

Nanotechnology Applications in Neuroscience: Advances, Opportunities and Challenges

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ÖZET:

Nörobilimde nanoteknoloji uygulamaları: Gelişmeler, fırsatlar ve sorunlar

Metrenin milyarda birine eşit olan "nanometre", 21. yüzyılın ikinci yarısında yaşamın her alanında duyulmaya başlamıştır. Santral sinir sistemi hastalıklarının insidansında gözlenen artış, bu alanda yeni tedavi ve profilaksi yöntemlerine ihtiyacı gündeme getirerek nanoteknoloji ve sinir bilim konseptlerini biraraya getirmiştir. Bu durumun temel sebebi, kan-beyin bariyerinin (KBB) yapısının konvansiyonel ilaç uygulamalarını etkisiz bırakmış olmasıdır. Nanoteknolojik ürünler, uyunçta ve biyoyararlanımda artma, ilaç moleküllerinin KBB'ye penetrasyonunu kolaylaştırma ve görülen yan etkilerde azalma sağlamıştır. Bu derleme, KBB'den geçişi kolaylaştıran bazı tedavi yaklaşımları ile kullanımı fark yaratan önemli nanoteknolojik ve mikro-elektro mekanik sistem örneklerini özetlemektedir. Ayrıca, bazı ürünlerin uygulanmasındaki invazif prosedürler ile mikroçip ve nano cihazların kullanımı hakkında temel tartışma konularından da bahsedilmiştir.

Anahtar sözcükler: Nörobilim, santral sinir sistemi hastalıkları, kan-beyin bariyeri, nanoteknoloji, mikro-elektromekanik sistemler

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ABSTRACT:

Nanotechnology applications in neuroscience: Advances, opportunities and challenges

New treatment and prophylaxis needs, which have emerged as the incidence of central nervous system disorders (CNSDs) has increased, have brought two concepts together: neuroscience and nanotechnology. Because of the restriction of the blood-brain barrier (BBB), conventional drug delivery systems do not always work to provide the levels of drug molecules to the CNS that are needed for the recovery from CNSDs. Nanotechnology products may provide increased compliance, enhanced bioavailability, better BBB penetration of drug molecules, and a minimized side effect profile. This review considers some important application examples of nanotechnology and micro-electromechanical systems in neuroscience, and drug delivery approaches across the BBB. The major controversies concerning invasive procedures for application of some products and the use of microchips and nanodevices are also discussed.

Key words: Neuroscience, central nervous system disorders, blood-brain barrier, nanotechnology, micro-electromechanical systems

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INTRODUCTION

In 1959, the Nobel Prize winning physicist Richard Feynman gave a lecture in which he described the idea of "nanotechnology," a discipline which he defined as "using machine tools to make smaller machine tools, these to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level." (1,2,3). Feynman also foresaw the possible use of nanotechnology in terms of medical applications: a nanomechanical surgeon which had to be inserted into a blood vessel to reach the heart in order to find the problem and slice it out via its nano-sized lancet (3). Today, nanomedicine has many applications, which can bring immediate benefits in research and the

practice of medicine to enhance the quality of human life. These benefits include better accuracy, control, versatility, reliability, cost-effectiveness, and speed (2). Nanotechnology techniques are especially adapted to be used in cases that require rapid interventions, such as cancer therapy, infection prevention and treatment and tissue regeneration.

Despite all the advances in neuroscience, particularly in the last decade of the 20th century, the pathological mechanisms of a number of central nervous system disorders (CNSDs) are not well understood, and there are challenges in the diagnosis and treatment of these disorders (4). Improvements in nanotechnology provide a perfect means to manipulate complex biological systems with

greater selectivity and simultaneously decrease undesirable side effects. These improvements will have a major impact in the field of neuroscience, leading especially to the development of newer and more specific therapeutic modalities (5). Nanotechnology has the potential to be used to facilitate the delivery of drugs and small molecules across the blood-brain barrier (BBB), to support the functional regeneration of neurons, and to improve neuroprotective strategies, especially those using fullerene (6).

USE of NANOTECHNOLOGY in DIAGNOSIS and TREATMENT of CENTRAL NERVOUS SYSTEM DISORDERS (CNSDs):

The prevalence of neurodegenerative disorders and psychiatric conditions will increase over the next decade due to changing demographics. Three aspects make this area particularly challenging: diseases are slowly progressing and difficult to detect early or predict, response to treatment strongly depends on the individual patient and often needs to be personalized, and all present and future medications must cross the blood brain barrier. The latter imposes in a literal sense a barrier to early diagnosis and the development of new medications. Today, Alzheimer's disease (AD) and Parkinson's disease (PD) are the most prevalent neurodegenerative disorders. Although the exact mechanisms of these disorders are elusive and current treatments focus on providing symptomatic relief, nanotechnology-based applications may alter the progress of the disease and improve the results following drug therapy. Drug delivery to the brain is still the main handicap in treatment of CNSDs. The multi-systemic pathophysiological nature of CNSDs, multiple pathways behind the neuron loss, the rigid structure of BBB, and peripheral side effects caused by drug release kinetics make the treatment of CNSDs a difficult subject (7).

The BBB, a selective barrier for the passage of drugs into cerebral tissue, is the main defense mechanism of the brain. The complexity of the serial membranes that the BBB contains originates from micro-vessel endothelial cells and the existence of tight junctions between the endothelial cells of the BBB. Drugs have to cross these membranes to enter the brain. Some molecules promise in vitro therapeutic efficacy, but their safe and effective

delivery to the central nervous system (CNS) is still unproven (7). Additionally, due to the high electrical impedance of the BBB, even the passage of ions is restricted by the endothelial cell layer (8). The transport mechanisms of the BBB may be manipulated through two basic paradigms: a molecular approach and a polymeric carrier approach. In the former, an appropriately designed drug can be targeted to a brain cell and may be activated by specific enzymes inside the target cell; however, the limited availability of drugs and potential prohibitive metabolic pathways may decrease the effect of the drug. In the latter approach, on which this review focuses, a polymeric carrier encapsulating the drug molecule is administered intravenously, intrathecally, or implanted as a device (7). Circumvention of the BBB via nanotechnology provides high levels of drug concentrations in the desired area, yet, reduced systemic toxicity compared with intravenous or oral administration. In addition, protecting labile drugs from rapid degradation and releasing multidrug preparations in a controlled manner are also important (9).

In the treatment of CNSDs, different types of nanotechnology products are in use. Some important nanostructured materials that may interface well with nanobiologically important systems and find use in the field are discussed below.

Nanoparticles

Adhesive nanoparticles are the most successful nanotechnology drug delivery system. These stable nanoparticles range from 10 to 100 nm and have high loading capacities, the ability to protect the drug molecule from degradation, and the ability to open tight junctions easily to cross the BBB. They also may be targeted to mutagenic proteins in AD and PD.

Adhesive nanoparticles provide entry into the brain mainly through their coating which is composed of a wide variety of surfactants. The coating ingredients determine the lipophilicity of the nanoparticle and therefore secure an earlier or later release of the particle's content. In general, the mechanism for the delivery across the BBB is endocytosis through the low density lipoprotein receptors on the endothelial cells. The process is mediated by the adsorption of apolipoprotein B and/or E from the blood. Therefore, it is stated that nanoparticles mimic lipoprotein particles, and act as "Trojan Horses." The drug,

encapsulated into the nanoparticle, may be released either within endothelial cells and then diffused passively into the brain, or be transported into the brain by transcytosis (10).

Clioquinol, a quinoline derivative, is known to be a $\text{Cu}^{2+}/\text{Zn}^{2+}$ chelator. It is able to solubilize the β -amyloid plaques in vitro, and inhibit accumulation of these plaques in AD transgenic mice in vivo (11). It has been shown that clioquinol-containing adhesive nanoparticles cross the BBB at a higher concentration than of the free drug and the carrier. These nanoparticles are administered to solubilize the β -amyloid plaques; therefore they also can be radiolabeled and utilized for in vivo imaging of senile plaques.

Gold particle usage in cancer therapy is a well known strategy due to their excellent targeting ability (12). In the case of AD, following the attachment of gold nanoparticles to β -amyloid plaques, the area is irradiated with low gigahertz electromagnetic fields. The energy level reached is too small to harm healthy cells. This radiation dissolves the plaques and prevents the re-arrangement for at least 1 week (13). This investigation is quite promising for treating other CNSDs involving protein aggregation. This technique functions as “molecular surgery.”

Acetylcholinesterase (AChE) acts as a ligand of β -amyloid in senile plaques. Therefore, hydrophilic, charged, and fluorescent AChE inhibitors, such as PE154 (14) and thioflavin-T (15), have an important role in the detection of these plaques in AD. The prepared nanoparticles have almost the same characteristics as adhesive particles. So far, this technique has only been applied intra-hippocampally, but not intravenously. Consequently, intravenous bioavailability is not clear. The accumulation of reactive iron, copper, and zinc in the aging brain results in macromolecular damage, and this results in oxidative stress-induced damage. Fibrillation and β -amyloid oligomerization are also induced by the accumulation of transition metals (16). All these are conditions that lead to the AD. Some metal chelators, such as deferipone and deferasirox, are approved by the FDA for clinical use; however, their properties are inappropriate to be delivered to the CNS (17). Conjugation of d-penicillamine, a Cu(I) chelator, to nanoparticles has been the subject of an in vitro study which aimed to reverse the accumulated metal-induced precipitation of β -amyloid protein. The results of the study proved that nanoparticle

encapsulated d-penicillamine resolubilized the plaques under reducing conditions (18).

Oxidative stress may produce various devastating cellular alterations, such as DNA fragmentation, peroxidation of membrane lipids, and transporter protein inactivation. This destruction may be avoided by developing fullerene-based neuroprotective compounds. Fullerenes are molecules composed entirely of carbon in different shapes. The hydroxyl functionalized derivatives of fullerenes (fullerenols) have antioxidant activity, meaning they are able to reduce glutamate, N-methyl-d-aspartate (NMDA), amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and kainite induced excitotoxic and apoptotic cell death (19). Despite these good properties of fullerenols, there are some reports of in vitro toxicity in human umbilical vein endothelial cells that were treated with 4.7-9.5 nm diameter- fullereneol nanoparticles.

Nanozymes

A “nanozyme” consists of a nanoparticle structure, an enzyme and a recognition moiety. In inflammation-induced PD, oxidative stress degrades the major dopaminergic pathways of the brain. Therefore, it is thought that the enzyme catalase is useful in treatment. In order to form the nanozyme, catalase is encapsulated by a nanoparticle, and bone-marrow-derived macrophages are attached as the recognition moiety. The macrophages direct the nanozyme towards the inflammation area in the brain. As a result, enhanced transport through the BBB and increased bioavailability are achieved (20).

Nanofibers

Nanofibers, produced especially by electrospinning, are fibers with a diameter less than 1000 nm. They are mainly used in wound healing and tissue repair, because they generate a perfect medium which has very similar characteristics to the extracellular fluid. In PD, polymer-based biodegradable nanofibers are engineered to form a scaffold that allows stem cells to repair damaged nerves instantly and effectively. The scaffold is injected into the body at the site where nerve regeneration is required. In general, applied stem cells adhere to the pre-formed and injected scaffold. In a study, the genes encoding

dopaminergic neurons were also expressed in order to obtain maximum performance through dopaminergic neuroblasts. The shortcoming of this method was the joint production of 10-20% of unwanted different types of cells in addition to dopaminergic neurons (21).

APPLICATIONS of MEMS in CNSDs

During the journey from “micro” to “nano,” biodegradable implants were the preparations that were initially used in neuroscience. Biodegradable implants had to be inserted directly into the brain via a precarious operation, and they were applied only in malignant gliomas that were not curable (22,23). The need for the sustained and reliable use of devices in CNSDs propelled scientists to new investigations. The focus of scientists has shifted to controlling drug delivery and improving the quality of life of patients with long-term diseases. Therefore, more innovative and practical products have emerged.

A once-daily applied transdermal patch, containing rotigotine, a non-ergolinic dopamine agonist, has brought some advantages to the treatment of PD: immediacy of onset of action as intestinal absorption is not needed, constant drug delivery, increased compliance (24), ease of use, decreased undesired effects due to drug use or disease progress (25) and the provision of a regular drug regimen for the elderly (26). Similarly, a once-daily applied transdermal patch, containing rivastigmine, an AChE inhibitor, is a good treatment option in AD because it is generally better tolerated than oral rivastigmine, especially in terms of gastrointestinal adverse events. It also has the potential for improving compliance, and its ease of use provides improved clinical benefit (27). More complex systems are usually used for adjunctive purposes. They aim to increase the patient's quality of life during regular treatment. These devices are mainly micro-fabricated and contain automatic control systems.

Medical therapies for epilepsy are usually oral drugs given daily on a fixed-schedule. It is very difficult to prevent seizures by regular treatment options. Many agents have been proposed as “rescue” therapies, which should be applied rapidly as soon as a clinical seizure or cluster of seizures start to forestall what would otherwise be a more prolonged or more severe clinical event. Currently, there are two choices of micro-electromechanical systems

available to use: the transcutaneous Vagus Nerve Stimulator (t-VNS) and the Responsive Neurostimulator System (RNS) (28).

The usual VNS System requires a small procedure to place a bipolar electrode pair around the left vagus nerve in the neck, near the carotid artery. It also contains a pulse generator and a lead system. Just like a cardiac pacemaker, the stimulator resides subcutaneously, and sends electrical impulses to the brain through implanted electrodes. This system is used to prevent seizures in epilepsy and is also effective in treating chronic or recurrent depression. The system should be used as an adjunctive therapy (29).

The t-VNS stimulators are brand new products in the market. This system does not require surgery, and it consists of a stimulator the size of a mobile phone and a dedicated ear electrode. Electrical impulses are targeted at the auricle, at the point where branches of the vagus nerve have a cutaneous representation. According to the severity of the seizures, the application must be done 3-4 sessions per day, each lasting at least one hour. This device is quite adaptable to the daily routine of the patient.

RNS is another interesting invention in this field, designed for the treatment of medically refractory partial epilepsy. Implantable components of the RNS include the RNS neurostimulator, a programmable device delivering electrical pulses, and cortical strip leads. It is claimed that it may “treat” epilepsy by detecting abnormal electrical activity in the brain and responding by delivering electrical stimulation to normalize brain activity before the patient experiences seizure symptoms. The neurostimulator should be implanted in the cranium, and electrodes should be implanted near the seizure focus. The control mechanism of RNS is an external laptop, which also keeps records of all changes in cerebral activity. A couple of studies using RNS on humans have been performed and the results are encouraging (30).

The patient wandering off and getting lost is the greatest concern of the families of elderly AD patients'. Radio Frequency Identification (RFID) chips may be implanted to track AD sufferers in the case of an emergency. The RFID chips can be detected by satellite systems via radio frequencies, and the exact location of the patient may be determined. Also, the chips can be read via a scanner to access the patient's personal and medical records. The use of these chips has been strongly opposed by some activists due to “invasion of privacy” issues (31).

CONCLUSION

In the last decade, nanotechnology has achieved some milestones in the field of neuroscience. Today, nanotechnology-based treatment, prophylaxis, and adjunctive therapy options are considered promising avenues for the treatment of CNSDs. Nanotechnology research focusing on the CNS will benefit from improvements in neurophysiology, neuroanatomy, and neuropathology (5). In order to provide useful nanotechnological treatment options for patients, advances in pharmaceutical chemistry, material science, molecular biology, neuropathology, neurophysiology, and neuroanatomy need to be examined in depth. Ethical issues have become the greatest handicap in this era, therefore strategies to provide effective solutions to these concerns should be developed carefully.

Before all else, detection of disease specific biomarkers will provide the ability to diagnose a degenerative condition and to prevent irreversible neural tissue damage. Imaging tracers passing through the BBB may assist in

indicating the condition of cerebral tissue. Additionally, choosing the right drug and determining the correct dose to treat a psychiatric condition relies a good deal on trial-and-error today. Use of antidepressants exemplifies this situation quite well. It often requires many trials of several weeks until the symptoms of the patient can be assessed and about 25% of the patients do not respond. Improved imaging techniques could allow an earlier recognition of patients who will not respond to a certain medication. In addition, data obtained from genomic and proteomic analysis may open a long-term opportunity to a more personalized treatment. Furthermore, the same methods could clarify the underlying specific defect mechanisms of several psychiatric conditions, which manifest with the similar symptoms. Nanotechnological improvements in imaging and drug delivery can provide important developments in psychiatry. In 1950s, Richard Feynman, who speculated that “There is plenty of room at the bottom,” foresaw what scientists are experiencing today. The truth is, there is more room at the bottom, as we try to reach particles smaller than “nano.”

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