Article

Spinal cord injury I: A synopsis of the basic science

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Abstract — Substantial knowledge has been gained in the pathological findings following naturally occurring spinal cord injury (SCI) in dogs and cats. The molecular mechanisms involved in failure of neural regeneration within the central nervous system, potential therapeutics including cellular transplantation therapy, neural plasticity, and prognostic indicators of recovery from SCI have been studied. This 2-part review summarizes 1) basic science perspectives regarding treating and curing spinal cord injury, 2) recent studies that shed light on prognosis and recovery from SCI, 3) current thinking regarding standards of care for dogs with SCI, 4) experimental approaches in the laboratory setting, and 5) current clinical trials being conducted in veterinary medicine. Part I presents timely information on the pathophysiology of spinal cord injury, challenges associated with promoting regeneration of neurons of the central nervous system, and experimental approaches aimed at developing treatments for spinal cord injury.

Résumé — Lésions de la moelle épinière I : Sommaire de la science fondamentale. Des connaissances considérables ont été acquises dans les constatations pathologiques suite à des lésions de la moelle épinière (LME) attribuées à des causes naturelles chez les chiens et les chats. Les mécanismes moléculaires en cause lors de l'absence de régénération neurale dans le système nerveux central, la thérapeutique potentielle incluant la thérapie par transplantation cellulaire, la plasticité neurale et les indicateurs de pronostic de rétablissement à la suite de LME ont été étudiés. Cette revue en deux parties résume : 1) les perspectives scientifiques fondamentales concernant le traitement et la guérison des lésions de la moelle épinière, 2) des études récentes qui apportent des précisions sur le pronostic et le rétablissement des LME, 3) le courant de pensée actuel concernant les normes de soins pour les chiens avec LME, 4) des approches expérimentales en laboratoire et 5) des essais cliniques en cours en médecine vétérinaire. La partie I présente des renseignements opportuns sur la pathophysiologie des lésions de la moelle épinière, les défis associés à la promotion de la régénération des neurones du système nerveux central et les approches expérimentales en vue de développer des traitements pour les lésions de la moelle épinière.

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Introduction

Traumatic spinal cord injury (SCI) is a devastating disease in human and veterinary medicine. In human medicine, approximately 50 per 1 million people are afflicted with SCI annually (1). The exact incidence of traumatic SCI in dogs and cats is unknown. Much of the epidemiological data pertaining to SCI in veterinary medicine is found in the older literature. Nevertheless, it has been estimated that up to 2% of all cases admitted to a veterinary hospital are afflicted by SCI resulting from intervertebral disc disease (IVDD) (2). For dogs not afflicted with IVDD, 60% of SCI result from motor vehicle accidents (3). When looking at dogs involved in motor vehicle accidents; however, 5% of the animals will have SCI (4). Other important causes of SCI in dogs are ischemia resulting from fibrocartilagenous embolism (5) and cervical spondylomyelopathy (6). In a retrospective study of cats with spinal cord disease, 7% had SCI injury due to vertebral column injury, 4% from intervertebral disc disease, 2% from a penetrating injury, and 7% had SCI resulting from

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ischemia or infarction (7). It is important to understand and appropriately manage dogs and cats with SCI. Substantial advances have been made in SCI research since the publication of veterinary review articles on SCI 10 y ago (8–10). Advances have been made in understanding 1) details of white matter changes occurring after naturally occurring SCI in dogs and cats; 2) the molecular mechanisms involved in failure of neural regeneration within the central nervous system (CNS); 3) potential therapeutics including cellular transplantation therapy; 4) neural plasticity; and 5) prognostic indicators of recovery from SCI in dogs. Given this, we review in 2 parts; 1) basic science perspectives regarding treating and curing spinal cord injury, 2) recent studies that shed light on prognosis and recovery from SCI, 3) current thinking on standards of care for dogs with SCI, 4) experimental approaches being investigated in the laboratory setting, and 5) current clinical trials being conducted in veterinary medicine. It is hoped that this information will provide both timely and topical information for veterinarians.

Spinal cord injury results from primary and secondary injury mechanisms

Traumatic SCI in dogs results from either endogenous or exogenous trauma, namely, intervertebral disc herniation and motor vehicle accidents, respectively. Regardless of the cause, the resultant pathology arises from both primary and secondary injury mechanisms. Primary injury is physical injury to the spinal cord and is the result of laceration, contusion, compression, and traction of the neural tissue. Pathological changes resulting from primary injury mechanisms include severed axons, direct mechanical damage to cells, and ruptured blood vessels. Secondary injury is of paramount importance and is responsible for expansion of the primary injury. Secondary injury results from alterations in local ionic concentrations (11); loss of regulation of local and systemic blood pressure (depending on the level of the injury) (12,13), reduced spinal cord blood flow (13), breakdown of the blood-brain barrier (12–14); production of free radicals (15), imbalance of activated metalloproteinases (16,17), and release of cytotoxic neurotransmitters (18,19). The results of both primary and secondary injury mechanisms are conduction block of neuronal impulses resulting from local ionic changes and demyelination, ischemia, necrosis, and apoptosis of spinal cord tissue, and characteristic pathological findings.

Though the pathological features of SCI have been previously described (20–23), neuropathological changes have recently been re-examined in dogs and cats following naturally occurring SCI (24). Neuropathological findings were characterized by hemorrhage and infarction, and gray matter damage. Detailed analysis of axonal and myelin changes revealed axonal swelling and myelin degeneration, that developed soon after the SCI. In particular, demyelination of axons developed by 2 wk following SCI. In the chronic phases of SCI the spinal cord reveals characteristic central areas of cavitation with peripheral rim sparing of white matter (24). These findings are similar to those in the chronic phases of SCI in humans and rats following natural and experimental injury, respectively. In fact, the pathological findings are so similar to those seen in traumatized human spinal cords that a strong argument has been made to consider using dogs with naturally occurring SCI as a translational model prior to evaluating potential therapies in humans (25).

Regeneration of axons is limited within the CNS

Physical injury to the spinal cord results in the mechanical disruption and degeneration of ascending and descending axons. Consequently, connections between neurons and their targets within the CNS are disrupted and various neurological abnormalities (notably paresis and paralysis) ensue. One of the main therapeutic strategies for SCI is to promote axonal regeneration. Although neuronal regeneration and neuronal sprouting are used interchangeably by some, we define neuronal regeneration, more specifically axonal regeneration, as regeneration of a previously lost axon. Meanwhile, we define neuronal sprouting as sprouting of an axon from an uninjured and viable neuron (explained more in subsequent sections). There are many confounding factors that contribute to the success of neuronal regeneration following SCI [for review see (26,27)].

These factors include the physical and biochemical barriers that are induced or inherent within the injured spinal cord and include inhibitory molecules in myelin [Nogo, myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp), ephrins, semaphorins, netrins, repulsive guidance molecule (RGM)] (26). Aside from the inhibitory properties of myelin, the astrocyte-lined glial scar is also an impediment for neural regeneration (28).

The glial scar helps seal the injury site from the spared tissue, possibly preventing spread of secondary injury. An undesirable effect of "walling-off" the injury site from intact axons is that axons are unable to cross the injury site. Further, and possibly more importantly, the glial scar itself produces a number of factors that make the biochemical milieu surrounding the injury site inhospitable for regenerating axons. These factors include tenascic acid, semaphorins, ephrins, and various proteoglycans (27).

In addition, mature CNS neurons themselves have limited regenerative capabilities compared with peripherally projecting neurons (29). In particular, various regeneration-associated genes (RAGs) are not upregulated or expressed appropriately in adult CNS neurons following injury (for reviews see 30,31). Regeneration-associated gene expression plays a role in the synthesis of various proteins that are important in regeneration. Such proteins include the regeneration-associated proteins GAP-43, CAP-23, and neurotrophins; the cellular downstream signaling molecules cyclic-AMP and CREB; and the integrins that are important in cell adhesion (30,31). Though neurons atrophy and have declining neuroregenerative capability after axotomy in the CNS, pathways important for regeneration can be stimulated with growth factors (see next section), up to at least 1 y after axotomy, and partially promote regeneration (32).

Experimental approaches for promoting recovery from spinal cord injury

Logically, research is aimed at overcoming the factors that are involved in impeding recovery from SCI. Specifically, research is conducted with the following aims: 1) preventing secondary

injury, 2) promoting regeneration and/or sprouting of remaining axons, 3) enhancing the purposeful function of remaining neural circuitry, 4) replacing destroyed spinal cord tissue, and 5) combining a number of the above approaches.

Preventing secondary injury. Primary injury mechanisms are minimized through surgical decompression of the spinal cord and/or stabilization of vertebrae (in the case of vertebral fractures) to prevent further damage to the spinal cord. Secondary injury, the cellular and molecular events resulting from primary injury, occurs predominantly in the acute (hours) and subacute (days to weeks) stages of SCI. The end result of secondary injury is the expansion of the size of the primary injury through a variety of mechanisms already mentioned. Given this, therapies aimed at controlling secondary injury mechanisms offer the potential to reduce the extent of the injury and thus improve the potential for recovery after SCI. Various potential therapeutics, aimed at reducing secondary injury, have been examined. In particular, a variety of approaches have been studied to alter neuroinflammation (administration of immunomodulator drugs such as minocycline or antibodies against leukocyte adhesion molecules) (33–36), reduce free radical damage (administration of glucocorticoids, iron chelators, and glutathione promoters) (15,37–40), reduce excitotoxic damage to neurons [administration of N-methyl-D-aspartate (NMDA) receptor antagonists] (41), improve blood flow (administration of opioid antagonists or calcium channel blockers) (42), seal damaged membranes (systemic administration of surfactants) (43,44), and counter the effects of local ionic imbalances (administration of sodium and calcium channel blocker) (45–49) [for a detailed review see (50)]. So far, none of these treatments have been useful for treating spinal cord injury.

Promoting regeneration and/or sprouting of remaining axons. Inhibitory molecules that reside near and at the site of SCI limit axonal regeneration. A variety of techniques have been used to counter the inhibitory aspects of the spinal cord microenvironment, or to promote regeneration of spinal cord axons.

There are a variety of proteins expressed in myelin that interfere with axonal regeneration. These molecules include MAG (51,52), OMgp (53), and Nogo (54). Consequently, a rational approach to improving neural regeneration would be to eliminate or immunologically prevent regenerating axons from coming in contact with these inhibitory substrates. In fact, such strategies have been performed experimentally and have resulted in variable improvement in neural regeneration and sensorimotor recovery (55–59).

An alternative approach to eliminating or immunologically preventing axons from encountering these inhibitory myelin proteins is to block interaction of these molecules with their receptors using a receptor antagonist. Alternatively, interfering with downstream signaling pathways would also be expected to ameliorate the inhibitory effects of these proteins on regenerating neurons. Fortunately, there is a common receptor known as the Nogo-66 receptor (NgR), through which MAG, OMgp, and Nogo act (60,61). Molecules that block the NgR promote modest regeneration and variable behavioral recovery in vivo (62–64).

Once myelin-associated inhibitors (MAIs) are activated, a downstream signal to RhoA GTPase (RhoA), an enzyme that is important in cytoskeletal regulation, is also activated (65). Subsequently, RhoA activation leads to recruitment of Rho kinase (ROCK) (an enzyme involved in phosphorylation of other molecules important in cytoskeletal regulation), triggering the reorganization of actin networks in the neuronal growth cone, and ultimately growth cone collapse and neurite inhibition (failed axonal regeneration) (65). Growth cones are found at the tips of developing axons, guiding neurite outgrowth (66). Inhibitors of RhoA and ROCK signaling promote neural regeneration in vitro and in vivo, and modest behavioral recovery (65–68).

Another inhibitory obstacle is the glial scar, formed by reactive astrocytes, that acts as both a physical and chemical barrier for regeneration and sprouting (69). Chondroitin sulphate proteoglycans (CSPGs), a component of the glial scar, are upregulated following CNS injury (70). Proteoglycans are made up of a glycoprotein and glycosaminoglycan (GAG) sugar side chains. Aggrecan, brevican, neurocan, and NG2, are examples of proteoglycans that contain the chondroitin sulphate side chains (28). CSPGs are found in the extracellular matrix, and interact with other matrix constituents by receptors on the GAG chains or the glycoprotein (71). Degradation of CSPG by the bacterial enzyme chondroitinase ABC (ChABC) permits CNS tissue to regenerate, in vitro (72). Application of ChABC-therapy has been beneficial for regeneration in vivo but such regeneration had mixed results in promoting behavioral recovery (73–76). The effects of blocking or degrading inhibitory molecules should be investigated for promoting recovery after SCI in veterinary medicine.

Many compelling studies using neurotrophins to promote axonal sprouting have been conducted. Neurotrophins are growth factor proteins that promote the development, growth, and survival of neurons. Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neutrophin-3 (NT-3), and neutrophin-4 (NT-4), are the core neurotrophins known to promote neuron survival (77). The common receptor for the core neurotrophins is known as p75, although the tropomyosin-receptor-kinase (Trk) family of receptor (Trk receptors) tyrosine kinases have higher affinity for specific neurotrophins (78). A variety of studies have reported that neurotrophins and neurotrophin receptors improve aspects of behavioral recovery following SCI (79–87). Furthermore, neurotrophins in combination with other treatments have also been useful in promoting behavioral recovery (88–95). Important side-effects of neurotrophin administration observed in human clinical trials for neurodegenerative diseases, and from experimental animal studies, that may preclude their use in SCI include weight loss, inappetance, nausea, and psychiatric disturbances (96). Though these side-effects may be due to route of administration of the neurotrophin and/or the particular neurotrophin being administered, these considerations will undoubtedly need to be taken into consideration when planning clinical trials investigating their use in SCI.

Enhancing the purposeful function of remaining neural circuitry. Physical activity has been linked with improved outcome following CNS trauma. It has been well-documented for more than 20 y that cats with a completely transected spinal

cord can be trained to step or stand on a treadmill (97). This phenomenon occurs because of the "retraining" of the spinal cord networks responsible for the alternating pattern of flexion and extension. Referred to central pattern generators (CPGs), the CPGs for hind limb stepping are located within the lower thoracic and upper-mid lumbar regions of the spinal cord in mice, rats, and cats (98–101). The ability to "learn" to step, in these cats, depends on a specific training regimen, however. In fact, spinal cord transected cats that are trained to stand are unable to walk on a treadmill, while those trained to walk are unable to stand (102). Albeit, stand-trained animals can be trained to step, and vice versa. An important aspect to this training is that the spinal cord "remembers" what it was trained to do. For instance, if a spinal cord transected cat was trained to walk on a treadmill, the cat is able to walk on the treadmill after a period of not being trained (103). Interestingly, a recent study showed that "training" of the CPG occurs in cats having only a partial SCI (104). Specifically, cats that received a partial SCI, and were treadmill-trained, regained bilateral stepping ability within hours after a subsequent complete spinal cord transection. Cats that did not receive any training prior to a complete transection were asymmetrical in their hind limb locomotor ability. Biochemical changes associated with training of the CPG have also been described (105,106). Specifically, spinal cord transected animals not trained to step on a treadmill had elevated levels of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) in spinal cord motor neurons, while those that were trained to step had reduced levels of the inhibitory neurotransmitter. Interestingly, it was originally thought, for specific physiological reasons that treadmill training was likely more efficacious compared to conventional rehabilitation step-training in SCI humans. A recent multicenter study in humans, however, indicated that treadmill training is good but no better at promoting recovery following SCI compared with conventional step-training physiotherapy (107).

Aside from the effects of training on the CPG, physical therapy also promotes recovery through sprouting of axons that remain following SCI. In particular, brain-derived neurotrophic factor (BDNF) and growth-associated protein (GAP-43) are thought to play a role in exercise-induced plasticity by promoting regeneration and axonal growth (108,109). GAP-43 is found in high concentrations in axonal growth cones, and thus, is thought to be associated with guiding the growth of axons and forming new connections after injury (110,111). However, overexpression can lead to motor neuron death even with continual growth of axons (110). Gomez-Pinilla et al (112) demonstrated that voluntary exercise increased the expression of BDNF and its receptors, and also increased GAP-43 (112). Experimentally, SCI rats also exhibit greater recovery when placed in enriched environments or where running wheels are provided to promote self-training and this is seen with enhanced neural regeneration (113,114).

In addition to exercising, recent findings show that dietary manipulations also affect recovery. Diet restriction increases levels of BDNF (115), and increases lifespan (116). In one study, rats provided with food every other day (beginning after the SCI) showed higher levels of performance after SCI than the control group (117). Importantly, the recovery that was observed with every other day food restriction in SCI rats was associated with a reduction in spinal cord lesion volume and increased sprouting of neurons within the spinal cord (118). In a non-SCI study, rats that were food restricted had significantly less neuronal loss in the hippocampus after excitotoxic-induced damage to their hippocampus (119). Interestingly, this effect was only present in rats that had been food restricted for longer than 8 wk. The mechanisms by which food restriction is associated with increased resistance of the brain after injury are still being investigated. The evidence suggests that neurodegenerative processes, including SCI, may be alleviated by dietary manipulations.

Taken together, exercise and a specific dietary regime may be advantageous for recovery from SCI. It is no longer appropriate to simply place a paraplegic animal in a harness with wheels without appropriate physical rehabilitation. Mounting evidence exists, however, that stress plays an important role in recovery in many diseases of the CNS. In particular, stress appears to impair recovery (120,121). Given this, rehabilitation therapy is important for spinal cord-injured patients and stress should be minimized. As for all clinical studies, future research into rehabilitation therapy, stress reduction, and food restriction for dogs affected with naturally occurring SCI is required, though stringent experimental rigour must be employed (studies should be blind, controlled, and use appropriate behavioral outcomes).

Replacing destroyed spinal cord tissue. Given that SCI results in necrosis and apoptosis of various cells within the spinal cord and that loss of this tissue is related, in part, to the loss of sensorimotor function, many researchers are involved in trying to replace this lost tissue in an effort to promote recovery. Recently, there has been substantial effort in transplanting stem cells, olfactory ensheathing glia, and Schwann cells into the spinal cord at or near the site of injury.

Stem cells can replace themselves (self-renewal) and are able to change into any type of cell in the body (pluripotent), albeit, the term "stem cells" is often used more broadly to encompass a variety of precursor or progenitor cells that may or may not be truly pluripotent (122,123). Nevertheless, stem cells are an attractive potential therapy for use in many diseases, not simply SCI. However, there are potential risks (such as, tumorigenesis) involved in introducing these cells into the spinal cord. Though there is controversy over the use of embryonic-derived stem cells for therapy, stem cells can be harvested from adults and offer the advantage of being used autologously. For example, pluripotent cells can be obtained from the adult bone marrow (124) and skin (125,126). There has been a significant amount of research investigating various aspects of stem cell therapy for SCI. It is unlikely that transplanted stem cells will bring about recovery by changing their phenotype to that of a functional neuron. Rather, there is clear evidence that using stem cells to produce a sufficient number of cells that have been forced into becoming a particular cell type, in vitro and prior to transplantation, is practical and useful for goal-directed therapies in SCI. For example, it has recently been demonstrated that Schwann cells derived from skin-derived precursor cells (127) and oligodendrocyte precursor cells (128) can be safely and successfully

transplanted, and remyelinate demyelinated axons, and bring about some sensorimotor recovery in rodents after experimental SCI. Given the number of different types of stem cells, much research is needed to identify safety and efficacy of stem cell therapy. Presently there are clinical trials in SCI in humans investigating the efficacy of bone marrow and peripheral blood stem cells (129).

Transplantation of olfactory ensheathing cells (OECs) has gained much attention in recent years. Olfactory ensheathing cells, glial cells found exclusively in the olfactory system, promote axonal regeneration (130,131), remyelination (132), and neural protection (133,134). These properties highlight why OECs are promising candidates for repairing the damaged spinal cord. The first use of these cells as a therapy for SCI demonstrated remarkable beneficial effects for regeneration and sensorimotor recovery in rats that had their spinal cords completely transected (135). The results were so phenomenal that many labs around the world began investigating the therapeutic potential of these cells for SCI. Disappointingly, the dramatic effects of these cells on sensorimotor recovery have not been replicated to the same degree. Nevertheless, recent studies have shown that OECs transplanted into experimentally spinal cord-injured rodents can promote neural regeneration and sensorimotor recovery (130,136,137). In vitro studies have demonstrated that OECs, in the presence of a demyelinated rat spinal cord, can remyelinate axons up to several millimeters in length, and bring axonal conduction velocities back to standard values (132). Other attempts at providing favorable microenvironments that facilitate axonal regeneration include the transplantation of Schwann cells (SCs).

The premise behind transplanting SCs into the spinal cord is that these cells provide a suitable environment for successful regeneration of neurons within the central nervous system (138,139). Although SCs can remyelinate axons (140) and do not contain NOGO (141), they have limited migratory capabilities to pass the lesion site and to gain access to the non-injured spinal cord caudal to the injury. Interestingly, cultured OECs can facilitate the migration of SCs, perhaps due to the secretion of nerve growth factor (NGF) by OECs (142). In fact, when NGF produced by OECs was blocked, SC migration was suppressed. After transplantation of OECs and SCs into the injured spinal cord, however, there is a lack of migration of the OECs and SCs although axonal growth and sprouting into the lesion site occur (143). Though the evidence for using SC therapy looks promising, especially in combination with other modalities, to date no studies have used this approach for SCI in veterinary medicine.

Combined approaches. The monomodal approaches for treating spinal cord injury, as described, have been modestly successful in treating experimental SCI. It will likely take multimodal approaches to succeed in curing SCI. There are now many investigators examining combinations and permutations of multi-modal therapies. Given the complexity of the factors that are involved, research into multi-modal therapies will require many years of investigation before identification of an appropriate therapy that could be tested in human and veterinary clinical trials. Nevertheless, efforts are presently underway to identify the most appropriate and efficacious multimodal therapy for SCI. CVJ

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