# Chondroitinase abc as a potential therapy for restoring motor function

Chondroitinase ABC as a potential therapy for restoring motor function after spinal cord injury

Introduction

Spinal cord injury (SCI) is a sudden and debilitating event, with life-changing consequences including loss of motor function, often resulting in paralysis, for which there is currently no adequate treatment. More than 2. 5 million people worldwide live with paralysis due to SCI – 50, 000 of these people in the UK. As well as the overwhelming effects of paralysis, including loss of bladder and bowel control and an inability to breathe independently, patients with SCI also experience multiple recurrent secondary medical complications such as infections, neuropathic pain and pressure sores (Sezer, et al., 2015).

After initial costs of the immediate injury, it is estimated that the average annual cost of treating these secondary issues sits at £2, 200 per patient in the UK. This, in addition to the devastating after effects of spinal cord injury, significantly impacts the functional, psychological and social well-being of patients and their carers, and with no cure, there is an ever-growing demand to find effective and clinically translatable therapies for spinal cord injury.

Developing such therapies is a complex task due to heterogenous injuries in terms of location and severity (Moon & Bradbury, 2018), however current clinical management of SCI through surgical stabilisation of the spine, neurological rehabilitation and prevention and treatment of acute and chronic complications has led to a considerable improvement in the prognosis of SCI, as well as enhancement of the quality of life of patients (Scholtes, et al., 2012). Despite huge research efforts, paralysis remains

uncurable and a practical, reproducible and functionally beneficial treatment has yet to be achieved (Sofroniew, 2018).

Presently, research is focused on inhibiting secondary injury, promoting regeneration and replacing destroyed spinal cord tissue (Varma, et al., 2013). This academic review will focus on regenerative therapies for SCI; in particular, the use of chondroitinase ABC as a gene therapy in restoring motor function after injury, the possible benefits it may provide and any set backs it could encounter.

Spinal cord injury

The spinal cord is an essential part of the central nervous system (CNS), allowing neuronal communication between the brain and the rest of the body to fulfil basic sensory, motor and autonomic functions such as muscle contraction and respiration. It is a tube-like bundle of nerve fibres, extending from the medulla oblongata to the lumbar region of the vertebral column and is made of two cell types, neurons and glia, and connective pathways called axons.

Immediate damage to the spinal cord in the form of laceration, compression or contusion is referred to as primary injury and involves cellular and vascular damage of neural tissue. In minutes, micro-haemorrhages occur in the central grey matter causing swelling of the spinal cord that leads to a cascade of damage including inflammation and loss of blood flow regulation (McDonald & Sadowsky, 2002). This triggers a secondary injury cascade involving damaged cells, axons and blood vessels producing toxic free

radicals that attack intact neighbouring tissue, eventually leading to ischemia, necrosis and apoptosis of neural tissue (Varma, et al., 2013).

It is understood that after an injury in the adult mammalian CNS, axons are unable to regenerate due to a combination of limited endogenous ability and an inhibitory region created at the site of injury (Lee & Zheng, 2008). Usually in the CNS, glial cells are responsible for the local immune response and wound healing (Moeendarbary, et al., 2017). However, after injury, accumulations of multiple hypertrophic cells including astrocytes, microglia and oligodendrocytes contribute to a toxic environment leading to glial scar formation. This creates a physical barrier for axon regeneration past the lesion, as well as a chemical barrier through the secretion of chondroitin sulphate proteoglycans (CSPGs) into the extracellular matrix (Burnside, et al., 2018).

High expression of the CSPG family of inhibitory extracellular matrix molecules can be seen during development for multiple processes including cell adhesion, migration and axon guidance. In comparison, CSPGs stay at relatively low levels in the mature CNS where they are concentrated in perineuronal nets, important for maintaining stability and plasticity (Bartus, et al., 2012).

But, when an injury to the spinal cord occurs, heavy upregulation of CSPGs cause undesirable side effects through restriction of neural plasticity and growth. This is due to covalent attachments of chondroitin sulphate glycosaminoglycan (CS-GAG) side-chains on CSPGs that are known to prevent neural regeneration within the spinal cord.

Chondroitinase ABC in restoring motor function- 100 more words

Chondroitinase ABC (ChABC) is a bacterial enzyme, when delivered via viral vector, is able to degrade the CS-GAG side chains comprising a major part of the glial scar that blocks axonal regeneration. Removal of CS-GAG side chains by chondroitinase ABC has been shown to oppose inhibition of neuronal growth in vitro and boost CNS axonal regeneration and neuroplasticity in vivo (Burnside, et al., 2018). The enzyme has shown positive outcomes through enhancing functional recovery in multiple sci models including rodents, cats and non-human primates, making it a potential therapeutic for restoring motor function after spinal cord injury (Hu, et al., 2018).

Obstacles to the translation of this potential therapy from animal models into human sci patients recently reviewed:

a) lack of thermal stability for mammalian body temperature to stop repeat administration

b) lack of control of chondroitinase gene expression once delivered by vector

c) demonstration of efficacy and safety in realistic models

First hurdle: (over the past 10 years, this has been achieved) Adjustment of the formula, preparation and delivery of the enzyme by using trehalose sugar and lipid molecules – render chondroitinase abc heat-stable and long-acting. (Look at results in more depth) (Hyunjung, et al., 2010)

Second hurdle: A preclinical study carried out by Burnside et al revealed that when a novel immune-evasive vector system is applied, in which the chondroitinase gene is under a doxycycline inducible switch, gene expression remains tightly controlled. With this new method of delivery, two positive outcomes were seen – first that short term treatment (2. 5 weeks), was sufficient in improvement of sensory axon conduction and ladder walking performance in rodents. Secondly, long term treatment (8 weeks) was vital for tasks requiring skilled reaching and grasping, leading to significantly improved function, with rats able to accurately grasp and retrieve sugar pellets. Overall novel gene therapy system indicates enhanced neuroplasticity and connectivity and provides an encouraging step towards generating a safer chondroitinase gene therapy.

Third hurdle: One recent randomised controlled canine clinical trial using dogs that had suffered naturally occurring spinal cord injuries e. g. road traffic accidents/herniated intervertebral discs (commonly occur in Dachshunds). Aimed to measure the effects of lipid microtubule-embedded chondroitinase abc in dogs with severe chronic clinical spinal cord injury this could be considered a final prelude to commencement of formal regulatory approval processes for translation into similarly-injured humans.

Results: improvement in limb coordination during walking – canine clinical trial

As these injuries varied in terms of spinal level, severity and time since injury, the canine clinical trial provided opportunity to evaluate a therapy in a hetereogenous population. (Moon & Bradbury, 2018)

What this means for potential therapies to be translated from the lab to the clinic – improvement of function for patients suffering from paralysis due to SCI  improvement in functional, psychological and social well-being.

Conclusion

Every eight hours someone is told they may never walk again due to paralysis caused by spinal cord injury. The complex and delicate nature of the central nervous system, and the spinal cord, means damage can be catastrophic, irreversible and as previously highlighted, can ultimately lead to a severe decrease in quality of life in all aspects of the biopsychosocial framework.

Overall, the combination of results outlining the potential benefits of chondroitinase ABC could have a significant impact for individuals suffering from spinal cord injury, for whom recovery of motor function is an important determinant of independence, and supports ongoing development of chondroitinase gene therapy towards clinical application for the treatment of spinal cord injury.

Bibliography


- Bartus, K., James, N. D., Bosch, K. D. & Bradbury, E. J., 2012. Chondroitin sulphate proteoglycans: Key modulators of spinal cord and brain plasticity. *Experimental Neurology,* 235(1), pp. 5-17.
- Burnside, E. R., De Winter, F., Didangelos, A. & James, N. D., 2018. Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury. *Brain,* 141(8), pp. 2362-2381.

- Hu, H. Z. et al., 2018. Therapeutic efficacy of microtube-embedded chondroitinase ABC in a canine clinical model of spinal cord injury. *Brain,* 141(4), pp. 1017-1027.
- Hyunjung, L., McKeon, R. J. & Bellamkonda, R. V., 2010. Sustained delivery of thermostabilized chABC enhances axonal sprouting and functional recovery after spinal cord injury. *PNAS,* 107(8), pp. 3340-3345.
- Lee, J. K. & Zheng, B., 2008. Axon regeneration after spinal cord injury: insight from genetically. *Restorative Neurology and Neuroscience,* 26(2-3), pp. 175-182.
- McDonald, J. W. & Sadowsky, C., 2002. Spinal-cord injury. *The Lancet,* 359(9304), pp. 417-425.
- Moeendarbary, E. et al., 2017. The soft mechanical signature of glial scars in the central nervous system. *Nature Communications,* Volume 8, p. 14787.
- Moon, L. D. F. & Bradbury, E. J., 2018. ‘ Chase’: in dogged pursuit of a therapy for spinal cord injury. *Brain,* 141(4), pp. 941-94.
- Scholtes, F., Brook, G. & Martin, D., 2012. Spinal cord injury and its treatment: current management and experimental perspectives. *Advances and Technical Standards in Neurosurgery,* Volume 38, pp. 29-56.
- Sezer, N., Akkus, S. & Ugurlu, F. G., 2015. Chronic complications of spinal cord injury. *World Journal of Orthopedics,* Volume 6, pp. 24-33.
- Sofroniew, M. V., 2018. Dissecting spinal cord regeneration. *Nature,* 557(7705), pp. 343-350.

- Varma, A. K., Das, A. & Wallace, G., 2013. Spinal Cord Injury: A Review of Current Therapy, Future Treatments, and Basic Science Frontiers. *Neurochemical Research,* 38(5), pp. 895-905.