TRANSPLANT OF OLFACTORY ENHANCED GLIA, STEM CELLS AND OVEREXPRESSING SCHWANN CELLS AS MODELS OF REGENERATIVE THERAPY IN SPINAL CORD INJURIES

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Abstract: New regenerative therapy in several pathological conditions of the spinal cord have been developed in animal models: transplant of olfactory enhancing glia (OEG), overexpressing schwann cells and stem cells, to increase the chances of therapeutic success in spinal cord injuries both in companion animals and in humans. The effect of transplanting neural stem cells for the treatment of spinal cord injuries has been studied with great interest during the last two decades. Studies regarding transplants in spinal cord injuries have been done and are still in a research stage. Passing from studies on experimental rat models to clinical studies in human gives new perspectives for the recovery of the patients (both human and animals) with spinal cord dysfunction.

INTRODUCTION

Many experimental models have been developed in an attempt to cure spinal cord injuries (SCI) in humans. Jeffery et all. (2006) highlight the case for using clinical SCI in dogs as an intermediate between rodent experiments and human clinical trials.

In veterinary clinics the most common causes of acute spinal cord injury include type I intervertebral disc herniation, vertebral fractures and luxation, vascular disease (e.g. fibrocartilaginous embolism (FCE) and haemorrhage), cervical stenotic myelopathy (Wobbler syndrome) and congenital malformation causing instability (e.g. atlantoaxial subluxation). Many chronic diseases, such as neoplasia, discospondylitis and inflammatory or infectious spinal cord disease, can, at a certain time, become acute. Acute onset of spinal cord dysfunction is most commonly caused by a combination of one or more events including concussion, compression, ischemia, or laceration of the spinal cord.

Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of spinal cord injury</th>
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<tbody>
<tr>
<td>Intervertebral disc disease</td>
<td>Concussion and compression</td>
</tr>
<tr>
<td>Vertebral fracture / luxation</td>
<td>Concussion, compression, laceration, Ongoing instability</td>
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<tr>
<td>Fibrocartilaginous embolism</td>
<td>Ischaemia</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Ischaemia and compression</td>
</tr>
<tr>
<td>Congenital instability (e.g. atlantoaxial subluxation)</td>
<td>Concussion, compression, laceration, Ongoing instability</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Compression, vertebral fracture</td>
</tr>
<tr>
<td>Discospondylitis</td>
<td>Compression, inflammation, vertebral fracture, Ongoing instability</td>
</tr>
<tr>
<td>Myelitis</td>
<td>Inflammation</td>
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RESULTS AND DISCUSSIONS

Acute concussion of the spinal cord initiates a series of biochemical and metabolic events that expand the primary zone of tissue necrosis.

The events are initiated by the initial mechanical insults, which causes release of neurotransmitters, damage to glial and neuronal cell membranes and of local vasculature. Spinal cord injuries result in severe and permanent neurological sequelae, and to date, there is no effective treatment. Transection of adult spinal cord causes extensive neuronal loss, acute axonal damage, demyelisation and scar formation. Furthermore, any potential functional restoration requires a re-establishment of local neuronal networks, synaptic connections, and descending/ascending neural pathways across the injury site (Zang Y. et all., 2007). (fig. 1)

Fig 1Schematic overview of the pathophysiology of spinal cord trauma, depicting the underlying vascular and biochemical components of secondary injury (Platt S.R., Olby N., 2004)

A correlation of reported data and current veterinary practice shows that spinal cord injury occurs commonly in dogs for two main reasons: first, they are frequently the victims of road traffic accidents; second, there is a high rate of disc degeneration (predominantly in smaller, condrodystrophic breeds) that can lead to acute nuclear extrusions associated a mixed contusive-compressive injury to the spinal cord similar to those in human patients. (Jeffrey ND et al., 2006)
During the last two decades, a large number of interventions have been successful in improving the outcome after spinal cord injuries in experimental rodents. Attempts to discard the lesions induced by the aggression of the trauma to the spinal cord tissue through the transplant of exogenous cells and tissues with a high capacity of regeneration and neural differentiation at the lesion site have been made.

The primary olfactory system has a remarkable capacity of forming olfactory neurons continuously throughout the animal’s life. An important factor in the high regenerative potential is represented by glial cells (olfactory ensheathing cells - OEG) which play a key role in regrowth and guidance of newly formed olfactory axons to the olfactory bulb. Studies on dogs showed that the transplants of cells from the frontal sinus mucosa (with a population of Schwann cells and OEG) have led to a positive response in spinal cord injury recuperation. (Skinner APC et al., 2004)

The effect of transplanting neural stem cells for the treatment of spinal cord injuries has been studied with great interest during the last two decades. In general, five beneficial effects of OEG, which all may contribute to increased functional recovery, have been reported:

1. stimulation of axonal outgrowth: After complete transection and OEG transplantation, descending as well as ascending axons traversed the lesion site and reached distances of 1.5 and 2.5 cm respectively. This is the largest distance observed for regrowing central axons after OEG implantation so far. Furthermore, the level of recovery of locomotor function and sensorimotor reflexes appeared to be correlated with the distance of axonal regeneration

2. axonal and tissue sparing;

3. the ability of OEG to migrate from the lesion site into the host scar tissue, An essential component of the mechanism behind the growth promoting properties of implanted OEG encompasses their potential ability to migrate through neural scar tissue. By migrating from the injection site, OEG might form a bridge crossing the lesion, thereby functioning as a scaffold for regrowing axons. This hypothesis implicates that implanted OEG are able to acquire properties which they do not display in their native environment. In the olfactory system, OEG appear to maintain their channel-like organization after an injury and do not migrate over long distances.

4. promotion of angiogenesis Angiogenesis is a process required for wound repair in general, since new blood vessels provide nutrients and enable the clearance of debris. In the injured spinal cord, a lack of sufficient blood supply has been hypothesized to contribute to the inability to regenerate. Furthermore, a correlation between angiogenesis and increased axon growth and functional recovery was shown after contusion injury. Several studies reported an increase in the formation of new blood vessels after OEG implantation. It has been proposed that formation of new blood vessels might function as a scaffold for migrating glia as well as for regrowing axons and could therefore contribute to positive effects on regeneration. New blood vessels after OEG implantation were directed towards the lesion site. Therefore blood vessels may form scaffolds for axons to extend along. In addition, OEG are known to express vascular endothelial growth factor (VEGF) and VEGF was upregulated after implantation in the photochemically injured spinal cord and

5. remyelisation of spinal cord axons. (Franssen EHP et al., 2007) In their natural environment, OEG do not myelinate olfactory axons. It was hypothesized that, like in the PNS, the thickness of the axons determines whether axons are myelinated by their surrounding glia. If so, OEG might be able to myelinate large-diameter axons
For the purpose of harvesting medullar stem cells (BMSCs), the canine species has many places of choice for medullar puncture: the proximal femoral epiphysis, the ilium, the sternum, the fourth rib and the humerus (Bienzle D., 2000). Their plasticity has been proven in regenerating neural cells. This could simplify the approach to cellular therapy of the nervous system by eliminating the necessity of harvesting autolog neural stem cells. At the same time, the facility of harvesting medullar stem cells, as well as the simplicity of culturing and in-vitro expansion procedures make them the ideal candidates for regenerative therapy (Paolo Bianco et. Al., 2001). Ji-Hey Lim et. Al. (2007) has induced spinal cord lesions on a canine model with the occlusion of the medullar canal on over 75% of its surface for 12 hours, the animals manifesting paraplegia. The experimental group treated with mesenchymal (umbilical) stem cells showed functional improvement, having much higher Olby scores. The histopathological data obtained suggested that the mesenchymal (umbilical) stem cell transplant can improve the functional recovery of the spine by creating new neural pathways through the scar fibrous tissue.

Passing from studies on experimental rat models to clinical studies in human gives new perspectives for the recovery of the patients (both human and animals) with spinal cord disfunctions.

CONCLUSIONS

Clinical SCI in dogs provides a model that is comparable in terms of mechanisms of injury, pathology, outcome, classification and functional monitoring to human SCI. The establishment of the canine model as an intermediate between rat and human intervention would aid and speed the transition of diverse therapy such as stem cell transplantation, chondroitin ABC, rolipram, co-transplantation of neural stem cells and NT-3-overexpressing schwann cells or combination therapy (3, 9)

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