IJAE
Vol. 115, n. 1/2: 91-94, 2010
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Plasticity and regeneration in the peripheral nervous system

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Presented at a meeting in honour of Prof. G. Orlandini, Florence, February 15, 2010

Summary

While in the central nervous system plasticity (in response to stimulus) and regeneration (in response to injury) are mainly based on adaptive changes in neural circuitries and synaptic reorganization, in the peripheral nervous system they are predominantly based on axonal (re)growth and neuron addition. In this paper, we will briefly overview the main investigation lines on plasticity and regeneration in the peripheral nervous system that have been carried out at the Laboratory of Human Anatomy of the Department of Clinical and Biological Sciences at the "San Luigi Gonzaga" Medical Faculty of the University of Turin. This body of research was mainly focused on the identification of the adaptive changes occurring to the sensory and autonomic neurons as a consequence of exceptional stimuli and/or damage at their periphery, as well as on the identification of effective new strategies for improving post-traumatic peripheral nerve fiber regeneration. These studies are in line with the long standing tradition on peripheral nervous system investigation carried out by the Anatomical School at the University of Turin since the times of Giuseppe Levi and we are honoured to have the occasion to present the results of our research on occasion of the appointment of Giovanni Orlandini as Emeritus Professor of the University of Florence.

Key words

Neuroplasticity, neural repair, myenteric plexus, dorsal root ganglia, peripheral nerve repair

Introduction

The study of the morphology of the nervous system at the Anatomical School of the University of Turin has a long lasting history which includes the work of some anatomical giants of the past, such as Luigi Rolando and Carlo Giacomini. The interest in the study of the peripheral nervous system, in particular, is based on the pioneering work of Giuseppe Levi, one of the fathers of modern neurobiology, who had among his distinguished discipuli some of the leading neuroscientists of the last century. One of them, Guido Filogamo focused his research interests mainly on the changes occurring in the peripheral nervous system in physiological and/or pathological conditions. Noteworthy are his studies on the occurrence of neuronal hyperplasia in the myenteric plexus, in which he postulated (about 50 years before the recent advancements on adult stem cells) the existence of an intestinal stem cell niche which justifies the marked increase (up to fourfold) in number of Auerbach's plexus ganglion neurons in the loops immediately upstream an obstruction (Filogamo and Vigliani, 1954).

In line with this research tradition, our research group has carried on the investigation of plasticity and regeneration in the peripheral nervous system in the Labora-

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tory of Human Anatomy of the Department of Clinical and Biological Sciences at the "San Luigi Gonzaga" Medical Faculty of the University of Turin. In this paper we will briefly overview these studies which can be ascribed to three main research lines: 1) neuroplasticity and regeneration in Auerbach's plexus; 2) neuron addition in dorsal root ganglia; 3) peripheral nerve repair and regeneration.

Neuroplasticity and Regeneration in Auerbach's Plexus

Hypertrophy of the intestinal wall, which follows partial stenosis, causes an increase in the workload of myenteric neurons that is accompanied by neuronal hypertrophy and hyperplasia (Gabella, 1984). We have carried out a series of studies, based on autoradiography after [3H]-thymidine administration and cytophotometry after Feulgen staining, which have showed that unscheduled DNA synthesis (i.e. not followed by cell division) occurs in myenteric neurons in the loops upstream from an intestinal stenosis in the rat and that this neosynthesis is associated with a hyperdiploid DNA content (Giacobini-Robecchi et al., 1988). In addition, we provided evidence, using electrophoretic analysis of the total genomic DNA, of the presence of extra-bands migrating below the high molecular weight DNA, suggesting that amplification may be the mechanism for the unscheduled DNA synthesis (Giacobini-Robecchi et al., 1995). Finally, in order to provide an unequivocal demonstration that of DNA neosynthesis occurs in myenteric neurons, we have showed by confocal imaging that, in the intestinal loops upstream of the stenosis, the proliferating cell nuclear antigen (PCNA) colocalizes with protein gene product 9.5 (PGP 9.5), a specific marker of intestinal nerve cells (Corvetti et al., 2001). These results are interesting in the perspective of understanding the etiology of various gastrointestinal diseases and identifying effective treatments.

Neuron Addition in Dorsal Root Ganglia

The first evidence of lifelong neuron addition in rat dorsal root ganglia (DRGs) can be found already in a paper published by Hatai in 1902 and has been further supported by other studies (Popken and Farel, 1997). Although these data have been disputed (Pover et al., 1994), the interest in neurogenesis within DRGs has recently increased due to the demonstration that neurospheres can be obtained from adult sensory ganglia explants (Lagares et al., 2007). We have been focusing our attention on the satellite cell population housed in DRGs, which we believe might represent the stem cell niche of DRGs. In fact, preliminary results suggest that, after nerve crush, DRG satellite cells can proliferate, change their differentiation lineage and give rise to new DRG neurons, thus revealing an unexpected plasticity of the peripheral sensory compartment in response to injury.

Peripheral Nerve Repair and Regeneration

The definition of effective new strategies for improving post-traumatic nerve regeneration is attracting much attention since, although peripheral nerves do spontaneously regenerate without any treatment, complete recovery of nerve function almost never occurs after microsurgical nerve repair and clinical results are still unsatisfactory (Battiston et al., 2009). Yet, in spite of the scientific advancements in tissue engineering and regenerative medicine, applications to the patients suffering from peripheral nerve damage are still limited. Our research in this field has been directed to the goal of bringing together the four main pillars of tissue engineering: i) reconstructive microsurgery, ii) transplantation; iii) material science, and iv) physical therapy.

As far as reconstructive microsurgery is concerned, we have investigated various microsurgical techniques and, in particular, have provided evidence on the effectiveness of termino-lateral neurorrhaphy as an alternative for nerve reconstruction in case of unavailability of proximal nerve stumps (Tos et al., 2009). Much attention is also attracted by the possibility to reconstruct nerve defects by tissue and cell transplantation. We have investigated the employment of combined autologous transplants made by autologous vein segments enriched with fresh skeletal muscle fibers, showing that basal lamina scaffolds of fresh muscle fibers facilitate Schwann cell migration and axon growth and that the NRG1/ErbB gliotrophic system is involved in improving regeneration along this type of conduits (Geuna et al., 2000; Battiston et al., 2009).

An alternative to tissue and cell transplantation for bridging nerve lesions with substance loss is the use of conduits made by biomaterials. We have investigated different types of artificial materials used to build up artificial nerve guides and the results suggest that biomimetic biomaterials (such as quitosane) are the most promising components for fashioning effective nerve scaffolds (Battiston et al., 2009). Finally, much interest is also attracted by physical therapy as an adjuvant to tissue engineering of peripheral nerves. In particular, we have shown that phototherapy improves axonal regeneration and reduces muscle atrophy after nerve injury and repair (Rochkind et al., 2009). It can be expected that an interdisciplinary and multitranslational approach could eventually allow to optimize the strategy for tissue engineering of peripheral nerves and lead to effective clinical applications.

Conclusions

The study of the plasticity and regeneration in the peripheral nervous system, although with a long lasting tradition, still represents a very lively and exciting research field for anatomists. Results obtained over the last years have thrown light on an unexpected regenerative potential and have opened exciting new perspectives for innovative clinical applications. In this paper we have briefly outlined some of the most promising research lines in this field, based on our experience over more than twenty years, and we are particularly honoured to contribute to this special issue of the Italian Journal of Anatomy and Histology published on the occasion of the appointment of Giovanni Orlandini as Emeritus Professor of the University of Florence.

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