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Neuropetides and adipose-derived mesenchymal stromal cells improve peripheral nerve regeneration in animal model

Although autologous nerve grafting remains the gold standard for nerve gap repair, entubulation techniques with artificial nerve conduits are considered a promising approach to peripheral nerve reconstruction (Strauch, 2000). Advances in bioengineering have led to the creation of autodegradable composite neural tubes lined with Schwann cells or infused intraluminally with neurotrophic factors (e.g., NGF, VEGF, FGF), which enhance the regeneration of nerve fibers and block the invasion of scar tissue, improving outcomes (Kim, et al., 2007; Yu et al., 2009; De Boer, et al., 2011). Recently, the potential therapeutic effect of adipose-derived mesenchymal cells (ASCs) that were transduced with the vasoactive intestinal peptide (VIP)-expressing lentivirus, a neuropeptide with neuroprotective, trophic and developmental regulatory actions, in peripheral nerve regeneration experimental model was demonstrated by Hernández-Cortés et al., 2014.

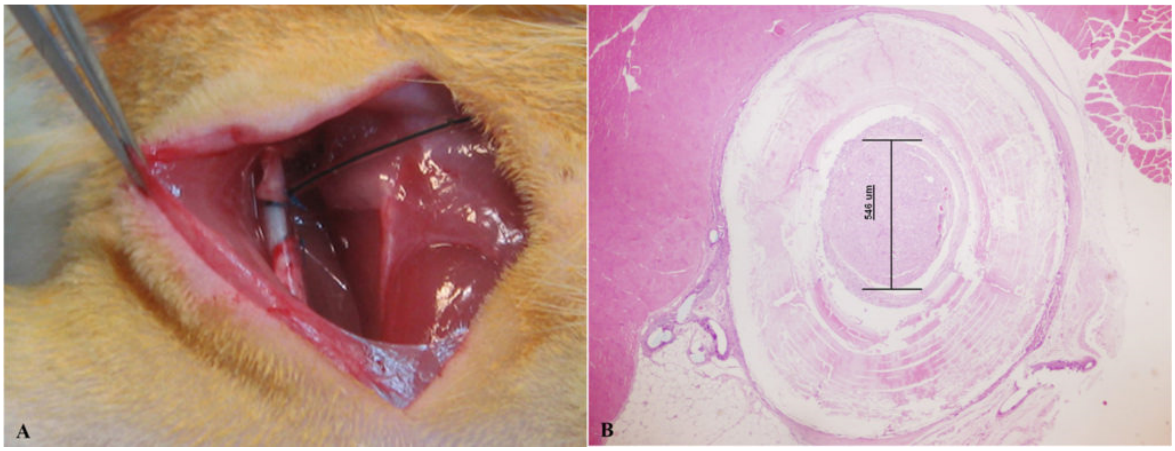

Fig. 1. A) Reconstruction of the sciatic injury defect in Wistar rats by suture with a 15-mm long DI-lactic-ε-caprolactone conduit. B) Cross-section of the middle segment of conduit of the sciatic nerve isolated from GHR group (Hematoxylin-eosin, original magnification x2).

Ghrelin (GHR) is a 28-aa neuropeptide that elicits a broad spectrum of biologic functions (Delporte, 2013). Initially related to appetite stimulation and growth hormone secretion, GHR has also been found to exert a neuroprotective effect in neurodegenerative diseases, regulate cognitive function, enhance synaptic function, and act as a potent neurotrophic factor in traumatic brain injury (Stoyanova et al., 2013; Qi et al., 2014. The positive effect of GHR on neural repair in the central nervous system is well documented, but its role in post-lesion peripheral nerve regeneration is poorly understood. Preliminary data suggest that GHR may play a role in promoting axonal regeneration after nerve injury (Raimondo et al., 2013).

ASCs have various characteristics that make their use attractive in the setting of peripheral nerve damage. First, they can differentiate to Schwann cells and produce trophic factors involved in nerve regeneration; second, they show preferential homing for sites of inflammation and tissue damage, as in an injured nerve (Gonzalez et al., 2009); third, they exert potent immunosuppressive and antifibrotic actions, favoring nerve

repair; and fourth, ASCs can be used in an allogeneic system, extending the applicability of this strategy. Infusion of ASCs or other mesenchymal stromal cells (MSCs) to nerve conduits has improved nerve repair in various experimental models (di Summa et al., 2010; Ao et al., 2011; Carriel et al., 2013).

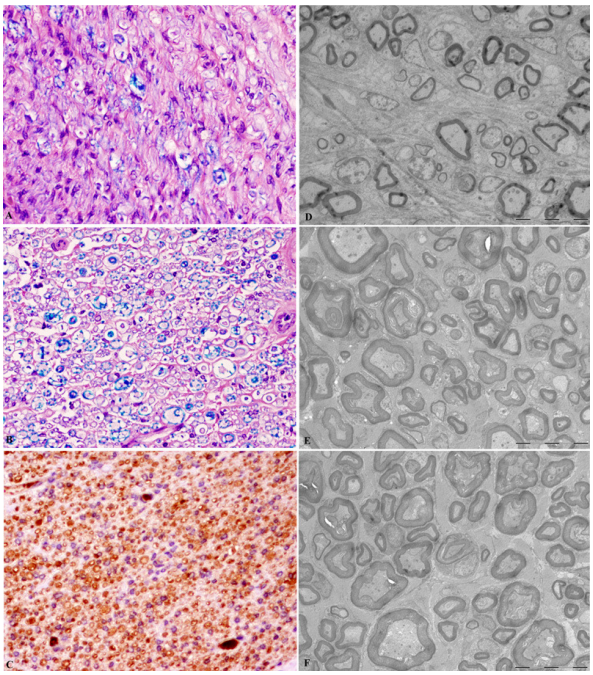

Fig. 2. Cross-section of the middle segment of conduit of the sciatic nerve isolated from: A CC group (Kluver-Barrera method, original magnification x40); B) CC-ASC group (Kluver-Barrera method, original magnification x40); C) CC-GHR group (Micropolymer-peroxidase-based method, original magnification x20). Ultrastructural cross-secction of the distal segment of the sciatic nerve isolated from D) CC-control group; E) CC-ASC group and F) CC-GHR group. Scale bars: 10µm.

We studied a unilateral peripheral nerve injury model, using Dl-lactic-ε-caprolactone conduits (CC) (Neurolac®, Polyganics, Groningen, Holland) to repair a 10-mm defect in the sciatic nerve of rats (Fig. 1). In addition to the controls a CC group plus instillation of 3 µg of GHR (AnaSpec, San Jose, CA, USA) once per week from weeks 2 to 6 (dissolved in 100 µL of saline at 30 µg/mL) at a site neighboring the lesion *via* temporary subcutaneous catheter, and CC-ASCs group, repaired as in the CC group plus 10^5 intratubular inoculation of ASCs.

Our recent study published in Histology and Histopathology in 2017 (Hernández-Cortés et al.) shows that although rats receiving GHR or ASCs showed no significant increased functional recovery in ankle stance angle (CC: 40.84°±4.26; CC-GHR: 49.70°±9.21; and CC-ASC group: 45.71°±9.35, p=0.372), they attenuated the percentage of reduction in the muscle fibers by the injury (CC: 65.31±52.57; CC-GHR:16.30±12.44; CC-ASC group:24.5±15.18, p=0.012), and a higher nerve area (CC: 0.44±0.35 mm^2; CC-GHR: 1.07±0.45mm^2; and CC-ASC group: 0.87±0.40mm^2, p=0.015), myelin area (CC: 0.09±0.04μm^2; CC-GHR: 0.25±0.08μm^2; and CC-ASC: 0.22±0.21μm^2, p=0.002) and number of myelinated fibers (CC: 21.10±7.21; CC-GHR: 35.89±3.23; and CC-ASC: 35.89±14.6, p=0.000) in the distal segment of operated

sciatic nerves in comparison to saline-treated control animals. These findings were confirmed by histochemical method, immunohistochemical analysis of myelin basic protein-positive nerve fibers, and by ultrastructural quantification of the myelin area and remyelination (g-ratio: CC: 0.72; CC-GHR: 0.58; and CC-ASC: 0.64, p=0.047) (Fig. 2).

Our results suggest that utilization of ghrelin or ASCs may improve nerve regeneration using Dl-lactic-ε-caprolactone conduits.

Hernández-Cortés P. [1], ***Delgado M.*** [2], ***Gonzalez-Rey E.*** [2], ***Aguilar M.*** [3], ***Aguilar D.*** [3], ***Padial-Molina M.*** [4], ***Galindo-Moreno P.*** [4], ***O'Valle F.*** [3]

[1]*Orthopedic Surgery, Complejo PTS Hospital and School of Medicine, University of Granada, Spain*
[2]*Institute of Parasitology and Biomedicine López-Neyra, CSIC, Granada Spain*
[3]*School of Medicine & Biopathology and Medicine Regenerative Institute (IBIMER, CIBM), University of Granada, Spain*
[4]*Department of Oral Surgery and Implant Dentistry. School of Dentistry, University of Granada, Spain*

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