodent TBI
  - was the first *in vivo* demonstration that brain trauma was different from ischaemia
  - identified that energy metabolism differed between brain and spinal cord injury
- First to apply proton magnetic resonance spectroscopy (MRS) to the study of TBI and SCI
  - identified that lactate concentration did not reach injury thresholds after brain trauma
  - first described that n-acetyl-aspartate was an unsuitable MRS concentration standard after brain injury
  - first described that n-acetyl-aspartate declined after brain injury
- Discovered that brain magnesium concentration declined after TBI
  - a seminal demonstration that intracellular free magnesium concentration can change *in vivo*
  - first to demonstrate that tissue total magnesium can decline after injury
  - first to calculate the impact of magnesium change on critical bioenergetic parameters *in vivo*
  - first to measure altered mitochondrial bioenergetics after TBI
- Discovered that magnesium treatment improved outcome after TBI
  - first description of magnesium as a neuroprotective agent after acute brain injury
  - first to demonstrate that lowering magnesium concentration was deleterious to outcome
  - first to demonstrate a dose-response effect for magnesium and define the therapeutic window after TBI
- First to apply diffusion weighted imaging to the study of TBI
  - identified critical early phase of vasogenic oedema following trauma
- Discovered that neuropeptides, and in particular substance P, are involved in early oedema formation after TBI and stroke
  - first to identify neurogenic inflammation as a characteristic feature of acute brain injury
  - first to describe NK1 antagonists as a novel therapeutic approach to treat oedema
  - first to describe beneficial effects of combined NK1 antagonists and tPA in stroke
  - first to describe the efficacy of NK1 antagonists in management of intracranial pressure
- Discovered that substance P may play a critical role in cell death in early Parkinson's disease
  - first to describe NK1 antagonists as a novel therapeutic approach to treat Parkinson's disease

- Over 6,500 citations according to Google Scholar
- "h" index of 41
- Associate Editor for the journal, *Magnesium Research*
- On the editorial boards of *Journal of Neurotrauma*, *Neurotherapeutics* and *Frontiers in Neurotrauma*

Detailed Statement

Introduction

Traumatic injury to the central nervous system (CNS) is the biggest killer of individuals under 44 years of age (for reviews see [202]). According to World Health Organisation statistics, traumatic brain injury alone is reported to now affect over 5 million individuals worldwide every year. The economic and social cost of brain injury to the community is enormous with billions of dollars being spent each year on the management and rehabilitation of trauma patients. Despite this, no effective treatment of CNS trauma currently exists. It is now accepted that CNS injury results in the development of neurologic deficits through two mechanisms [193]. The first of these is known as primary mechanisms. These occur at the time of the traumatic event and include mechanical processes such as laceration, tearing and stretching of nerve fibres. The second mechanism is termed secondary injury, and is made up of biochemical and physiological processes initiated by the primary insult and manifesting with time after the injury. It has been demonstrated that much of the morbidity after brain injury is associated with the development of this secondary injury (for reviews see [202]). Given that the secondary injury develops from minutes to days after the primary event, there potentially exists a window of opportunity to pharmacologically prevent this type of injury and significantly improve resultant outcome. However, the factors that make up secondary injury must first be identified and then "anti-factors" developed to inhibit the injury process.

Much has been learnt about CNS injury over the last 30 years [200], with a considerable amount of research effort being directed toward understanding primary and secondary injury and their respective roles in determining outcome. As the importance of secondary injury became evident, initial efforts in developing a pharmacological intervention were based on a "magic bullet" approach that would ideally inhibit the single, most important secondary injury factor and result in a major improvement in outcome [123]. Despite the excitement of several candidates being quickly identified, including excitatory amino acids, free radicals, lactate, and calcium, amongst others [74], the subsequent failure of clinical trials made it clear that such an approach was unlikely to succeed. Indeed, it is now widely accepted that "multipotential" therapies that simultaneously inhibit a number of secondary injury factors are more likely to deliver a successful outcome [111]. To develop such compounds, a complete and thorough understanding of secondary injury factors after CNS injury is essential. In the following paragraphs, I summarise my personal contributions over 25 years to characterising secondary injury after CNS trauma.

Personal contributions

My PhD training was in the application of magnetic resonance spectroscopy (MRS) to bacterial bioenergetics [1-5] and in 1985 I was recruited by the Department of Neurology at the University of California, San Francisco to adapt and apply the technology to the study of bioenergetics following traumatic brain injury (TBI). After personally building the appropriate radiofrequency surface coils, I quickly obtained the first phosphorus MRS spectra of traumatically injured brain and published the results in a series of papers appearing in the late 1980s [6,10,14]. These publications demonstrated that unlike in ischaemia, there is no overt loss of high energy phosphates following TBI, and no profound tissue acidosis, unless the injury was of a lethal severity [14]. This discovery was one of the first demonstrating fundamental differences between TBI and stroke, and led to a re-evaluation of how TBI should be conceptualised. At the time, TBI was widely considered as a sub-group of brain injuries that resulted in ischaemia; this is no longer the case. The MRS studies of TBI also initiated the development of the rodent, lateral fluid percussion injury model [20], largely in an attempt to better localise the injury and be able to detect small changes in energy metabolism [195]. This model of rodent TBI has since become one of the most widely used experimental TBI models in the world [195,200].

Following on from the success of the phosphorus MRS studies, I subsequently built double-tuned radiofrequency surface coils and applied proton MRS to brain injury [7]. By programing a lactate editing pulse sequence within a water suppression sequence, I was able to perform the first reported lactate editing after traumatic brain injury [9,15]. The resulting publications were the first to demonstrate that lactate levels did not reach injurious concentrations after mild-severe brain injury, and that the mild acidosis after trauma could be correlated with brain lactic acid formation [9]. It was clear from these studies that therapies targeting lactic acidosis were therefore of little potential benefit in the treatment of TBI. In performing the proton MRS studies, I also became the first to demonstrate that the commonly used internal standard for brain proton MRS, n-acetyl aspartate, decreased after TBI and could not be used as an internal MRS standard [15]. Use of this metabolite as a concentration standard was subsequently abandoned, and further studies by others have since shown that the decline is, in fact, a neuronal marker of mitochondrial dysfunction and/or cell death.

My ability to develop and build highly sensitive radiofrequency surface coils was then directed toward spinal cord injury (SCI). After designing a saddle-shaped radiofrequency coil for use on the spinal vertebrae, I became the first scientist to publish an MRS characterization of experimental SCI [21,24,33]. These studies showed that SCI was always associated with a loss of high energy phosphates, and that even mild mechanical pressure was sufficient to cause energy depletion. The difference between TBI and SCI was quite profound and had clear implications with respect to therapeutic approaches. Despite both making up the CNS, brain and spinal cord injury could not be regarded as the same.

Whilst using phosphorus MRS to characterise the energetic response after CNS trauma, I also discovered that brain free magnesium concentration declined after injury [11,12,13,22,24]. At the time, intracellular free magnesium concentration was always considered to be constant. This discovery was therefore a controversial finding, and led to a number of invited presentations at international conferences. My characterisation of changes in intracellular free magnesium concentration after trauma [12,13] was accepted as the first publication in the world to demonstrate *in vivo* changes in free magnesium concentration. This proved to be a seminal finding and has led to a paradigm shift with respect to understanding the role of intracellular magnesium in cell physiology and metabolism. By declining in concentration, magnesium shifted the equilibrium of multiple enzymatic reactions, particularly those related to energy metabolism. Having published the effects of these magnesium changes on the equilibrium constants of the energy reactions and their bioenergetic consequences [19], I then published the first full characterisation of oxidative metabolism following TBI [41], including the first description of the role of mitochondrial metabolism after TBI [29]. These publications demonstrated that profound changes in energy metabolism occurred after trauma, despite the fact that high energy phosphates did not significantly alter in their concentration. Nonetheless, with magnesium decline, the high energy metabolites became unavailable for injury repair. Numerous publications have since been published by others confirming the initial observations in trauma, and demonstrating that magnesium decline also occurred in other brain pathologies such as stroke, hypoxia, migraine, and drug intoxication, amongst others. I was often contacted by these investigators to consult on the interpretation of the acquired data.

Having characterised that brain free (and total) magnesium concentration declined after trauma, I was then the first to demonstrate that treatment with magnesium salts after TBI led to a marked improvement in neurological outcome [13,17]. Subsequent publications further characterising this effect became amongst the most highly cited in the field [22,23]. Interestingly, treatments that reduced brain free magnesium concentration prior to injury (diet, alcohol), exacerbated injury [17,32,44,47], confirming that brain magnesium homeostasis was a critical factor in determining

outcome. This was further supported by a number of studies that showed that drugs that improved outcome after TBI [16,27,30] also improved brain free magnesium concentration [18,31,35], with the degree of magnesium improvement correlating with the degree of improvement in functional outcome. This was a highly significant finding that initiated a plethora of studies by others examining the neuroprotective properties of magnesium salts in acute brain injuries (for reviews see [64,170,192,199,201]). To this day, this avenue of investigation continues, with a number of clinical trials now in progress in TBI, premature infant brain injury, stroke, and subarachnoid haemorrhage, amongst others [203].

After 2.5 years in the USA, I was awarded a Queen Elizabeth II Fellowship to return to Australia (James Cook University) so as to continue with my TBI studies using one of the first high-field, 7.0 tesla MR instruments to be installed in the world. In my new role as a supervisor of graduate research students undertaking their PhD studies, I was able to further characterise magnesium changes over time in the fluid percussion model [51], as well as introduce alternative models of TBI into the lab to characterise magnesium changes in these models [48,52,53,58,63,67,76]. I established that changes in brain intracellular free magnesium concentration were a ubiquitous feature of TBI irrespective of the model or species of animal. Further studies of magnesium therapy determined the optimal magnesium dose for treatment [55,56,91], as well as the therapeutic window [59,60]. Examining different magnesium salts [56,94] supported the hypothesis that it was the magnesium ion that was important, and not the form in which it was administered. While we had some indications as to what caused brain magnesium decline after trauma [28], we turned our attention to free magnesium changes in other body compartments (the blood) in an effort to understand whole body magnesium homeostasis after TBI [57]. We also began investigating other aspects of secondary injury including gender differences [37,39,65,78], other potentially neuroprotective agents [42,43,45,77], as well as general secondary injury factors [38,46,54,70,72]. By the late 90s, I was widely regarded as an expert in secondary injury factors after TBI, and the world's foremost expert on magnesium in brain, as evidenced by regular invitations to give oral presentations at international neurotrauma and magnesium meetings.

The access to a high-field MR instrument at James Cook University allowed me to supplement my ongoing spectroscopy studies with advanced MR imaging techniques to study brain oedema. My interest in brain oedema was in response to several reports suggesting that magnesium might reduce oedema after TBI [201]. I became the first to apply diffusion-weighted imaging to TBI [40] and demonstrate that oedema following TBI was initially vasogenic in nature as opposed to cytotoxic, the latter being the widely held view at the time. Classical studies using blood brain barrier markers and wet weight/dry weight techniques subsequently confirmed this conclusion [81]. The outcome of the MR studies sparked an interest in oedema formation after TBI and its regulation. After initially focussing on gender related steroids [96,97,102] and classical inflammation [69,75], it became increasingly apparent that classical inflammation could not account for the observed speed of changes in blood brain barrier permeability and oedema formation after TBI. Since studies of peripheral oedema had shown an association between neurogenic inflammation and oedema, my studies then focussed on neurogenic inflammation. At this time, I relocated to the University of Adelaide where large animal models of trauma had been developed and human post-mortem tissue was readily available. While I still continued with studies of magnesium in brain injury [85,91,92,93,98,119,120,129,142] and other diseases [80,95,105,107,112], I became increasingly interested in neurogenic inflammation in TBI and was subsequently the first to demonstrate that neurogenic inflammation was strongly associated with post-traumatic oedema formation [81,82,121]. I furthermore demonstrated that this could be rapidly and effectively attenuated using substance P, NK1 receptor antagonists [93,103,116,124,133,146]. Similar observations were made using a reversible stroke model of brain injury [99,101,137,157], thus establishing that substance P release was an integral component of neuroinflammation following acute brain injury.

While continuing to investigate mechanisms of secondary injury in various models of brain injury [84,87,89,90,100,104,114,131,134,147,150,151,154], including the role of substance P [109,127,130,136,153,157], the interplay between substance P, oedema formation and the development of increased intracranial pressure after TBI was becoming increasingly important if clinical translation of a new pharmacotherapy was to be pursued. Intracranial pressure control remains one of the most important management targets in clinical TBI [202].

I therefore focussed our subsequent studies on oedema and intracranial pressure development. We quickly discovered that rodent models of trauma could not consistently reproduce the intracranial pressure profile observed clinically [139], implying that while they might be excellent for biochemical characterisation of secondary injury, rodents may not be appropriate for the development of therapies that target intracranial pressure. We therefore examined the changes in intracranial pressure and brain oxygenation after TBI in a number of alternative animal species, and have demonstrated that an ovine, large animal model of traumatic brain injury most successfully mimics the post-traumatic changes in these variables seen clinically [108,115,143]. Most importantly, the model is able to reproduce the clinical effects of the commonly used hyperosmotic therapies, mannitol and hypertonic saline, on intracranial pressure after TBI. Our most recent results (manuscripts in preparation) show that NK1 antagonists are more effective than currently used therapies in reducing elevated intracranial pressure and restoring brain oxygenation, while the experimental agents, magnesium and progesterone, are ineffective. The negative effect of magnesium in the ovine model is consistent with the outcome of a previous clinical TBI trial, while the results of the progesterone clinical TBI trial are not expected for a couple more years. Ours is the first demonstration of a pharmacotherapy that restores both intracranial pressure and brain oxygenation to normal levels in a large animal model of TBI. The results have been patented and were licensed to a pharmaceutical company for clinical development.

Conclusion

When I graduated from my PhD studies in 1985, it was widely accepted that intracellular free magnesium concentration was fixed and constant. Now, it is accepted that magnesium is a dynamic cation whose changes in concentration regulate a vast array of cellular biochemical and physiological processes [203]. This paradigm shift has come about largely in response to my studies demonstrating declines in free magnesium concentration following TBI. Since then, numerous studies by other laboratories have shown declines in various neuropathologies including ischaemia, subarachnoid haemorrhage, hypoxia, mitochondrial disorders, migraine, Parkinson's disease, psychiatric disorders, drug abuse and addiction, with potential therapeutic effects having also been reported for hearing loss, cerebral palsy, depression, pain, autism, and potentially Alzheimer's disease. These reports have all been encapsulated in my recently edited book, *Magnesium in the Central Nervous System* [203], which has been downloaded over 3,500 times since publication 6 months ago.

My more recent studies demonstrating a central role for substance P in neurogenic inflammation following traumatic brain injury and stroke has also triggered a variety of studies further examining the neuropeptide's contribution to other CNS disorders. In my own laboratory, we have begun investigating Parkinson's disease and brain metastasis, both of which demonstrate increased blood brain barrier permeability and high levels of neuroinflammation [132,198]. We have now demonstrated, for the first time, that an increase in substance P potentially plays a critical role in dopaminergic cell death [128], and that its attenuation with NK1 antagonists may offer a novel therapeutic approach to intervention in early Parkinson's disease [148]. Similarly, we have

demonstrated that blood-borne tumour cells may increase blood brain barrier substance P concentration to facilitate brain invasion [155]. Other laboratories have recently reported similar findings, and with further research into other neuropathologies just starting, only time will tell whether substance P is an integral player in all CNS associated neuroinflammation.

Over the years, I have developed an international reputation in the field of traumatic brain injury, being on the editorial boards of the major journals in that specific discipline, and an invited co-contributor to the chapter on trauma in the prestigious textbook, *Greenfield's Neuropathology* [193]. Indeed, in a recent review published in the journal *Neurotherapeutics*, I was described as "one of the pioneers" in the field of trauma-related secondary injury (Cekic and Stein, 2010). I am also widely considered as an international authority on the role of magnesium in the central nervous system, and am an associate editor for the journal, *Magnesium Research*. In honour of my research contributions over the years, I was recognised by both the International Neurotrauma Society and the International Society for the Development of Magnesium Research by being named the Chair and President, respectively, of both the 7th International Neurotrauma Symposium and the 10th International Magnesium Symposium, recently hosted in Australia. Now with my postdoctoral fellows and research students, I continue to investigate secondary injury following CNS trauma, and still hope to successfully develop a pharmacological treatment that will vastly improve the quality of life of affected individuals.

Cekic M, Stein DG (2010) Traumatic brain injury and aging: is a combination of progesterone and vitamin D hormone a simple solution to a complex problem. *Neurotherapeutics*, 7:81-90.

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