JOURNAL OF NANO- AND ELECTRONIC PHYSICS *ЖУРНАЛ НАНО- ТА ЕЛЕКТРОННОЇ ФІЗИКИ*
Vol. **15** No 3, 03035(7pp) (2023) Том **15** № 3, 03035(7cc) (2023)

Biodegradable Conductive Nerve Conduits Based on Carbon Apatite-Biopolymer Biomaterials: Synthesis and Properties

L.F. Sukhodub*, M.O. Kumeda, L.B. Sukhodub

Sumy State University, 2, Mykoly Sumtsova st., 40007 Sumy, Ukraine

(Received 20 April 2023; revised manuscript received 17 June 2023; published online 30 June 2023)

The mini-review examines the current state of the problem of peripheral nerve (PN) regeneration, including details of the internal structure of PN, types of their damage, biochemical aspects, in particular the function of Schwann cells, macrophages, intermolecular interactions of cell membrane receptors with extracellular matrix proteins, which are involved in the peripheral nerve regeneration process. The development of artificial nerve tubes (conduits) to suture the distal and proximal ends of the damaged nerve with an artificial conduit is the main strategy for PN recovery. Emphasis is placed on the use of leading biomaterials of the new generation, in particular, based on natural polysaccharides (alginate - Alg and chitosan - CS) and carbon nanoparticles CNP (single and multi wall carbon nanotubes – SWCNTs/MWCNTs, graphene - G, graphene oxide - GO or fullerene - C_{60}) obtained in the Sumy State University laboratory "Bionanocomposite" (Ukraine) to solve the PN regeneration problem. The results of studies of the obtained materials with carbon nanoparticles such as C_{60} and SWCNTs on electrical conductivity, swelling ability, and the ability to adsorb tryptophan (an amino acid that is indispensable for the functioning of the central nervous system) are presented. The peculiarities of the effect of carbon-based materials on the restoration of the functions of damaged nerve tissue are considered. Also, the usefulness of CNTs in neuroscience has been noted due to their specific properties, namely strength, flexibility, and electrical conductivity, in particular for mediating the growth and differentiation of neurons. This characteristics of the recently created polymer samples with CNP showed that these biomaterials have properties beneficial for neural tissue engineering.

Keywords: Peripheral nerve injury, Carbon nanoparticles, Hydroxyapatite, Biopolymers.

DOI: 10.21272/jnep.15(3).03035 PACS number(s): 61.41. + e, 61.46. – w

1. INTRODUCTION

The nervous system is an important part of the human body. Traumatic and disease-induced peripheral nerves and spinal cord injuries (PNI) cause various functional disorders. PNI threatens motility and sensory function because cell division does not occur in mature neurons because they are fully differentiated. Millions of people around the world suffer from non-regeneration of nerve tissue and therefore the problem of PN regeneration remains one of the biggest challenges in tissue engineering and regenerative medicine. The development of artificial nerve tubes (conduits) to suture the distal and proximal ends of the damaged nerve with an artificial conduit is the main strategy for PN recovery [1]. Functionalized neuro tubes are third-generation channels with chemical or architectural bioactivity engineered for axonal proliferation. Thanks to the improvement of bioengineering and microsurgery, in the future neuro tubes, can increase the level of regeneration and functional restoration of a critical nerve gap. At the same time, there is a lack of studies that would show that the results of neural tube transplantation were better than the results of autologous nerve transplantation.

Nowadays, commercial silicone nerve conduits, which had a low ability to degrade, have been replaced by some alternative materials. These materials include natural biopolymers (chitosan, alginate, collagen, gelatin, and hyaluronic acid) and synthetic polymers (polylactide (PLA), polyglycolide (PGA), poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL)). Biopolymers are more compatible with cells, less toxic, and can positively affect cell proliferation and migration. Therefore, natural polymers occupy a leading position among candidates for peripheral nerve regeneration [2,3].

Recent studies have shown that electrical stimulation plays a vital role in the regeneration of nerve tissue. Direct intraoperative electrical stimulation of damaged nerve tissue enhances and accelerates its functional recovery [4]. There is a wide range of applications of electrical stimulation, which is considered an important scheme of the regeneration process functionalization of nervous tissue. It is believed that the optimal properties for nerve regeneration have passive electrical stimulators. This goal can be achieved both by applying an electric field and by introducing conductive materials into the conduits.

Among the leading materials, special attention is paid to carbon-based materials, namely graphene, its oxide, fullerenes, and carbon nanotubes. These materials promote the interaction of cells and material due to the high ratio of surface area to volume [5]. It has been shown that nerve conductors consisting of graphene oxide to achieve electrical stimulation can affect cell adhesion and motility under an electric field. However, the rate of degradation of such conduits remains unfavorable. Also, the mechanism underlying the electrical stimulation function is still unclear [3].

Given the above, the main attention of this mini-review will be drawn to the problem of PN regeneration using leading bionanomaterials of the new generation, in particular, based on natural biopolymers - alginate

* l_sukhodub@yahoo.com

 © 2023 Sumy State University

and chitosan polysaccharides - and carbon nanoparticles (SWCNTs, G, C60), synthesized in the "Bionanocomposite" laboratory of the Sumy State University of the MES Ukraine.

2. PERIPHERAL NERVES REGENERATION

The peripheral nervous system connects the brain and spinal cord to the tissues and organs of the human body. Each nerve consists of several bundles, up to several hundreds of microns in diameter, while each bundle contains numerous axons and Schwann cells that extend the myelin sheaths around the axons [6] (Fig. 1).

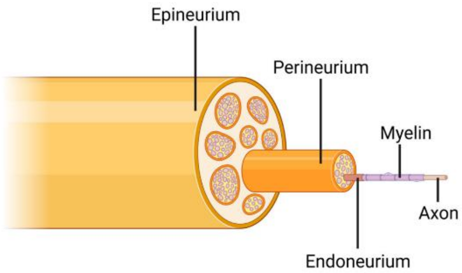

Fig. 1 – Internal structures of a peripheral nerve. The entire nerve is surrounded by a membrane epineurium. Each bundle of axons is separated from the surrounding tissue by its perineurial membrane. Each axon together with its myelin sheath is covered with a thin endoneurial membrane [7]

Trauma is the cause of 87% of all cases PNI [8]. Damage to the myelin sheath is the least severe type of nerve damage that spontaneously recovers through remyelination [6]. A more serious type of injury is axonotmesis: damaged axons undergo so-called Wallerian degeneration [6]. Complete transection of nerve tissue with obliteration of all three collagen membranes the most severe type of PNI. Peripheral nerve injury induces retrograde signals from axons to cells that activate the expression of several regeneration genes [7]. Damage to the axon activates Schwann cells, which, together with macrophages, clear the way for its regeneration [6]. But not all PNIs heal spontaneously: with mild axonotmesis, intact endoneurium, and perineurium are perceived by Schwann cells and regenerating axons that repeat the microarchitecture of connective collagen tissue. At the same time, with severe axonotmesis, the absence of structural collagen membranes hinders the recovery process, i.e. disorganized growth (formation of a painful nerve) occurs [6].

Intermolecular interactions of cell membrane receptors with components of the extracellular matrix (ECM) are the basis of PN regeneration. Membrane receptors that attach cells to ECM proteins are integrins – heterodimeric macrostructures of the cell membrane [9]. One of the most important proteins included in the composition of the ECM is collagen, which provides the structural strength of the tissue against tearing. Laminins are another group of ECM proteins, which are large glycoproteins, and they form the main part of the ECM of the nervous system. Fibronectin also enters the nervous system with an arginine-glycine-aspartic acid (RGD) domain that binds various integrin molecules, of which there are about 24 types [10]. In the process of obtaining PNI, the structure of collagen membranes is destroyed, which leads to complications in peripheral nervous system regeneration [6].

3. NEW GENERATION BIONANOMATERIALS FOR REGENERATION AND STIMULATION OF NERVOUS TISSUE

To solve the problem of nerve tissue regeneration, biomaterials (BM) are used, which in a certain way imitate the architecture of the ECM, that is, they act as substrates to which axons are attached [7]. Biomaterials can be either natural or synthetic. Among the natural BMs that contain ECM proteins and are used in tissue engineering, including the peripheral nervous system, are collagen hydrogels, and laminin hydrogels [11]. At the same time, these hydrogels are quickly resorbed *in vivo* and have low mechanical strength [12]. Natural biopolymers include those that are not part of ECM. For example, the polysaccharides alginate or chitosan, which will be discussed in the following sections of the review.

Synthetic BMs are polylactic acid, polycaprolactone, polyethylene glycol, and others. Their properties (porosity, stiffness, degradation rate) are easier to "adjust" compared to natural BM [13]. But at the same time, synthetic biopolymers require a certain surface modification and do not contain binding macromolecules.

Hydrogel scaffolds can provide mechanical support for cell growth, proliferation, and differentiation, and their porosity facilitates nutrient diffusion. The mechanical strength and porosity of hydrogels are flexible and adjustable characteristics, so they have great prospects for use in peripheral nerve regeneration. Hollow tubular PNs (conduits) are another form of transplanted material for PN regeneration. They are produced from various biomaterials, for example, collagen or PLGA [14]. The conduit serves as a connecting bridge between stumps of the peripheral nerve. It also isolates the lesion site from the environment and prevents spurious regeneration beyond the peripheral nerve passage. It was concluded that combined plastic surgery using Schwann cells matrigel and polylactate caprolactone tubes is a worthy alternative to traditional autoneuroplasty [15]. However, the desired restoration of PN in the clinic cannot be achieved due to the absence of Schwann cells in synthetic tubes, which are regulators of the directed growth of axons [16]. However, Schwann cells of neural origin are not readily available. Given these limitations, these cells are not an ideal source for experimental procedures or clinical applications.

4. CARBON BIOMATERIALS BASED ON HYDROXYAPATITE AND NATURAL POLYSACCHARIDES

4.1 Carbon Nanotubes

Carbon nanotubes (CNTs) have attracted great scientific interest in the last decade due to their mechanical, electronic, and physicochemical properties [17]. CNTs can be classified as multi-walled carbon nanotubes (MWCNTs) and single-walled carbon nanotubes (SWCNTs) depending on the number of internal layers, which are rolled graphene sheets. The diameter of CNTs can vary from 0.4 to 2 nm for SWNTs and from 1.4 to 100 nm for MWCNTs [18]. Biological applications of CNTs are limited by their initial hydrophobic surface, which is prone to aggregation when exposed to aqueous solutions. Thus, for the use of CNTs in biomedical research, their chemical functionalization is necessary both to reduce toxicity and to provide the desired characteristics of CNTs in the biological environment [19]. After surface modification of CNTs with targeting ligands and drugs, the resulting functionalized CNTs (f-CNTs) are less toxic and immunogenic and show great advantage as drug delivery systems for the treatment of cancer *in vivo* [20]. Due to their physicochemical properties, CNTs are widely used in many scientific fields, including composite biomaterials, nanoelectronics, drug delivery and others [21]. At the same time, the potential application of CNTs as therapeutic agents in the field of neuroscience is carried out on a much smaller scale.

4.2 Graphene and Its Derivatives

Graphene (G) is an allotrope of carbon that forms a two-dimensional hexagonal lattice at the atomic scale that can conduct heat and electricity efficiently. The electronic configuration of carbon is $1s^2 2s^2 2p^2$. In the excited state, four equivalent quantum mechanical states are formed due to sp^n hybridization, which plays an essential role in four covalent bonds between carbon atoms [22]. The stability of G depends on how densely packed the carbon atoms are during sp^2 hybridization. The attractive properties of graphene are due to its high surface area in combination with electronic and thermal conductivity, as well as mechanical strength. Due to the high ratio of the surface area to the volume of the material (S/V parameter) and high conductivity, graphene is very promising for hybrid biomaterials. Due to its unique microstructure, graphene exhibits enhanced physical and chemical properties. For example, Young's modulus and internal strength G are approximately 1TPa and 130 GPa, respectively. The electron mobility of graphene at room temperature is $2.5 \cdot 10^5$ $cm^2V^{-1}s^{-1}$, and thermal conductivity is about 3000 WmK^{-1}. Oxygen functional groups on the surface of graphene oxide (GO) provide sites for a variety of interactions to bind molecules such as polymers, and nanoparticles (NPs). GO is obtained from graphite oxide using the Hammer method, the reduced form of GO is graphene through an oxidant such as hydrazine or ascorbic acid [22].

4.3 Fullerene C60

A fullerene is an allotrope of carbon whose molecule consists of carbon atoms joined by single and double bonds to form a closed or partially closed network with fused rings of five to seven atoms. A molecule can be a hollow sphere, an ellipsoid, a tube, or many other shapes and sizes. Fullerenes with a closed lattice topology are informally denoted by their empirical formula C*n*, where *n* is the number of carbon atoms. Fullerene C_{60} is the best-known member of the family, named after Buckminster Fuller. Closed fullerenes, especially C_{60}, are also informally called buckyballs for their resemblance to a standard soccer ball. Nested closed fullerenes are called bucky onions. Cylindrical fullerenes are also called carbon nanotubes or buckytubes [23].

4.4 Hydroxyapatite

Among the family of calcium orthophosphates (CaOPs), hydroxyapatite (HA) is of greatest interest, as it is a close crystal-chemical analog of the mineral component of the bone tissue of the human and animal skeleton, as well as one of the most thermodynamically stable and least soluble CaOPs. Synthetic hydroxyapatite $Ca_5(PO_4)_3(OH)$, commonly referred to as $Ca_{10}(PO_4)_6(OH)_2$, demonstrates the presence of two molecules in the crystalline unit cell and is most similar to biological apatites. That is why HA is widely used for biomedical applications, particularly bone engineering [24]. The crystal structure of HA belongs to the space group P63/m of hexagonal syngony with lattice parameters a = 0.9432 nm, c = 0.6881 nm.

4.5 Natural Polysaccharides

Nerve conductors must meet several requirements, namely, be non-toxic, have good mechanical strength and elasticity, have a less immunogenic reaction, be biodegradable, and ensure rapid regeneration of the nerve. Therefore, natural polymers occupy a leading position among candidates for the regeneration of peripheral nerves [2,3]. Alginate and chitosan are often used among natural polymers in nerve tissue engineering. Alg is a structural polymer of brown seaweed that contains the monosaccharides d-mannuronic acid and α-l-glucuronic acid, which are linked by β-(1–4) glycosidic linkages. The main advantage of this material is its structural proximity to connective tissue. This makes it possible to provide an appropriate microenvironment for stimulating the regeneration of defective distal and proximal segments. In addition, the rate of alginate degradation can ensure axonal sprouting [5]. CS is a natural cationic molecule and a structural element of chitin present in the cytoskeleton of crustaceans. It consists of 35 repeating glucosamine and N-acetylglucosamine groups linked by a glycosidic bond. The unique properties of CS have attracted many researchers in the field of peripheral tissue engineering.

5. METHODS OF MANUFACTURING CONDUCTIVE CARBON BIOMATERIALS

Since the function of neurons is to conduct electrical signals, conductive coatings or materials with conductive particles are popular applications for nerve regeneration. Electrical stimulation has been shown to modulate growth factor production [25]. Popular conductive particles include carbon nanotubes or composites based on graphene oxide. The use of temporary electrical stimulation (ES) increases the speed of functional recovery due to the enhancement of nerve conduction. At the same time, nerve defects of critical size require the use of conductive conduits, and the application of ES in clinical conditions is a certain problem [26]. An alternative to ES is a pharmacological approach, namely the delayed release of a certain drug that promotes the conduction of nerve impulses. For example, the drug 4-aminopyridine (4AP), known as a blocker of voltagedependent potassium channels, as well as an enhancer neurotrophin release, was found to be suitable for the treatment of PNI and spinal cord injuries. Among the nano- and microparticles of inorganic origin, which can potentially be included in the composition of nerve conductors, there are particles of calcium orthophosphates, including hydroxyapatite, as well as zinc oxide (ZnO), magnetite, and carbon NPs. The issue of the effect of these NPs of inorganic origin on several properties of nerve conductors is one of the key issues for modern regenerative medicine in general.

Let us consider in more detail the process of creating model samples of nerve conductors based on sodium alginate with incorporated NPs and their properties studies results: electrical conductivity, hydration, and absorption capacity of organic bioactive substances using the tryptophan (Trp) amino acid [27]. In the cited work [27] the authors used the following synthesis of conductive conduits: a 3% solution of sodium alginate was prepared by dissolving the powder in ultrapure water for 24 hours at a temperature of 37°C. An appropriate amount of C_{60} fullerene powders and SWCNTs were added to the obtained solution to obtain carbon nanoparticle concentrations of 0.005 and 0.01 mg/l. The resulting colloidal suspension was homogenized in an ultrasonic bath for 5 hours, then poured into plastic cylinders with a diameter of 1 cm. The suspension was subjected to freezing followed by lyophilization for 24 hours. Then the lyophilized samples were cross-linked for 4 hours. For this, they were put into a 1.5% solution of chitosan with polyethylene glycol, which was used as a plasticizer (10% by volume of chitosan). The samples were washed in ethyl alcohol and ultrapure water and dried at 37°C. For some of the samples, a final treatment was applied - the application of a hydrophobic layer of PLA (polylactic acid) to the surface of the samples. The samples were immersed three times for 5 seconds in a 10% solution of PLA in cyclohexanone and dried in air. Depending on the content of carbon nanoparticles (0.005, 0.01), the samples were named Alg_0.005Full, Alg_0.005SWCNTs, and the control sample without carbon nanoparticles was named Alg_control. Schematically, the structure of the resulting conductive conduit is shown in Fig. 2.

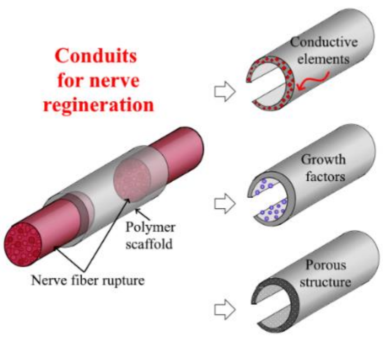

Fig. 2 – Schematic representation of the obtained nerve conduit [27]

6. RESULTS AND DISCUSSION

6.1 Conductivity Research

Samples of different compositions were tested for their conductive properties. The direct current (DC) insulation resistance of the materials was measured with an M 4100/4 type megohmmeter and the M 9508 MASTECH device. The current flowing through the samples was measured using a MASTECH MS 8040. To determine the current, a special G6-34 signal generator was used. The value of the amplitude of the alternating current (AC) signal is set equal to 60 mV. The frequency of the applied voltage varied in the range of 50-1500 Hz. Sinusoidal, rectangular, and triangular waveforms were used. Before the study, the samples were moistened with a phosphate-buffered solution, that is, their condition was close to physiological. The results of electrical conductivity measurements of the obtained samples (Fig. 3) together with literature data are presented in Table 1.

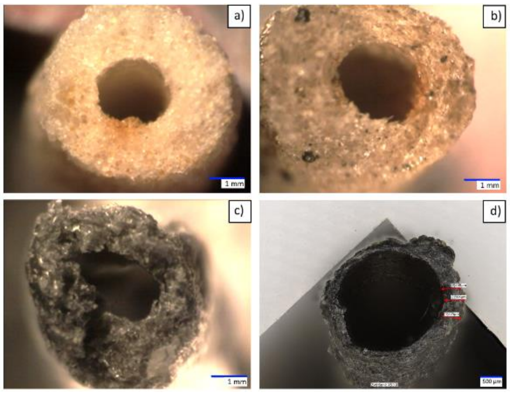

Fig. 3 – EM results of the synthesized samples before cross-linking a) Alg_control, b) Alg_0.005 Full, c) Alg_0.005 SWCNTs, and after cross-linking – d) Alg_0.005 SWCNTs

Table 1 – Composition and conductive properties of experimental samples

Sample	Conductivity, S/cm	Current, μA	Capacity, pF
Alg_control	$1.25\cdot10^{-3}$	0.01	4.3
Alg_0.005 Full	$1.54\cdot10^{-3}$	0.02	4.5
Alg_0.005 SWCNTs	$3.49\cdot10^{-3}$	0.04	4.3
Electroactive colloidal hydrogels for neural tissue engineering (literature data)	$3\cdot10^{-4}$ [28]	No data	
	$6\cdot10^{-2}$ [29]		
	$2.41\cdot10^{-5}$ – $8\cdot10^{-3}$ [30]		
	$1.5\cdot10^{-3}$ – $5.7\cdot10^{-3}$ [31]		

Since the obtained tubular samples are designed to function *in vivo*, namely to create a nerve signal, their ability to conduct electricity plays an important role in this process. It was found that for these samples with an outer diameter of 5 mm and a wall thickness of 1 mm, the best conductivity was observed for the sample with SWCNTs [27]. At the same time, additional studies showed that the highest resistance and the lowest current are characteristic of samples with ZnO particles [27], the semiconductor properties of which are well known [32]. These data correlate with studies in [24], from which it follows that the presence of ZnO particles in the apatite-biopolymer composite reduces swelling and porosity by 1.5 and 1.4 times, respectively. A similar situation is typical for composites with C60 fullerene

[33]. Swelling and porosity parameters affect the degree of hydration, and since water itself is a conductor, its content affects the overall conductive properties of apatite biopolymer samples.

6.2 Study of Adsorption on the Example of Tryptophan (Trp)

The adsorption capacity (q_e) of the sample was determined by the formula $q_e = (C_i - C_e)V/M$, where C_i and C_e are the initial and the experimental concentrations of Trp (mmol/L), while M and V - are the weight of the adsorbate (204.2 g/mol) and the volume of the solution. Trp adsorption data were analyzed using 4 isotherms: Langmuir, Freundlich, Sips, and Henry [27]. The average percentage deviation between experimental and predicted data was determined by minimizing the objective function. The reliability of each model was checked by the corresponding correlation coefficient (r^2). As a result, it was found that the Sips isotherm (a combination of the Langmuir and Freundlich isotherms), which predicts the heterogeneity of the adsorption surface, best correlates with the experimental data for all the samples listed in Table 1 ($r^2 = 0.97$-0.94).

6.3 Features of Conducting Materials Based on Graphene

Currently, it has been established that G-based materials, due to their high electrical conductivity, mechanical strength, elasticity, and biocompatibility, have found wide application in tissue engineering. In particular, G has been widely applied to the regeneration of the PNS by improving the interaction between neurons. Strong bonds and large specific surface area with high electrical conductivity favor the use of G-based composite materials for PNI regeneration [1]. Oxidation of G to GO increases the hydrophilicity of the surface and creates functional groups (OH, COOH, C=O), which, in turn, opens up the possibilities of selecting material properties necessary for bioprinting [1]. Scaffolds based on G and GO, due to the transmission of electrical signals, provide electrical stimulation of axon restoration processes [34]. But at the same time, the concentration of G in the composite should not exceed 50 µg/ml, since higher concentrations cause toxicity, low cell adhesion, and cell apoptosis [35].

Recently, three-layer tubular conduits with graphene nanoparticles have attracted attention. For example, one such construct contains alginate-polyvinyl alcohol as an inner layer, a polycaprolactone membrane as a middle layer, and a double outer layer consisting of polycaprolactone fumarate and eggshell [36]. This engineering design provides the direction of movement for PC12 cells through the electrical conductivity of these frameworks. Electrical stimulation increased cell proliferation 1.8 times compared to the unstimulated group [36]. GO with a conductivity of about $4.5 \cdot 10^{-4}$ S/cm was also successfully used to repair a sciatic nerve defect (15 mm) due to its ability to support the proliferation of Schwann cells, as well as its angiogenic effect [37]. By changing the state of conductivity, it is possible to regulate the adsorption of fibronectin, which affects the shape and growth of the cell [38], electrical stimulation increases the adsorption of this protein, which accelerates the expansion of neurites [39].

HA-based conduits were found to enhance Schwann cells expression by overexpressing neural proteins (Tuj1, GFAP) on the conducting scaffolds. Graphene-PCL promotes the emergence of more axons and neuron area compared to non-conductive conduits (Fig. 4) [1].

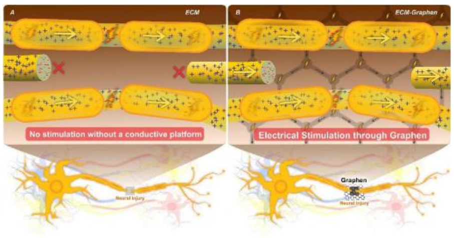

Fig. 4 – Neuron regeneration alongside graphene as conductive. The injured neuron exposed conductive platform vs. The injured neuron without the conductive platform, conductive platform along with the injured neuron results in nerve regeneration because of electrical stimulation [1]

6.4 Biological Mechanisms that are Mediated by CNTs

Some diseases of the nervous system are treated by restoring the structure of neurons by slowing the growth of neurons. Several neurotrophic factors have been identified that affect the growth of neurons. At the same time, there is a problem of how to regulate this process, since there are no methods of controlling the growth environment on a nanometric scale [18]. CNTs have alternatively demonstrated potential utility in neuroscience due to their specific properties, including strength, flexibility, and electrical conductivity. It was demonstrated that the level of specific conductivity of PN is important for mediating the growth and differentiation of neurons: cells on substrates with a conductivity of 0.43-0.5 S/cm showed the strongest adhesion, cell migration, and protein expression [40]. To maintain the physiological state of neuronal cells, MWCNTs were coated with bioactive molecules (4-hydroxynonenal) to increase neuronal branching. The results of the functionalized MWCNTs effect study on the morphology of the cytoskeleton of neurons showed abnormal growth of neurons, and therefore there was a need to modify the surface of MWCNTs to achieve proper cellular activity. The blood-brain barrier (BBB) (Fig. 5) [40], which separates the blood from the cerebrospinal fluid and the internal environment of the CNS, is the main obstacle to the delivery of drugs in cases of its disorder.

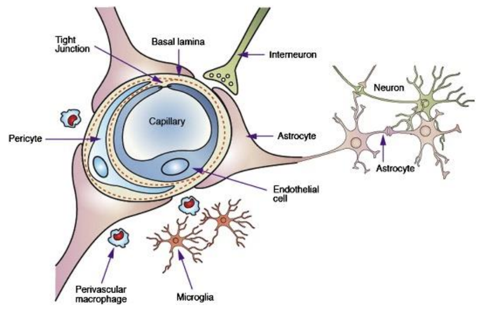

Fig. 5 – Schematic representation of the blood-brain barrier (BBB) and other components of the vascular-nerve unit (NV) [40]

CNTs, which have attractive properties, are an excellent example of solving this problem. They can be used as separate scaffolds or in combination with other biomaterials to stimulate and regenerate nervous system damage, for example, being used as drug carriers to neurons or directly interacting with biomolecules that are associated with CNS diseases [40]. At the same time, it should be remembered that CNTs are intrinsically toxic, which is related to the ability of fullerenes to induce lipid peroxidation, the formation of free radicals, the tendency to aggregate and interact with cell membranes, and DNA damage. All these are obstacles to the potentially wide use of CNTs in the therapy of neurological diseases [18,40].

7. CONCLUSIONS AND NEW CHALLENGES

The development and production of new generation composite biomaterials that can promote the healing process of damaged nerves is the main goal of researchers in the field of regenerative medicine. In this mini-review, attention was focused on the preparation of alginate-based porous, double-layer conduits with carbon nanoparticles such as fullerene C_{60} and SWCNTs. The obtained characteristics of these samples showed that these biomaterials have properties useful for neural tissue engineering. Carbon particles, as well as the created PLA layer, significantly reduce the degree of swelling of the synthesized materials. The sample containing SWCNTs has twice the electrical conductivity compared to fullerene C_{60}. Experimental data on electrical conductivity correspond to the relevant characteristics of polymer hydrogels, which are candidates for use in nerve tissue engineering. These results showed that the obtained porous composites, due to their internal electrical conductivity, can be used as a bioactive material to improve the regeneration of damaged peripheral nerves after biological studies. At the same time, for example, G-based composites have both positive (increased neuronal activity) and negative (strong π -bonds pose a threat to membrane integrity) effect on PNI regeneration. Therefore, the focus of further research should be to optimize the use of both graphene and its derivatives, as well as other carbon nanoparticles to achieve optimal regeneration of PNI.

ACKNOWLEDGMENT

The research was financially supported by the National Research Foundation of Ukraine within the framework of the program Science for Security and Sustainable Development of Ukraine 0122U001154 and the Ministry of Science of Ukraine in the frame of a research topic 0122U000775.

REFERENCES

1. P. Zarrintaj, E. Zangene, S. Manouchehri, L.M. Amirabad, N. Baheiraei, M.R. Hadjighasem, M. Farokhi, M.R. Ganjali, B.W. Walker, M.R. Saeb, M. Mozafari, S. Thomas, N. Annabi, *Appl. Mater. Today* **20**, 100784 (2020).
2. P.-X. Zhang, N. Han, Y.-H. Kou, Q.-T. Zhu, X.-L. Liu, D.-P. Quan, J.-G. Chen, B.-G. Jiang, *Neural Regen. Res.* **14**, 51 (2019).
3. Y. Yan, R. Yao, J. Zhao, K. Chen, L. Duan, T. Wang, S. Zhang, J. Guan, Z. Zheng, X. Wang, Z. Liu, Y. Li, G. Li, *Bioact. Mater.* **11**, 57 (2022).
4. T. Gordon, *Neurotherapeutics* **13**, 295 (2016).
5. M. Farokhi, F. Mottaghitalab, M.A. Shokrgozar, D.L. Kaplan, H.-W. Kim, S.C. Kundu, *Int. Mater. Rev.* **62**, 367 (2017).
6. H. Khan, N. Perera, *Orthop. Trauma* **34**, 168 (2020).
7. B. Kaplan, S. Levenberg, *Int. J. Mol. Sci.* **23**, 1244 (2022).
8. B.J. Pfister, T. Gordon, J.R. Loverde, A.S. Kochar, S.E. Mackinnon, D.K. Cullen, *Crit. Rev. Biomed. Eng.* **39**, 81 (2011).
9. J.P. Myers, M. Santiago-Medina, T.M. Gomez, *Dev. Neurobiol.* **71**, 901 (2011).
10. K.A. Venstrom, L.F. Reichardt, *FASEB J.* **7**, 996 (1993).
11. Y. Yang, Y. Fan, H. Zhang, Q. Zhang, Y. Zhao, Z. Xiao, W. Liu, B. Chen, L. Gao, Z. Sun, X. Xue, M. Shu, J. Dai, *Biomaterials* **269**, 120479 (2021).
12. T. Führmann, P.N. Anandakumaran, M.S. Shoichet, *Adv. Healthc. Mater.* **6**, 1601130 (2017).
13. B. Kaplan, U. Merdler, A.A. Szklanny, I. Redenski, S. Guo, Z. Bar-Mucha, N. Michael, S. Levenberg, *Biomaterials* **251**, 120062 (2020).
14. E.B. Saltzman, J.C. Villa, S.B. Doty, J.H. Feinberg, S.K. Lee, S.W. Wolfe, *J. Hand Surg. Am.* **44**, 700.e1 (2019).
15. B. García-Medrano, N. Mesuro Domínguez, C. Simón Pérez, M. Garrosa García, S. Gayoso del Villar, A. Mayo Íscar, M.J. Gayoso Rodríguez, M.A. Martín Ferrero, *Rev. Esp. Cir. Ortop. Traumatol.* **61**, 359 (2017).
16. A. Faroni, S.A. Mobasseri, P.J. Kingham, A.J. Reid, *Adv. Drug Deliv. Rev.* **82–83**, 160 (2015).
17. N. Saito, Y. Usui, K. Aoki, N. Narita, M. Shimizu, K. Hara, N. Ogiwara, K. Nakamura, N. Ishigaki, H. Kato, S. Taruta, M. Endo, *Chem. Soc. Rev.* **38**, 1897 (2009).
18. C. Xiang, Y. Zhang, W. Guo, X.-J. Liang, *Acta Pharm. Sin. B* **10**, 239 (2020).
19. A. Battigelli, C. Ménard-Moyon, T. Da Ros, M. Prato, A. Bianco, *Adv. Drug Deliv. Rev.* **65**, 1899 (2013).
20. Z. Liu, K. Chen, C. Davis, S. Sherlock, Q. Cao, X. Chen, H. Dai, *Cancer Res.* **68**, 6652 (2008).
21. L.B. Sukhodub, L.F. Sukhodub, M.O. Kumeda, Y.I. Prylutskyy, M. V. Pogorielov, M.P. Evstigneev, V.V. Kostjukov, N.Y. Strutynska, L.L. Vovchenko, S.V. Khrapatiy, U. Ritter, *Prog. Biomater.* **9**, 1 (2020).
22. A. Balaji, J. Zhang, *Cancer Nanotechnol.* **8**, 10 (2017).
23. P.R. Buseck, S.J. Tsipursky, R. Hettich, *Science* **257**, 215 (1992).
24. L.B. Sukhodub, M. Kumeda, V. Bielai, L.F. Sukhodub, *Carbohydr. Polym.* **266**, 118137 (2021).
25. J. Huang, X. Hu, L. Lu, Z. Ye, Q. Zhang, Z. Luo, *J. Biomed. Mater. Res. Part A* **9999A**, NA (2009).
26. M. Sakuma, I.R. Minev, S. Gribi, B. Singh, C.J. Woolf, S.P. Lacour, *Bioelectron. Med.* **2**, 43 (2015).
27. M. Kumeda, L. Sukhodub, L. Sukhodub, O. Potapov, O. Tsyndrenko, O. Kmyta, *11th IEEE International Conference "Nanomaterials: Applications and Properties" (NAP 2021)*, 176891 (2021).
28. P. Zarrintaj, A.M. Urbanska, S.S. Gholizadeh, V. Goodarzi, M.R. Saeb, M. Mozafari, *J. Colloid Interface Sci.* **516**, 57 (2018).
29. S. Homaeigohar, T.-Y. Tsai, T.-H. Young, H.J. Yang, Y.-R. Ji, *Carbohydr. Polym.* **224**, 115112 (2019).
30. S. Vandghanooni, M. Eskandani, *Int. J. Biol. Macromol.* **141**, 636 (2019).
31. J. Qu, Y. Liang, M. Shi, B. Guo, Y. Gao, Z. Yin, *Int. J. Biol. Macromol.* **140**, 255 (2019).
32. A. Pogrebnjak, L. Sukhodub, L. Sukhodub, O. Bondar, M. Kumeda, B. Shaimardanova, Z. Shaimardanov, A. Turlybekuly, *Ceram. Int.* 45, 7504 (2019).
33. L.B. Sukhodub, L.F. Sukhodub, M.O. Kumeda, S.V. Prylutska, V. Deineka, Y.I. Prylutskyy, U. Ritter,

Carbohydr. Polym. **223**, 115067 (2019).
34. R. Guo, S. Zhang, M. Xiao, F. Qian, Z. He, D. Li, X. Zhang, H. Li, X. Yang, M. Wang, R. Chai, M. Tang, *Biomaterials* **106**, 193 (2016).
35. A. Raslan, L. Saenz del Burgo, J. Ciriza, J.L. Pedraz, *Int. J. Pharm.* **580**, 119226 (2020).
36. N. Golafshan, M. Kharaziha, M. Alehosseini, *Biomed. Mater.* **13**, 065005 (2018).
37. Y. Qian, J. Song, X. Zhao, W. Chen, Y. Ouyang, W. Yuan, C. Fan, *Adv. Sci.* **5**, 1700499 (2018).
38. B.E. Beck-Broichsitter, A. Lamia, S. Geuna, F. Fregnan, R. Smeets, S.T. Becker, N. Sinis, *Biomed Res. Int.* **2014**, 401760 (2014).
39. A. Kotwal, *Biomaterials* **22**, 1055 (2001).
40. S.A. Mezzasalma, L. Grassi, M. Grassi, *Mater. Sci. Eng. C* **131**, 112480 (2021).

Біорозкладні провідні нервові канали на основі вуглецево-апатит-біополімерних біоматеріалів: синтез та властивості

Л.Ф. Суходуб, М.О. Кумеда, Л.Б. Суходуб

Сумський державний університет, вул. Миколи Сумцова, 2, 40007 Суми, Україна

В міні-огляді розглянуто сучасний стан проблеми регенерації периферичних нервів (PN), включаючи деталі внутрішньої структури PN, види їх пошкоджень, біохімічні аспекти, зокрема функцію Schwann-клітин, макрофагів, міжмолекулярних взаємодій рецепторів клітинної мембрани з білками ECM, які задіяні в процесі регенерації периферичних нервів. Розробка штучних нервових трубок (кондуїтів) для зшивання дистальних і проксимальних кінців пошкодженого нерва є основною стратегією відновлення PN. Зроблено акцент на використання провідних біоматеріалів нового покоління, зокрема на основі природних полісахаридів (альгінат – Alg, хітозан – CS) та вуглецевих наночастинок (одностінні карбонові нанотрубки – SWCNTs, графен – G, оксид графену – GO чи фулерен – C_{60}) отриманих в лабораторії «Біонанокомпозит» Сумського державного університету (Україна) для вирішення проблеми регенерації PN. Приведені результати досліджень отриманих матеріалів з наночастинками вуглецю C_{60} та SWCNTs на електропровідність, набрякання та здатність до адсорбції триптофану (амінокислоти, що є незамінною для функціонування центральної нервової системи). Розглянуто особливості впливу вуглецевих матеріалів на відновлення функцій пошкодженої нервової тканини. Також, відмічена корисність CNTs в нейронауках завдяки їх специфічним властивостям, а саме міцності, гнучкості та електропровідності, зокрема для опосередкування росту та диференціюванню нейронів. Ці характеристики нещодавно створених зразків полімерів з CNP показали, що ці біоматеріали мають властивості, корисні для інженерії нервової тканини.

Ключові слова: Пошкодження периферичних нервів, Карбонові наночастинки, Гідроксиапатит, Біополімери.