RESEARCH REVIEW JOURNALS
Volume-04
Issue-06
June-2019

ISSN: 2455-3085 (Online)
RESEARCH REVIEW International Journal of Multidisciplinary
www.rrjournals.com[UGC Listed Journal]

A Study of Nano Particles and Therapies for Alzheimer's Disease

[1]Pradnya Sanjay Lokhande & [2]Dr. Rohit Saraswat

[1]*Research Scholar, OPJS University, Churu, Rajasthan (India)*
[2]*Assistant Professor, OPJS University, Churu, Rajasthan (India)*

ARTICLE DETAILS

Article History
Published Online: 12 June 2019

Keywords
Alzheimer's disease, dementia, drug delivery, nanoparticles, neuroprotection.

ABSTRACT

Alzheimer's disease (AD) typically affects behavior, memory and thinking. The change in brain has been reported to begin approx. 10-20 years before the appearance of actual symptoms and diagnosis of AD. An early stage diagnosis and treatment of this lethal disease is the prime challenge, which is mainly halted by the lack of validated biomarkers. Recent Nano technological advancements have the potential to offer large scale effective diagnostic and therapeutic options. Targeted drug (e.g. Rivastigmine) delivery with the help of nanoparticles (NPs) in the range of 1-100 nm diameters can effectively cross the blood brain barrier with minimized side effects. Moreover, biocompatible nanomaterials with increased magnetic and optical properties can act as excellent alternative agents for an early diagnosis. With the high volume of research coming in support of the effective usage of NP based drug delivery in critical environment of CNS, it is quite likely that this approach can end up providing remarkable breakthroughs in early stage diagnosis and therapy of AD. In the current review, we have presented a comprehensive outlook on the current challenges in diagnosis and therapy of AD, with an emphasis on the effective options provided by biocompatible NPs as imaging contrast agents and drug carriers.

1. Introduction

Alzheimer disease (AD) is the most prevalent neurodegenerative disorder (NDD) affecting more than 35 million people worldwide, with no full proof diagnosis apart from the post-mortem identification of neurofibrillary tangles (NFTs) and senile plaques (SP) in the brain [1, 2]. The premortem diagnosis of AD that is based primarily on neurological, cognitive and neuropsychological tests, in vivo brain imaging and patient's clinical history has been reported to provide a maximum 85% accuracy. The soluble AD markers can be detected by two general approaches. The first approach which measures the total amyloid-β (Aβ) or tau pro-tein in the plasma or cerebrospinal fluid (CSF) has been hampered by a remarkable overlap of these markers in healthy as well as affected individuals, thus leading to not so conclusive results [3]. The second approach which utilizes the pathogenic markers like Aβ-derived diffusible ligands (ADDLs) and phosphorylated and cleaved tau protein may provide more conclusive findings, but their low CSF concentrations in early AD make it very tough to accurately identify them by ELISA or blotting assays [2, 4].

Nanotechnological advances have now started to exert a remarkable impact in neurology and neurodegeneration [5]. These approaches based on the engineering of nanoparticles (NPs) specific for brain specific endothelial cells (EC) are now gaining attention in AD diagnosis and therapy [6, 7]. The NPs which are highly specific for circulating Aβ may improve the AD condition by inducing a "sink effect" [8, 9]. The new in vitro developments related to AD diagnostics include scanning, tunneling microscopy procedures, immune sensors, and ultrasensitive NP-based bio-barcodes, which are capable of detecting Aβ (1-40) and Aβ (1-42) [8, 10]. Despite these advances, some major concerns related to the initiation of NP-mediated adverse events in AD demand the engineering of precisely assembled biocompatible Nano constructs [8]. Biocompatible Nano constructs (Fig. 1) can be synthesized from biopolymers, chitosan [11], gelatin [11, 12], and polymers, or from the semi-conductive metals-gold and cadmium [15] though adverse effects such as cytotoxicity or inhibition of cytokinesis, which can result from physiological applications. Quantum dots synthesized from the more commonly used cadmium are cytotoxic due to the liberation of Cd2+ ions during the deterioration of the CdSe crystal lattice. Others have demonstrated in vitro the disruption of tubulin orientation leading to cell cycle arrest and prevention of cytokinesis caused by the internalization of polymeric NPs as small as 10s of nanometers. However, since the emergence of Nano science and nanotechnology some 20 years ago, there have been many developments to counteract some of these affects. For example, the modification of quantum dots with shells have not only lowered the toxicity but also provided functional groups for ligand, DNA, or peptide bio conjugation.

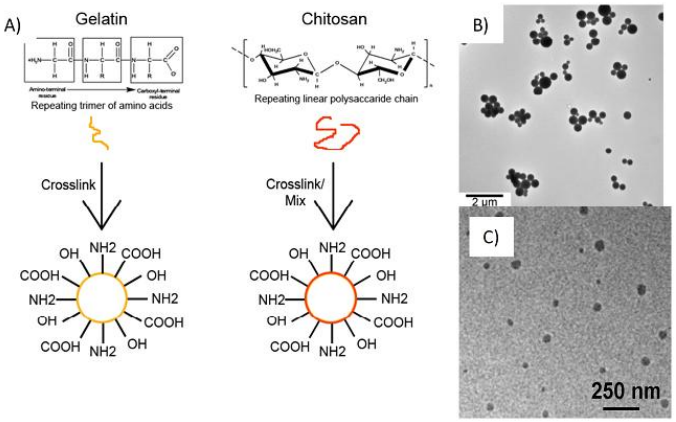

Fig. (1). Example of nanoparticles constructed from biocompatible molecules

2. Nanotechnology In the Diagnosis of AD:

Since neuron invasiveness and degenerative changes have begun before the onset of AD symptoms, early diagnosis is the key to effective treatment of AD. Most studies focus on magnetic resonance imaging (MRI) using contrast-doped NPs or labeling NPs with fluorescent probes to detect and identify amyloid plaques.

Iron oxide NPs

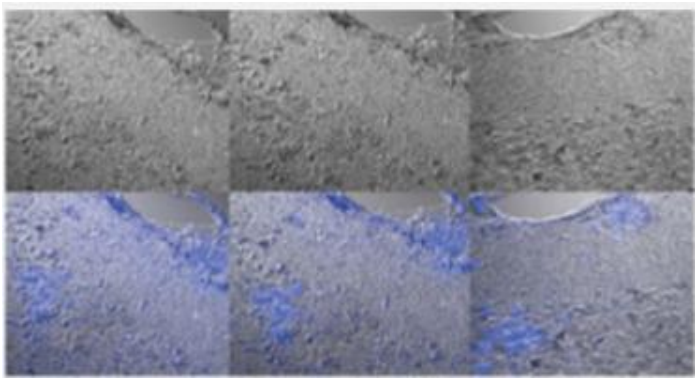

Figure 2: Histochemical stained Aβ plaques on serial brain sections of Tg2576 mice

Magnetic iron oxide NPs have gained wide attention due to their large surface area, good magnetic properties, low toxicity, and good biocompatibility and degradability. For example, Cheng et al. [6] synthesized superparamagnetic iron oxide nanoparticles (SPIONs) connected with curcumin which coated with polyethylene glycol (PEG)-lactic acid (PLA). The material is non-cytotoxic and has the ability to detect amyloid plaques in the brain of Tg2576 mice with AD [7] (Figure 2). Both top and bottom images were viewed by confocal microscopy. Top images were bright view and bottom images were fluorescence signal from stained chemical (from left to right stain by thioflavin T, curcumin or curcumin-MNPs)

Gold NPs

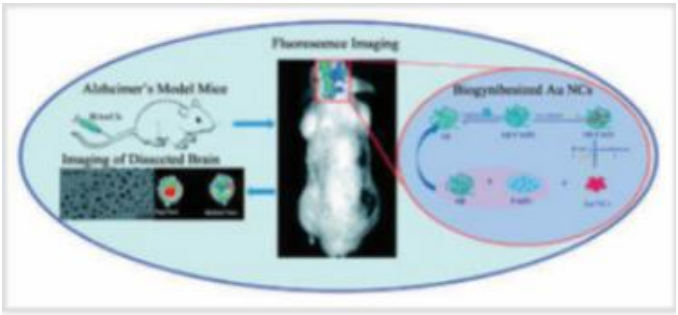

Figure 3: This diagram showed that intravenous injection of aqueous HAuCl4 through the AD mice tails showed exact bright fluorescence labeling around the affected sites of the Alzheimer's brain

Lai et al exposed these sites to an aqueous solution of chloroauric acid to form a gold salt by targeting the site of infection [8]. These salts are assembled into gold nanoclusters (AuNC) for fluorescence imaging. Within a few hours after the injection of chloroauric acid by the tail vein of AD mice, there was a clear fluorescent label around the affected part of the brain, whereas the control mice did not show any fluorescent area after intravenous injection of chloroauric acid for 24 hr (Figure 3).

3. Nanotechnology in the treatment of AD:

BBB is the primary barrier to the delivery of therapeutic drugs to the brain. Some treatments have forced them to open by causing structural damage to the BBB, at which point the BBB has lost its selectivity for drug passage. The carrier system combined with nanotechnology is the most promising treatment strategy for delivering drugs to the brain through the BBB. The current common delivery systems are shown in (Table 1) [9].

Table 1: Several commonly used Nano carrier systems

Nanocarrier Systems	Structure	Effect
Liposomes	Small vesicles composed of single or multi-layered bilayer lipids surrounding a central aqueous chamber	Targeted delivery therapy; prolonged circulation time in the body; sustained release
Micellar	Hydrophobic core and hydrophilic polymer shell	The core is incorporated with a lipophilic compound; the shell is used to stabilize the micelles and hide the drug
Nanogel	Composed of ionic and nonionic polymer chains	High load capacity and stability; Respond to ionic strength, temperature, pH, etc.; Reduce drug absorption in liver and spleen
Dendritic macromolecule	Polymer formed by crosslinking of repeating monomer units	Internal nanostructures can embed several therapeutic agents; external groups can be combined with ligand

Cholinergic anti-inflammatory effects play an important role in preventing the development of learning and memory disorders in AD patients, so acetyl cholinesterase (AChE) inhibitors can be used for symptomatic treatment of AD. As an inhibitor of AchE and butyrylcholinesterase, rivastigmine was approved by the FDA in 2000 for the treatment of AD. Studies have shown that coating the drug in nanoparticles enhances the targeted delivery of rivastigmine and reduces the side effects of free drug administration. Curcumin can enhance mitochondrial function and may be suitable for preventing AD. However, the bioavailability of curcumin is low. Some studies have suggested that the bioavailability of curcumin micelles is higher than that of naturalcurcumin, and the encapsulation of nanoparticles can increase the solubility of curcumin, prolong the circulation time in the body, and improve the Targeted release within brain. There is also evidence that metals have the effect of damaging neurons. The level of metal ions can be reduced by the use of chelating agents that target the interaction between Aβ and metal ions in the brain of AD patients.

4. Diagnosing AD: Nanotechnology-Based Developments:

AD pathogenesis is primarily typified as the gradual loss of neurons and synapses, thus causing gross atrophy in multiple regions of the affected brain. At present, the reliable early diagnosis of AD is very tough and is often mistaken with other age/stress-related conditions. All the available clinical methods of AD diagnosis including neuropsychological testing and brain imaging can provide a maximum of 85% accuracy, and that too at a much later stage of the disease. The accurate diagnosis can only be obtained postmortem by examining the brain issue in an autopsy. Early detection of the disease remains important for the reason that it can determine the treatment efficacy and help in proper evaluation of experimental treatments. The clinical symptoms (memory/cognition decline) of AD appear usually much after the beginning of deterioration of neural tissues, thus proclaiming the need of much more sensitive and reliable approaches for an early detection of neurodegeneration. Being neurotoxic and hypothesized as causative agent of AD related memory loss, ADDLs have been implicated in AD pathogenesis. A significant difference in CSF concentrations of ADDLs in normal and AD patients proclaims them as a potentially reliable marker. However, the weak signal due to low concentration of these biomarkers is not detected reliably by ELSIA, but can be detected by a newly developed ultrasensitive method called bio-barcode assay. The barcode technique utilizes magnetic iron oxide core micro particles and gold NPs (attached to a large number of “barcode” DNA oligonucleotide strands) suspended in solution and conjugated with ADDL specific antibodies. The authors used the term “barcode” DNA because of the unique label specific to the target protein (ADDL in this case). In procedures similar to the traditional ELISA, the particle-ADDL-particle sandwich is removed magnetically from the solution, the barcode DNA is released from the sandwich with elevated temperature and low-salt conditions and then read using standard DNA detection methods such as gel electrophoresis, fluorescent probes in real time PCR, electrochemistry, scanometric detection, etc. The high sensitivity enabled measurement of ADDL levels of about 200 AM (autopolar, 200 x 10-18 moles/L) in CSF of healthy people, whereas in AD patients, the levels were markedly higher, about 1.7 FM (femtomolar, 1.7 x 10-15 moles/L) [4]. Using this novel assay, approx. 10 times higher ADDL concentration was observed in the AD-CSF samples as compared to healthy-CSF samples [4]. The fact that CSF samples are not easily available is encouraging the researchers to investigate the possibility of adapting this method for blood samples, which would greatly simplify the effective usage of this promising diagnostic tool. The optical property named localized surface plasmon resonance (LSPR) possessed by silver and gold NPs is now being utilized in diagnostic approach targeting the ADDL biomarkers. The systematic analysis of an assay utilizing triangular silver NPs prepared by Nano spheres lithography employing UV-VIS spectroscopy exhibited noticeable shifts in the maximum excitation wavelength via changes in refractive index on the addition of even Nano molar concentrations of ADDLs; with remarkably varying responses to CSF and brain extracts from healthy and AD individuals. There are many other studies utilizing nanomaterials for novel imaging methods, thus generating new in vivo ways to study and detect new pathological markers and help evaluate the clinical efficacy of new drugs in clearing the toxic plaques.

5. Potential Nano-Enabled Routes To Therapy For AD

At present, there is no definitive cure available to reverse the AD induced neurodegeneration. The medications available in the market can at the most provide some degree of symptomatic relief, which can slightly improve the brain cells’ communication but cannot halt the process of degeneration. However, continuous research efforts are being made to identify and develop the “disease modifying” strategies which can catch the root cause of AD and halt neurodegeneration. The most obvious hurdle in the effective transfer of therapeutic agents from blood to brain is the blood brain barrier (BBB), which is a two way selectivefilter between neural tissues and blood capillaries. BBB performs the crucial role as protective barrier for “foreign substances” like disease causing agents and toxins circulating in bloodstream and also for large active molecules which may be of good therapeutic value. Hence, a new strategy to overcome this natural physiological barrier is quite desirable. In this attempt, a number of new options for engineering Nano-carriers laced with desirable surface properties are being explored to facilitate effective, safe and targeted delivery of active molecules across BBB and their sustained release in the brain. These Nano systems could act as “Trojan horses” by masking the physicochemical properties of the encapsulated/embedded therapeutic agents, thus promoting the transport of such molecules across the BBB. Additionally, these Nano carriers can enhance the bioavailability of encapsulated molecules by shielding them against enzymatic degradation and hence enhancing their half-life. These modifications would naturally enhance the efficacy of the Nano carriers, and with drastic reduction in the quantity of therapeutic agent required, any probable undesired side effect would also be minimized.

6. Nano-Mediated Drug Delivery

Rivastigmine is one of the few drugs which are used for the alleviation of symptoms related to mild to moderate

dementia, making it a target candidate for NP-mediated drug delivery in brain. A 3.82 fold enhanced uptake was observed when rivastigmine bound to Poly(n-butyl cyanoacrylate) (PnBCA) coated with chemical polysorbate 80 was injected intravenously. This in turn could be attributed to the binding of blood lipoproteins to the surface of NPs. In another pharmacodynamics study on amnesic mice, rivastigmine bound to PnBCA-NPs and poly(lactide-coglycolide) (PLGA)-NPs induced faster memory reversal in AD patients, thus indicating an enhanced delivery in mouse brain. Based on the use of single wall carbon nanotubes (SWCNTs) as carrier, a new approach has been proposed to deliver acetylcholine (ACh) to brain to alleviate the disrupted cholinergic neurotransmission in AD patients. Indeed, many other anti-ACHE or AChEI have been encapsulated in NPs to improve its brain delivery. Earlier studies have raised concerns regarding the toxicity of SWCNTs towards the mitochondria in cells, but this study demonstrated that a safer delivery of Ach to target organelles is possible by carefully monitoring the dosage. Moreover, the functionalization of carbon nanotubes with biomolecules like branched Polyethylene glycol (PEG) chains provides an enhanced suitability and biocompatibility as a drug delivery vehicle.

7. Direct Interaction of Nanostructures with Aβ Peptide

The application of Nano constructs in AD is not only limited to carrying active agents across the BBB and delivering them to the brain, but many studies also aim at engineering brain specific NPs with Aβ peptides. Such nanomaterials can interact directly with the Aβ peptides to either break the already existing amyloid aggregates or suppress the self-assembly into febrile plaques or toxic oligomers, thus eliminating their deleterious effects. Aβ self-assembly has reported to be inhibited by PEGylated phospholipid Nano micelles by inducing a conformational change which makes the peptide reluctant to aggregation; a diminished neurotoxicity was observed in cytotoxic studies on human neuroblastoma cells [50]. The complexes of polyampholyte and fluorinated dodecanoic acid (fluorinated NPs) were also found to inhibit the formation of Aβ fibrils [86, 87]. Nano constructs formed by salvation and suffocation of polystyrene were also reported to exhibit similar inhibitory effect. The studies utilizing fairly low concentrations of quantum dot Nano crystals capped with appropriate organic compounds like dihydrolipoeic acid and Nacetyl-L-cysteine have also been reported to be quite effective in inhibiting the formation of amyloid fibrils.

8. Towards Regenerative Therapy

The limited regeneration ability of central nervous system makes the gradual loss of brain cells (caused by toxic amyloid species) irreversible, thus limiting the potential of medical therapies targeting amyloid aggregation. However, some novel approaches based on stem cells and tissue engineering offers some hope for the reversal of neural loss. A plethora of nanotechnology based applications have emerged, which include the development of Nano-scaffolds mimicking the extracellular matrix to promote and support the growth and controlled differentiation of neural progenitor cells in vivo to repair the damages. One such recent development is stem cell therapy, which utilizes few stem cells harvested from the patients and grown in laboratory to generate a good volume to initiate the process of tissue regeneration by re-injection inside the patients' body. However, the tendency of stem cells (in culturing process on standard plastic surface) to spontaneously differentiate into other cells and thus lose their regenerative ability, has been a major drawback of this method. A recent study on the use of a novel surface patterned with an ordered arrangement of Nano scale pits (prepared by injection molding + electron beam lithography) was found to be quite effective in permitting the stem cells to proliferate while maintaining their original properties over long period for therapeutic usage [96]. Such nano-patterned surfaces may provide the basis for a large scale stem cell culture "factories", which may enable therapy for various NDDs.

9. Conclusion:

Nano technological approaches are being used for designing and engineering novel Nano-scale devices and materials with controllable functional characteristics. It is also noteworthy that many NPs having the theranostics characteristics have been effectively used in AD diagnosis and drug delivery/therapy. The Nano constructs can provide new ways to efficiently carry and deliver drugs/neuroprotective/ therapeutic molecules to the brain, and can also be tailored to counter and eliminate the AD pathogenic factors. The nanomaterials are now being used as the basis for approaching the challenges of early and sensitive detection of AD. More recently, the use of non-invasive diagnostic imaging has been assessed. For example, the use of probes targeting amyloid fibrils by positron emission tomography might represent a powerful tool to assess early-stage of AD onset. With many promising results mentioned above now being obtained by in vitro studies, it has become important to confirm the efficacy of these nanotechnology based approaches in representative in vivo AD models.

References

[1] Mirza Z, Ali A, Ashraf GM, Kamal MA, Abuzenadah AM, Choudhary AG, et al. Proteomics approaches to understand linkage between Alzheimer's disease and type 2 diabetes mellitus. CNS NeurolDisord Drug Targets 13(2): 213-25 (2014).

[2] Ashraf GM, Greig NH, Khan TA, Hassan I, Tabrez S, Shakil S, et al. Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. CNS NeurolDisord Drug Targets 13(7): 1280-93 (2014).

[3] Fazili NA, Naeem A, Md Ashraf G, Gan SH, Kamal MA. Therapeutic Interventions for the Suppression of Alzheimer's disease: Quest for a Remedy. Curr Drug Metab (2014).

[4] Georganopoulou DG, Chang L, Nam JM, Thaxton CS, Mufson EJ, Klein WL, et al. Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proc Nat AcadSci U S A 102(7): 2273-6 (2005).

[5] Ansari SA, Satar R, Perveen A, Ashraf GM. Current opinion in Alzheimer's disease therapy by nanotechnology-based approaches. CurrOpin Psychiatry 1 : (2016).

[6] Aliev G, Daza J, Herrera AS, Carmen Arias Esparza MD, Morales L, Echeverria V, et al. Nanoparticles as Alternative Strategies for Drug Delivery to the Alzheimer Brain: Electron Microscopy Ultrastructural Analysis. CNS NeurolDisord Drug Targets 14(9): 1235-42 (2015).

[7] Ali A, Ahmed SI, Mirza Z, Hua GS, Amjad KM, Abuzenadah A, et al. Application of Proteomic Tools in Modern Nanotechnological Approaches Towards Effective Management of Neurodegenerative Disorders. Curr Drug Metab 16(5): 376-88 (2015).

[8] Brambilla D, Le Droumaguet B, Nicolas J, Hashemi SH, Wu LP, Moghimi SM, et al. Nanotechnologies for Alzheimer's disease: diagnosis, therapy, and safety issues. Nanomedicine 7(5): 521-40 (2011).

[9] Nikalje AP. Nanotechnology and its Applications in Medicine. Med Chem (2015).

[10] Parveen S, Misra R, Sahoo SK. Nanoparticles: A boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine: NanotechnolBiol Med 8(2): 147-66 (2012).

[11] Leong KW, Mao HQ, Truong-Le VL, Roy K, Walsh SM, August JT. DNA-polycationnanospheres as non-viral gene delivery vehicles. J Control Release 53(1-3): 183-93 (1998).

[12] Azarmi S, Huang Y, Chen H, McQuarrie S, Abrams D, Roa W, et al. Optimization of a two-step desolvation method for preparing gelatin nanoparticles and cell uptake studies in 143B osteosarcoma cancer cells. J Pharm PharmSci 9(1): 124-32 (2006).

