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RESEARCH ARTICLE

Nanotechnologies for Alzheimer's disease (AD) treatment

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LETTER TO EDITOR

Alzheimer's disease (AD) is a devastating neurodegenerative disorder and the most common form of dementia among people over the age of 65 years. This neuropathological condition is characterized by a progressive loss of cognitive function and presents two established pathophysiological hallmarks in the brain. These include extracellular acscumulations mainly composed of amyloid-β (Aβ) peptide (also referred to as senile plaques) and intracellular neurofibrillar tangles of hyperphosphorylated τ protein.[1] Today, millions of people are affected by this neuropathology, posing a heavy economic and social burden. It is predicted that in the next few decades, AD will exert a huge societal and economic impact if no efficient therapeutic and/or early-diagnosis approaches become available.

Moreover, considering the increase in population aging and survival, the impact of AD on the health care systems will be even more pronounced. Therefore, strategies for early detection as well as treatment of AD are among the most challenging and timely areas in modern medicine.

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The blood-brain barrier (BBB) is a formidable gatekeeper in the body toward exogenous substances that maintains the chemical composition of the neuronal “milieu” for proper functioning of neuronal circuits and synaptic transmission. This barrier is formed at the level of the endothelial cells of the cerebral capillaries and essentially composes the major interface between the blood and the brain. The most important factor limiting the development of new drugs and biologics for the central nervous system (CNS) is the BBB. Generally,

pharmaceuticals, including most small molecules, do not cross the BBB.[2] During the past decade numerous attempts have focused on this pivotal problem by designing different strategies that aid drug passage across the BBB. Among these, nanotechnology-based strategies have gained tremendous importance as some of them are capable of overcoming the limitations inherent to BBB passage. These include various types of lipidic, polymeric, inorganic, and other types of anoparticles (NPs) for controlled drug delivery and release pertinent to various CNS conditions.[3,4]

DELIVERY OF BIOACTIVE MOLECULES TO THE BRAIN:

A healthy BBB is a major obstacle for the development of both small and large neurotherapeutic olecules (e.g., recombinant recombinant peptides, Ab fragments, antisense oligonucleotides, viral vectors).[4] In addition, the BBB also negatively affects drug efficacy and tolerance, because large doses of drugs are needed to reach levels above the minimum effective concentration in the brain. anoparticulate systems offer an opportunity to overcome such problems and can be used as "Trojan systems" for transporting active molecules across the BBB, thus reducing toxicity and mproving therapeutic efficacy.[5]

ACHE INHIBITORS AND ACETYLCHOLINE (ACH):

The deficiency in cholinergic neurotransmission is considered to play an important role in the learning and memory impairment of AD patients.[5] So far, cholinergic neurotransmission enhancement remains the most effective therapeutic approach to treat AD. Accordingly, rivastigmine, a noncompetitive and reversibl inhibitor of both AChE and butyrylcholinesterase, was approved in 2000 by the FDA for the treatment of AD. Experimentally, this drug has been shown at least to maintain-if not to improve– cognitive function, global function, and behavior in AD patients. However, its clinical efficacy remains limited mainly due to poor brain translocation, which requires frequent injections, and its adverse cholinergic effects on peripheral organs.[6]

An interesting approach for the delivery of ACh to the brain for AD treatment was proposed by Yang et al, using single-wall carbon nanotubes. However, single-wall carbon nanotubes are nonbiodegradable materials, and not much is known regarding their acute and chronic toxicity.

Estrogens and androgens

There is ample preclinical evidence that gonadal steroids (estrogens and androgens) play an important role in CNS development and

functions. Estrogen treatment can decrease the risk of AD. Experimentally, estradiol may promote the growth and survival of cholinergic neurons and reduce significantly cerebral amyloid deposition.[7]

Curcuminoids

Curcuminoids, obtained from Curcuma longa (turmeric), the most commonly used natural yellow photoconstituents in the food industry, have been widely screened in the past decade for biological activities such as anti-inflammatory, antioxidant (see also "Antioxidant Species" below), neuroprotective, hepatoprotective, anticarcinogenic, antiviral activities, and many others. Numerous investigators have reported that curcumin can significantly reduce Aβ aggregaterelated toxicity on neurons.[8]

Non-functionalized NPs

Two parallel studies investigated the encapsulation of curcumin into polymeric PnBCA NPs, and it was demonstrated that the encapsulation procedure dramatically increased curcumin half-life and concentration in the brain when compared with free curcumin.

Targeted NPs

Another approach has utilized NPs decorated with appropriate ligands for curcumin brain delivery.54 This strategy was based on the preparation of curcumin-loaded PnBCA NPs decorated with ApoE3 ligands to exploit LDL-r-mediated transcytosis across the BBB and through SH-SY5Y neuroblastoma cells.[9]

Chelating ligands

There are suggestions that aberrant copper homeostasis has implications in AD. Accordingly, Treiber et al have engineered hyperbranched polyethyleneimine constructs with encapsulated Cu(II) ions, which were not only internalized by cells but also increased cytosolic concentrations of Cu(II) (by releasing the metal cations) and induced weaker Aβ turnovers. Unfortunately, no in vivo experiments have been conducted, presumably because of polyethyleneimine toxicity.[10]

α-, β-, and γ-secretase inhibitors

Aβ peptides originate from proteolysis of the APP by the sequential enzymatic actions of β-site APP-cleaving enzyme 1 (BACE-1, a β-secretase) and γ-secretase (i.e., a protein complex with presenilin 1 at its catalytic core). Instead, the nonamyloidogenic pathway involves successive APP cleavages by α- secretase (thus precluding Aβ formation) and γ-secretase, leading to the formation of nonamyloidogenic fragments.

Antioxidant species

Another strategy regarding the treatment of AD is directed toward the delivery of antioxidant species to the brain, because of their ability to quench the reactivity of reactive oxygen species (see also "Antioxidant Sponges" below). Glutathione-Antioxidant sponges

Fullerenes

Specific carbon-based nanostructures have shown some promising therapeutic effects in AD. For instance, radical scavenging entities, such as carboxyfullerenes (C60) could trap multiple radicals and have been consequently exploited as "radical sponges." In this view, Dugan et al investigated the ability of water-soluble C60 carboxylic acid derivatives, containing three malonic acid groups per molecule, to reduce the apoptotic neuronal death induced by exposure to Aβ1-42. In this way, fullerenes could be an interesting alternative to reduce damage caused by Aβ toxicity.

Nanocerias

Nanocerias (i.e., mixed-valence-state cerium) were used to drastically reduce the reactive oxygen intermediates intracellular concentration in vitro and in vivo, so as to prevent the loss of vision due to light-induced degeneration of photoreceptor cells. These results indicated that nanoceria particles were active for the inhibition of reactive oxygen intermediate intermediate-mediated cell death that is involved, among other species in AD pathogenesis.[11]

Physical interaction with Aβ peptide

Protein and peptide conformation is often altered following adsorption onto the surface of NPs, and this may affect their biological functions accordingly. This has been utilized to advantage by designing brain-specific NPs with affinity for Aβ peptides, thus affecting their aggregation or nucleation. The γ-glutamylcysteinylglycine (also called glutathione, GSH), a water-soluble endogenous antioxidant composed of glutamic acid, glycine, and cysteine, is one of the most important intracellular antioxidants. Physical interaction with Aβ peptide Protein and peptide conformation is often altered following adsorption onto the surface of NPs, and this may affect their biological functions accordingly. This has been utilized to advantage by designing brain-specific NPs with affinity for Aβ peptides, thus affecting their aggregation or nucleation.[11]

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