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Review

Carbon nanomaterials for nerve tissue stimulation and regeneration

Aneta Fraczek-Szczypta *

AGH University of Science and Technology, Faculty of Materials Science and Ceramics, Department of Biomaterials, Al. Mickiewicza 30, 30-059 Krakow, Poland

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ABSTRACT

Nanotechnology offers new perspectives in the field of innovative medicine, especially for reparation and regeneration of irreversibly damaged or diseased nerve tissues due to lack of effective self-repair mechanisms in the peripheral and central nervous systems (PNS and CNS, respectively) of the human body. Carbon nanomaterials, due to their unique physical, chemical and biological properties, are currently considered as promising candidates for applications in regenerative medicine. This chapter discusses the potential applications of various carbon nanomaterials including carbon nanotubes, nanofibers and graphene for regeneration and stimulation of nerve tissue, as well as in drug delivery systems for nerve disease therapy.

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1. Introduction

Due to the complexity of the nervous system anatomy and function, repairing damaged nerves, as well as recovering the full function of injured nerves, have been challenging compared with the treatment of other tissues. Worldwide, approximately two million people live with a spinal cord injury [1]. In the United States alone, there are about 250,000–400,000 people living with a spinal cord injury and nearly 13,000 additional people are subjected to spinal cord injuries each year [2]. Patients are typically in two age groups: young people up to the age of 15 and middle-aged between 30 and 50 years of age [3]. Injury in the peripheral nervous system (PNS), though generally less potentially debilitating than injury to the central nervous system (CNS), is much more common. Tens of thousands of peripheral nerve repair procedures are performed each year [4]. With the increasing age and population of the world, a greater number of patients will need various neural implants allowing for the full restoration of damaged nerve function.

* Corresponding author. Tel.: +48 126173759.
E-mail address: afraczek@agh.edu.pl.

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The human nerve system consists of the CNS, including the brain and spinal cord, and the PNS consisting of the nerves and ganglia outside of the brain and spinal cord. Nerve injuries are complicated and are serious clinical and social problems in the world. Injuries of the PNS are often capable of spontaneously healing after traumatic injury; damaged CNS tissue does not regenerate in the same manner. The current treatment of CNS injury, particularly that of the spinal cord, relies on minimizing secondary injury and implementing physical therapy designed to help a patient function with limited mobility. Treatment to restore healthy tissue and regain sensory and motor function is still not a reality. Developments in CNS tissue regeneration aim to ultimately provide a method for repairing functional tissue and restoring sensory and motor function [4]. The CNS system lacks Schwann cells to promote axonal growth and, more importantly, the thick glial scar tissue may be formed mainly by astrocyte and meningeal cell activity resulting in an unfavorable environment, which inhibits neural regeneration [5].

Nerve tissue defects within the PNS may heal without surgical intervention if the loss is small. However, where the defect is greater, it is required to connect the nerve stumps with tubular prostheses. Usually allografts and autografts, such as cutaneous nerves or blood vessels, serve as connectors. However, very often the allografts and autografts are not sufficient, therefore, tubular implants are used. Despite intensive research on tubular implants with natural and synthetic polymers, an implant that meets all the requirements for nerve regeneration has still not been designed.

There are high hopes for the progress of research on regeneration and stimulation of the nervous system associated with nanotechnology, in particular nanomaterials. It is expected that nanomaterials will be able, on the one hand, to prevent the activity of astrocytes (in CNS) and, on the other, to stimulate axon growth and the restoration of synaptic connections.

Carbon nanomaterials are proposed as promising candidates for nerve stimulation and regeneration. Currently, the best known are the three types of carbon nanostructures: carbon nanotubes (CNTs), carbon nanofibers (CNFs) and graphene. Carbon nanostructures have unique mechanical, electrical and physicochemical properties, and their shape (CNTs and CNFs) is similar to neurites. Biostable CNTs are attempted to be used as implants where long-term extracellular molecular cues for neurite outgrowth are necessary, e.g. in regeneration after spinal cord or brain injury [6].

Moreover, these materials can be fictionalized and modified chemically using biomolecules stimulating neurite growth. The chemical and biological modification of carbon nanomaterials produces various surface charges affecting the nerve response. Moreover, the surface charge can influence the length of neurite outgrowth, their number, branching and the number of synaptic connections.

2. Central and peripheral nerve regeneration

Problems with regeneration in the CNS are the result of several processes that take place after injury. These processes are designed to restore the blood–brain barrier and prevent further (secondary) tissue damage as well as to create an environment that is not favorable for nerve regeneration. Nerve damage induces astrocytes (glial cells) to increase their activity and, thus, to create a glial scar. Astrocytes migrate, proliferate, increase in size, and produce a glial scar rich in extracellular matrix (ECM) proteins, myelin and oligodendrocytes. Active astrocytes release proteoglycans including chondroitin sulfate proteoglycans (CSPGs), which are known as aggressive inhibitors of axon outgrowth. Glial scars can prevent axon regrowth through the creation of chemical and physical barriers. To be able to rebuild nerves, it is necessary to have free space through which axons can grow. The goals of all regeneration strategies in the CNS are generally to moderate reactive gliosis while promoting axon growth and tissue regeneration [4].

Peripheral nerve damage is typically, but not exclusively, caused by traumatic injury. It may also be a result of complications of orthopedic surgery. The peripheral nerve regeneration process runs in a few phases. In the first phase, multiple pathophysiologic events occur that are described as Wallerian degeneration. This process is connected with myelin sheaths and nerve fibers break up that greatly depends on cells called macrophages. These cells, excluding their phagocytic properties, play an important role in supporting the nerve fiber reconstruction process, called regeneration. They produce various cytokines, which stimulate Schwann cell proliferation and also production of neurotrophic substances, such as NGF (Nerve Growth Factor). These substances reach the cell body by retrograde axonal transport and stimulate the expression of genes whose products are responsible for axonal regeneration. Schwann cells build characteristic bands, or tubes of Büngner, within which axons grow [1,7,8].

The axon growth rate is estimated at about 0.5–1 mm/day [9]. It follows that in a few days several millimeters of distance can be overcome; however, reinnervation of target tissues may take place months. It is important to note that mature neurons do not undergo mitosis. Thus, supporting the regrowth of axons from existing cells to distal targets is the goal of a nerve guidance channel (NGC) [10]. Very often defects of peripheral nerves are greater than 2 cm, therefore, the implant should be designed to provide directional axon growth from the proximal to the distal nerve stumps to allow for synaptic connections. Usually allografts and autografts, such as cutaneous nerves or blood vessels, are used as nerve conduits. Among the materials of no biological origin, natural and synthetic polymers are the most common for producing peripheral nerve prostheses. These materials include polymers such as silicone, collagen, alginate, laminin, chitosan, hyaluronic acid, polylactide (PLA), polyglycolide (PGA), copolymers PLA with PGA and polycaprolactone (PCL) and others [11–13].

Surgery and implantation in the nervous system have a variety of problems not currently satisfying the high-performance demands necessary for today's patient. Specifically, for autografts taken from other sites of the body, it is frequently difficult to obtain enough donor nerves, and this deficiency of available tissue may result in functional impairment [14,15]. In addition, allografts and xenografts are associated with a risk of transmission of diseases and stimulation of the foreign body response, which is often the main cause of implantation failure [16,17]. Some implants e.g., silicone prostheses, strongly stimulate fibrous tissue formation, which consumes tube space limits or even stops regeneration and the migration of axons from the proximal to distal stump.

Silicon probes or other metal alloys of neural electrode-based prostheses are frequently encapsulated by a dense glial scar tissue in the brain [18,19]; this significantly decreases the electrical conductivity between the probe and tissue, significantly impairs the efficiency of electrostimulation and makes the probes useless during therapy. Other biomaterials, including various polymers used for manufacture of nerve conduits, may be limited by their mismatch of mechanical and electrical properties as well as lowered biocompatibility [2].

In contrast, in recent years, nanomaterials have become promising candidates for a variety of tissue engineering applications. Nanomaterials are materials that perform structural configuration and morphology at the nanometric range i.e., at least one dimension less than 100 nm. Due to a large range of properties, nanomaterials can be engineered to interact with cells and proteins with a greater degree of specificity [4].

3. Nanomaterials as next generation biomaterials for nerve tissue regeneration and stimulation

Nanoscale materials have a number of unusual properties that are unreachable for the materials at the microscale. Thanks to these properties, nanomaterials have the opportunity for use in areas of far reach of traditional materials. First, nanomaterials have a larger surface area in comparison with conventional materials. The specific surface area of a given mass of nanoparticles is greater than the specific surface area of the same dose of microscale particles. The increased