We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

4,300
Open access books available

116,000
International authors and editors

130M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter 6

The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

Agon Mekaj and Ymer Mekaj

Abstract

Peripheral nerve injuries are frequent and represent a significant pathology of the peripheral nervous system because, despite operative techniques and successful microsurgical repair, in most cases, the nerve repair is followed by scar formation. Numerous investigations have been carried out with the aim of finding pharmacological substances that can prevent scar formation and speed up the regeneration of repaired nerves. This chapter is dedicated to the efforts of many researchers to find different pharmacological agents with local effects on the improvement of nerve regeneration. Numerous experiments have been carried out in mice and rabbits using hyaluronic acid, tacrolimus, cyclosporin A, melatonin, vitamin B12, methylprednisolone, riluzole and potassium and calcium channel blockers. In the experimental animal studies, topical pharmacological agents were used at the site of peripheral nerve repair. The effect of these substances is most commonly studied in sciatic nerve injury in experimental animals. Their effects were evaluated using a variety of methods, such as morphological, biomechanical, electrophysiological and functional evaluation, and the above-mentioned substances, have been shown to have neuroprotective and neuroregenerative properties though different mechanisms.

Keywords: nerve injury, nerve regeneration, pharmacological agents, scar formation

1. Introduction

The peripheral nervous system (PNS) is very complex, being composed of the cranial nerves and the spinal nerves, which project from the spinal cord and pass through the intervertebral foramina of the vertebrae [1]. Peripheral nerves, composed of motor and sensory neurons, are considered as complex organs and are present in nearly all parts of the human body [2]. Motor neurons transmit processed information from the central nervous systems (CNS) to
skeletal muscles via efferent pathways, whereas collected information from periphery travels to the brain via afferent pathways, after they are translated into nerve signals [3]. Neurons are the main cells of the PNS, but there are two kinds of neuroglia in the PNS, namely Schwann cells and satellite cells. Neurons are made up of the body (soma) and their thin processes of the cell, which are called dendrites and axons. In the soma of the neuron, there are many types of organelles [4]. Based on the number of extensions that arise from the cell body, neurons can be multipolar (three or more extensions), bipolar (two extensions, one axon and one dendrite) or unipolar (only one extension), which are very short and divided in the form of a letter T [5].

Peripheral nerve injuries (PNIs) are very common, and automobile accidents are the most common cause of nerve trauma [6], with most cases (75%) occurring in the upper limbs [7]. However, the etiological factors of PNI are different in peace and conflict periods, and, historically, most knowledge of PNIs was developed during wars [8]. Nerve injuries can be caused by lacerations with sharp objects, penetrating trauma, stretching or crushing trauma, fractures and wounds [9]. Lacerations, especially those which were caused by a knife blade, are another common cause of PNIs, comprising 30% of serious injuries in some series [10]. Compression is another common cause of PNIs, including ‘Saturday Night Palsy’ caused by radial nerve compression, which causes entrapment neuropathies [11]. The most severe form of nerve injury is a transection, which is known as grade V neurotmesis, usually owing to a laceration from a knife, firearm or glass shard [12]. The neurotmesis is characterised with a full transection of the axons and connective tissue layers wherein complete discontinuity of the nerve is observed [13]. There are numerous classifications of nerve injuries, but of these classifications, the most widely accepted are those developed by Seddon and Sunderland [14, 15].

After a peripheral nerve sustains a traumatic injury, complex pathophysiologic changes, such as morphologic and metabolic changes, occur at the injury site [16]. Furthermore, these complex changes occur in the nerve cell body, in the proximal and distal segments to the injury site, as well as in the distal endings of both muscle end-plates and sensory receptors [17]. These changes are characterised by axonal degeneration, which follows a sequence of events within the zone of trauma extending both proximally and distally [18]. Disconnected axons and cell bodies (in proximal axon injuries) degenerate via chromatolysis [19]. The degenerative changes in the distal segment were first described by Waller in 1850 based on observations of frog glossopharyngeal and hypoglossal nerves after injury [20]. Wallerian degeneration starts almost immediately after axotomy and lasts for 3–6 weeks [17].

The regenerative process begins almost immediately after nerve injury. The first wave of axonal sprouting occurs within hours of axotomy [21]. Two days after this first wave of axonal sprouting, a second wave of this process of regeneration starts [22]. According to some authors, axons may branch once they reach the distal stump, and in these cases, one axon may give rise to several branches [23]. It is known that Schwann cells play an important role in nerve regeneration at the site of nerve injury because they elaborate processes that include physical conduits that lead axons to their targets [17]. The extension of Schwann cells’ processes can limit the rate of axon regeneration more than axonal growth [24]. Regeneration of the damaged peripheral nerve depends on the microsurgical procedure performed. Currently, there are several operating techniques that can be used to repair injured nerves, such as direct epineural repair,
grouped fascicular repair, fascicular repair and nerve grafting [25]. However, there are some factors that influence the regeneration process after nerve repair, such as the nature, location and extent of damage, the extent and timing of repair, fascicular anatomy and patient factors (age, physical condition, metabolic disorders, avitaminosis and the presence of any disease).

In addition, recently some experimental studies have shown that nerve regeneration after its repair can be improved by some pharmaceutical agents, mainly used locally at the site of nerve repair. Drugs commonly used for this purpose include tacrolimus [26–29], hyaluronic acid and its derivatives [30–32], melatonin [33–35], methylprednisolone [36–39], vitamin B complex and vitamin B12, [40–42], calcium and potassium channel blockers [43, 44] and riluzole [45, 46]. These substances have neuroprotective and neuroregenerative properties, though different mechanisms contribute markedly to nerve regeneration.

Therefore, the main aim of this chapter is to present new insights into the mechanisms of action of many of the above-mentioned pharmacological agents on the prevention of perineural scar formation and on nerve regeneration after peripheral nerve surgery. However, it is understandable that complete regeneration and functional recovery will almost never be achieved, regardless of the operative technique used or the type of pharmacological agent applied.

2. Hyaluronic acid

Hyaluronic acid (HA) (CAS No. 9004-61-9) is a natural glycosaminoglycan formed by bonding N-acetyl-α-glucosamine with glucuronic acid [47]. It is a mucopolysaccharide, which occurs naturally in all living organisms, and is several thousands of sugars (carbohydrates) long. Disaccharide units are formed at the plasma membrane in vertebrates and some bacteria [48, 49]. HA is characterised by a very large number of disaccharide pairs (10,000 or more), so its molecular mass is approximately 4 million Da [50]. HA was discovered in bovine vitreous humour by Meyer and Palmer in 1934. These authors found that the HA contained two sugar molecules, one of which was uronic acid, and they proposed the name ‘hyaluronic acid’ [51], while the term ‘hyaluronan’ was introduced in 1986 by Endre Balazs to conform with the international nomenclature of polysaccharides [52]. HA is a major primary component in the extracellular matrix, but it has also been found intracellularly. HA has been isolated from many other sources, and its physicochemical structural properties and biological role have been studied in numerous laboratories [53]. The biosynthesis of HA has been studied for over six decades, but our understanding of the biochemical details of HA assembly is still incomplete. The enzyme responsible, HA synthase (HAS), is a membrane protein that requires only Mg²⁺ and two sugar-UDP substrates (GlcUA-UDP and GlcNAc-UDP) to polymerise HA chains [54]. In 1993, the hasA gene was identified and cloned, and the HAS protein from Streptococcus pyogenes was expressed [55, 56]. It was also demonstrated that only the HAS protein was required to synthesise HA [57]. It is known that mammalian genomes have three different HAS genes (HAS1, HAS2 and HAS3) that are expressed at specific times and in specific tissues during development, ageing and wound healing, as well as under normal and some pathologic conditions [58, 59].
HA has numerous biological functions, such as maintenance of the elastoviscosity of liquid connective tissues, for example, in joint synovial and eye vitreous fluid, control of tissue hydration and water transport, as well as supramolecular assembly of proteoglycans in the extracellular matrix. Furthermore, HA has various receptor-mediated roles in cell detachment, mitosis, migration, tumour development and metastasis, and inflammation [52, 60]. The predominant role of HA in organisms is unknown, but some clinical studies have demonstrated various physiological effects of exogenous HA. Exogenous HA enhances chondrocyte HA and proteoglycan synthesis, reduces the reproduction and activity of proinflammatory mediators, such as matrix metalloproteinases, and alters the behaviour of immune cells [61]. HA has also been successfully used in peripheral nerve surgery to reduce nerve adhesions during wound healing after nerve injury, which occur during ophthalmological, cardiovascular and dermatological procedures, including supplementing joint fluid in arthritis [32, 62, 63]. HA is known to reduce the extent of scar formation and nerve adhesions via the inhibition of lymphocyte migration, proliferation and chemotaxis of granulocyte phagocytosis and degradation, and macrophage motility in order improve peripheral nerve regeneration [31, 64]. These functions are manifested during scavenging of reactive oxygen-derived free radicals, the inhibition of immune complex adherence to polymorphonuclear cells, the inhibition of leucocyte and macrophage migration and aggregation, and the regulation of fibroblast proliferation [65]. HA is an endogenous stimulator of interleukin-1 (IL-1) production, and IL-1 affects fibroblasts proliferation and collagenase production [30]. Therefore, according to Hiro et al., HA is an endogenous IL-1 inducer and may play important roles in the pathological and/or physiological changes of connective tissues [30]. It is known that HA is highly non-antigenic and non-immunogenic, because it has high structural homology across species and weak interactions with blood components [66]. HA’s degradation products are thought to contribute in scar formation because the increased amounts of HA fragments from the action of hyaluronidase in HA induce increased scar formation. There are various commercial preparations of HA in different forms, such as films, microspheres, liposomes, fibres and hydrogels, which have been used for more than 20 years worldwide [63]. Although the above-mentioned commercial preparations of HA have mainly been used in animal studies, it also provides useful information regarding the effect of hyaluronate in the prevention of post-operative peridural scar adhesion after laminectomy in spine surgery; however, additional clinical trials regarding the use of HA-based gels should be performed to confirm its effects in human subjects [67, 68]. Use of the hyaluronic acid-carboxymethylcellulose membrane Seprafilm as a solid anti-adhesion barrier agent is one of the therapeutic approaches used to reduce postoperative scar formation and is effective in promoting peripheral nerve regeneration at the repair site [69]. In addition, HA-carboxymethylcellulose solutions improve nerve regeneration and reduce perineural scar formation and adhesion after sciatic nerve repair [70]. It has been confirmed that direct application of HA-carboxymethylcellulose in transected nerves may limit axonal outgrowth by contact with regenerating axons; therefore, HA-carboxymethylcellulose barriers may prove to be a tool to prevent neuroma formation through inhibiting axonal growth [71]. On the contrary, according to some other studies, the role of HA solution in axonal outgrowth is dose-dependent, because high dose of HA (100–1000 μg/ml) topically used is characterised by significantly increased axonal outgrowth compared with HA solution (10 μg/ml) applied in the control group, in which axonal outgrowth did not
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378

169
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378

169
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378

169
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378

169
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378
The Role of Pharmacological Agents in Nerve Regeneration after Peripheral Nerve Repair

http://dx.doi.org/10.5772/intechopen.68378


[85] Toll EC, Seifalian AM, Birchall MA. The role of immunophilin ligands in nerve regeneration. Regenerative Medicine. 2011;6:635-652. DOI: 10.2217/rme.11.43


DOI: 10.1006/exnr.1998.6974


[121] Li H, Zhang L, Xu M. Dexamethasone prevents vascular damage in early-stage non-freezing cold injury of the sciatic nerve. Neural Regeneration Research. 2016;11:163-167. DOI: 10.4103/1673-5374.175064


