Research Models of Spinal Cord Injury

An Overview of Commonly Referenced Spinal Cord Injury Models in Pre-clinical Research and Examples of Their Use

Opportunities for Improvement

Throughout the world, between 250,000 - 500,000 people suffer a spinal cord injury (SCI) every year.[1] Most SCIs are attributed to preventable causes, such as motor vehicle accidents, violence, falls, and contact sports injuries. Immediate treatment typically involves maintaining critical bodily function and reducing the secondary injury cascade caused by inflammation and hemorrhage. While there have been many advancements in SCI research over the past 30 years, individuals who suffer from SCIs are twice as likely to die prematurely, with the rate of mortality being highest during the first-year post injury. Many patients will experience acute and chronic health difficulties, particularly respiratory and cardiovascular complications. These occur in 80% of cases and are most prevalent during the acute phase.[2] Due to the physical and financial burden SCIs put on patients and their families, research must continue to find solutions that increase quality of life and are conducted in translatable environments to ensure the best patient outcomes.

Understanding SCI Research Models

Physiological changes to multiple organ systems and the complexity of secondary injury pathology cannot be effectively studied with *in vitro* methods, making *in vivo* models essential. Development of an experimental *in vivo* model of spinal trauma requires researchers to replicate SCI in humans as closely as possible. A 2014 publication in the journal Neural Regeneration Research cites the following conditions as necessary for an adequate animal model "(1) simulate damage that is similar to clinical SCI; (2) be controlled, reproducible, and stable; (3) involve a simple technique that is easy to study; (4) the equipment used to make a model is straightforward and quick to produce."[3] Considerations when designing a studying should include identifying various elements based on the objectives of the study, including optimal species, location of injury, type of injury, and outcome assessments.

Animal Models

Both small and large animal models are used in SCI research. Rodents are the most common, with rats making up 72.4% of all SCI pre-clinical studies.[4] Rats provide similar pathology to humans with the development of a fluid filled cyst. Mice, on the other hand, have been shown to experience a moderate amount of regeneration following injury, with no formation of the cyst. With the wide availability of genetic mouse models, mice are most typically used when looking at biological and molecular processes in axon regeneration. Although large animal models provide the most translational accuracy to human trauma, the cost, ethical concerns, and regulatory requirements associated with them limit their use. They are primarily used for treatment evaluation in later stages of development.

Location of Injury

The four regions (cervical, thoracic, lumbar, sacral) of the spinal cord each contain neurons which branch out to send and receive signals throughout the body. Trauma to the spinal cord can result in altered function and/or sensation below the point of injury. The cervical region is the most common area of injury in humans. Due to animal welfare concerns, as well as reliability and reproducibility, cervical injury is less frequently used in pre-clinical research. Thoracic injury is the most common area of spinal cord injury and is used in 81% of animal studies.[4] Researchers studying commonly affected organ systems (e.g. cardiovascular and respiratory), perform high thoracic injuries, greatly decreasing risk of mortality associated with cervical trauma. This method also allows the animals to maintain use of their forelimbs.

Injury Methods

No one method of inducing injury can fully represent all characteristics of human SCI. Proper model development should include:

- Mimicking human pathology as much as possible
- Reproducibility
- Consistency

The following sections outline current methods employed by researchers to induce SCI in animal models.

Contusion is the most used injury model and replicates injuries from falls or impact on the spinal cord. A laminectomy is performed on anesthetized subjects and researchers employ the weight drop method or an impactor on a specified region. This inflicts an acute injury onto the spinal cord and may be done bilaterally or unilaterally. The impactor technique is preferred, as it is performed in a controlled manner that limits variability across subjects and laboratories. In addition, impactors are also considered a more humane method for inducing injury.[5] There are many types of impactor models, including the MASCIS, the Ohio State University impactor, air gun, and Infinite Horizon.

Compression is another method used in SCI research and involves prolonged cord compression. This method can be used in conjunction with contusion after impact to mimic dislocations and burst fractures. Compressing of the spinal cord can be done using a variety of validated methods, including aneurysm clips, forceps, balloons, spacers, and strapping. Each method has pros and cons that should be closely evaluated during study design. Though less common, compression method can also be used in ischemic models of SCI.

Transection models involve either complete or partial severing of the spinal cord. As transection injuries are not commonly seen in the clinical setting, they are typically not useful when studying mechanisms of SCI pathophysiology. Researchers may choose transection models to study axon regeneration, degeneration, cell transplantation, or neuroplasticity. These models do not require any special equipment and are relatively easy to perform.

Less commonly used techniques include distraction (stretching of the spinal cord), dislocation, and chemical injuries.

Biomarkers of SCI

SCI can lead to multiple organ and physiological dysfunction during the acute and chronic phases, making measuring multiple endpoints incredibly valuable. A multi-faceted approach allows for study refinement by recognizing that organ systems work together and influence one and other. It also allows for better characterization of the model being studied and improved understanding of pathology variation across subjects. To improve translation from animal model to the clinical environment, DSI recommends careful consideration of study length, selection of injury models, choice of animal model, and proper solutions that allow for a comprehensive assessment of the model being studied. Throughout all injury models, a broad range of physiologic parameters are used for quantifying acute and chronic impact of SCI. These physiologic endpoints are most measured in mice, rats, guinea pigs, rabbits, felines, canines, swine, and nonhuman primates. Various telemetric and hardwired solutions are available depending on the animal model used. Below are a list of applications and their commonly collected endpoints that are being used to advance SCI research.

Cardiovascular

Injury to the high thoracic and cervical regions can lead to impairment of the autonomic nervous system and dysregulation of the cardiovascular system. This presents as autonomic dysreflexia, hypotension, orthostatic intolerance, bradycardia, cardiomyopathy, and increased risks for coronary heart disease. Researchers are collecting endpoints such as systemic blood pressure, heart rate, pressure-volume loops and cardiac contractility via left ventricular pressure, blood flow, and electrocardiogram in SCI models to better understand acute and chronic effects.

Respiratory

Pulmonary complications mostly occur in the acute stage following SCI and are the number one cause of mortality throughout the first-year post-injury. Mechanical ventilation is necessary with high cervical, complete injuries, typically occurring in C1 – C5 trauma. Injuries at T1 – T12 can affect the control of breathing in the intercoastal and abdominal muscles. Respiratory related biomarkers that are commonly assessed

include breathing frequency, inspiratory and expiratory duration, peak airflow rates, tidal volume, vital capacity, functional residual capacity, expiratory reserve volume, cough, lung and chest wall compliance, respiratory muscle functions, and respiratory metabolism. These endpoints are measured using either direct or indirect methods.

Neurophysiology

SCI can lead to severed nerves within the spinal cord leading health care providers to look at the neurophysiology of subjects to determine the level of injury as early as possible. Eventually, neurophysiology will be used for prognostic and rehabilitation purposes. Many of the endpoints collected in the clinical setting can also be collected in pre-clinical models. These include nerve conduction studies, electromyography, F-Wave method, sympathetic skin response, bulbocavernosus reflex, and H reflex methods. Neurostimulation is an up and coming technique which is showing real promise in possibly restoring some autonomic functions in pre-clinical models.

Sleep

Sleep disorders are commonly reported in patients following SCI and can lead to decreased quality of life. Many complications occur due to pain, circadian rhythm disturbances, breathing difficulties, abnormal leg movements, pharmacological effects, and depression. Sleep can be measured in animal models through electroencephalogram (EEG) that measures the electrical signals in the brain to identify different sleep stages. Sleep is determined by physiological changes in EEG together with the EMG (electromyogram – muscle movement). Other variables including temperature, blood pressure and neuroendocrine function can be added to gain extra information. Another way to measure sleep is by physical activity correlated to resting periods. Noninvasive respiratory measurements can also be collected during sleep to evaluate breathing difficulties or sleep apnea.

Behavioral Assessment

Assessing behavior in pre-clinical models can help researchers identify extent of injury, mechanisms for recovery, rehabilitation techniques, and methods for evaluating new treatment options. Typically, researchers will assess locomotion, motor, sensory, autonomic, and reflex responses.[6] There are many types of behavioral equipment available to researchers studying SCI and methods are based on a variety of factors including the severity of injury, location of injury, and animal model used. Common behavioral products include but are not limited to open field-testing, video tracking, kinetic weight bearing, hot cold plate, forced swimming, inclined plane, grip strength, and beam walking.

Sexual Function

Up to 95% of men with SCI experience some sort of sexual dysfunction, particularly erectile and ejaculatory issues.[7] With many SCI studies focusing on the more critical physiological functions, very little pre-clinical research is done on sexual function following SCI. Studying the chronic effects can help generate new treatments and therapeutics to increase patient's long-term well-being. Types of assessments done to measure sexual function in animal models following SCI include activity-based training, penile reflexes, and telemetry monitoring of penile pressure.

Temperature

Patients with a SCI in the higher thoracic or cervical region are more likely to experience dysfunction with temperature regulation below the point of injury. Extreme temperature is a known cause of autonomic dysreflexia, a phenomenon that leads to incredibly high blood pressure which can cause pulmonary embolism, stroke, and death in patients with cervical SCIs. Temperature can be taken acutely or chronically in animal models, depending on the goals of the study. Continuous measurement provides the largest opportunity to correlate temperature with other physiological changes.

Suggested SCI Publications Studying Various Physiological Biomarkers

Neurophysiology
Masood, F.; Abdullah, H.A.; Seth, N.; Simmons, H.; Brunner, K.; Sejdic, E.; Schalk, D.R.; Graham, W.A.; Hoggatt, A.F.; Rosene, D.L.; Sledge, J.B.; Nesathurai, S. Neurophysiological Characterization of a Non-Human Primate Model of Traumatic Spinal Cord Injury Utilizing Fine-Wire EMG Electrodes. Sensors 2019, 19, 3303

Neurostimulation
Taccola, G., Gad, P., Culaclii, S., Ichiyama, R. M., Liu, W., & Edgerton, V. R. (2020). Using EMG to deliver lumbar dynamic electrical stimulation to facilitate cortico-spinal excitability. Brain Stimulation, 13(1), 20-34.

Sleep
Lujan, H. L., & DiCarlo, S. E. (2020). Direct comparison of cervical and high thoracic spinal cord injury reveals distinct autonomic and cardiovascular consequences. Journal of Applied Physiology, 128(3), 554-564.

Autonomic Dysreflexia
Mironets, E., Osei-Owusu, P., Bracchi-Ricard, V., Fischer, R., Owens, E. A., Ricard, J., Wu, D., Saltos, T., Collyer, E., Hou, S., Bethea, J. R., & Tom, V. J. (2018). Soluble TNFα Signaling within the Spinal Cord Contributes to the Development of Autonomic Dysreflexia and Ensuing Vascular and Immune Dysfunction after Spinal Cord Injury. The Journal of neuroscience : the official journal of the Society for Neuroscience, 38(17), 4146–4162.

Cardiovascular Responses
Harman, K. A., States, G., Wade, A., Stepp, C., Wainwright, G., DeVeau, K., ... & Magnuson, D. S. (2018). Temporal analysis of cardiovascular control and function following incomplete T3 and T10 spinal cord injury in rodents. Physiological Reports, 6(6), e13634.

Sexual Dysfunction
Steadman, C. J., Vangoor, S. S., & Hubscher, C. H. (2019). Telemetric monitoring of penile pressure during mating in rats after chronic spinal cord injury. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 317(5), R673-R683.

Respiratory
Lee, K. Z. (2019). Impact of cervical spinal cord contusion on the breathing pattern across the sleep-wake cycle in the rat. Journal of Applied Physiology, 126(1), 111-123.

Acute Hypoxia Treatment
Komnenov, D., Solarewicz, J. Z., Afzal, F., Nantwi, K. D., Kuhn, D. M., & Mateika, J. H. (2016). Intermittent hypoxia promotes recovery of respiratory motor function in spinal cord-injured mice depleted of serotonin in the central nervous system. Journal of applied physiology, 121(2), 545-557.

Spinal Cord Microdialysis
Streijger, F., So, K., Manouchehri, N., Tigchelaar, S., Lee, J. H., Okon, E. B., ... & Kwon, B. K. (2017). Changes in pressure, hemodynamics, and metabolism within the spinal cord during the first 7 days after injury using a porcine model. Journal of neurotrauma, 34(24), 3336-3350.

Motor Coordination
Chung, E., Yoon, T. G., Kim, S., Kang, M., Kim, H. J., & Son, Y. (2017). Intravenous Administration of Substance P Attenuates Mechanical Allodynia Following Nerve Injury by Regulating Neuropathic Pain-Related Factors. Biomolecules & therapeutics, 25(3), 259–265.

Behavior Evaluation
Harel, N. Y., Song, K. H., Tang, X., & Strittmatter, S. M. (2010). Nogo receptor deletion and multimodal exercise improve distinct aspects of recovery in cervical spinal cord injury. Journal of neurotrauma, 27(11), 2055-2066.

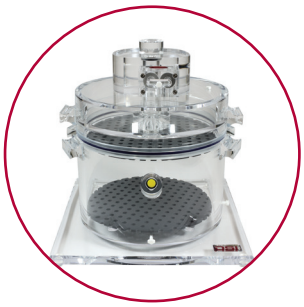
Motor Function
Ellman, D. G., Degn, M., Lund, M. C., Clausen, B. H., Novrup, H. G., Flæng, S. B., ... & Lambertsen, K. L. (2016). Genetic ablation of soluble TNF does not affect lesion size and functional recovery after moderate spinal cord injury in mice. Mediators of inflammation, 2016.

Temperature
Järve, A., Todiras, M., Kny, M., Fischer, F. I., Kraemer, J. F., Wessel, N., . . . Bader, M. (2019). Angiotensin-(1-7) Receptor Mas in Hemodynamic and Thermoregulatory Dysfunction After High-Level Spinal Cord Injury in Mice: A Pilot Study. Frontiers in Physiology, 9

Solutions for Spinal Cord Injury Research

Telemetry
PhysioTel™ Implantable telemetry is designed for stress-free continuous data collection in small and large animals.

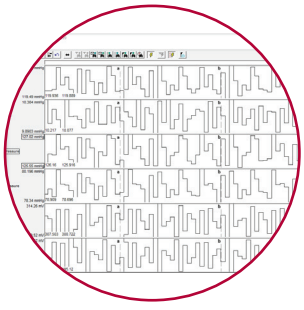
Respiratory
Buxco® hardware and software are for collecting respiratory data and reporting results in the fastest, most reliable manner.



Hardwired
DSI amplifiers accelerate research with better resolution of data using the latest Digital Signal Processors.

Behavior
Panlab and Coulbourn Instruments offer industry leading behavioral assessment solutions including grip strength meters, forced and voluntary exercise, mazes, and more.

Software
DSI offers powerful data acquisition and analysis software packages for applications including cardiovascular, respiratory, neurological, and more.



References

[1]Spinal cord injury. (n.d.). Retrieved July 29, 2020, from https://www.who.int/news-room/fact-sheets/detail/spinal-cord-injury

[2]Tollefsen, E., & Fondenes, O. (2012). Respiratory complications associated with spinal cord injury. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke, 132(9), 1111-1114. https://doi.org/10.4045/tidsskr.10.0922

[3]Zhang, N., Fang, M., Chen, H., Gou, F., & Ding, M. (2014). Evaluation of spinal cord injury animal models. Neural regeneration research, 9(22), 2008–2012. https://doi.org/10.4103/1673-5374.143436

[4]Sharif-Alhoseini, M., Khormali, M., Rezaei, M. et al. Animal models of spinal cord injury: a systematic review. Spinal Cord 55, 714–721 (2017). https://doi.org/10.1038/sc.2016.187

[5]Verma, R., Virdi, J. K., Singh, N., & Jaggi, A. S. (2019). Animals models of spinal cord contusion injury. The Korean journal of pain, 32(1), 12–21. https://doi.org/10.3344/kjp.2019.32.1.12

[6]Mahdi Sharif-Alhoseini and Vafa Rahimi-Movaghar (July 2nd 2014). Animal Models in Traumatic Spinal Cord Injury, Topics in Paraplegia, Yannis Dionyssiotis, IntechOpen, DOI: 10.5772/57189. Available from: https://www.intechopen.com/books/topics-in-paraplegia/animal-models-in-traumatic-spinal-cord-injury

[7]Hess, M. J., & Hough, S. (2012). Impact of spinal cord injury on sexuality: broad-based clinical practice intervention and practical application. The journal of spinal cord medicine, 35(4), 211–218. https://doi.org/10.1179/2045772312Y.0000000025