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Approaches on Nano-based drug delivery for Alzheimer's Disease: Methods for Diagnosis, Pharmacology and Safety matter

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A B S T R A C T

The large number of people diagnosed with a neurodegenerative disorder i.e. Alzheimer's disease (ADs), a increasing rapidly. AD is the most common form of dementia worldwide, affecting more than more than 35 million people. It is characterized by memory dysfunction, spatial and temporal orientation, and loss of lexical access. Although clinical development of drugs for the symptomatic and disease modifying treatment of AD. A large number of drugs with different mode of targets and their mechanism were investigated. The targeted nano based drug (eg. Nanoparticles: NPs) delivery to the central nervous system (CNS), for diagnosis and treatment of AD, due to limitations posed by the restrictive blood brain barrier (BBB). This review literature provides a concise approach into the current and future applications of nano based medicine for the treatment of ADs, besides reviewing and discussing the literature on the drug delivery, their diagnosis and treatment for safety point of view in Alzheimer's.

Introduction

The application of nano based medicine in neurological research areas are expected to have a major impact leading to the exploration of newer therapeutic modalities. Nanotechnological devices with the smallest functional organization on the nano-meter scale (1-100 nm) that are the able to interact with biological systems at molecular level, they may stimulate and interact with target tissues and cells. Nanotechnology offers ways to manipulate complex biological systems with greater selectivity and specificity than the conventional pharmacological approaches such as the blood brain barrier (BBB) in Alzheimer's disease (AD).

Alzheimer's disease is a neurodegerative disorder (ND) are specific category of brain disease, common form of dementia among people elderly ages more than 65 years and encompasses a variety of conditions that

familial or sporadic characterized by the persistent loss of neuronal activity. Due to the aging of the human population AD affects 24.3 million people worldwide and increases socio-economic, financial and medical burden. (Ferri *et al.,* 2005). The National Institutes of Health (NIH) estimates that 4.5 million Americans are affected by AD. In this continuation, the estimated annual cost of healthcare is over $ 100 billion every year and in the coming time, estimate that by 2050, 13.2 million over age Americans are expected to have AD.

AD is mainly characterized by three major pathophysiological characteristics; The dysregulation of the cholinergic systems, (Teipel *et al.,* 2011; Parent *et al.,* 2013). the senile plaque accumulation made of β-amyloid peptide aggregates and the apparition of neurofibrillary tangles resulting from the hyperphosphorylation of Tau protein (Augustinack *et al.,* 2002). β-Amyloid peptides are derived from amyloid precursors that can undergo several cleavages by β-, γ- and α-secretase. In AD, β-amyloid peptides accumulate and lead to toxic fibrillary aggregation also known as senile plaques (Sinha and Lieberburg, 1999). Those aggregates severely impair the viability of neurons by disrupting brain parts composed of unmyelinated neurons, dendrites and glial cells also known as neuropil (Murphy and LeVine, 2010). On the other hand internal cell dysregulations observed in AD patients cause a hyperphosphorylation of Tau, which severely impairs the axon integrity and the neurotransmitter transport (Sun *et al.,* 2003). Moreover, there is increasing evidence showing that those three hallmarks are closely interconnected, which tend to indicate that upcoming therapeutic measures should act simultaneously on all of them (Busciglio *et al.,* 1995; Ferreira *et al.,* 1997; Zheng *et al.,* 2002).

The current treatments for AD are mostly acetylcholine esterase inhibitors (Rivastigmine, Dopenezil, Galantamine) or NMDAR inhibitor (Memantine). Those inhibitors show only transient effects without stopping the progression of the disease and are mainly administered orally or transdermally (Hansen *et al.,* 2008; Molino *et al.,* 2013).

Drug delivery to the brain still remains a highly challenging for the treatment of AD. The development of new practical treatment modalities for the treatment of AD is currently a highly active research area among the scientific community.

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 NPs for controlled drug delivery to various CNS conditions (Silva, 2010).

Some strategies have been directed towards encapsulation of several types of biologically active molecules into NPs for their (targeted) delivery to the brain. Others some have focused on the use of nanovectors to overcome the toxicity of amyloid clusters by promoting their clearance or by altering their aggregation kinetics in the brain and in the blood, peripheral treatment with molecules that have high affinity for Aβ can reduce the level of Aβ in the brain through the sink effect. Engineered NPs exhibiting high affinity for Aβ, where sequestered plasma Aβ will be routed to hepatic and splenic macrophages for destruction. This approach could potentially reduce or prevent brain amyloidosis. It should also be emphasized that NPs can be introduced into the body through different routes of administration.

Notably, some efforts suggest that orally delivered NPs can improve bioavailability of certain drugs used in AD.

Current Pharmacotherapy and Targeted NPS for the Treatment of AD

Drug development of new agents for the symptomatic and disease-modifying treatment of AD has resulted in both promise and disappointment. Since, a large number of drugs with differing targets and mechanisms of action are available for the treatment of AD. For instance, Phase III trials of nonsteroidal anti-inflammatory drugs (NSAIDs), phenserine, statins, tarenflurbil, tramiprosate, Ginkgo biloba and xaliproden have been completed. However, none of them has demonstrated a significant efficacy. Different randomized clinical trials in patients with MCI (Thal *et al.,* 2005), at high risk for AD have found that NSAIDs were not effective treatments (Rogers *et al.,* 1993; Scharf *et al.,* 1999; Aisen *et al.,* 2003). Phenserine is a selective choline esterase inhibitor (ChEI) that was found to inhibit the formation of Aβ in animal studies (Thatte and Axonyx, 2006). It is well established that high cholesterol levels are associated with an increased risk of AD (Kivipelto and Solomon, 2006). Moreover, in animal models, hypercholesterolemia promotes Aβ production and deposition (Sparks, 2008). Tarenflurbil is a γ-secretase inhibitor, results in the formation a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1684 patients with mild AD have shown no significant effects after 18 months of treatment (Green *et al.,* 2009). Tramiprosate is a modified amino acid taurine that functions as a glycosaminoglycan mimetic which can bind soluble Aβ peptides, and thus act as an antifibrillar agent that inhibits the formation of amyloid plaques (Greenberg *et al.,* 2006). Due to the insufficiency in conventional delivery mechanisms intensive research done over the last few years has focused on the development of new strategies to more effectively deliver drug molecules across the BBB (Gabathuler, 2010). To overcome the limited access of drugs to the brain different strategies have been investigated that achieve BBB penetration including the osmotic BBB opening (Rapoport, 1996), biologically active agents (e.g., histamine, serotonin, substance P, metalloproteinases, etc.) (Abbott and Revest, 1991), liposomes and NPs. Among the various nanocarriers used polymeric NPs are promising

Physiochemical Properties of Brain Targeted Nanoparticles

The size, surface and charge of the prepared NPs are important characteristics properties (Davis *et al.,* 1997). NPs with a size greater than 100 nm are easily captured by Küpffer cells or other phagocytic cell populations which thus restrict their biodistribution. Hydrophilic nanoparticles with particle size less than 100 nm have been reported to avoid opsonization (Allemann *et al.,* 1993) with a consequent prolonged circulation times to facilitate enhanced targeting of the drug to specific sites (Banerjee *et al.,* 2002). Sonavane *et al* (2008) have evaluated the effect of increasing particle size on the biological distribution of NPs following i.v. administration (1 g/kg) of the NPs suspension prepared in sodium alginate solution (0.5%w/v) in mice. By varying the citrate ion concentration, gold NPs with 15 nm, 50 nm, 100 nm and 200 nm size were synthesized. Higher amount of NPs with 15 nm particle size was observed in all tissues including the blood, liver, lung, spleen, kidney, brain, heart and stomach. As compared to particles with size 15 nm and 50 nm, which could pass the BBB easily, NPs with size 200 nm were present at the

minimum level in different organs including the blood, brain, stomach and pancreas (Sonavane *et al.,* 2008).

Mechanism of Brain and Cellular Uptake of NPs

Drug delivery to the brain for the treatment of NDs related to aging still remains a challenging task because traditional drug delivery systems have limited application due to the restrictions posed by the BBB with their low bioavailability. Over the last few decades, nanotechnology has been explored extensively as an area of potential research for the development of newer therapeutic modalities for the treatment of neurological disorders (table-2).

A concentration gradient due to an increased retention of NPs in the brain blood capillaries combined with an adsorption to capillary walls that would increase the transport of NPs across the endothelial cell layer for drug delivery; solubilization of endothelial cell membrane lipids leading to membrane fluidization; opening of tight junctions between endothelial cells thus leading to enhanced permeation of the drug in the nanoparticulate; endocytosis of the NP by endothelial cells followed by drug release within these cells of the brain; transcytosis of the NPs with attached drug across the endothelial cell layer; inhibition of the P-glycoprotein efflux system by coating the NPs with polysorbate 80 are some of the mechanisms proposed for the penetration of the NPs to the brain (Lockman *et al.,* 2003).

Although, the exact mechanism(s) of transport are not known, the absence of toxicity at the BBB both in vitro and in situ suggests that NPs may be transported through the barrier by endocytosis or transcytosis or by passive diffusion in the absence of barrier opening. They may be designed to mimic low density lipoproteins and interact with their receptors, thereby triggering uptake by the endothelial cells of the brain (Faraji and Wipf, 2009).

Different Approaches Used In The Treatment Of Alzheimer' Disease

(Imaging - based nanotechnologies for Alzheimer's diagnosis).

Thioflavin T

Thioflavin T (ThT) is a molecule capable of recognizing β- sheet structures related to Aβ aggregates both in vitro and in vivo. A recent attempt described the encapsulation of ThT into PS-b-PnBCA NPs, its release into the brain after intracerebral injection, and its interaction with Aβ species, thereby showing clear visualization of amyloid aggregates (Siegemund et al., 2006).

Quantum dots – AB Complex

Fluorescent semiconductor nanocrystals (quantum dots, QDs) have evolved over the past decade as highly useful fluorescent probes for biological labeling and diagnostics. QD features include long-term photostability and physicochemical stability, nanoscale size, and size-dependent emission wavelength (Dubertret *et al.,* 2002). Tokuraku *et al* designed poly(ethylene glycol) (PEG)-QDcrosslinked Aβ peptide as a tool to monitor and to quantitatively describe the formation of fibrils and oligomers in solution and in a cellular system. This approach allowed the study of the Aβ peptide aggregation kinetics but could also be used to follow the in vivo peptide aggregation (Tokuraku *et al.,* 2009). The authors have considered the functionalization of these nanoassemblies with appropriate ligands such as transferring for BBB-crossing (Xu et al. 2008).

Gold NPs

Gold NPs (Au NPs) also represent an interesting tool for studying Aβ peptide aggregation kinetics. Choi et al described the synthesis of heterodimeric NPs consisting of a cobalt(II) magnetic core and a platinum shell directly fused onto Au NPs and stabilized by lipoic acid–polyethylene glycol coating (Choi *et al.*, 2008).

The results with terminal carboxyl groups of the PEG chains enabled covalent binding with lysine residues of neutravidin at the surface of the NPs. The Co @ Pt-Au nano assemblies presented a high magnetization value [63 emu g-1 (Co) at 3 T], making them appropriate for T2-weighted spin echo MRI measurements and also clearly showed that these NPs can be used in MRI to monitor key structural stages of Aβ self-assembly. (Choi *et al.*, 2008).

However, several important parameters should be considered before a viable application is foreseen. Indeed, the intrinsic in vitro, in vivo cytotoxicity of the employed materials used to prepare the NPs should be thoroughly evaluated before further investigations. The feasibility of these approaches will further depend on developments that do not depend on invasive procedures.

Iron oxide NPs

Magnetic iron oxide NPs have gained much interest because of their large surface area, magnetic properties, and limited toxicity. They have already been approved by the U.S. Food and Drug Administration (FDA) as MRI contrast agents in liver imaging (de Vries *et al.*, 2005).

The synthesis of monocrystalline iron oxide NPs (MIONs) covalently tethered to the N terminus of Aβ1-40 peptide through amide coupling and their development for the concomitant targeting and imaging of senile plaques has been reported (Wadghiri *et al.*, 2003). These MRI agents, by means of longitudinal MRI, were able to recognize high-affinity Aβ plaques in the brains of amyloid precursor protein (APP) and APP/PS1 transgenic mice when coinjected with mannitol (used to transiently open the BBB). Although this study is very encouraging and demonstrates the proof of concept, manipulation of the BBB remains questionable for human testing.

Metal Chelators as Therapeutic Agents in Alzheimer's

Iron (940 μM), copper (390 μM) and zinc (1055μM) have been reported to be elevated by several-folds in AD brain as compared to normal age-matched samples [copper (70 μM), zinc (350 μM) and iron (340 μM)] (Adlard and Bush, 2006; Lovell *et al.*, 1998; Bush,2003). Zinc, copper, and iron have been shown in multiple studies to be markedly enriched in Aβ plaques in transgenic mice (Castellani *et al.*, 1999; Dong *et al.*, 2003; Lee *et al.*, 1999).

Metal chelators bind strongly to two or more metal ions and form a cyclic ring, which converts the metal ions into an inert form and depletes the total pool of bioavailable transition metals. The first such agent to enter clinical investigations for the treatment of AD is Desferrioxamine (DFO), an iron chelator with high binding affinities for zinc, copper and aluminum (Kebre, 1964). However, DFO is a large hydrophilic molecule, which is not orally bioavailable and does not normally penetrate the BBB. Cropper McLachlan *et al* (1991) have studied the beneficial effect seen with the DFO treatment in patients with AD was due to the drug's interaction or chelation of metals.

Beneficial Effects of Curcumin and Catechins on the Amyloid Cascade

Polyphenols are among the new treatment options because numerous epidemiological studies have suggested an association between the consumption of polyphenolic phytochemical-rich foods or beverages and the prevention of certain neurological diseases, including AD (Singh *et al.*, 2008). These compounds not only exhibit potent anti-oxidative and anti-inflammatory effects but can also target different pathways implicated in the pathogenesis of AD such as the attenuation of the production of the Aβ, are given in the Table 1).

Green tea is rich in flavonoids (a class of polyphenol) with 30% of dry weight of a leaf (Graham,1992) and also it have shown beneficial effects in animal models of stroke/cerebral ischemia, AD and PD. Neuroprotection in ischemia by EGCG may be mediated through reducing iNOS expression, peroxynitrite formation, preservation ofmitochondrial complex activity and integrity, or ferric iron chelation (Suzuki *et al.*, 2004; Mandel *et al.*, 2005; Sutherland *et al.*, 2005). There are several in vitro studies that suggest green tea extract could protect neurons from the Aβ-induced damages (Bastianetto *et al.*, 2006; Choi *et al.*, 2001; Levites, 2003)

Table.1 Description of some Properties and Targets of Catechins and Curcumin for their Potential Beneficial Effects against AD

Properties of targets	Selected polyphenols	References
Effect on the Aβ pathway		
➢ Reduction in β secretase activity	Catechins	Jeon *et al.*, 2003
➢ Increase α secretase activity	Catechins	Rezai Zadeh *et al.*, 2005
➢ Reduction of BACE-1 mRNA	Curcumin	Liu *et al.*, 2010
➢ Reduction of the formation of Aβ Fibrils	Curcumin	Ono *et al.*, 2004
➢ Reduction of Aβ deposits and senile plaques	Curcumin	Garcia-Allozaetal,2007 in Tg2576 mice models
Cytoprotection		
➢ Reduction in Aβ- induced caspase activity in hippocampal neuronal cells	Catechins	Choi *et al.*, 2001
➢ Protect cells from Aβ- induced toxicity	Catechins	Levites *et al.*,2003,
➢ Protect cells from Aβ- induced toxicity	Curcumin	Kim *et al.*, 2001
Effect on the inflammatory pathways		
➢ Reduction of Aβ- induced expression of cytokines and chemokines	Curcumin	Giri *et al.*, 2004
➢ Reduction in Aβ- induced cytokines in human astrocytoma U373MG cells	Catechins	Kim *et al.*, 2007
Oxidative stress markers		
➢ Reduction in oxidized proteins in TG2576 mice model	Curcumin	Lim *et al.*, 2001
➢ Reduction in Aβ- induced levels of lipid oxidation in hippocampal newuronal cells	Catechins	Choi *et al.*, 2001

Table.2 Drug Loaded –NPs Tested for the Treatment of AD

S.No.	Drug	Types of nanoparticle	Model	Route of administration	Applications	Particle size (nm)	Reference
1.	ChEIs —Tacrine	a) Polysorbate-80 coated poly (n-butylcyanoacrylate) Chitosan nanoparticles) b) Chitosan nanoparticles	Rats	I.v. injection	Enhanced concentration of the drug in the brain A new drug delivery system for increasing bioavailability of the drug in the brain	35.5± 4.64 41±7	Wilson *et al.*, 2008 Wilson *et al.*, 2010
2.	Amyloid β targeted drugs -Thioflavin T and S	Core–shell nanoparticles composed of a polystyrene core and a degradable PBCA [poly (butyl-2-cyanoacrylate)] shell	APP/PS 1 mice	Intracerebroventri-cular injections	Tools to trace and clear Aβ in the brain	-	Siegemund *et al.*, 2006
3	Poly-phenol EGCG	Nanolipidic particles	Rats	Oral	Prevent brain beta amyloid plaque formation	30–80	Smith *et al.*, 2010
4.	Amyloid-beta	Chitosan nanoparticles	Mice	Systemic administration	Nano-vaccine delivery system could be used as a potential carrier for Abeta	15.23±10.97	Songjiang and Lixiang, 2009
5.	Gold nano-particles	-	-	-	The prepared nanoparticles dissolve toxic protein deposits of Aβ1–42 by the combined use of weak microwave fields and gold nanoparticles (AuNP) without any bulk heating	-	Bastus *et al.*, 2007
6.	Proteins and pepides-VIP	Poly (ethylene glycol)-poly (lactic acid) nanoparticles modified with wheat germ agglutinin	Mice	Intranasal administration	Improvement in brain delivery of estradiol using wheat germ agglutinin nanoparticles	90-120	Gao et al., 2007

Curcumin is a low molecular weight molecule with highly potential for antioxidant and anti-inflammatory activities. Its yellow curry spice is part and parcel of Indian vegetables. When fed to aged Tg2576 mice, curcumin reduced Aβ levels and

plaques (Yang *et al.,* 2005). However, curcumin also blocked Aβ aggregation and fibril formation in vitro model (IC50=0.8 μM) (Yang *et al.,* 2005) and this property could be implicated in the reduction of amyloid plaques burden observed in vivo after curcumin treatment of Tg2576 mice models. This antioxidant is also a good inhibitor of expression of inflammatory cytokines and cyclo-oxygenase-2 likely by the inhibition of JNK/AP-1 and NF-kB mediated gene transcription (Aggarwal *et al.,* 2003). However, it has restrictive pharmaceutical role because of its extremely low aqueous solubility, rapid systemic elimination, inadequate tissue absorption, poor absorption from the gut and degradation at alkaline pH, which severely curtails its bioavailability (Anand *et al.,* 2007; Wahlstrom and Blennow, 1978).

Some Other Types of Nano Effective Drug Delivery System in the Treatment of Alzheimer's Disease

Polymeric Nanogels

Nanogels are network of crosslinked polymers that often combine ionic and non-ionic polymers chains that are prepared using an emulsification solvent evaporation approach (Bronich *et al.,* 2006; Bontha *et al.,* 2006). Nanogels swell in water and are able to incorporate molecules such as oligonucleotids, DNA, proteins and low molecular-mass drug. The drug-loading capacity is up to 40-60% have encapsulated within oligonucleotides within a cross linked nanogel for delivery across the BBB (Vinogradov *et al.,* 2005). Nanogels are promising carriers for CNS drug delivery.

Polymeric Nanoparticles

Polymeric noparticles range from 10 nm to 1000 nm (Muller and Keck, 2004), nanoparticles possess high drug loading capacities if appropriately designed and are able to protect the incorporated drug-load against degradation and efficient targeting to the brain. Polymeric nanoparticles have been used for the CNS delivery of several drugs such as doxorubicin (Alyaudtin *et al.,* 2001; Steiniger *et al.,* 2004).

Polymeric Nano-micelles

Polymeric nano-micelles have core-shell structure with a hydrophilic core and a shell of hydrophilic polymer blocks. The core can incorporate up to 20-30% (w/w) of hydrophobic drugs,

Thus preventing premature drug release and degradation. Polymeric nano-micelles are versatile and have been shown to efficiently deliver DNA molecules in *vitro* and *vivo,* moreover, no successful study on their delivery to the CNS has been reported (Oishi *et al.,* 2007; Nguyen *et al.,* 2000).

Conclusion

Nanotechnology has a high potentially evolutionary impact on the basic understanding and pharmaco therapeutic approaches of neuroscience. It may contribute significantly towards the development of nano based effective drug system for the treatment of AD. Nanotechnologies have emerged that can manipulate Aβ aggregation both in the brain and in the peripheral circulation, thus aiding experimental AD therapy. However, three important open questions remain to be answered before engaging in further research toward clinical investigations: (1) the efficiency of symptom alleviation by these nanoparticulate systems must be validated in representative AD in case of vivo models, (2) FDA-approved macromolecules for nanoconstructs must be

employed, and (3) non invasive administrations of NPs must be considered for repeated and prolonged therapeutic purposes. These requirements are also relevant when considering the development of a strategy based on the development of NPs for physical interactions with Aβ peptide. In this case the majority of the above-discussed studies were performed in buffer environments, a considerable simplification of physiological conditions. Recent achievements also described the synthesis of drug and the use of imaging agents and drugs based on nanoparticulate systems. Therefore, in order for nanotechnology applications directed towards AD to be fully exploited, it would be important for neurosurgeons, neurologists, and neuroscientists to participate and contribute to the scientific process along with pharmaceutical scientists and medical engineers. True to the highly interdisciplinary nature of this area of research, it is also important that nano technological advancements occur in conjunction with basic and clinical advancements in the field of neuroscience.

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