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REVIEW

Recent advances in nanotechnology based drug delivery to the brain

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Abstract Drug delivery into the brain was difficult due to the existence of blood brain barrier, which only permits some molecules to pass through freely. In past decades, nanotechnology has enabled many technical advances including drug delivery into the brain with high efficiency and accuracy. In the present paper, we summarize recent important advances in employing nanotechnology for drug delivery to the brain as well as controlled drug release.

Keywords Nanotechnology · Nanoparticle · Drug delivery · Blood–brain barrier

Introduction

Feynman suggested: "there's plenty of room at the bottom". Nanotechnology has emerged to be one of the most powerful technologies in applied biomedical sciences. The applications of nanotechnology to neurobiology and neurological sciences would include nano-material based tissue engineering, diagnostics and drug delivery, nanorobotics for nano-surgery, as well as nano-chips for memory storage. Drug delivery into the brain has been one of the most important questions in not only clinical neuroscience areas, but also the basic tools for neuropharmacology analyses. In this manuscript we discuss the nanotechnology-enabled drug delivery into the brain, particularly nanoparticle based approaches as well as their current advances.

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Different routes for brain drug delivery with nanotechnology

Circulation across blood–brain barrier

One of the most well-known structures that separate the extracellular fluid of neuron from circulation is the blood–brain barrier (BBB). It is composed of endfeets of astrocytes that cover blood vessels, pericytes and tight junctions between endothelial cells (Abbott et al. 2010). In physiological conditions, BBB is critical for the hemostasis of the brain internal environment and normal functions (Palmer 2010). Only limited areas such as circumventricular organs are "blind" of BBB, which provide the sensor of the pH of blood. Most large molecules such as proteins cannot cross the BBB; therefore brain is most resistant to bacterial infections normally (Banks and Erickson 2010). However this characteristic also weakened the efficiency of drug delivery into the brain, as antibiotics and antibodies are too large to pass the BBB (Jeffrey and Summerfield 2010).

Targeted brain drug delivery after vein administration therefore requires the drug molecules to cross BBB efficiently to reach the effective concentration. Two questions have to be solved: first the drugs must be enabled for brain entry; second the drugs won't be expelled out of the brain by transporters such as P-glycoprotein easily (Gabathuler 2010). In ideal situations, the BBB-permeable ligands should be able to target groups of cells or specific brain regions as well (Silva 2007).

Currently there are several major applications of nanodelivery into the brain with vein injection and across BBB. The first would be targeting brain tumors with therapeutic drugs given that most tumor blood vessels are more permeable and "leaky" in comparison to well built vessels in normal tissues. Conceivably the nanoparticles carrying antineoplastic drugs would reach brain tumors, and PEG-coated nanoparticles were found to be with more than 10 times of efficiency in delivery tested by accumulation in tumor tissues when compared to routine delivery through circulation (Brigger et al. 2002; Feng et al. 2004). Also, the polysorbate coated nanoparticles that can be taken up by brain endothelial cells have been shown to target tumor tissues efficiently (Alyautdin et al. 1997). The second general application of drug delivery would be the treatment of many types of brain disorders, including neurodegenerative diseases. For instance, many growth factors and neuropeptides are effective when administrated into the ventricle, but lack efficiency for systemic application, explained by their failure in crossing the BBB. Now people have successfully delivered PEG-coated nanoparticles to brain and spinal cord in rat model of experimental allergic encephalomyelitis, for instance (Calvo et al. 2002). It is believed that in the future more and more other brain diseases could be treated in similar manners. The third aspect would be delivery of diagnosis agents into the brain for imaging purposes. For instance, the classic superparamagnetic magnetic resonance imaging (MRI) contrast agents, many iron oxides, when coated and combined with nanoparticles, could be put into the body for long-term and stable detection (Peira et al. 2003).

Some newly emerged techniques in penetrating the BBB would further expand the current repertoire of nanoparticle based delivery into the brain. For instance, the signaling peptide of rabies virus could penetrate BBB efficiently and deliver small interfering RNA to local regions in the brain (Kumar et al. 2007). It would be interesting to develop nanoparticles coated with this peptide for BBB-crossing delivery in the future. The engineering of this signaling peptide would help to generate more powerful tools in crossing BBB. Additionally, because the viral infection to the brain often associates with neuroinflammation and BBB disruption, people have also proposed to employ other types of virus-based nanodelivery system that could disrupt the BBB to enhance the drug targeting into the brain (Shriver et al. 2009). The use of neurotrophic virus during brain drug delivery greatly enhanced the BBB permeability as well as the drug delivery into the brain.

Intranasal delivery

Olfactory nerves project directly from the olfactory epithelium to the olfactory bulb of the brain. It has been found for a very long time that small particles such as metal dusts could accumulate in the brain of mine workers since 1920s. Further, some neurotrophic viruses could invade the brain through olfactory nerves, and propagate even into deeper regions of the brain. These discoveries brought the idea of intranasal delivery of small molecules into the brain following administration of the solutions directly into nostril.

Some difficulties still remain in processes of intranasal delivery. For example, some drugs cannot be internalized by olfactory sensory neurons in the olfactory epithelium efficiently, therefore weakened their further entry into the brain; or they lack the characteristic of long-term persistence, and attached less firmly to the epithelium. Nanoparticles as the drug carriers have emerged to be applicable in this area without such defects (Mistry et al. 2009). For instance, 30 nm diameter salts of manganese have been found to propagate into very deep regions in the brain (Elder et al. 2006). ^{13}C containing nanoparticles of similar size have been tested in other studies as well (Oberdorster et al. 2004). It was believed that these nanoparticles were transported because they are small sized. Interestingly other evidences implied that the size does not mean everything, some bigger sized nanoparticles (280 nm) were found in deep regions including hippocampus after intranasal administration (Wang et al. 2007), though these particles could reach the brain through circulation indirectly as well.

Several types of modifications of nanoparticles were found to be useful in enhancing the efficiency of delivery and penetration into deep brain regions. Most times these modifications include ways to change the surface properties of nanoparticles, so that the interaction with biological systems could be promoted. For example, chitosan modified molecules showed much longer residency time on the olfactory epithelium (Charlton et al. 2007), as well as enhanced permeability due to their interaction with tight junction complexes (Smith et al. 2004). Additionally, PEG coated nanoparticles showed increased diffusion in tissues (Lai et al. 2007), and lectins isolated from plants could greatly upregulate the uptake of coated nanoparticles without clear evidences of toxicity (Gao et al. 2006; Gao et al. 2007). It is hoped that other small molecules and peptides, such as cholera toxin subunit B (CTB) (Zhang et al. 2008), could provide more possibilities in further improvement of nanoparticles based intranasal drug delivery. Last but not least, when combined with other nanomaterials such as nanofiber scaffold gels which showed high biocompatibility, nanoparticles could reach maximum persistence over the olfactory epithelium, as tested in several previous studies (Dhuria et al. 2010; Jogani et al. 2008; Nochi et al. 2010).

Cerebral-spinal fluid (CSF) or directly into the brain areas

As mentioned above, many big molecules including trophic factors and neuropeptides are only effective when injected into ventricle or directly into the brain, if not helped with BBB-permeable ligands. Though invasive, the direct drug administration led to most precise concentration control with spatial and temporal accuracy. There are many ways to further improve the approaches with nanotechnology. Coating with ligands could enhance the tissue compatibility and residence of the drug carriers with reduced immune rejection effects (Mundt et al. 2009). Also, particles could be conjugated with targeting ligands for specific neuronal populations, challenged dopamine neuron in Parkinson's disease, for example. However direct administration of nano-drug carriers could also bring unwanted effects, as they may disrupt normal brain metabolism much more than the bigger particles, as proven previously (Yamada et al. 2008). Proper coating must be carefully chosen as direct ventricle administration led to significant increase of these nano-carriers inside the brain; even minimal toxicity could accumulate and bring catastrophic results.

Therefore, drugs embedded in slow-releasing nano-gels could provide alternative choices without acute effect on the brain. Many natural and artificial gels have been developed as drug-releasing carriers in brain tissues. For example, some self-assembly peptide nanofiber scaffolds have been found to be helpful for brain recovery after trauma and could even downregulate immune reactions (Ellis-Behnke et al. 2006; Guo et al. 2009). It was suggested that when seeded with stem cells or drug-carrying capsules (Guo et al. 2007), such bio-gels could exert long-term effects during degradation and absorption.

Summary

Why nano, when nano, and how nano? It was believed that nanotechnology would be the most powerful technology in coming decades. We will be able to apply nanotechnology to most, if not all, aspects of neurobiology research and clinical neuroscience studies. To employ nanotechnology in your own study, try to ask the question how can nanotechnology facilitate this process whenever meeting a question. Brain drug delivery has been a very old area, but few major progresses have been achieved in the past century. In the present essay we summarized how nanotechnology has made this area further advanced, and how many new opportunities emerged for further discoveries and technical applications. Currently there lacks clinical studies on human subjects, but some progresses have been achieved with primate models (Heidel et al. 2007). We believe that in coming years nanotechnology would make drug delivery into the brain much easier than nowadays.

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