

Bibliographic review on the application of biomaterials in neurological disorders

Actualización bibliográfica sobre el uso de biomateriales en afecciones neurológicas

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Cite as

Auza-Santivañez JC, Condori-Villca N, Oberson Santander I, Tecuatl Gómez LM, Mamani Manzaneda LP, Condo-Gutierrez AR, et al. Bibliographic review on the application of biomaterials in neurological disorders. SAP Biomedical & Chemical Engineering Innovation. 2025; 4:169. <https://doi.org/10.56294/evk2025169>

Publication History

Submitted: 28-01-2024

Revised: 03-03-2024

Accepted: 16-05-2024

Published: 17-05-2024

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ABSTRACT

Introduction: the process of endogenous neurogenesis is not capable of replenishing lost cells after an injury that can result in massive cell loss. Biomaterials are being developed to mimic the brain's extracellular matrix, providing scaffolds that promote tissue repair and regeneration. The objective was to characterize the application of biomaterials in neurological affections.

Method: a literature review was conducted, where 20 articles in English and Spanish were selected, published in the last five years on the subject, in databases such as: Scopus, PubMed, Springer.

Results: biomaterials play an essential role in the human body by serving as artificial substitutes or implants that interact with living tissues, organs, and bodily fluids. Emerging approaches, including stem cell therapy, biomaterials, immune cell therapy, and exosome-based treatments, show promise in modulating the inflammatory response while avoiding broad suppression of immune function. With that in mind, researchers are exploring how these materials could help repair nerve damage once thought to be permanent, boost brain function, and play a key role in fields like neuro-oncology and neuro-rehabilitation.

Conclusions: biomaterials enable safe contact with living tissue and offer promise in neuroscience. Research is still needed to address ethics and ensure safe use.

Keywords: Biomaterials in Neuroscience; Neural Tissue Engineering; Neuroregeneration; Hydrogels for Brain Repair; Neural Stem Cells.

RESUMEN

Introducción: el proceso de neurogénesis endógena no es capaz de reemplazar las células perdidas tras una lesión que puede causar una pérdida celular masiva. Se están desarrollando biomateriales que imitan la matriz extracelular del cerebro, proporcionando andamios que favorecen la reparación y regeneración del tejido. El objetivo fue caracterizar la aplicación de biomateriales en afecciones neurológicas.

Método: se realizó una revisión bibliográfica en la que se seleccionaron 20 artículos en inglés y español, publicados en los últimos cinco años sobre el tema, en bases de datos como Scopus, PubMed y Springer.

Resultados: los biomateriales desempeñan un papel esencial en el cuerpo humano al actuar como sustitutos artificiales o implantes que interactúan con tejidos, órganos y fluidos corporales. Nuevas estrategias, como la terapia con células madre, los biomateriales, la inmunoterapia celular y los tratamientos basados en exosomas, muestran potencial para modular la respuesta inflamatoria sin suprimir de forma generalizada la función inmune. Con base en ello, los

investigadores están explorando cómo estos materiales podrían ayudar a reparar daños neuronales antes considerados irreversibles, mejorar la función cerebral y tener un rol clave en áreas como la neurooncología y la rehabilitación neurológica.

Conclusiones: los biomateriales permiten un contacto seguro con el tejido vivo y representan una promesa dentro de la neurociencia. Sin embargo, aún es necesario avanzar en la investigación para abordar aspectos éticos y garantizar un uso seguro.

Palabras clave: Biomateriales en Neurociencia; Ingeniería de Tejido neural; Neuroregeneración; Hidrogeles para Reparación Cerebral; Células Madre Neurales.

INTRODUCTION

The brain has the most complex architecture of all the tissues in the body with a spongy anisotropic microstructure. Brain tissue can be divided into two types, gray and white matter. Gray matter forms the outer layer of the brain which contains cell bodies, dendrites, and unmyelinated axons, whereas the white matter forms the central structure with anisotropically arranged myelinated axons. Brain disorders such as stroke can lead to irreversible cell loss due to the brain's limited capability of regeneration leaving a stroke survivor to live with lifelong impairments. Traumatic events such as car accidents, falls, and assaults are also the leading causes of adult disability worldwide.⁽¹⁾

Other neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's disease, and amyotrophic lateral sclerosis (ALS) mainly affect the elderly population and also responsible for disability similar to stroke. The process of endogenous neurogenesis is not capable of replenishing lost cells after an injury that can result in massive cell loss.⁽¹⁾

Traditional interventions, such as anti-inflammatory drugs, neuroprotective agents, anticoagulants, and surgical procedures like decompressive craniectomy and hematoma evacuation, are critical for managing the immediate consequences of brain injuries and preventing further complications. However, these treatments fail to address the underlying processes of neural degeneration and do not promote long-term recovery of brain function.⁽²⁾ In contrast, during the chronic stage, physical and cognitive rehabilitation therapies might work in a minority of patients, especially in subjects with less extensive damage after the initial insult.⁽³⁾

The primary obstacle in patient's recuperation is the complex healing process of the central nervous system (CNS). The lack of understanding about it complicates the design of effective therapeutic strategies. Moreover, the blood brain barrier (BBB), a highly selective barrier that protects the CNS, limits the delivery of many therapeutic agents to the brain and spinal cord.⁽²⁾ The restrictive permeability of the BBB and, in particular, the abundance of tight junctions that encircle endothelial cells, complicates the entrance of biomolecules into the brain by crossing the luminal and antiluminal lipid membranes that face the blood lumen and the brain parenchyma, respectively.⁽³⁾ Systemic administration of therapeutic molecules to stimulate endogenous neural progenitor cells proliferation and to prevent glial scar formation are also not possible due to the presence of the BBB.⁽¹⁾

Biomaterials, both natural and synthetic in origin, are constantly used in the medical field and can be defined as "materials that present new properties that make them suitable to come into direct contact with living tissue without causing an immune rejection or an adverse reaction".^(1,4,5,6)

Although the concept of biomaterials as we understand them today was not fully developed, ancient societies intuitively utilized natural materials with desirable properties for medical purposes. In ancient Egypt, linen and papyrus were employed as bandages and wound dressings, providing protection and aiding in healing.⁽⁴⁾ The first generation of biomaterials emerged in the 1950s and 1960s and primarily consisted of industrial materials that were not specifically developed for medical use.⁽⁴⁾

The integration of tissue engineering and regenerative medicine has marked a significant shift in the treatment of central nervous system injuries, moving beyond symptom management toward promoting long-term recovery and functional restoration at both the cellular and tissue levels.⁽²⁾ The evaluation of the state of the art in the use of biomaterials and stem and precursor cells is a crucial point in order to establish the goals and objectives in addressing new scientific and clinical challenges.^(7,8)

A bibliographic review was carried out, to characterize the application of biomaterials in neurological disorders.

METHOD

A bibliographic investigation was carried out. To this end, a search was conducted in databases such as PubMed, Scopus, and Springer using the following keywords: Biomaterials in neuroscience; Neural tissue engineering; Neuroregeneration; Hydrogels for brain repair; Neural stem cells. These terms were used in combination with the connector "and." A total of 20 articles were selected, more than 60 % of which were published in the last five years, in both Spanish and English. Relevant information was extracted, and after organizing and synthesizing it, a well-structured development was achieved.

RESULTS

Biomaterials are being developed to mimic the brain's extracellular matrix, providing scaffolds that promote tissue repair and regeneration. These biomaterials can help reduce inhibitory signals from glial scars, creating an environment conducive to axonal regrowth and neural repair.⁽²⁾ Tissue engineering adopts principles and methods from the engineering and medical sciences to design artificial tissue substitutes that can potentially provide structural and functional support to the host tissue. The fundamental aim of

tissue engineering is to re-establish the function of a specific tissue lost to disease or an accident in a minimally invasive way.⁽¹⁾

Biomaterials play an essential role in the human body by serving as artificial substitutes or implants that interact with living tissues, organs, and bodily fluids. They contribute to various medical treatments, therapies, and interventions, improving patient health and quality of life.⁽⁴⁾ The broad utilization of biomaterials across diverse medical specialties underscores their indispensable role in enhancing patient care, promoting medical innovation, and improving overall quality of life.⁽⁴⁾ It's becoming clear that the surface properties and chemical composition of a biomaterial can strongly influence how neurons and glial cells respond during experiments.

Systemic administration of neurotrophic factors for a treatment, requires comparatively higher concentrations that increase the risk of off-target effects. On the contrary, invasiveness, risk of infection, and short half-life of neuro trophic factors challenge the effectiveness of local delivery via catheter or mini osmotic pump.⁽¹⁾ An alternative route for systemic administration is intracerebral. Although this route is more invasive, an intracerebral injection offers significant advantages, e.g., the direct administration of drugs in the area/s of interest, although these drugs are also exposed to rapid degradation and clearance, which is a strong limitation if persistent pharmacological effects are needed.⁽³⁾ Despite all the advances, there are still concerns about long-term compatibility, especially when these materials are implanted into sensitive areas like the brain or spinal cord.

Applications

Specifically, biomaterials derived from natural sources have been shown to enhance the survival of the transplanted cells, exhibiting better integration with the designated host tissue, neuro genesis, angiogenesis, and functional recovery in rodent models.⁽⁹⁾

Effective therapeutic strategies for neuronal damage require precise modulation of the inflammatory response while avoiding broad suppression of immune function. Emerging approaches, including stem cell therapy, biomaterials, immune cell therapy, and exosome-based treatments, show promise in achieving this balance. Stem cells have been shown to migrate to injury sites, modulate inflammation, and promote tissue repair. Despite their promise, these approaches face challenges such as immune rejection, scalability limitations, and the lack of standardized clinical protocols.⁽²⁾

The application of biomaterials for targeted delivery and neuroprotection has led to the development of several promising systems that are revolutionizing the treatment of CNS disorders. These biomaterials, such as GelMA-PPS/PC hydrogels, release neurotrophic factors like brain derived neurotrophic factor directly at the injury site, scavenging reactive oxygen species (ROS) and reducing pro-inflammatory cytokines to promote neuroprotection and neuronal survival. The Triglycerol monostearate loaded procyanidins system combines ROS-scavenging agents with curcumin, promoting neurogenesis and upregulating neurogenesis markers such as doublecortin (DCX).⁽²⁾

Neural Stem Cells

Neural stem cells can differentiate into neurons, astrocytes, and oligo dendrocytes; however, their success depends on the ability to secrete neurotrophic factors and to modulate the immune response.⁽¹⁰⁾

Esteban-Garcia et al.⁽¹¹⁾ describe in their review the use of biomaterials for neurorestoration after ischemic stroke. One of the most common strategies to target this problem is biomaterials combined with cellular therapy. The authors address the limitations and consequences that originate after stroke, the endogenous repair mechanisms and the critical keys that can contribute to a successful therapy using biomaterials and stem cells.

Neural stem cells (NSCs) derived from various sources including embryonic stem cells (ESC), mesenchymal stem cells (MSC), induced-pluripotent stem cells (iPSC), and hematopoietic stem cells (HSC) have been evaluated for their potential in neuro-regeneration. However, poor cell survival, uncontrolled differentiation, lack of extracellular matrix (ECM) support, graft rejection due to the host immune response are some of the critical issues limiting the success of transplantation as a therapeutic approach.⁽¹⁾ As a solution, implantation of a brain-like biomaterial into the lesion cavity could create a microenvironment that would serve as a scaffold for the transplantation of neural stem-like cells or the delivery of neurotrophic factors or therapeutic molecules.⁽¹⁾

Chemically defined platforms with adaptable mechanical properties can modulate a series of cellular properties such as proliferation, differentiation, maturation, and cytoarchitecture in 2D and 3D CNS in vitro models. ^(1,12,13) Using biomaterials to create 3D models of brain tissue has made it easier to explore how neurons behave in health and disease, without always relying on animal models.

Biomaterials are carving out a unique space in neuroscience because they offer more than just structural support. They're becoming active players in modulating cellular behavior, which is especially useful when working with delicate neural tissues that are highly reactive to changes in their surroundings.

Witherick et al, demonstrated the role of MSCs in modulating cytotoxic reactive oxygen species through the secretion of the extracellular antioxidant molecule superoxide dismutase 3. This molecule eliminates excess superoxide produced by the microglia after demyelination, improving symptoms of the disease.⁽¹⁰⁾

Another beneficial effect reported with MSC administration is the secretion of such neurotrophic factors as nerve growth factor, ciliary neurotrophic factor, and brain-derived neurotrophic factor (BDNF). In an animal model of EAE, administration of MSCs is reported to increase levels of these molecules, leading to neurological improvement.⁽¹⁰⁾

Hydrogel

Hydrogels are porous structures composed of 30–90 % water of their dry weight. Porosity of the hydrogels can be modulated

by adjusting the degree of crosslinking between each molecule. The porous structure of the hydrogel assists in promoting local neoangiogenesis to supply nutrients and oxygen to the newly formed tissue.⁽¹⁾

Both natural and synthetic biomaterials can form a hydrogel in an aqueous solution via crosslinking, hydrogen-bonding, photopolymerization, or self-assembly as a function of temperature and pH.⁽¹⁾ Hydrogels have emerged as promising materials for Human Machine Interfacing due to their tissue mimicking properties, tunability, and biocompatibility. Hydrogel-based interfaces have advanced significantly in both research and commercial applications. Ultrasound coupling hydrogels are now standard in medical imaging and therapy.⁽¹⁴⁾

By creating a biocompatible environment, hydrogels support localized repair and enhance the delivery of growth factors and neural stem cells (NSCs) to injury sites—both of which are critical for tissue regeneration.⁽²⁾ Laboratory evaluations of the organo-hydrogel's toxicity to human skin revealed minimal cytotoxic effects, supporting its suitability for direct skin contact in wearable medical devices.⁽¹⁴⁾

Implantation of a hyaluronic acid hydrogel scaffold developed by the Segura lab, containing highly clustered vascular endothelial growth factor (VEGF) into the infarct cavity has shown enhanced angiogenesis and neurogenesis, and improved motor functions after two weeks in mid-cerebral artery occlusion (MCAO) model of ischemic stroke and after 16 weeks in photothrombotic model of ischemic stroke in mice.⁽¹⁾

A hydrogel developed by the Shoichet lab promoted synaptic plasticity and recovery of motor functions in rat models of ischemic stroke by co-delivering the anti-inflammatory drug cyclosporine and neurotrophic factor erythropoietin into an infarct cavity located within the motor cortex.⁽¹⁾

For brain stroke, hydrogels have been preferentially designed for direct cerebral administration, although hydrogels have also been applied via the intranasal route. In cerebral applications, hydrogels can be injected in a pregel state (liquid) to achieve *in situ* gelation over a time window of a few minutes. This strategy reduces invasiveness, prevents subsequent damage of viable functional tissue, and is very appropriate for cell encapsulation. Different hydrogel-based biomaterials have been implanted in the striatum, in the stroke cavity, or epicortically above the brain's surface. *A priori*, the implantation of static hydrogels could be more able to treat focal injuries, although alternative approaches should be explored for global damage caused by severe stroke or neurodegenerative disorders, affecting several brain structures, such as the cortex, hippocampus, and striatum (e.g., Alzheimer's disease).⁽³⁾

Biocompatible antifreeze hydrogels offer dual advantages by maintaining operational stability at low temperatures and providing robust protection to the skin. These hydrogels are designed to function effectively in various environmental conditions, making them suitable for applications such as wearable sensors and electronic skin.⁽¹⁴⁾

Growth promoting signal cues

Previous studies have shown that a critical threshold level of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) is required to continue damage-induced neurogenesis and migration of newly synthesized neurons to damaged regions of the brain. Local delivery of BDNF by adeno-associated virus (AAV) was also reported to enhance neurogenesis in Huntington's disease model rats.⁽¹⁾

That said, there's still a long road ahead in terms of standardization, especially since results can vary a lot between *in vitro* setups and real-world application. Balancing innovation with reliability is a challenge that the field continues to face.

Exosomes

It has been demonstrated that most benefits of stem cell therapy are mediated by the paracrine modulatory effect rather than cell replacement.⁽¹⁵⁾ A very attractive material format for biomedical applications is the nano particles (NPs), which usually results from the association of bioactive compounds and molecules, drugs, peptides, protein factors, antibodies, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and interfering RNA, with a core structure formed by natural or artificial polymers, lipids, or a combination thereof.⁽³⁾ Stem cell-derived exosomes, which are nano-sized vesicles secreted by stem cells, that can freely cross the BBB, penetrate different target tissues, and diffuse into the blood.⁽¹⁵⁾ These exosomes carry bioactive molecules, such as growth factors, genetic material, and RNA, which can directly promote tissue regeneration.^(2,16)

One of the most intriguing aspects is how certain biomaterials can be fine-tuned to release therapeutic agents in response to specific cellular cues. This "smart" behavior could eventually lead to more targeted interventions with fewer side effects, especially in complex diseases like multiple sclerosis or glioblastoma.

Heterogeneous compositions of proteins, lipids, and nucleic acids are selectively packaged into extracellular vesicles. These components play a role in the cross talk communications between cells and participate in tissue repair and regeneration processes. Among them, exosomes are considered key players in the molecule transfer between cells.⁽¹⁵⁾ These nanocarriers have shown the ability to reduce mitochondrial dysfunction, alleviate neural inflammation, and restore cognitive function, offering a more targeted and controlled therapeutic approach than traditional pharmacological treatments.⁽²⁾

The functionalization of exosomes with different molecules such as antibodies or other therapeutic components could significantly increase their homing capacity and therapeutic.⁽¹⁵⁾ The actual technology with NPs allows their surfaces to be decorated with chemical and biological motifs to prevent the rapid decay of the drug concentration in circulation as a consequence of excessive degradation and poor stability due to the body's clearance/excretion and metabolism. NPs can be externally decorated with targeting ligands, and it is possible to change the quantity and density of these molecules (e.g., antibodies) to identify specific subsets of native or pathological cells in tissues and organs and ensure the subsequent delivery of NPs in these selected targets.⁽³⁾

The integration of nanomaterials, such as graphene, carbon nanotubes, and MXenes, into hydrogel matrices has significantly

improved their electrical conductivity, mechanical strength, and responsiveness to external stimuli, opening new possibilities for soft robotics and neural interfaces.⁽¹⁴⁾

The work presented by Lara-Velazquez et al.⁽¹⁷⁾ describes multiple studies highlighting the advantages and challenges of chitosan-based gene and drug delivery systems (nanocapsules, nanospheres, solid-gel formulations, nanoemulsions, microspheres, and micelles) for the treatment of brain tumors. The work presented by Ruiz-García et al.⁽¹⁸⁾ addresses potential and newest developments in the area of bioengineering and cell therapy. It is an exquisite work, exploring state of the art approaches in the therapy of glioma.

Álvarez et al.⁽¹²⁾ found that nanofibers with greater intensity of internal supramolecular motion have enhanced bioactivity toward motor and cortical neurons. Proteomic, biochemical, and functional assays reveal that highly mobile peptide amphiphile scaffolds caused enhanced $\beta 1$ -integrin pathway activation, reduced aggregation, increased arborization, and matured electrophysiological activity of neurons.

Organoids

Different cell types have been used to generate organoids in vitro, including primary cultured cells from human tissues, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). iPSC cultures have provided invaluable information for modeling neurological and neuromuscular disorders. Basic research has benefited from the use of neural organoids, particularly in the field of disease modeling and target identification in the context of neuropsychiatric and neurological disorders.⁽¹⁹⁾

Nickels et al.⁽¹⁹⁾ have recently optimized the generation of midbrain organoids by modifying the timing of maturation, the patterning strategy, and the starting number and type of cells. Particularly, the optimization of timing and the use of a more committed cell line consistently increased the reproducibility of the model, reducing the variation among batches while maintaining the cellular complexity of midbrain organoids.

Biomaterials research has been buzzing with innovation lately, especially in areas like neuroscience. The following are additional advancements in the field.

Recent therapeutic strategies have been focusing on reprogramming the body's immune response—particularly by tapping into the role of regulatory T cells and macrophages—to help steer inflammation toward healing and tissue repair. Alongside that, exosomes derived from mesenchymal stem cells (MSCs) have emerged as promising carriers of anti-inflammatory agents, offering the benefits of cell-based therapy without the potential complications that come with transplanting whole cells.⁽²⁾

On another front, ⁽²⁰⁾ Gazarian and colleagues made a notable breakthrough by identifying both tau protein and its mRNA in Dental Pulp Stem Cells (DPSCs) using an in vitro model. This system now provides a novel platform for examining the underlying molecular processes that drive tau protein clumping and the eventual formation of neurofibrillary tangles—hallmarks of neurodegenerative diseases.

Innovations in biomaterials have also opened the door to 3D in vitro modeling of neurological disorders like Alzheimer's. This approach allows researchers to simulate disease mechanisms in a more lifelike microenvironment, offering a new lens through which to study disease progression and potential treatments.⁽⁷⁾

In terms of surgical applications, well-established polymers such as hydroxyapatite and poly (methyl methacrylate) continue to play a key role in cranial reconstruction, particularly in patients undergoing craniectomy following ischemic or hemorrhagic stroke.⁽³⁾

CONCLUSIONS

Biomaterials present new properties that make them suitable to come into direct contact with living tissue without causing an immune rejection or an adverse reaction. They emerge as an alternative to the limitations of traditional treatments in the neurosciences. Despite showing major advances in forms such as hydrogels, exosomes, and neural stem cells, it is necessary to promote research in this area to navigate ethical conflicts and spread this approach as a safe alternative.

FUNDING

None.

CONFLICT OF INTEREST

None.

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