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SPINAL CORD INJURY: CURRENT MAMMALIAN MODELS

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ABSTRACT

It is estimated that approximately 2.5 million people are affected by Spinal Cord Injury (SCI), with more than 130,000 new cases reported each year (International Campaign for Cures of Spinal Cord Injury Paralysis). Although there is currently no cure for SCI, various strategies including rehabilitative, cellular and molecular therapies have been tested in a variety of animal models. But questions remain as to the validity of animal models and whether they relate to the clinical conditions found in humans. This review aims to look at the different and most current models that are used to study SCI and their potential uses in mimicking the human condition. Several different animal models have been developed to study the problems of SCI, allowing exploration of mechanisms and properties of specific pathways such as; the MAPK pathway and spinal cord diseases such as; Syringomyelia and Central Cord Syndrome to name a few to be elucidated. SCI is complicated by cavitation and a glial scar that lines the cavity, reducing the possibility of axon regeneration. Mammalian models, particularly in mice and rats, have been used for many years to study the impact of SCI and potential therapies, however, questions remain as to the validity of these models and their potential usefulness.

Keywords: Spinal Cord Injury (SCI), Cavitation, Axon Regeneration, Glial Scar, CNS

1. INTRODUCTION

SCI affects more than 2.5 million people worldwide and 130,000 new cases are reported each year (International Campaign for Cures of Spinal Cord Injury Paralysis). Although advances have been made through research, there are currently no fully restorative therapies for SCI and therefore, safety measures especially in the sports industry have been put in place to reduce the risk of developing any new cases (Ogungbo, 2011). SCI can lead to devastating long term effects and Methylprednisolone; the only treatment for acute human SCI (Akhtar *et al.*, 2008) helps to reduce

inflammation and pain (Gorio *et al.*, 2005; Bracken, 2012) for the individual. The life expectancy of an individual diagnosed with SCI can be significantly reduced, impacting on their quality of life (Middleton *et al.*, 2007; 2012), which results in income loss if the severity of the condition worsens. This further impact's on the economic burden along with the high costs associated with primary care of the individual (French *et al.*, 2007; Nakae *et al.*, 2011). After SCI, pathological changes at the lesion site ultimately play a part in nerve conduction loss and prolonged demyelination. These changes include increased inflammation (Zhang *et al.*, 2012), disruption of Blood-Spinal Cord Barrier (BSCB) and

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extensive haemorrhage (Echeverry *et al.*, 2011; Lee *et al.*, 2012) along with an increase in necrosis, apoptosis, cavitation and ischemia (Byrnes *et al.*, 2010; James *et al.*, 2011). An up-regulation of all these factors results in detrimental effects on axon regeneration after injury.

SCI can result from three main causes which ultimately lead to tissue damage; (1), compression caused by spinal discs or bone material pressing against the cord; (2), destruction from direct trauma; and (3), reduction in blood flow from the initial damage i.e., ischemia. SCI is a two-step process marked by distinct changes during the primary and secondary injury phases. 'Primary injury refers to damage sustained by the neural elements at the time of trauma through shear forces to axons or blood vessels and results (Cadotte and Fehlings, 2011). The secondary injury phase refers to the body's response to the primary injury and involves a host of cellular processes that occur immediately after injury and persists for months to years' (Cadotte and Fehlings, 2011). During the primary injury phase astrocytes become activated and increase the expression of GFAP as a result of the trauma sustained to the cord and fluid-filled cysts containing Extracellular Tissue Matrix (ECM) proteins such as laminin, collagen 1, 2 and 3 and fibronectin begin to appear at the lesion site. During the secondary injury phase, macrophages, monocytes and immune cells invade the lesion site in an attempt to clean up the debris in the lesion site while astrocytes increase the flow of ions from neurones to the extracellular fluids allowing astrocytes to enlarge and proliferate into the spaces provided. This reaction of the astrocytes forms the glial scar lining that surrounds cavities; a major inhibitory environment for axons (**Fig. 1A and B**). The injured area suffers demyelination due to a loss in oligodendrocytes and it's this prolonged demyelination that causes axonal degeneration. Along with demyelination there is also an increase in apoptosis and necrosis around the lesion site causing further detrimental effects.

SCI can be sub-divided into two main categories; complete and incomplete. According to the AASCIN (2004) neurological classification, complete SCI refers to 'no preservation of motor and/or sensory function that exists more than three segments below the level of injury, where as incomplete SCI refers to 'some preservation of motor and/or sensory function existing more than three segments below the level of the injury'.

Animal models have been developed with the aim of recreating features of either complete or incomplete SCI allowing understanding of the anatomical and biological consequences of SCI to be investigated. Animal models have several obvious advantages over their human

counterpart: for example, the specified tissue needed can be used and processed for histological purposes to investigate co-localisation of proteins of interest, mRNA analysis (microarray) to give expression of proteins and protein analysis (western blotting) to give levels of protein. Rat models are most widely used to study SCI since they are inexpensive, have few surgical infections, are easy to care for and can be studied in large numbers but increasingly mouse models have also been implemented in SCI research (Nakae *et al.*, 2011). Larger mammals such as dogs and cats are also used but very rarely and are less experienced models based in SCI research, requiring expensive after care and housing as well as stringent ethical considerations.

Currently there are range of models that are used by researchers (**Table 1**) that include contusion, compression and transection-based models amongst others. The limitation of these different animal models is that they can never truly express the clinical characteristics of the human condition (Davoody *et al.*, 2011), but the real question is 'have animal models contributed to actual therapies? The only actual therapy for the treatment of acute SCI in humans is Methyl Prednisolone (MP) (Akhtar *et al.*, 2008, Pandya *et al.*, 2010) and even though it has shown a significant benefit in animal models (Merola *et al.*, 2002) the benefits on human SCI remain unproven and is not considered a regulatory treatment for SCI (Sharma, 2012). This review aims to establish the current animal models that are used to study SCI and the advantages and disadvantages of the techniques and therefore the potential outcomes in relation to the human condition.

1.1. Contusion Models

The vast majority of human SCI are caused as a result of motor vehicle accidents, falls and sporting injuries involving a sudden compression of the spinal cord, resulting in vertebral damage that allows the bone or vertebral disc to encroach on the spinal canal space. Other instances include laceration of the spinal cord, bullet wounds and slow compression injuries that can result from tumour growth. The contusion model is the most widely used animal model that relies on an impactor device, such as weight-drop from a specified height. The impact of the weight can vary depending on the distance moved by the weight. The first tightly controlled contusion model of SCI was described by Allen (1911), in which a specified weight could be dropped from a defined height, delivering a defined amount of energy to the exposed spinal cord. This caused injury to the spinal cord as a result of compression and displacement and was used to study the effects of myelotomy on the outcome of SCI (Allen, 1911).

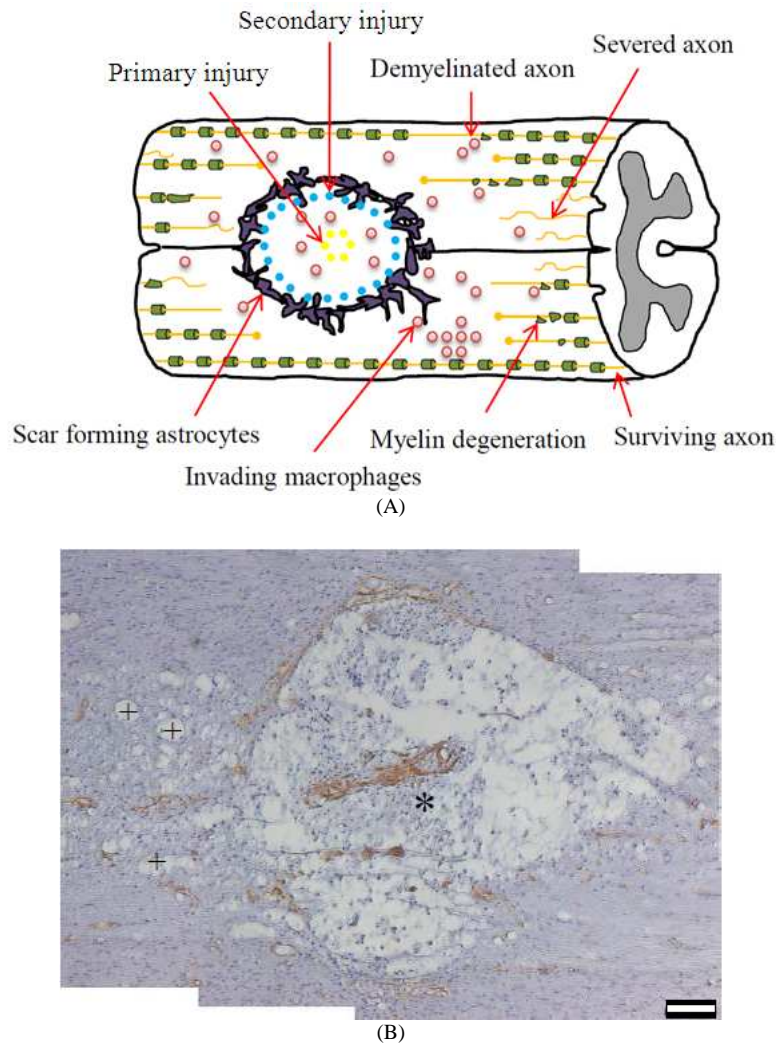


Fig. 1. The formation of cavities after SCI. (A) Diagrammatic representation of the formation of fluid-filled cysts after SCI. (Adapted from Springer Images www.springerimages.com/Images/Biomedicine/1-10.1007_978-3-642-02824-3_12-0), the primary injury is the initial lesion sustained to the cord causing an influx of immune cells and macrophages into the lesion site. It is the constant influx of these invading immune cells and macrophages that leads to the formation of fluid-filled cysts or cavities, which bring about the secondary injury, causing the up-regulation of reactive astrocytes that divide and fill the vacant spaces with glial scar tissue lining the cavity. The glial scar then acts as an inhibitory factor leading to myelin degradation and nerve conduction loss, (B) Longitudinal section from a T8 dorsal column crush injured rat spinal cord demonstrating laminin Immunostaining (brown) at 8 days post lesion (counterstained with Haematoxylin) and the extent of the cavitation at the lesion site, (A) large cavity is observed at the epicentre of the lesion (*) while smaller cavities are observed in adjacent areas (+). These cavities lead to destruction of axons and eventual loss of function. Scale bar = 100 μ m

Later, a modification to this model was introduced in the form of the New York University Impactor (Gruner, 1992) and more recently the Ohio State University Spinal Cord Research Centre has produced a weight-drop device controlled by a computer to closely control a particular level of spinal cord

compression (Stokes *et al.*, 1992; Behrmann *et al.*, 1993; Jakeman *et al.*, 2000). A variety of slow rapid compression models have been used but it is the extent of the cord displacement that determines the severity of the injury. However, the clinical relevance of such contusion models has not been established.

Table 1. Summary of the current SCI animal models that are used in research to mimic the clinical human SCI these animal models are used to assess pain, behaviour, histology and genetic alterations following SCI, but more importantly to assess neural and molecular outcomes. These models are more frequently developed on Rat and Mice and less frequently on larger animals such as Cats and Dogs

Model	Description	Advantages/Disadvantages
Contusion	Induced with an impactor i.e. weight-drop from a Specified height (Allen, 1911), thoracic contusion is most commonly used (Behrmann <i>et al.</i> , 1993; Jakeman <i>et al.</i> , 2000) Clip Induced with clips calibrated to exert a force of 50/35g-	Impact from contusion can be difficult to assess pain behaviour due to variation of distance
Clip compression	Induced with clips calibrated to exert a force of 50/35g -50g = severe response and 35g = moderate response The clip is closed over the entire cord for 1 minute (Bruce <i>et al.</i> , 2002)	Allows for precise control of injury Does not resemble injury seen in humans
Balloon compression	Uses different volumes of balloon inflation and different compression durations of expression to create contusion (Lim <i>et al.</i> , 2007)	Controlled environment Non-invasive method of creating SCI
Computer controlled contusion	Uses an animal trap that delivers a set weight to the exposed spinal cord; the computer monitors the (Stokes and Jakeman, 2002)	Reproducible, controlled environment But equipment is expensive
Spinal cord displacement	impact attempts to regulate trauma impact by Controlling displacement length of the spinal cord (Nakae <i>et al.</i> , 2011)	Controlled displacement and monitoring of biochemical parameters at the time of impact helps reduce outcome variability-controlled environment
Transection	Complete spinal transection, performed using spring scissors (Kang <i>et al.</i> , 2011; Nakae <i>et al.</i> , 2011)	Widely used to assess regeneration (Talac <i>et al.</i> , 2004) but it is clinically irrelevant (Poon <i>et al.</i> , 2007)
Photochemical	The use of a dye induces the photochemical reaction by activating an argon laser to produce single oxygen molecules on the endothelial surface of spinal cord vessels (Watson <i>et al.</i> , 1986)	Reliable and reproducible Does not induce mechanical trauma to the cord Extent of injury is difficult to control
Excitotoxic	Intraspinal/intrathecal injection of excitotoxins e.g., quisqualic acid (Bhatoe, 2009)	Long-lasting spontaneous pain, thermal hyperalgesia and mechanical allodynia (Fairbanks <i>et al.</i> , 2000; Yezierski <i>et al.</i> , 1998) Has ability to correlate specific areas of tissue damage
Spinothalamic tract lesions	Lesions core pain pathway; spinothalamic tract area using tungsten microelectrode (Nakae <i>et al.</i> , 2011; Zeilig <i>et al.</i> , 2011)	Resembles allodynia and hyperalgesia Provides useful and novel insights into the underlying biological mechanisms of SCI
Canal stenosis	Is entrapment of the cauda equine and/or lumbar Nerve roots by hypertrophy of osseous and soft tissue structures surrounding the lumbar spinal cord that reduces blood flow (Sekido <i>et al.</i> , 2012)	This model helps clarify pathophysiology of chronic, light pressure to the spinal cord (Sekiguchi <i>et al.</i> , 2004)

Nonetheless, the contusion model has been used in a variety of studies that include: (1), the use of CM101, a polysaccharide derived from group B streptococcus which inhibited inflammatory angiogenesis, protecting axons from Wallerian degeneration and improving functional outcome in mice (Wamil *et al.*, 1998; Nanney *et al.*, 2001) (2), suppression of CD47, an inhibitor of angiogenesis improved functional outcomes in knockout mice (Myers *et al.*, 2011; 2012) (3), implantation of human CNS stem cells after a moderate contusion injury improved locomotor recovery in mice (Hooshmand *et al.*, 2009); and (4), transplantation of Bone Marrow Mesenchymal Stem Cells (BMSCs) also increased

motor function in rats by the up-regulation of VEGF expression and induced angiogenesis (Yu *et al.*, 2011).

However, this initial model has been modified to use other devices that bring about compression to injure the cord; such as clip compression, balloon compression, computer controlled contusion and spinal cord displacement. These are all examples that bring about incomplete SCI.

1.2. Clip Compression

The clip compression model in some ways resembles the contusion model as the injury is caused by pressure to the cord. The injury is induced using clips calibrated to

exert a specific force. A force of 50 g is normally used to produce an outcome that would have a severe response and a force of 35 g is used to produce an outcome that would have a moderate response. The clip is then closed over the cord for 1 min (Bruce *et al.*, 2002) allowing precise control over the pressure exerted and the time that the pressure is used for, but this model does not truly mimic the injury seen in humans. Despite this the model is reproducible in rats at the thoracic level (Poon *et al.*, 2007).

The clip compression model has also been applied to the cervical region of the cord in rats to evaluate the efficacy of antagonising the Fas receptor using a soluble Fas receptor post-injury (Robins-Steele *et al.*, 2012). This study showed behavioural recovery along with enhanced cell survival, tissue sparing and integrity of descending fibre tracts when soluble Fas was administered via an intrathecal catheter either 8 or 24 h post-injury. Clip compression has also been applied to the cord at the thoracic level (Marsh *et al.*, 2002) in rats to test if neutralization of Nerve Growth Factor (NGF) with a fusion protein to Trk-A, blocked the development of autonomic dysreflexia, a life-threatening condition caused by aberrant primary afferent sprouting in the dorsal horn that is NGF-dependent.

The model has also been used to carry out kinematic studies to assess locomotor recovery following spinal cord clip compression in adult rats (Alluin *et al.*, 2011), suggesting that kinematic parameters (e.g., daily training on a treadmill over a six week period) should be taken into account when looking at new strategies to improve locomotor function after SCI.

1.3. Balloon Compression

The Balloon Compression model was first described by Tarlov in 1953 and has been modified since then. The method uses different volumes of balloon inflation and different durations of expression (Lim *et al.*, 2007), allowing for a controlled environment. Later methods did not require laminectomy and therefore were non-invasive and like the clip compression model, allowed for precise control of injury parameters. In an initial description of the balloon compression model, an embelectomy catheter was inserted into the epidural space through a hemilaminectomy hole at the vertebral arches and balloons were then inflated with varying amounts of contrast agents, causing direct compression to the spinal cord (Lim *et al.*, 2007). This method was further adapted and improved such that hemilaminectomy was not required, but that balloons were inserted through the lumbosacral space into the epidural space, where balloons

were then inflated (Lee *et al.*, 2008). A variety of different species from canine to monkeys (Guizar-Sahagun *et al.*, 2011) have been assessed through this model to gain a controlled compression model of SCI.

1.4. Computer Controlled Contusion

A computer controlled contusion model consists of an animal trap that reproducibly delivers a defined weight to the exposed spinal cord, with a computer monitoring the dynamics of the impact (Stokes *et al.*, 1992; Stokes and Jakeman, 2002). The device allows the researcher to take control of the degree of the injury produced and shown that a well controlled contusion injury can be seen observed in mice (Jakeman *et al.*, 2000) as it reduces the variability of the experiment and allows monitoring of biochemical parameters as well as assessments of behavioural and histological outcomes following contusion injury (Ma *et al.*, 2001).

1.5. Spinal Cord Displacement

Spinal cord displacement allows the cord to be exposed to a single rapid and calibrated displacement at the site of a laminectomy. The injury is initiated at the tip of a vertical shaft driven by an electromagnetic shaker. Transducers are arranged in series with the shaft recording the patterns of displacement and force during the impact (Jakeman *et al.*, 2000). The results demonstrate that the electromagnetic device can be used to produce a well-controlled contusion injury. The model attempts to regulate trauma impact by controlling displacement length of the spinal cord (Nakae *et al.*, 2011) and therefore helps to reduce outcome variability.

Sensory testing after SCI in rats has been carried out (Detloff *et al.*, 2010) and it is thought that SCI injury impairs sensory systems causing allodynia, showing that early detection of this provoked pain pathway can identify mechanisms that are responsible for its development. Hypothermia improves mobility in rodents and experiments have reported the preservation of neurons immediately after injury and a faster rate of recovery occurs after cervical displacement when hyperthermia is implemented (Lo *et al.*, 2009).

1.6. Transection Models

The transection model is referred to as a complete spinal transection which is performed using spring scissors following laminectomy, producing a laceration of the cord. This model may reflect complete SCI in patients (Nakae *et al.*, 2011) but this type of injury is rarely seen in the clinic (Talac *et al.*, 2004; Poon *et al.*,

2007); however, partial transection (hemisection) is also modelled and has become popular for studies in the mechanisms of pain. Transection models are also increasingly used to model the effects of scaffolds and biomaterials on axon regeneration after injury. For example, a polymer scaffold with rat bone marrow stem cells has been used to promote plasticity and limited regeneration in spinal cords after injury (Kang *et al.*, 2011). Combinatorial therapies have also been used where (Fan *et al.*, 2011) neurotrophic factors have been combined with biomaterials after complete transection of the spinal cord in rats. Enhancing axonal regrowth appears to be a promising therapeutic approach to repair the injured spinal cord. To allow for regeneration, sterile gel foams have been placed between the two ends of transected cords with variable degree of success (Nakae *et al.*, 2011).

Neurotrophic factors have also been used in studies by Garcia-Alias *et al.* (2011) after a lateral hemisection to the spinal cord, combining NT-3 with Chondroitinase ABC treatment as it restores plasticity in the adult CNS. They found that these animals displayed inter-limb coordination and improved body stability. Furthermore, Neural Stem/Progenitor Cells (NSPCs) have been used to deliver soluble Nogo66 (Guo *et al.*, 2012) receptor protein (blocks the inhibitory effects of myelin-based inhibitors) and growth factors to rat spinal cord following complete transection. Results show an increase in survival of transplanted NSPCs while soluble Nogo66 enhanced axonal regeneration, although no effect on functional recovery was observed, since a small number of descending corticospinal tract axons grew into the central portions of the bridges. Nogo-66 has been discussed previously by Wei *et al.* (2010) following hemisection in rats to show the effects of using hyaluronic acid hydrogels modified with Nogo66 receptor antibodies in supporting angiogenesis and inhibiting the glial scar at the lesion site (Wei *et al.*, 2010). Despite the fact that transection is rarely seen in the clinic, these models have served useful purposes in allowing the use of biomaterials, stem cells and neural progenitor cells to show that some of these therapies, when used in combination can restore some degree of function through mainly plasticity-related changes to spinal circuits.

1.7. Photochemical Models

This method was first developed by (Watson *et al.*, 1986), which showed a photochemical-based model of SCI and is now widely used to study neurotrauma (Gaviria *et al.*, 2002). To bring about the injury, a dye is used to induce the photochemical reaction by activating an argon laser to produce single oxygen molecules on the endothelial surface of spinal cord vessels. This causes

intense platelet responses, vessel occlusion and damage to parenchymal tissues (Hao *et al.*, 1991). The model is reliable and reproducible and does not require mechanical trauma and therefore there is no need for a laminectomy since the injury is caused purely by ischemia. Once the injury has been induced, behavioural studies can be performed.

The model reproduces the phenomenon of secondary lesions such as; cavitation that is seen after SCI. Using this model, motor recovery after photochemical SCI, induced before or after intrathecal injection of bupivacaine (anaesthetic drug belonging to an amino amide group that blocks sodium channels and therefore preventing the influx of sodium resulting in preventing depolarisation) resulted in improved motor recovery in rats (Lopez *et al.*, 2004). The model has also been successfully adapted in the mouse showing that it is reproducible and reliable (Gaviria *et al.*, 2002; Piao *et al.*, 2009). Different exposures to a cold light source correlated with the extent and severity of the injury, while histopathological analysis showed cavity formation in the ischemic environment. How these models relate to the human condition needs further investigation but these studies can model some of the features of the secondary injury phase and thus may be beneficial.

1.8. Excitotoxic Models

An excitotoxic model is induced via intraspinal/intrathecal injection of excitotoxins such as, quiscolic acid. The use of excitotoxins produces long-lasting spontaneous pain, thermal hyperalgesia and mechanical allodynia but also produce cavity formation, neuronal loss and astrocytic scarring (glial scar tissue which correlates with the general environment observed after SCI). The advantage of this model is that it has the ability to correlate specific areas of tissue damage with behavioral changes (Nakae *et al.*, 2011). Animals that are exposed to SCI using this method do exhibit pain that is much greater than any other model (Leem *et al.*, 2010; Nakae *et al.*, 2011) injected AMPA-metabotropic receptor agonist quiscolic acid to stimulate injury, resembling ischemic events and cavitation observed after SCI, characteristic of the clinical condition known as post-traumatic Syringomyelia. Intraspinal injection of quiscolic acid has also been used to induce excitotoxic SCI in rats (Bhatoo, 2009) demonstrating pathological changes that correlate with clinical SCI; such as, neuronal loss, haemorrhage and cavitation (Schwartz *et al.*, 1999; Berens *et al.*, 2005). Although the excitotoxic model is a non-traumatic model it displays the characteristic pathological differences that would be seen after clip-

compression and contusion models that are more commonly used. Therefore, the model is useful in investigating excitotoxic-mediated changes after SCI.

1.9. Spinothalamic Tract Model

This model restricts injury to the spinothalamic tract, which is the main pain pathway in animals, using tungsten microelectrodes (Nakae *et al.*, 2011). The model provides useful and novel insights into the underlying biological mechanisms of SCI, resembling some features of SCI in humans including hyperalgesia and allodynia (Wang and Thompson, 2008). The model is particularly useful in studying pain behaviour, as it works with the central pain pathway, although (Finnerup *et al.*, 2007) claimed that the loss of spinothalamic functions in patients with neuropathic pain does not appear to be a predictor for central pain in SCI, but is a contributor.

Zeilig *et al.* (2011) showed that the hyperexcitability of neurones may be due to damage to the spinothalamic tract where the central pain pathway causes a buildup in response. Spinothalamic tract neurones show an increased expression of metabotropic glutamate receptor subtype 1 (Mills and Hulsebosch, 2002), which parallels the development of hyperalgesia and allodynia, both of which contribute to central pain after injury.

1.10. Canal Stenosis

Canal stenosis is described as the entrapment and narrowing of the cauda equine and/or lumbar nerve roots by hypertrophy of osseous and soft tissue structures surrounding the lumbar spinal cord, causing ischemia at the site of injury (Nakae *et al.*, 2011). The model therefore causes demyelination and subsequent axonal degeneration. Canal stenosis can be termed a model (Sekiguchi *et al.*, 2004; Ito *et al.*, 2007), which helps to clarify pathophysiology of chronic, light pressure on the spinal cord. Only recently an animal model has been developed known as, rat Lumbar spinal Canal Stenosis (LCS) model (Sekido *et al.*, 2012) which can be used to study mainly bladder function after injury. Trauma contributes to the primary injury sustained but age can play a major factor (Akuthota *et al.*, 2003) in narrowing the spinal canal. Injury to the nerve does not always occur in this model but factors such as degeneration of neurones, ischemia and inflammation around the site of injury play major contributions to the injury of the nerve. It remains to be seen how useful this model will be in understanding some of the pathological changes that occur after SCI.

1.11. Limitations of Spinal Cord Injury Models

As previously discussed, each model presents itself with various limitations with the major holdback being that animal models never truly express the injury seen in humans for a variety of reasons. For example, it may be difficult to assess pain using a contusion model, as sometimes pain behaviour is not always apparent if the weight is released on the specified area from a short distance. The contusion model is also performed mainly in the thoracic region, as cervical contusion can be life-threatening (Nakae *et al.*, 2011) due to respiratory and cardiovascular functions being compromised at the level of injury (Yisheng *et al.*, 2007). For example, upper cervical SCI can disrupt the transmission of respiratory signals from the brain stem to the phrenic motor neurones (transmit signals to the diaphragm) therefore causing paralysis (Zimmer *et al.*, 2007). Using computer controlled contusion as a method to obtaining reproducible and reliable SCI, it is also an expensive method due to the sophisticated equipment that is required. The method also produces lesions that is difficult to distinguish between spared and regenerating axons, especially if the focus of the study is axon regeneration (Talac *et al.*, 2004). Although complete transection models are widely used to assess regeneration with the help of biomaterials and scaffolds, it does produce a large scar at the epicentre (Winter *et al.*, 2002) and therefore represents a severe model and so animals require intensive post-operative care (Talac *et al.*, 2004). However, transection models are difficult to standardise if several segments of the cord are removed (Blight, 2000). In addition this model is rarely seen in humans and therefore has no clinical relevance except to evaluate implantation devices and axon regeneration (Talac *et al.*, 2004). Hemisection models however, do not completely cut the corticospinal tract due to the injury being incomplete. It is also difficult to control the extent of injury if SCI is induced through the photochemical method since large areas may be affected by the ischemic environment created as a result of this model.

The anatomical location of injury between experimental animal models and clinical human SCI differ greatly. As discussed above, experimental SCI is potentially dangerous at the cervical level as it may lead to life threatening complications to the animal. SCI at the thoracic level is more commonly used in experimental models, however humans commonly present with SCI at the cervical region (Akhtar *et al.*, 2008) and therefore the site of injury can greatly affect the pathology and the severity of the injury presented in a clinical setting.

Two other factors play a crucial role in experimental SCI not mimicking the clinical injury presented by humans; laminectomy and anaesthesia. If laminectomy is performed on a patient, it not only increases the local trauma but can cause spinal instability. This can also occur in animal models of SCI as surrounding muscle, bone and ligaments are removed during induction of injury. Removal of specific components at the region of injury can have a major impact and alter the physiological responses to injury. In some ways, laminectomy free methods such as, balloon compression models may mimic the human condition more accurately.

Anaesthesia on the other hand, affects the CNS pathology and recovery following injury, either directly or indirectly (Akhtar *et al.*, 2008). It can affect blood pressure, respiratory rate and metabolism as each individual can react differently under different concentrations of the same anaesthetic. As stated above motor recovery following photochemical SCI being induced before or after intrathecal injection of bupivacaine (Lopez *et al.*, 2004) shows that anaesthesia can affect recovery and functional outcomes after SCI.

Functional outcomes and behavioural assessments between clinical models and experimental models of SCI also vary. It is very easy for human's to express the pain and symptoms that the injury presents but very difficult to do so with animal models. Therefore, specific tests and analysis methods are carried out post-injury to correlate the injury with their behavioural patterns and specific biomarkers. The behavioural patterns often correlate with the severity of the injury produced and is a measurement that is quite reasonable to carry out in a clinical environment but for animal models it is quite limited and indirect (Blight, 2000). The main way that functional outcomes are assessed in animals is by using the BBB score, which is a locomotor activity evaluation, originally developed at the Ohio State University (Basso *et al.*, 1995; 1996). The BBB score evaluates the movements of the hind limb of an animal after injury to express recovery. Although this analysis is reliable and reproducible, researchers have tested it through the severity of the condition (Filho and Molina, 2008), where the BBB score is reproducible in animals with mild severity but as the condition becomes more severe, reproducibility is reduced. While the BBB score only assess hind limb function, it does not take into account pain, bladder and bowel function which are other symptoms that require coordinated spinal cord activity (Akhtar *et al.*, 2008). Other ways of evaluating locomotor recovery are also commonly used, such as grid walking, which tests the animal's ability to deal

with challenging limb control problems (Blight, 2000). In patients, sensory assessment can be performed by testing whether they can distinguish between a sharp or dull edge of a pin but this cannot accurately be reproduced in animals and researchers solely attempt to assess sensory function based on the loss of motor functions (Akhtar *et al.*, 2008).

2. CONCLUSION

In summary, there is a vast amount of research that is available on different models that are used to present experimental SCI that are also reproducible, reliable and in some ways resemble the injury seen in humans. However, the most common methods of producing an SCI in animal models is; contusion/compression and transection. These models express some of the features of the injury response that is seen in humans and are routinely used in research to assess, pain pathways, biochemical markers, morphology and path physiology. Limitations do exist between clinical and experimental SCI from functional and behavioural assessments to the anatomical location of the injury sustained, but advances in research continue to push forward with many of these limitations still present.

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