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Review article

Nanomedicines: a therapeutic alternative in development for seizure control

Nanomedicinas: una alternativa terapéutica en desarrollo para el control de las crisis epilépticas

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Abstract
Nanomedicine is the term used to define nanometric technologies applied to health care, which have allowed the development of innovative strategies for treating and diagnosing various diseases, including those that affect the central nervous system. In particular, due to the advantages conferred by their intrinsic characteristics, nanomedicines have been explored as a possible therapeutic alternative that allows optimizing the control of seizures and epilepsy through various approaches, which may include improving the pharmacokinetics of anticonvulsants, reducing their adverse effects, increasing their efficacy for seizure control, and, in some cases, overcoming drug resistance. These advantages position nanomedicine as a very attractive tool that helps overcome various challenges for optimal seizure control, sometimes impossible in some particular cases, such as drug resistance. This review addresses general aspects of epilepsy, providing some context on its pathophysiology and the challenges associated with developing treatments for this disease. Furthermore, in this review, we compile the evidence that has evaluated the potential use of different nanomedicines in animal models of seizures and models of responsive and refractory epilepsy from the basic science perspective. These studies provide fundamental evidence, focusing on translational medicine, that establishes the foundation for future applications with the potential for the clinical treatment of epileptic disorders.

Keywords: central nervous system; refractory epilepsy; nanomedicine; nanocarriers.

Resumen
La nanomedicina es el nombre que se asigna a las tecnologías nanométricas aplicadas al cuidado de la salud, las cuales han permitido el desarrollo de estrategias innovadoras para el tratamiento y diagnóstico de diversas enfermedades, incluidas aquellas que afectan al sistema nervioso central. En particular, debido a las ventajas conferidas por sus características intrínsecas, las nanomedicinas se han explorado como una posible alternativa terapéutica que permita optimizar el control de las crisis epilépticas y la epilepsia a través de diversos enfoques, que pueden incluir el mejorar la farmacocinética de los fármacos anticrisis, reducir sus efectos adversos, aumentar su eficacia para el control de las crisis y, en algunos casos, superar la farmacorresistencia. Estas ventajas posicionan a la nanomedicina como una herramienta muy atractiva que ayude a superar diversos desafíos que han imposibilitado el control óptimo de las crisis en ciertos casos particulares, como la farmacorresistencia. Esta revisión aborda aspectos generales sobre la epilepsia, proporcionando un contexto sobre su fisiopatología y los desafíos asociados con el desarrollo de diversos tratamientos para esta enfermedad. Además, en esta revisión se recopilan las evidencias que han evaluado el uso potencial de diferentes nanomedicinas en modelos animales de crisis agudas, así como en modelos de epilepsia responsiva y refractaria al tratamiento, desde el enfoque de la ciencia básica. Estos estudios proporcionan evidencia fundamental, desde el ámbito de la medicina traslacional, que sienta las bases para futuras aplicaciones con potencial de trasladarse eventualmente a la práctica clínica en el tratamiento de trastornos epilépticos.

Palabras clave: sistema nervioso central; epilepsia; epilepsia refractaria; nanomedicina; nanotransportadores.

1. Introduction

Technological innovation in the health sector refers to using scientific and technological knowledge to address issues in different fields and improve assisted individual´s diagnosis, treatment, and prognosis.[1] One such innovation is nanomedicine.

Nanomedicine is a rapidly evolving branch of nanotechnology that has produced great interest due to its advancements and benefits for disease treatment. This technology enables the precise manipulation of structures and compounds at a nanoscale level, conferring their unique characteristics for improving drug delivery, enhancing their bioavailability, and facilitating tissue targeting that is otherwise difficult to reach, such as different areas in the brain.[2] Accordingly, the potential of nanomedicines as therapeutic tools for treating some central nervous system (CNS) diseases, such as seizures and epilepsy, has been explored.[3]

The use of nanomedicines in treating seizures and epilepsy holds great potential to overcome several issues that impact the appropriate treatment of this condition. These nanodevices-based therapies can significantly improve treatment efficacy by protecting antiseizure therapeutic molecules from degradation and ensuring a more precise targeting of their pharmacological sites of action.[4,5] Additionally, they can increase the bioavailability of drugs, optimizing their absorption and distribution throughout the body.[6-8] As a result, the treatment's effectiveness is heightened, and the need for higher doses may also be reduced.[9] This contributes to a reduction in the development of side effects and improves the epileptic patient's quality of life.

One of the most relevant advantages of nanomedicines is their ability to transport therapeutic molecules into the brain, which is challenging to access because of the blood-brain barrier (BBB) function.[10,11] This capability is significant for treating refractory epilepsy, as it helps overcome the overexpression of non-selective transporters that impede drug penetration.[12,13] Nanodeliery systems can optimize drug delivery, enhancing their effectiveness and creating new opportunities for treating epilepsy that do not respond to conventional treatments.

This manuscript will review some general information about epilepsy and current therapeutic alternatives. It is intended to provide an update on using nanomedicines for treating seizures and epilepsy from a basic science perspective. This manuscript compiles a series of evidence highlighting how nanomedicines can shield therapeutic molecules with anticonvulsant properties from degradation and the evaluation of their effectiveness in preventing epileptic seizures in animal models. Additionally, this review discusses recent advancements in nanotechnology as a promising approach to address refractoriness in epilepsy, proposing innovative strategies.

2. Epilepsy

The International League Against Epilepsy (ILAE) defines a seizure as a temporary occurrence of signs and/or symptoms caused by abnormal, excessive, or synchronous neuronal activity in the brain. Epilepsy is a brain disorder characterized by an enduring predisposition to generate epileptic seizures that are accompanied by neurobiological, cognitive, psychological, and social significant consequences.[14] However, due to the need to align the concept of epilepsy with clinical practice, it was redefined in 2014, making it increasingly descriptive through the inclusion of different clinical criteria, including the number of unprovoked seizures, the probability of recurrence in a given period, and defining properly it as a disease.[15]

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Epilepsy is a disease that, according to the World Health Organization (WHO), affects approximately 50 million people worldwide,[16] with an incidence rate of 61.4 per 100,000 person-years[17] and a prevalence of 0.7%.[18] Interestingly, this pathology occurs more frequently in people at the extremes of life, i.e., children and older adults.[15]

The general pathophysiological mechanisms of epilepsy are associated with an imbalance between excitation and inhibition in specific brain areas, manifested by alterations in electrochemical properties that lead to abnormal synchronous neuronal activity. Because the mechanisms involved in regulating these properties are diverse, any factor that alters the regular firing pattern of neurons can contribute to the development of epilepsy.[19] In this sense, it has been established that the etiology of this disease is multifactorial. Some conditions that have been identified as pro-epileptic include brain infections, congenital malformations, the presence of brain tumors, traumatic brain injury, genetic factors, and strokes, among others.[19,20]

Over the years, much research has been done with multiple approaches focused on studying epilepsy. Although it is recognized as a disease that can be controlled through different therapeutic strategies, there is still no cure. This situation generates a negative impact on various aspects of the lives of both patients and their families. The unpredictability of seizures can make participating in daily activities such as work, academics, or social activities challenging.[21] In addition, epilepsy carries an economic burden due to multiple direct and indirect costs that are constantly generated due to the chronic nature of the disease. A study reported in 2022 estimated that epilepsy has a total annual cost of US$119.27 billion worldwide.[22] At the same time, due to the stigmatization of the disease, there also is a negative impact on emotional health, self-esteem, and social integration.[23] On the other hand, epilepsy also has repercussions on physiological processes such as memory, attention, and information processing, which translates into a negative impact on cognitive functions, in addition to the frequent occurrence of psychiatric comorbidities such as depression and anxiety. In general, it is known that patients with epilepsy have a lower quality of life, with several limitations in their everyday lifestyle.[24]

As already mentioned, there is still no treatment that can cure the disease. However, different therapeutic strategies have been developed for its control, such as pharmacological and nonpharmacological therapeutic strategies. Among the nonpharmacological, some of the more representative types include neurostimulation (vagus nerve, trigeminal nerve, deep brain, and transcranial), epilepsy surgery, gene therapies, or alternative therapies, such as ketogenic diet, yoga, aerobic exercise, music therapy, or acupuncture.[25] These types of treatments are often used as adjuvants to pharmacotherapy, especially in patients who do not respond well to medication or who develop severe side effects derived from continued use of antiseizure drugs (ASDs) (previously called antiepileptic drugs). Although there is evidence that these nonpharmacological therapies help control seizures and improve patient's quality of life, these approaches present variable efficacy, depending on the type of epilepsy and the individual response to treatment.[25,26]

Regarding the pharmacological approaches, data indicate that the U.S. Food and Drug Administration (FDA) has approved more than 30 ASDs, which act on different therapeutic targets through various mechanisms of action, ranging from the more classical ones, such as blocking Na^+ channels or glutamate receptors, modulation of Ca^{2+} or K^+ channels, improvement of GABAergic inhibitory

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function, among others; to the most novel ones such as inhibition of excitatory neurotransmitter release, slow inactivation of Na^+ channels, or maintenance of the inactivated state of voltage-gated Na^+ channels. The use of drugs is, in many cases, the first treatment option for seizure control, and it has been estimated that appropriate pharmacological schemes contribute to keeping around 70% of patient's seizures-free.[27] Although the efficacy of pharmacotherapy is high, it may vary depending on the etiology of the condition causing the seizures. In addition, it is well known that the use of ASDs is associated with some disadvantages, such as a short therapeutic interval, in addition to causing various mild side effects (headache, dizziness, nausea, etc.) or some more serious ones, such as the development of visual problems, liver and kidney damage, skin rashes and teratogenic effects. These alterations have been associated with high doses and long-term use of ASDs.[28]

In addition to the disadvantages associated with pharmacotherapy, another critical issue that requires attention is the lack of response to certain ASDs. Despite all the efforts that have been made to generate more effective therapies that allow patients to be seizure-free, there is still a high proportion of patients (~40%) who do not respond to pharmacotherapy, not even to the most modern therapeutic molecules.[29] This condition is known as refractory epilepsy and still represents a challenging obstacle to overcome in research development and clinical treatment of epilepsy, which urgently needs to be resolved. Among the proposals for the control of this refractory condition, the use of polytherapy, the use of cannabidiol,[30] epilepsy surgery, and neurostimulation[31] have been studied.

Nanotechnology is a proposed solution to address the challenges and disadvantages of treating and managing epilepsy. ASDs combined with nanodevices could enhance the pharmacokinetics of these medications, leading to more precise drug delivery, reduced side effects, and ultimately improved treatment effectiveness.[31] Additionally, nanodevices can potentially deliver therapeutic molecules to specific, hard-to-reach targets. This capability is significant for challenging pharmacological targets, such as those involved in refractory epilepsy. By enhancing the delivery of therapeutic molecules to these specific locations, nanotechnology through nanomedicine may provide a new approach to overcoming existing limitations in epilepsy management.

The following section discusses concepts related to the nano field, the properties of nanometer-scale materials, and how these characteristics benefit various applications in healthcare.

3. Nanomedicine

Three concepts should be distinguished when discussing nanomedicine: nanoscience, nanotechnology, and nanomedicine. Nanoscience studies structures and molecules with sizes within the nanoscale (1 nm = $1x10^{-9}$ m). Nanotechnology is the application of nanoscience to create new materials and devices (known as nanomaterials or nanodevices, respectively) between 1 and 100 nm in at least one dimension, which have properties that depend on those dimensions. In general terms, nanomedicine is a new field that uses advances in nanotechnology and nanoscience to improve treatments that enhance health.[32] The use of nanomaterials for disease diagnosis, monitoring, control, prevention, and treatment of diseases is the precise definition of nanomedicine.[33]

Due to their minuscule size, nanomaterials offer novel properties that prove to be helpful in various technological

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fields, including nanomedicine or medical applications, as they allow, among other things, more precise treatment, more effective interventions, and fewer side effects. The size of nanometric materials is their most crucial characteristic, as it is linked to a fundamental and significant property, the surface-to-volume ratio. According to this property, the surface of a material grows as its size decreases; as a result, nanometric materials have huge surfaces. This large surface generates many reactive sites on the surface, which influences the physicochemical properties of a substance, making the same substance inert in its bulk or macrometric forms and reactive when it is nanometric in size.[34] This exceptional quality makes nanometric-scale materials attractive and establishes them as an effective instrument for various healthcare applications. The ability of these materials to interact with biomolecules, cells, and tissues improves drug adsorption and optimizes processes such as the controlled release of therapeutic molecules or biomedical imaging techniques.[35] Due to their small size, nanomaterials also have the advantage of crossing biological barriers, such as cell membranes and the BBB, through passive or active transport.[36] This ability increases the delivery efficiency, improves the bioavailability of therapeutic agents, and reduces side effects when reaching challenging therapeutic targets.[2]

In addition to size, nanomaterials have other properties, such as shape, surface charge, porosity, and chemical composition, affecting how they interact with biological systems. These physicochemical properties can be beneficial, detrimental, or inert in biomedical applications. Nanosized materials can be produced using one, two, or more molecules and various chemical synthesis methods. The selection of a molecule or combination of molecules and the synthesis method yield many nanomaterials exhibiting a wide range of properties.[35,37] Inorganic (Fe, Au, SiO_2) and polymeric nanoparticles, micelles, dendrimers, nanocapsules, nanotubes, liposomes, and nanocrystals are examples of nanomaterials (Figure 1).[38] These materials can be optimized to enhance their interactions with biological systems, enabling the development of innovative solutions for a broad spectrum of biomedical applications. These applications include gene therapy, tissue engineering, medical imaging, and the targeted delivery and release of therapeutic molecules, tissue engineering, medical imaging, and the targeted delivery and release of therapeutic molecules.[39]

Some nanomaterials tested in medical imaging include coated or functionalized carbon nanotubes, nanodiamonds, and gold or copper sulfide nanoparticles. Using nanosized materials generally results in higher-quality images obtained through positron emission tomography (PET) and magnetic resonance imaging (MRI). This contributes to generating more accurate diagnoses.[40] Tissue engineering is another field in which nanomaterials have emerged as a promising strategy for repairing tissues, such as bone, skin, dental, and neural tissue. The properties of nanomaterials allow them to mimic the structural and functional characteristics of natural tissues, stimulate cell regeneration, and enhance microscopic integration with surrounding tissues, which makes them useful in tissue engineering.[37] Another application of nanotechnology in healthcare is developing therapeutic systems to prevent or treat diseases. One promising approach in preventive therapeutics is the use of nanovaccines. Recently, nanotechnology has significantly contributed to vaccine development, particularly with the approval of various SARS-CoV-2 vaccines that incorporate nanotechnology-based delivery systems.

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Different nanovaccines based on nanogels, liposomes, lipid, or polymeric nanoparticles have been developed to prevent diseases caused by infections such as brucellosis, hepatitis, malaria, and COVID-19.[41] Compared to their traditional counterparts, nanovaccines offer some benefits, such as better immunogen stability, controlled antigen release, and reduced adjuvant use. These properties are beneficial because they improve prevention and vaccine effectiveness, minimize adverse effects, maximize the immune response, and enhance the effectiveness of infectious disease prevention. Despite the promising nature of this field, only a small number of nanovaccines have progressed to clinical research, and even fewer have received approval for clinical use.[42]

Drug-loaded nanocarriers are therapeutic systems designed for disease treatment. These nanoscale materials serve as vehicles for the targeted, sustained, and prolonged delivery of therapeutic molecules. These nanoscale materials act as vehicles for the targeted, sustained, and/or prolonged delivery and release of therapeutic molecules. They have shown great promise in overcoming the limitations of traditional treatments and delivering therapeutic agents across various biological barriers, reducing drug toxicity, increasing targeting delivery efficacy, and improving pharmacokinetic properties.[43] Nanotechnology has also been used to improve the treatment of genetic diseases through gene therapy. Some disadvantages of naked gene therapy have been addressed using nanomaterials such as liposomes, cationic polymer nanoparticles, inorganic nanocarriers, etc. These advancements offer several benefits, including protection against degradation, transport to the drug targeted transport to specific (such as specific organelles) where they are required, longer circulation times, increased treatment efficacy, improved binding affinity, and the development of more biocompatible materials.[44] Given these advantages, nanomaterials' diagnostic and therapeutic potential has been explored across a wide range of pathologies, including cardiovascular diseases,[45] metabolic disorders,[46] autoimmune conditions,[47] genetic disorders,[44] and diseases of the CNS.[48] Health authorities in multiple nations and regions, including the FDA, the European Medicines Agency (EMA), and the National Medical Products Administration (NMPA), have authorized many nanomedicines for clinical practice.[49]

The versatility of nanomaterials increases the effectiveness of currently available treatments and opens up new avenues for precision medicine. This promising future will involve the creation of sophisticated, highly specific diagnostic tools, preventive alternatives, and therapies for complex or difficult-to-treat diseases, such as those affecting the CNS. The following section reviews the characteristics contributing to the ongoing challenges in diagnosing and treating CNS disorders and diseases and discusses how nanomedicine can help address these challenges.

4. Nanomedicines for the Central Nervous System

The CNS is anatomically and physiologically well-protected. The BBB acts as a boundary between the abluminal brain and the lumen of blood vessels.[50] This structure contains a variety of mechanisms that allow the maintenance of brain homeostasis, such as the restriction of the passage of serum proteins and electrolytes, the enzymatic degradation of polar compounds to avoid their brain uptake, and the removal of xenobiotic compounds by the efflux transporters which returns these molecules to the bloodstream.[51,52] The importance of the BBB is unquestionable, as this structure

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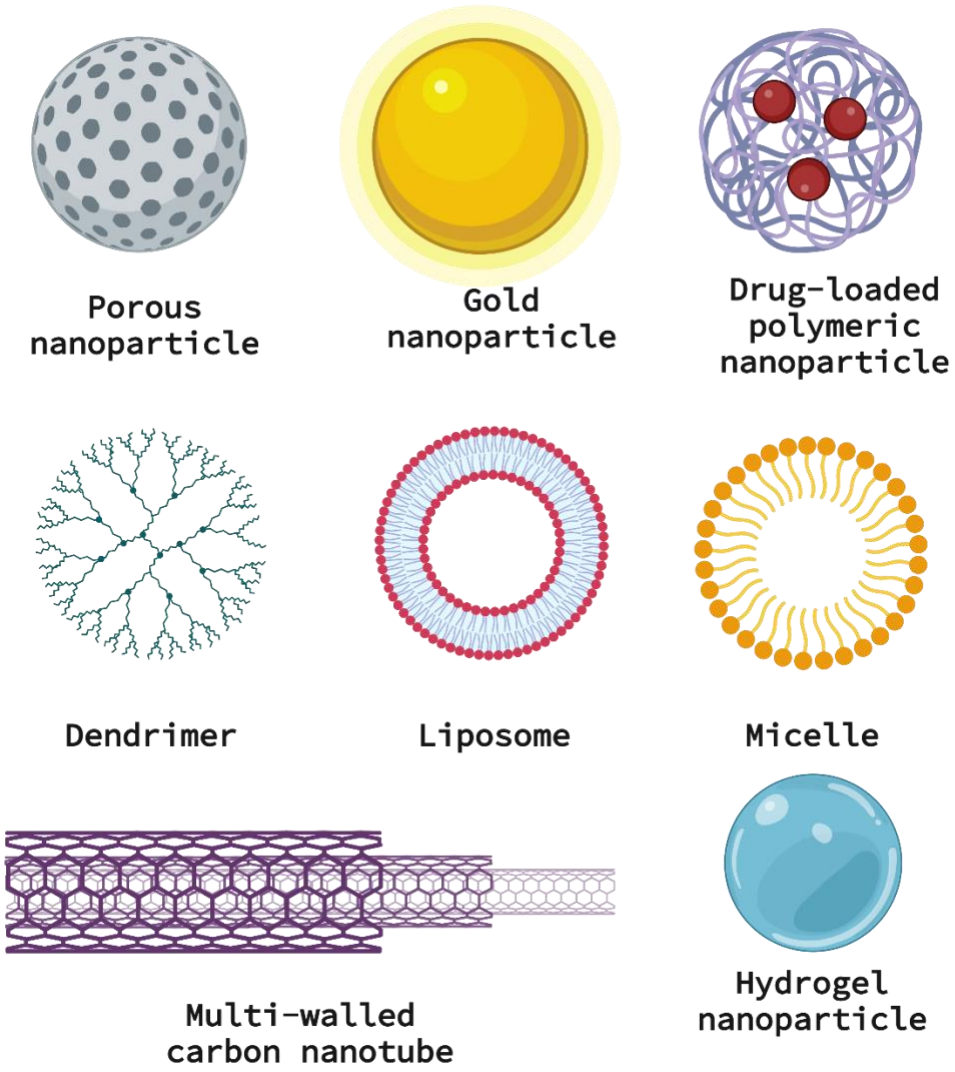
functions as a brain defense and detoxification mechanism that ensures a stable and safe neuronal environment for brain function.[10] However, this same BBB becomes the main barrier to pharmacological treatment when pathological changes occur at the neuronal level because it complicates or prevents restoring its normal nervous function when using pharmacological tools. Pharmacotherapy is necessary to treat diseases. However, its effectiveness is diminished by its limited ability to cross the BBB or the inactivation of therapeutic molecules caused by catabolic enzymes in brain tissue.[11] Thus, the same barrier that protects the vital organ becomes a challenge to overcome.

The use of nanotechnology to develop strategies to improve the diagnosis or treatment of CNS diseases and disorders has emerged as a promising tool. This arises from the need to generate strategies that can overcome the obstacles presented by the protection provided by the BBB.

The proposal to use nanometric materials for therapy and diagnostic applications in the CNS is supported by the properties



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outlined in the previous section (i.e., size, shape, surface charge, loading capacity, etc.).[3] These characteristics provide benefits such as ease of penetration into the brain tissue, higher concentration of therapeutic molecules in neural tissues, greater efficacy and bioavailability of drugs, better stability, control of their release kinetics, longer duration

Figure 1. Schematic representation of the most commonly used nanomedicines for CNS diseases.

in the bloodstream, low or no toxicity, high biocompatibility and biosafety, as well as high biodegradability and non-immunogenicity.[53] Carbon-based nanomaterials like nanotubes and fullerenes, ceramic oxide nanoparticles (SiO_2 or ZnO), polymeric nanoparticles, nanocapsules, metallic nanoparticles, quantum dots, lipid liposomes, solid lipid nanoparticles, protein-based nanoparticles, dendrimers, nanoemulsions, nanosuspensions, and nanogels are examples of nanomaterials that have been investigated for this purpose.[54]

Diagnosing CNS diseases and disorders remains a challenge, as early detection continues to be a critical goal. However, efforts are underway to develop nanodiagnostic tools, such as using MnO nanoparticles or protein (IL-3)-functionalized iron oxide nanoparticles as contrast agents to improve magnetic resonance imaging's ability to detect brain tumors.[55,56] Advances in the early diagnosis of Alzheimer's disease using magnetic (MNP) and superparamagnetic nanoparticles (SPIONS) for detecting amyloid plaques are of great benefit for the timely diagnosis of this pathology using MRI.[57,58] The zinc oxide (ZnO) nanowires are a promising nanodiagnostic tool with high sensitivity and selectivity, enabling the detection of very low dopamine concentrations (1 nM) in the serum of patients with Parkinson's disease.[59] Perfluorocarbon (PFC) nanoparticles have been used as a synthetic biomarker that can detect changes in circulating thrombin levels, making these nanoparticles a potential method for diagnosing stroke.[60] These are just a few examples of how nanomaterials have been applied to improve the diagnosis of CNS disorders and diseases.

Nanotechnological tools have also been developed to treat CNS diseases and disorders, such as depression, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and brain tumors. Various nanopharmacotherapy approaches, such as solid lipid nanoparticles or SPIONS, have been proposed for treating brain tumors.[61] Polymeric nanoparticles have been explored as therapeutic strategies for Alzheimer's disease.[62] On the other hand, nanocarriers are used to treat multiple sclerosis to improve the delivery of FDA-approved drugs, such as dimethyl fumarate (DMF).[63]

A common approach involves using nanomedicines to improve the pharmacokinetic properties of antidepressants.[64] Other nanotechnological innovations have been explored for the diagnosis and treatment of schizophrenia,[65] anxiety,[66] and bipolar disorder.[67] In the following section, this review will focus on technological proposals to improve epilepsy control from various approaches, summarizing the key findings from a basic science perspective.

5. Nanomedicine proposals to improve epilepsy control

As mentioned above, pharmacotherapy is the first choice for seizure control in epilepsy. Although many medications are now available,[68] the treatment of epilepsy presents several challenges due to the

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pharmacokinetic properties of ASDs, including protein binding, limited absorption, irregular distribution, short half-life, and difficulty in crossing the BBB.[69] Nanometric technologies have been proposed as a solution to these challenges in epilepsy. These technologies aim to address the limitations of conventional administration by facilitating penetration through the BBB, increasing therapeutic concentrations, improving targeting, efficacy, and bioavailability, and helping to reduce adverse effects.[70] The following text discusses findings related to proposals for developing nanomedicines to enhance the treatment of seizures and epilepsy from a basic science perspective. These studies include verifying the ability of nanomedicines to penetrate the BBB, comparing the effectiveness of nanomedicines with their free-drug counterparts, assessing the efficacy of molecules in reducing seizures and epileptic seizures, and evaluating new routes of administration.

1. *Nanomedicine for BBB Crossing*. As a first approach, it was confirmed that nanoparticles could cross the BBB. In this regard, a study employed nanoparticles coated and loaded with cholesterol and dipalmitoyl phosphatidylcholine, examined in an *in vitro* BBB model involving astrocytes and endothelial cells. The results demonstrated that coated and uncoated nanoparticles could cross the synthetic BBB. However, coated nanoparticles exhibited three- to four-fold greater penetration than uncoated nanoparticles. It has been proposed that the choline transporter in endothelial cells may have facilitated the crossing of the BBB.[71] These findings show that these nanosystems could overcome the challenges the BBB poses. Since then, several studies have focused on creating and refining nanosystems as potential treatments for epilepsy.[4,9,72]

2. *Nanomedicine for improved pharmacokinetics*. One goal of nanomedicines is to enhance the pharmacokinetic properties of ASDs, decrease side effects, and improve therapeutic outcomes. A study by Darius et al. (2000) encapsulated the ASD valproic acid (VPA) in nanoparticles and evaluated the nanosystems *in vivo*. Their findings showed that the application of nanoparticles decreased the dangerous side effects of VPA therapy by preventing the production of harmful metabolites.[73]

Some investigations have examined the efficacy of non-conventional molecules (ZLM 2/576, thyrotropin-releasing hormone, β-carotene) for controlling seizures, comparing their effects when administered alone or with nanomaterials.[72,74] These studies aim to increase drugs' bioavailability, stability, and therapeutic precision with potential antiseizure effects. In the maximal electroshock (MES) animal model, one of the earliest investigations assessed the anticonvulsant efficacy of ZLM 2/576, a non-competitive N-Methyl-D-Aspartate (NMDA) receptor antagonist.[72] The findings indicated that the antiseizure activity was considerably enhanced by the molecule encapsulated in poly-(n-butylcyanoacrylate) nanoparticles coated with polysorbate-80.[72] Another investigation used two seizure models (MES- and pentylenetetrazole (PTZ)-induced seizures) to evaluate the antiseizure properties of beta-carotene encapsulated in polymeric nanocarriers with and without polysorbate-80 coating.[74] Compared to the control, beta-carotene-loaded nanoparticles dramatically reduced seizure duration and increased seizure latency. Coated nanoparticles exhibited enhanced effects compared to uncoated nanoparticles, effectively reducing

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seizure duration and increasing seizure latency.[74]

A study aimed at increasing the bioavailability of thyrotropin-releasing hormone (TRH) by encapsulating it in nanoparticles to prevent its degradation described a nanosized system that delayed the onset of epileptogenesis. The findings included increased electrical stimuli required to reach stage V kindling seizures, along with a shorter after discharge duration.[6] Additionally, other studies have shown how nanoformulations enhance the protective effect of ASDs, such as oxcarbazepine (OXC)[7] and carbamazepine (CBZ),[8] by maximizing their bioavailability and controlled release.

In contrast to the findings mentioned above, some preparations do not show any significant effect, as demonstrated by Holtman et al. (2014), who tested the effect of methylprednisolone. This glucocorticoid has been demonstrated to prevent seizures and was delivered using liposome-based nanotechnology. No significant differences were found when using the nanosized liposomes compared to the vehicle-treated group.[75]

3. *Enhanced therapeutic effects with nanomedicine*. Over the past 20 years, numerous studies have compared the *in vivo* effectiveness of ASDs when administered freely or in combination with nanomaterials.[4,5,76] Here are some studies that utilized seizure models to assess the therapeutic efficacy of nanomedicines. Nair et al. (2012) compared the effect of CBZ-loaded chitosan nanoparticles and free CBZ on seizure onset after exposure to a chemoconvulsant or electrical stimulation. According to the study, the onset of seizures was longer in the groups treated with CBZ-loaded nanoparticles than in those treated with free CBZ.[4] Another study also developed CBZ nanoformulations composed of nanostructured lipids.[5] This nanoformulation demonstrated an excellent protective effect over time, with animals remaining protected against the MES for up to 4 h.[5] Another study investigated the effect of polysorbate-80 coating on gabapentin (GBP)-loaded nanoparticles, focusing on brain drug concentrations and anticonvulsant effects.[76] Seizure duration was shortened in animals tested in both models MES and PTZ, and GBP concentrations were three-fold higher in polysorbate-80-coated nanoparticles.[76]

Some epilepsy models have been used to assess the efficacy of nanocarriers. Glucose-coated gold nanoparticles were employed as lacosamide carriers (LCM) in a model of temporal lobe epilepsy. The LCM-loaded nanocarrier dramatically reduced the frequency and amplitude of electrographic discharges in both the ictal and interictal phases. In addition, a trend toward reduced seizure frequency was observed.[77]

4. *Nanocarriers for multidrug delivery*. Some studies have investigated the nanoencapsulation of at least two ASDs into a single system; the encapsulation of CBZ and levetiracetam (LEV) in poly(lactic-co-glycolic acid) (PLGA) polymeric nanoparticles was evaluated in the chemical kindling model with PTZ.[78] The results show that the combination of these drugs led to less severe seizures; however, there were no differences between the groups that received the free combination or those that were encapsulated in the nanoparticles.[78] This approach aims to increase the effectiveness of the treatment by controlling delivery, enhancing brain penetration, and minimizing the side effects of the drugs.

5. *Nanomedicine for alternative routes of administration*. Nanosystems can also be used to investigate alternative routes of administration that simplify and accelerate

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the delivery of therapeutic molecules to the brain, as well as improve the pharmacokinetic characteristics of ASD. In this context, some drugs have been administered via the intranasal route since it allows rapid and direct absorption through the nasal cavity, avoiding the BBB and facilitating their arrival to the CNS.[79,80] However, drugs must possess specific properties, including stability, solubility, a high mucosal clearance rate, and the ability to produce minimal nasal irritation. Nanosystems are positioned as one potential option for intranasal delivery of brain-targeted drugs because they offer many features.[81] In line with this, a study compared two administration routes for VPA-loaded lipid nanocarriers (liposomes). Intranasally administered liposomes provide better protection against seizures in the MES than those administered intraperitoneally.[79] In addition, nanostructured lipid carriers were employed to increase the amount of lamotrigine (LMT) in the brain after intranasal administration.[80] The findings demonstrated a significant accumulation of LMT in the brain that persisted for 24 hours after intranasal administration, and the animals were protected by the nanosystems, which reduced the seizure duration and prolonged the latency of seizures.[80]

6. *Smart nanomaterials for stimulus-responsive therapy*. Responsive systems are sophisticated nanosystems that respond to particular stimuli. Until recently, developing a system that provides on-demand treatment during epileptic seizures was a distant goal. However, a recent advancement has led to the creation an electrosensitive or smart system that responds to stimuli using phenytoin (PHT)-loaded hydrogel nanoparticles.[82] This innovative system was designed to release PHT in response to an external electric field stimulus. The after-discharge duration and the frequency of generalized seizures in the amygdala kindling model were the two parameters used to confirm the antiseizure efficacy of this system.[82] The subsequent optimization of this system confirmed its responsiveness by demonstrating its ability to release the ASD when epileptic seizures occurred, thereby enhancing the antiseizure effect with lower doses and improving the drug's therapeutic index.[9] SPIONs exhibit magnetic properties only in an external magnetic field and lose their magnetization when the field is removed. This feature enhances the targeting of nanocarriers to specific areas of pharmacological interest. This approach was used in designing a responsive system made up of SPION-loaded lipid nanocarriers for transporting Clonazepam (CZ). The nanoformulation exhibited a protective effect by delaying the onset of the first seizure approximately 7.5 times and the time of death 14 times in the presence of the magnetic field.[83]

Previous research has mainly relied on particle or nanoparticle systems, which are effective. However, alternative systems, such as polymers and nanogels, have also been tested in addition to these methods.[84,85] An injectable thermogel based on ethosuximide (ESM)-loaded chitosan nanocapsules (nanogels) effectively suppressed spike-wave discharges (SWD) in an *in vivo* model.[84] Another study developed a CBZ-loaded nanoemulgel that can be administered intranasally to enhance the amount of ASD available in the brain.[85] A chemical and an electrical seizure model were used to evaluate this system's anticonvulsive effects. In the chemical model, the system showed its efficacy by significantly delaying the onset of seizures. Likewise, in the electrical model, the nanoemulgel protected the animals by improving their survival rate.[85]

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6. Nanomedicine for overcoming epilepsy refractoriness associated with overexpression of multidrug transporters

Even today, controlling refractory epilepsy remains a challenge. Drug resistance exacerbates the adverse effects of epilepsy, and in refractory patients, conditions such as unintentional injuries, premature death, and psychosocial dysfunction are common.[86] Although therapeutic options such as neuromodulation or surgery exist to manage this condition, access to these treatments is limited by high costs and strict inclusion criteria.[87] To address the issue of drug resistance, an efficient, affordable, and accessible treatment is needed. In this context, nanomedicine has been explored as a potentially beneficial approach.

Several hypotheses have been proposed to explain the etiology of drug refractoriness in epilepsy. These hypotheses suggest that genetic mutations affecting drug targets, the intrinsic severity of seizures, alterations in mitochondrial function, and the presence of multidrug-resistant transporters may all play a significant role.[88] The suggestion that drug resistance in epilepsy could be overcome by nanotechnology is grounded in the transporter hypothesis, which attributes this condition to the increased expression of multidrug resistance proteins, such as P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1), located on the luminal side of endothelial cells forming the BBB. Due to this limitation, achieving therapeutic concentrations of ASD in the CNS is challenging.[89] Therefore, nanocarriers may potentially enhance the delivery and therapeutic concentrations of ASD in the epileptic foci by masking them against the modified BBB (Figure 2).

One study proposed using silica-coated iron oxide nanoparticles for PHT transport in an animal model with P-gp overexpression.[12] This research demonstrated that the nanoparticles could reach the brain despite P-gp overexpression at the BBB, release PHT, and exert their antiseizure effect. The protective effect of this nanosystem was demonstrated by an increase in the post-discharge threshold and a reduction in the prevalence of seizures in the animals that received the PHT-loaded nanoparticles.[12] Another proposal evaluated PHT-loaded Pluronic P85-coated poly(butylcyanoacrylate) nanoparticles to overcome PHT resistance in a TLE model with P-gp overexpression. The nanoparticles-treated group achieved significantly higher levels of intracerebral PHT than those treated with free PHT and those administered with a P-gp inhibitor (tariquidar, TQD). Moreover, in contrast to the group treated with ASD without nanocarriers, the nanomedicine dramatically decreased spontaneous recurrent seizures. These findings established this nanotechnological approach as a powerful tool to overcome drug resistance, at least for PHT.[13]

On the other hand, one research group proposed that CBZ-loaded PLGA nanoparticles emerge as a promising approach for the treatment of refractory epilepsy.[90] The findings showed that almost all the evaluated doses of loaded nanomedicines (except the smallest one, >1 mg/kg) considerably decreased the frequency and duration of seizures and increased latency to seizures, suggesting that this approach might be feasible for the delivery of ASD.[90] However, the animal model did not replicate the features of drug refractoriness. In addition, there is insufficient evidence that CBZ interacts with P-gp. Therefore, the suggestion that this nanotechnology can be used to treat refractory epilepsy should be taken cautiously.

An alternative approach involves using nanomaterials to modulate the P-gp

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function and/or expression. In this regard, one study aimed to reduce the overactivity of the pregnane X receptor (PXR), a common regulatory transcription factor of P-gp and cytochrome P450 3A4 genes. PEG-PLA nanoparticles containing ketoconazole (KCZ), a PXR antagonist that could block the expression of P-gp, were created to achieve this. The findings demonstrated that the nanomedicine significantly increased brain concentrations of a specific ASD, i.e., CBZ, decreased the frequency and duration of seizures, and attenuated electroencephalographic activity.[91] A sophisticated approach involves mixed Pluronic P123/F127 micelles functionalized with a tryptophan derivate (TD) and encapsulated with LTG. The first goal of this system was to use the polymer Pluronic P123 to modulate P-gp activity. The second goal was to use the modified amino acid (TD) to guide the nanosystem to the epileptic foci and enhance the delivery of LTG encapsulated in the micelles. Evidence showed that the TD-functionalized nanosystems predominantly target the hippocampus and other epileptogenic brain regions associated with epilepsy. Furthermore, LTG's brain/plasma ratio was increased in animals treated with the nanoformulation, particularly in brain regions where P-gp was overexpressed. This dual-function system holds great promise as a method for delivering ASD.[92]

Other methods have been developed to create accurate and noninvasive diagnostic systems. In this regard, nanomaterials have been designed to detect P-gp, the most prevalent biomarker of drug resistance.[93,94] These nanotechnological systems can improve and simplify the diagnosis of refractoriness, creating new avenues for its management and treatment.

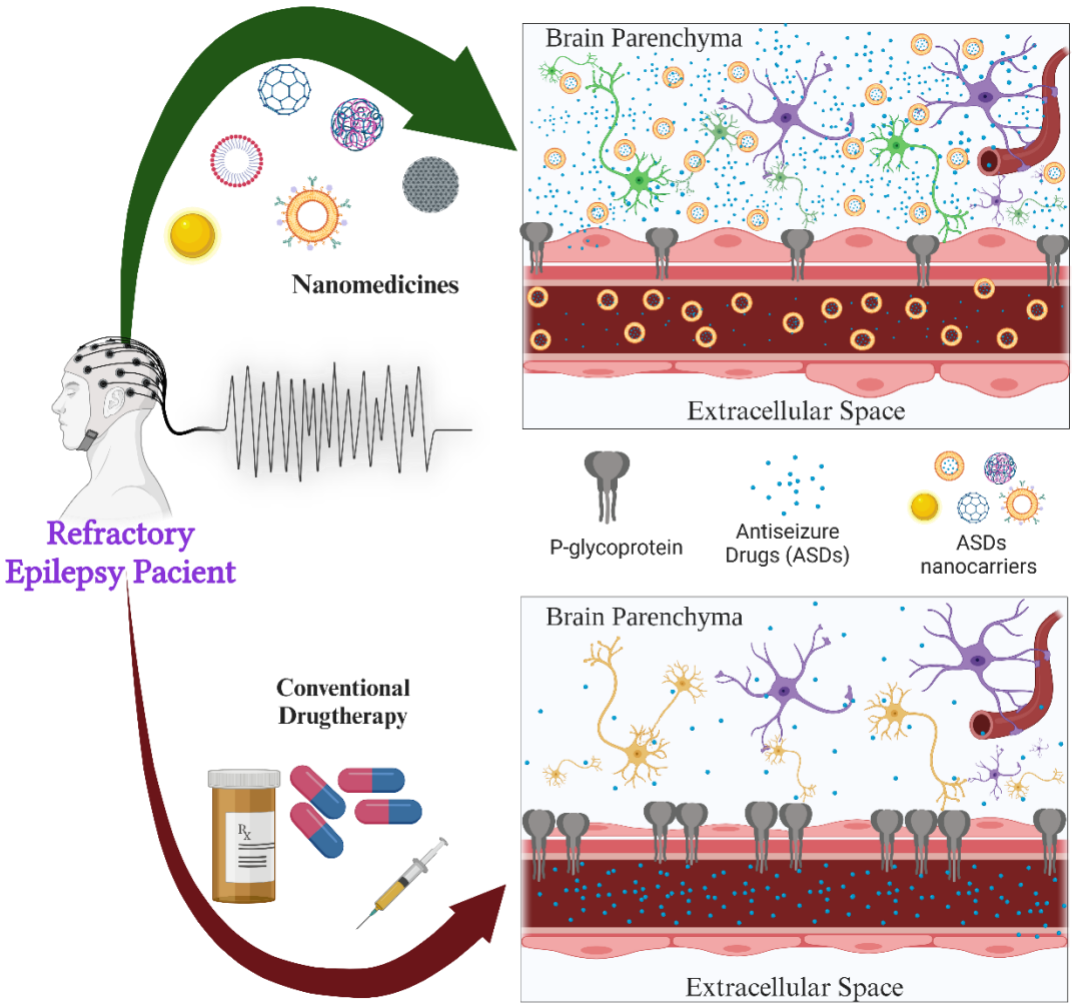

Figure 2. Schematic representation of ASDs concentration in brain parenchyma of refractory epilepsy patients treated using nanomedicines (upper panel) or conventional pharmacotherapy (lower panel). After ASD-loaded nanocarrier administration, ASD is increased at the brain parenchyma and allows for achieving therapeutic effective concentration for epilepsy control. In contrast, ASDs do not protect refractory patients against seizures because ASDs therapeutic concentration cannot be achieved due to the overexpression of P-gp at the BBB.

7. Conclusions

Several studies demonstrate that nanosystems can improve drug delivery, increase therapeutic efficacy, decrease side effects, enhance BBB penetration, and increase brain concentrations of ASDs, making them a novel and promising option for treating seizures and epilepsy. Furthermore, due to the wide variety of nanomedicines available, another advantage is that it could be a customized therapy tailored to each patient's needs. Additionally, nanosystems could be designed not only to treat epilepsy but also to address its comorbidities, providing a more comprehensive approach to managing

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the condition. These findings highlight the advantages these technological innovations could bring to improve current treatments and provide new solutions that are not yet available. However, it is crucial to remember that these developments are still experimental and that further research is needed to verify their efficacy and safety.

Furthermore, since these alternatives would be used chronically, while pharmacotherapy would only control the disease, biosafety must be guaranteed; otherwise, it could become a counterproductive option, presenting disadvantages such as high reactivity or tissue accumulation, which could lead to toxicity. Another significant drawback is the lack of regulation in nanotechnology and nanomedicine. The absence of clear and standardized regulatory frameworks hinders these technologies' safe and effective implementation in clinical settings. Additionally, the lack of regulations could lead to the commercialization of unproven or ineffective therapies, putting patient health at risk and potentially hindering research progress. As a result, there is a risk that advances in nanomedicine may be applied without adequate oversight, leading to unforeseen side effects or even severe complications in patients. Therefore, appropriate nanosystem development and clinical application regulations must be established to avoid unexpected side effects. These regulations should ensure rigorous testing, safety protocols, and quality control to maximize the benefits of nanomedicine while minimizing potential risks. A comprehensive approach to applying nanotechnology will allow the exploitation of these technologies' full potential without compromising patients' health.

8. Conflicts of Interest

Apart from those already disclosed, the authors have no other relevant affiliations or financial relationships with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in the manuscript.

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