Review Article

Nanotechnology in neurology: Genesis, current status, and future prospects

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Abstract

Nanotechnology is a promising, novel field of technological development. There is great potential in research and clinical applications for neurological diseases. Here we chronicle the inception of nanotechnology, discuss its integration with neurology, and highlight the challenges in current application. Some of the problems involving practical use of neuronanotechnology are direct biological toxicity, visualization of the nanodevice, and the short life expectancy of nanomachinery. Neuron cell therapy is an upcoming field for the treatment of challenging problems in neurology. Peptide nanofibers based on amphiphilic molecules have been developed that can autoregulate their structure depending on the conditions of the surrounding milieu. Such frameworks are promising for serving as drug delivery systems or communication bridges between damaged neurons. For common disabling diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), recent developments have seen revolutionary nanotech-based novelties, which are discussed here in detail. Bioimaging integrated with nanoneuromedicine has opened up new doors for cancer and infection therapeutics.

Key Words

Amphiphile, nanomedicine, nanotechnology, neurology

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Introduction

The future is upon us, and it has brought us the gift of nanotechnology. In the metric system, a nanometer (nm) is one billionth of a meter (m). Though this scale is too small for the naked eye, this is the realm of the biological cell and its organelles. Truly speaking, all the real action happens at the molecular or cellular level. Nanotechnology involves the manipulation of technological machinery at the atomic scale. For perspective, a nucleus is about 6 μm across, a ribosome 20 nm in diameter, and a single strand of DNA 2 nm wide. A typical human being is composed of 100 trillion cells. Nanotechnology has created novel devices for the treatment of various neurological diseases. Shrinkage of machinery, chip-based technologies, and the creation of unprecedented nanomaterials are contributing immensely to the reduction of morbidity. Novel nanotechnological inventions have driven human excitement and curiosity to a new high. Judging from the pace of nanotechnological innovation and research, one can safely assume that the future is headed toward the integration of therapeutic neurology and nanotechnology.[1,2]

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The Founding Forefather

On December 29, 1959 the famous physicist Richard Feynman delivered a lecture on quantum mechanics at the California Institute of Technology. Little did he know that this talk would become the cornerstone for technological revolution in the field of nanotechnology. Feynman proposed writing the entire 24 volumes of Encyclopaedia Britannica on the head of a mere pin.[3]

Another radical idea suggested by his friend Albert Hibbs was that of micromachines, dubbed as the "swallowable surgeon," that could be controlled from the outside to perform surgery at the cellular level.[3] This device could be used to eliminate malignant neoplasms at their inception or repair defective heart valves. Among the boons of working at the nano level are the minimal friction and mechanical wear and tear. In addition, as the mass of the device is negligible, gravitational forces in turn become trivial.

Potential of peptide nanofibers in neurology

Amphiphilic molecules are used to create auto-assembling nanofibers, having alternate positive and negative L-amino acids. These amino acids when placed in a physiological salt solution reassemble into a semisolid nanofiber mesh.[4]

The relative concentration of ions in the internal milieu of a cell regulates the strength and shape of such a nanofiber matrix. Thus, it can be safely assumed that such materials can be easily introduced inside the cells for drug delivery, etc., without the needless hassle of complicated surgery. Many doors to therapeutic interventions can be opened using this approach.

This novel approach has been used to attempt to treat optic tract transection. Self-assembling peptides were introduced into the trauma site. After some time, some axonal growth was documented, leading to the partial return of functional vision in experimental animals with removed brachiums.[5]

Neural engineering at the cellular level is an upcoming field. Carbon-based nanomaterials are excellent electrical conductors without many adverse effects on biological tissue. In one study, astrocyte adhesion was markedly decreased on using carbon nanofibers, while neuronal cell growth was boosted.[6]

Cell attachment and cell differentiation have been measurably seen following use of peptide frameworks. Functional ligands can be introduced using simple techniques, for instance, with (RGD) Arg-Glyc-Asp (IKVAV) Isoleucine-Lysine-Valine-Alanine-Valine (RADA peptide gel backbone) AcNRADARADARADARADA-$CONH_2$, which are epitopes with integrin receptor binding sites. Outgrowth processes from cultured neural cells were produced from direct application of peptide amphiphilic molecules with IKVAV sequences. Moreover, astrocytic differentiation of progenitor cells was thwarted using the same approach.[7]

RADA16-I–incorporated peptide mesh resulted in the formation of functional synapses. This was due to the growth of PC12 cells, primarily in rat hippocampal neurons.[8]

In one study, astrogliosis was found to be reduced and the frequency of oligodendrocytes increased at the site of trauma.[9]

As potential implantable biomedical devices, carbon-based nanotubes have shown promise in the role of subcellular neuroelectral bridges.[10]

The challenge that is neuronanomedicine

Neurological illnesses pose strange and unique dilemmas for human morbidity. Inflammation, infection, neoplasia, autoimmunity, and degeneration are important harbingers of mortality.

Though science has given us novel technological wonders such as nanotubes, nanowires, miniature robots, and nanospheres, the challenges facing their implementation in order to thwart neurological pathogenesis are myriad.[11]

Some of the problems are as follows:

Manufacturing

Any facility that hopes to manufacture nanomachines on a large scale has to be efficient and extremely clean. The slightest amount of contamination in the manufacturing process can result in faulty nanoinfrastructure. The *in vivo* repercussions of this can easily be disastrous.

Drexler, one of the great pioneers of nanotechnology, proposed in 1986 that such nanomachines can be used for self-manufacture and assembly, thus resulting in a "billion tiny factories."

Life of nanomaterials inside biological environments

The life expectancy of a nanomaterial inside a cell is questionable. No long-term data are available to give a safe and conclusive answer. The long-term effects of a foreign body inside a living cell are unknown as well.[12]

Visualization of the nanoparticle

Another problem is locating the nanomachine inside large areas of tissue. Massive amounts of resolution are needed to amplify subcellular structures. Transmission electron microscopy is the best bet so far to visualize such suboptimal structures, but at the cellular level even scanning a few cells for a nanoparticle is akin to surveying expansive fields of land via an airplane.

Biological side effects

One might presume that the unintended effect of something as minuscule as a nanomachine would at best be trivial at the cellular level. On the other hand, it might just translate into symptoms manifesting at the level of the patient. The truth is that no reliable database exists to justify any such conclusion. Safety protocols and tests have been laid down to truncate any such risk, but currently the identification of hazards is made on a case-by-case basis.[13]

Direct toxicity

The most obvious and straightforward risk to a cellular environment is from the chemical makeup of the nanoparticle. In general, the toxicity of nanoparticles reflects their chemistry.[14] For instance, the toxicity of carbon nanotubes

is a direct result of the external framework, dimensions, type of carbon isotope used, coating on the surface, and relative amounts of carbon used.[15]

Damage to the DNA of the cell has also been reported in some studies. In one study, mutation frequency in mouse embryonic stem cells doubled after the use of multiwalled carbon nanotubes.[16]

Automatic regulation of drug delivery at neuron level

Injecting accurate amounts of a drug in minuscule quantities to subcellular targets can be staggeringly challenging. *In situ* placement of special genes maneuvered by biological sensors can control the concentration of a drug as per requirements, in concordance with a feedback loop. This is just one of the various approaches that have been suggested for the drug delivery problem.[17]

A glimpse into the future of nanoneuromedicine

Considerable efforts are being focused in the research laboratory on using nanoneuromedicine for disease treatment. In case of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), nanomedicines have emerged as promising treatment options. Pathophysiological processes involving neuron inflammation and protein misfolding initiate a degeneration cycle within the cell. This can be thwarted using better drug targeting. Diagnosing and monitoring the end-effects of therapeutics is possible using nanoneurotechnology.

Common presentations of AD include poor memory and decreased cognition due to brain atrophy and the destruction of cortical and subcortical neurons.[18] AD can be diagnosed using tau and amyloidogenic Ab42 forms, and Ab-derived diffusible ligands (ADDL). Cerebrospinal fluid (CSF) can be scanned for ADDL levels using "biobarcodes" that make use of ADDL-specific antibodies with gold nanoparticles.[19] Detection of immunocomplexes can be augmented by the application of scanning tunneling microscopy and anti–Ab40-gold conjugation system.[20] Gold nanoparticles can also be engineered as multispot-localized surface plasmon resonance immunochips.[21] Nanotechnology is being used this way to detect Ab deposition.[22] Anti–Ab antibody-coated fluorescent quantum dots are being used to track Ab accumulation.[23] Ab aggregation inside neurons is inhibited by nanocarbon fullerenes, which eventually results in stopping cognitive decline.[24] Ab fragment-conjugated gold nanoparticles can be incorporated into Ab complexes. Laser is then used to selectively ablate Ab aggregates.[25] Nanomedicine can be used to create drugs for more efficient brain delivery. Magnetic chitosan nanoparticles incorporated with tacrine can be homed into specific target locations with the help of external magnets.[26]

PD is characterized by resting, tremors, bradykinesia, and postural instability, due to the destruction of dopaminergic neurons in the substantia nigra pars compacta. Striatal projections are typically lost.[27] Lewy bodies, protein-filled inclusions in neurons, are characteristic. They are made of misfolded a-synuclein (a-syn) and ubiquitin. Gold- and titanium dioxide-incorporated nanotube arrays detect a-syn using photoelectrochemical immunosensors.[28]

Atomic force microscopy in tandem with nanoneurotechnology can detect protein misfolding of single a-syn molecules.[29] Plasmonic nanogoldparticles for quantization of neurotransmitter concentrations can indirectly gauge PD pathogenesis.[30] To aid in symptomatic treatment, ascorbic acid-functionalized carbon fullerenes encase levodopa molecules in drug manufacturing. This augments an antioxidant effect inside neurons.[31] Neuroinflammation and neurodegeneration inside neurons is adequately inhibited by using catalase-packaged polyethyleneimine nanoparticles, which effectively diminishes hydrogen peroxide.[32] Bromocriptine was incorporated as a nanoparticle with tristearin/tricaprin lipid combination to thwart neurodegeneration.[33] Lactoferrin-containing nanoparticles that cover the human neurotrophic factor gene modulate locomotor function and decrease dopaminergic neuronal loss.[34]

In addition, anti–α-syn-conjugated polybutylcyanoacrylate nanoparticles helped in neuronal a-syn clearance.[35]

ALS is a disease of motor neurons that leads to the loss of neuromuscular control with fatal outcomes.[36] Motor neuron degeneration takes place predominantly in the upper and lower motor neurons.

Protein inclusions made of ubiquitin and ALS-associated proteins, such as superoxide dismutase 1 (SOD1), are found in neurons and axons. For speedy diagnosis, gold particles coated with SOD1 can be combined with SOD1 aggregates to produce a colorimetric detection system.[37]

Carboxyfullerene nanotubes with SOD incorporates are neuroprotective of pathology.[38] Carbon nanoparticles with large carrying capacity can deliver riluzole, a glutamate inhibitor, to pathogenic sites more accurately.[39]

In MS, immunocytes act against self-antigens of the nervous system, associated with myelin and oligodendrocytes. Lesions of demyelinated white matter or perivascular inflammatory plaques are seen.[40] A water-soluble fullerene incorporated with an *N*-methyl-D-aspartate receptor antagonist inhibited MS disease progression as well as myeloid neuronal infiltrates.[41]

Nanomedicine and bioimaging

Curiously, positron emission tomography (PET) provides both diagnostic and therapeutic nanomedicine capabilities, otherwise known as theranostics.

Lack of blood supply in stroke models can be seen using liposome-encapsulated hemoglobin molecules, which can permeate ischemic territories.[42]

Prompt fibrinolysis can be provided by liquid perfluorocarbon nanoparticles incorporated with plasminogen activator streptokinase.[43] Cerium oxide nanomaterials can scavenge reactive oxygen species and give neuroprotection.[11]

Quick assessment of drug pharmacokinetics is possible by contrast magnetic resonance (MRI) agents, such as superparamagnetic iron oxide (SPIO): A 100-μm isotropic resolution can detect single nanoparticles.[44] Magnetite

targeting is utilized in cancer therapy. Easy visualization is done by SPIO-loaded nanoparticles, and then specifically targeted within the brain tissue. Tumors can be then accessed after nanomaterials cross the blood/brain barrier (BBB).[45]

Carmustine (hydrophilic polymeric coating)-combined nanoparticles can be "steered" within brain tumors using magnetism to achieve significant reduction of tumor volume.[46] Theranostic nanomaterials have been developed that contain antiretroviral drugs and SPIO particles. These are called "small magnetite antiretroviral therapy" or "SMART" particles. New developments in targeting ligands and nanoformulated SPIO particles to adequately quantize drug dose reductions hold promise.[47]

Conclusion

The application of nanotechnology is promising in view of frustrating problems in therapeutic neurology. As it involves cellular biology, many roadblocks lie ahead. However, the rapid pace of technological innovation and an increasing interest in both funding and curiosity are enabling scientists to explore this field further. Even for currently incurable diseases such as AD and PD, new hope has been found in the form of nanotechnological treatment options. The future of nanoneuromedicine for both bioimaging and therapeutics is indeed very exciting.

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Conflicts of interest
There are no conflicts of interest.

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