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Review Article

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A Review of the Protective Effects of Nanoparticles in the Treatment of Nervous System Injuries

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ABSTRACT

One of the most vital organs in the body is the nervous system. Damage to the nervous system may lead to a variety of issues and illnesses in people, and each year, both the affected person and society incur significant financial, human-life, and spiritual expenses as a result. Although the activity in the field of nerve repair and regeneration is growing rapidly, until now, nerve repair is not done completely. A chain of events, including inflammation, elevated oxidative stress, and the progression of damage, occur after the initial insult to the nervous system. Damage to mitochondria, proteins, and cell membrane structures, damage to adipose tissue, and eventually illnesses of the nervous system can all be a result of oxidative stress, which is brought on by an imbalance between the creation of free radicals and metabolic responses. As a result of inadequate antioxidant levels or excessive formation of free radicals, damage to nerve cells might worsen. Nerve cells require a lot of oxygen and antioxidants. To stop oxidative stress and its harmful consequences, antioxidants—either synthetic or natural—must be used. In this context, the treatment of illnesses of the neurological system may hold promise for nanoparticles with a long half-life. As a result, the biological use of nanoparticles has been stressed as a novel therapeutic strategy for the treatment of neurological disorders and lesions, which is still in its early phases. Therefore, the purpose of this review is to ascertain how protective nanoparticles are in the therapy of nervous system damage.

Key words: *Nanoparticles, Nervous system injuries, Protective effects, Treatment*

INTRODUCTION

Peripheral nerves are usually subject to physical damage. Usually, construction and transportation accidents, natural disasters, injuries caused by war, and other traumas such as diseases and complications caused by surgery cause peripheral nerve damage [1, 2]. Following peripheral damage, a series of pathophysiological events occur, which leads to valerian disintegration in the distal part and the loss of a small part of the proximal part of the axon. Together, macrophages, monocytes, and Schwann cells remove the myelin sheath and axon debris. Schwann cells multiply and form a bridge called the band of Bungner [3, 4]. These cells produce extracellular matrix molecules and neurotrophic factors to stimulate axon regeneration [5]. Axon sprouts are formed by the nodes of Rannoia

and the new myelin sheath is formed by Schwann cells. Axon sprouts grow until the axon can perform its functions again. Spontaneous repair of the peripheral nerve is almost always incomplete and the function of the nerve does not completely return to its original state [6, 7]. Strokes, head trauma, spinal cord injuries, and retinal degeneration are some examples of central nervous system injuries. These lesions in children are often traumatic or congenital defects, while in adults they are traumatic or degenerative. Following damage to the central nervous system, events such as the death of nerve cells, destruction of nerve fibers and glycolysis, and an excessive increase in the number of glial cells (such as astrocytes, oligodendrocytes, and microglia) occur. Neurons cannot divide, so if a neuron is destroyed, a new neuron will not replace it, as a result, the central nervous system, unlike the peripheral nervous system, does not have the inherent ability to repair itself [8-10].

Regenerative medicine is a branch of modern medical science whose goal is to restore and restore damaged or lost tissue or organs, which, according to the type of treatment approach and method, includes cell therapy, treatment using the patient's cells, treatment using non-autologous donor cells, treatment with growth factors, use of recombinant proteins, use of small molecules, tissue engineering, and gene therapy [11-13].

One of the more recent and useful fields that has caught the interest of academics and offered several chances for advancement in the medical sciences is nanotechnology. This technology is employed in the medical field as well as in the military, agriculture, diagnostic procedures, magnetic imaging, sensors, and fast material detection. These days, scientists employ this technology to identify and treat a wide range of illnesses, including cancer. Thus, by concentrating on molecular techniques, this discipline has gained recognition as a significant branch that has made remarkable developments in recent years [14]. Materials that are utilized in surgery, dentistry, all types of experimental science studies, biomechanical biosystems, the battle against germs, etc. may be created using nanotechnology, which is based on the utilization of atoms and molecules. Scientists currently have little control over the scope of nanoparticle impacts, despite the fact that there have been several studies on the subject [15-17].

Less intrusive techniques are more appropriate for the discussion of imaging methods, making nanoparticles the best possible candidates for the creation of such techniques. In nanotechnology, they utilize specially designed materials that can interact with biological systems at the molecular level and stimulate the nervous system while causing the fewest possible adverse effects. Contrary to conventional systems like pills and liquids, nanoparticles intelligently regulate and sustain the distribution of medications in various organs, resulting in more and better effects [18, 19]. Nanoparticles are used for imaging in neuroscience and also to investigate the fate of adult stem cells in nervous systems and in the treatment of many nervous system disorders [20, 21].

Today, much research is conducted on smart materials that can help in the regeneration and treatment of nerves through various methods such as antioxidant effects, stimulating the proliferation of nerve cells, modulating inflammatory factors, etc. Therefore, due to their chemical and morphological characteristics, some nanoparticles are promising therapeutic methods that can have neuroprotective and antioxidant properties depending on the dose and size [22]. So, the purpose of this study is to look at how nanoparticles might help guard against nervous system damage.

Nanoparticles as new drug delivery systems in the nervous system

Protective barriers make it difficult for biologists to deliver drugs to the central nervous system. Drugs must be able to penetrate the blood-brain barrier and enter therapeutic concentrations in the brain after administration for them to be effective in the central nervous system [23]; otherwise, they won't be able to do their jobs [23]. As a result, ineffectiveness in the treatment of illnesses of the central nervous system is frequently not a result of a medicine's insufficient potency but rather of an issue with the way the drug is delivered. Recently, interesting results have been observed in the field of nanotechnology, particularly when nanoparticles are used to transport drugs [24]. Typically, for a pharmacological therapy to be successful, it has to have a long shelf life in the blood. It is now possible to functionalize the surface of nanoparticles with positively charged biomolecules to create an electrostatic interaction, which facilitates the passage of nanoparticles through the blood-brain barrier because endothelial cells have negative charges on their surface. Transferrin and lipoprotein receptors in the cell allow nanoparticles to absorb and cross the blood-brain barrier [25]. Additionally, the prolonged circulation of modified nanoparticles in the blood makes it simpler for them to interact with and enter endothelial cells, which opens up the prospect of greater control over the actions of the cells. The use of nanoparticles in medicine is still plagued by issues including unknown tissue interactions and unpredictable outcomes, despite the current advancements in the field of nanoscience. In this context, high-penetrating-power cerium oxide nanoparticles can inhibit the development of scar tissue that hinders healing in spinal cord lesions [26]. As opposed to anionic nanoparticles,

cationic nanoparticles are more permeable to the central nervous system and can remain in circulation for extended periods of time without having hazardous consequences. For instance, cationic gold nanoparticles may enter cells without using energy and by avoiding processes like endocytosis, which might have an impact on cell function [27].

Enzyme carriers for antioxidants can be made from nanomaterials. Antioxidant enzymes can lower reactive oxygen species (ROS), but because of their transient presence in the blood and subsequent decomposition, they have a hard time crossing the blood-brain barrier [28]. Polymer nanoparticles are the most common type of medication delivery technology because they can cross cells' tight connections. Additionally, they have a high drug-loading capacity and boost the efficiency of medications taken in combination. In this aspect, nanocapsules are crucial to current drug delivery because they can preserve the medication and have a high drug-loading capacity, increasing the likelihood that the drug will reach the brain. Additionally, the reticuloendothelial system's macrophages are protected from drug detection by these nanoparticles [29].

Nanoparticles in the treatment of central nervous system diseases

Ischemia

A stroke caused by a lack of blood supply to a part of the brain is a neurological disorder. One of the most typical stroke symptoms is the generation of free radicals [30]. Some nanoparticles have the potential to inhibit reactive oxygen species in stroke. Nanoparticles of platinum and cerium oxide, due to their antioxidant properties, have been promising answers for improving and treating stroke. These nanoparticles mimic the activity of antioxidant enzymes and destroy free radicals [31]. The use of these nanoparticles significantly reduces the volume of the damaged area. The use of gold nanoparticles in the treatment of stroke depends on the size of the nanoparticles. A study showed that gold nanoparticles with a size of 20 nm reduced the volume of the damaged area, while the same nanoparticles with a size of 5 nm can cause damage to nucleic acids by accumulating in the nucleus, so the antioxidant property depends on the size of the nanoparticles. Also, in another study, it was shown that cerium oxide nanoparticles reduced the death of rats by reducing the induction of nitric oxide synthesis in the hippocampus of rats [32].

Research has shown that the use of nanoparticles causes the neutrophils that cause the immune response to be inhibited and prevent severe brain damage in brain models [33]. Increased nestin protein is effective in post-injury repair mechanisms. Also, this protein is expressed in large amounts during the early stages of development of the central and peripheral nervous system [34]. Researchers showed an increase in the number of cells expressing Nestin as a result of treatment with silver nanoparticles in mouse models of stroke, which indicated the effectiveness of these nanoparticles in neurogenesis [35].

Alzheimer

Alzheimer's disease (AD) or amnestic disease is a type of brain disorder with a gradual weakening in which the functions and mental abilities of the patient are degraded. In Alzheimer's disease, a recent event usually occurs first, and unfortunately, a cause or a suitable treatment is not available. Accumulated evidence supports the hypothesis that oxidative stress produced by different mechanisms may be among the main factors promoting neurodegeneration [36].

The accumulation of amyloid plaques is one of the known causes of Alzheimer's disease, which is found in all parts of the brain of these patients, and in laboratory environments, beta-amyloid is used to induce Alzheimer's disease in mice. In their research, D'Angelo *et al*. found that treatment with cerium oxide nanoparticles protects brain neurons against oxidative stress induced by beta-amyloid. The obtained results emphasized the neurotrophic role of these nanoparticles as a factor that can modulate the important pathways of nerve cell survival. Also, Das *et al*. investigated the antioxidant and neuroprotective properties of cerium oxide nanoparticles in spinal cord injuries. In this research, it was observed that treatment with this nanoparticle causes the growth and survival of nerve cells in the spinal cord [37].

Among the factors of accumulation of amyloid beta proteins, we can mention metal ions such as copper and iron, which increase with age in the brain. Nanoparticles can remove metals from the body or prevent their undesirable functions through their specific bonds. Nanogels have been considered due to their high stability, ability to respond to external stimuli, and high and accurate loading of active substances such as drugs. In Alzheimer's disease, nanogels are also used to prevent the accumulation of amyloid beta plaques [34]. In research that investigated the effects of silver nanoparticles on Alzheimer's disease, the results showed that the surfaces of

silver nanoparticles can act as a nano chaperone and inhibit the formation of amyloid fibers. As a result, the medicinal use of these nanoparticles can be useful for the treatment of Alzheimer's disease. Dowding J and his colleagues showed that cerium oxide nanoparticles can switch between their Ce3+ and Ce4+ states and in this way can destroy superoxide anions and hydrogen peroxide. Also, these nanoparticles accumulate in the outer membrane of the mitochondria and prevent the collapse of the mitochondrial structure due to the toxicity caused by beta-amyloid. Therefore, cerium oxide nanoparticles have antioxidant properties, and drug treatment by this nanoparticle can prevent the destruction and death of nerve cells in Alzheimer's disease [38].

Parkinson

Parkinson's disease (PD) mainly affects brain dopaminergic cells. Parkinson's disease is a multifactorial cascade of destructive factors that usually affects people over 65 years old. Loss of dopaminergic neurons leads to tremors, speech, and memory impairment. A subset of patients appears to follow an autosomal dominant inheritance pattern, although in most cases the inheritance pattern is not discernible [39]. Researchers used a method based on nanoparticles to prevent neurodegeneration in animal models of Parkinson's disease to transfer plasmids containing desired genes to the brain. This approach discovered a gene therapy-based method for the treatment of Parkinson's disease that had the potential to repair defective genes [40].

Iron oxide nanoparticles, by affecting the interaction of neurons and surrounding cells, play a significant role in increasing the regeneration capacity of neurons after spinal cord injury. The ability of magnetic iron oxide nanoparticles to track the migration of leukocytes and track cells inside the body can be useful in the study of central nervous system lesions such as Parkinson's, stroke, brain tumors, epilepsy, and Alzheimer's. Stressed or disabled neurons need more energy to survive and repair and improve their function. Improving the metabolic pathways and improving the level of adenosine triphosphate (ATP) (Adenosine triphosphate; and Nicotinamide adenine dinucleotide; NADH)) is one of the characteristics of nanoparticles in the brain [41]. For example, introducing a suspension containing gold nanoparticles into the body of rats has been effective in improving the symptoms of Alzheimer's and Parkinson's disease [42].

Multiple sclerosis

Although the cause of multiple sclerosis (MS) is unknown, it seems to be caused by the interaction of genes and the environment, and diet, sunlight, infections, and genetics are important factors in MS patients. Despite promising advances in the understanding of modern diseases, precise details about the inflammatory processes are still not available [43]. MS is an inflammatory disease that destroys the central nervous system, especially in adults, which causes numbness and vision loss. In early definitions, MS was described as a disease characterized by inflammation around blood vessels and damage to myelin. This disease has been identified in more than 2 million people worldwide, mainly based on medical history and clinical examination of the patient [44].

Obstruction of blood flow in narrow vessels and increased production and accumulation of reactive oxygen species in MS lead to the activation of macrophages and apoptosis in oligodendrocytes [45]. The use of nanoliposomes in modern drug delivery systems, along with their structural similarity to biological membranes, can show fewer side effects and better treatment processes in the target tissue with controlled release and accurate targeting. In research, the use of nanocarriers such as nanoliposomes has shown promising results in improving MS symptoms [46].

For the purpose of describing autoimmune illness in humans and understanding MS, Eitan and his colleagues used mouse models to show the impact of cerium oxide nanoparticles. Clinical symptoms, damage to the white matter of the central nervous system, and inflammation of the central nervous system were all decreased by drug therapy using nanoparticles [47].

Nanoparticles in the treatment of peripheral nervous system diseases

Considering that different mechanisms are involved in the repair of peripheral nerves, as a result, various molecular signals can be effective in these processes. These signals can play a role in these complex processes separately or in cooperation with each other using specific methods such as a specific expression or deletion of genes in nerve tissue cells or using specific antibodies. Several factors can cause damage to peripheral nerves, in addition to causing changes in the axon of damaged neurons, damage to peripheral nerves can also cause dysfunction of the organs associated with them [48].

As a consequence of the nanoparticles' tiny size, which increases their surface-to-volume ratio and allows them to absorb more free radicals, they may be an effective technique to deal with free radicals produced as a result of

nerve injury. It should be emphasized that because such modeling in mice is reasonably affordable, peripheral nerve researchers frequently employ the sciatic nerve as a study tool for nerve healing using varied dosages [49]. The effects of cerium oxide nanoparticles on enhancing motor function and tissue alterations after sciatic nerve damage in rats were studied by Soluki *et al*. When compared to the control group, the groups that received cerium oxide treatment recovered considerably faster and had improved motor function. Additionally, it was shown that cerium oxide nanoparticles decreased cell apoptosis and were successful in peripheral nerve healing in a study that examined the effects of oxidative stress on endothelial cells and nerve cells. Reducing oxidative damage also increases the lifespan of neuron cells, and because cerium oxide has antioxidant properties, cerium oxide nanoparticles can swiftly act and absorb reactive oxygen species during this process. Additionally, this chemical has been shown to have impacts on angiogenesis, nervous system modulation, anti-cancer applications, decreasing high blood pressure, antimicrobial properties, lowering cholesterol levels, and preventing damage to injured tissue [11].

There is a lot of optimism for developing medical diagnostic and therapeutic facilities thanks to the characteristics of nanoparticles. Magnetic nanoparticles are a popular molecule for diagnostic and therapeutic applications because they may deliver medications to desired areas using a magnetic field [50].

Scientists are trying to repair nerves by optimizing the properties of nanoparticles and stimulation parameters. Gold nanoparticles, as a substrate and matrix that is electrically conductive, are a promising material for the regeneration of peripheral nerves [42]. In diseases of the nervous system, it is also possible to disperse drug particles in a very small size in an external liquid phase using nanosuspensions. Ease of manufacturing process, much lower toxicity, and increased efficiency are the advantages of nanosuspensions [18]. Nanocarbon formulation can also be used for various applications such as cancer diagnosis, imaging drug delivery, and tissue engineering [51].

CONCLUSION

Following damage to the nervous system, the use of neuroprotective agents is a suitable strategy to control the damage and restore the system. Nowadays, the use of nanoparticles as a new factor has been widely considered. Some nanoparticles have neuroprotective properties due to their antioxidant properties and other chemical and morphological characteristics. In general, nanoparticles are promising therapeutic methods that are still in the early stages, but considering extensive studies in this field, this therapeutic approach is expected to be one of the useful therapeutic agents in the treatment of neurological lesions in the future.

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