EDITORIAL

Nanomedicine and Nanotechnology: A New Advanced Therapeutic Path for the Treatment, Diagnosis and Prevention of Alzheimer's Disease

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ABSTRACT

Nanomedicine and nanotechnology offer many new and advanced therapeutic options in imaging, diagnosis, monitoring of disease, treatment and prevention for Alzheimer's Disease (AD). Alzheimer's disease is a heterogeneous disabling disease which has no known treatment for cure. In 1959, Nobel prize winner R.P. Feynman suggested the idea of studying things at the atomic level and nanoscience was evolved[1-4]. Nanomedicine and nanotechnology are the science behind the ability to employ nanotechnology for the manipulation of atomic, molecular and macromolecular scales; which makes it a novel tool to treat, diagnose and prevent AD[5-8].

Because nanotechnology works in many areas of medicine, The National Institute of Health in the USA coined the word "nanoscience". The future hope of nanomedicine and nanotechnology is early diagnosis of AD and other diseases. For AD patients the earliest possible diagnosis and the therapeutic pathway described in this paper, will markedly change the treatment and prevention of AD.

INTRODUCTION

Alzheimer's disease is a heterogeneous disabling chronic disease which has no known treatment for cure. In 1959, Nobel prize winner R.P. Feynman suggested the idea of studying things at the atomic level, and nanoscience evolved[1-4]. Nanomedicine and nanotechnology offer many new and advanced therapeutic options in imaging, diagnosis, monitoring of disease, treatment and prevention for Alzheimer's Disease (AD). Nanomedicine and nanotechnology are the science behind the ability to employ nanotechnology for the manipulation of atomic, molecular and macromolecular scales; which makes it a novel tool to treat, diagnose and prevent AD[5-8].

NANOTECHNOLOGY FOR DIAGNOSIS

At present diagnosis in AD is primarily based on neuropharmacological testing. However, clinical diagnosis in AD needs neuroimaging monitoring, accepted biomarkers and total hyperphosphorylated proteins in cerebrospinal fluid (CSF). Accumulation of oligomers and plaques need to be imaged. However, for the comfort of patients, non-invasive imaging is of great help. MRI use is becoming essential. Synthetic nanoparticles of diverse surface character started to be successfully used in biomedical science[5-16]. Use of MRI contrast medium is very useful in AD[7,10,11,14]. Nanoparticles, particularly Fermoxytol[10] is endorsed by the FDA to be used for this purpose as a first iron oxide conjugate. Recent research has demonstrated that nanoparticles may be variable in-vivo in diagnosis of AD. This also facilitates in the early detection of amyloid plaques with the use of MRI. Thus, MRI can be used for recognizing and detecting amyloid plaques utilizing iron oxide nanoparticles[11].

Aβ fibrils can also be selectively removed. Gold nanoparticles have been used as a contrasting agent to study structural stages[6,7,12,14] in Aβ assembly[7,12]. Nanoparticles remove selectively Aβ fibrils with the help of scanning tunneling microscopy[7,13]. Blood brain barrier (BBB) is an important factor for limiting the effectiveness in AD. Nanotechnology and nanoparticles provide an alternative delivery path for the therapeutic use and treatment for AD[5,6,14-17].

Nanotechnological solutions like Liposomes, dendrimers, carbon dots, polymeric nanoparticles, micelles and magnetic nanoparticles all provide innovative methods for the treatment of AD[5,6,11,14,16,17] drug delivery. Nanoparticle system containing chelating agents have exceptional capability for penetrating BBB. These methods are not only safe and efficient but also provide nerve tissue exposure of metal nanoparticles; thus, preventing any harmful effects[12].

Examples are polymeric nanoparticles which are capable of reducing Aβ disposition, neuronal loss, and vesicular cerebral process including autogenesis. Nanoliposomes containing curcumin inhibit formation of fibrous or oligomer Aβ in-vitro, and also includes neurogenesis, and removes cognitive deficit in AD[5,14,16,18,19].

Nanoparticles are becoming an important route in research for drug delivery and in diagnosis and treatment of AD and various diseases. Use of nanoparticles enhances drug stability, has positive effects on pharmacokinetics and pharmacodynamics, is gaining ground as treatment for reducing side effects, and is increasing viability in AD and other Central Nervous System (CNS) diseases.

The use of nanoparticles in AD and various CNS diseases has brought continued modification for meeting their requirements and suitability. The increasing use of liposomes, polymeric, micelles, gold nanoparticles, metal oxide nanoparticles and quantum dots are enlarging

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the therapeutic path in more diseases; particularly in the diagnosis, treatment and prevention in some diseases. Nanoparticles are between one to one hundred millimeters (mm) and their size makes them penetrate the BBB satisfactorily[20-28]. The interesting formulation makes the nanoparticles non-toxic, biodegradable and suitable for target treatments[22-24]. Nanoparticles in general hold and distribute drugs and other neuroprotective molecules to AD patients. Nanoparticles can also be used by IV, nasal and dermal routes[25-31] to reach the target treatment area through BBB in the brain to improve viability pharmacodynamically with much less adverse reactions[29-31] in comparison to oral drugs.

The common mechanisms of nanoparticle utilization are: endocytosis (like receptor endocytosis), phagocytosis and pinocytosis. Receptor mediated endocytosis is usually the preferable method. Quantum dots have been modified, which helps to maintain stable peptide-quantum dots to interact and allow the passing of antibodies to occur[32-34]. Amyloid fibrils have high affinity with nanoparticles; and nanoparticles can be used in the inhibition of Aβ peptide[32-36]. Graphene quantum dots (gold)[35-37] have been studied to act as carriers for drug molecules, particularly due to their small size; making drug delivery to the brain, simple.

In the mitochondria, as a targeted therapy for the correction of mitochondrial dysfunction, nanotechnology provides a new path of delivering the therapeutic agents to mitochondria[37-41]. In comparison to the nanotechnological path, oral therapeutic drugs used for AD are administered in higher doses; because some portion of the drug is lost in the GI tract, as well as for metabolism in the hepatic region. These drugs also need to bind with serum albumin in the bloodstream in order to sustain needed half-life before it reaches BBB. Besides, these drugs also have side-effects which AD patients have to tolerate. Thus, it is clear that nanoparticles help in overcoming the above difficulties, and make it easier to transmit through BBB drug delivery. In AD patients, nanoparticles also provide mitochondrial therapy if required[42]. Though recent research has shown drug delivery can easily and safely cross BBB, their safety issues need more in-detail investigation.

TOXICITY

Nanoparticle use in medicine is increasing markedly in various diseases and in various applications. Therefore, the need to evaluate the toxicity[43,44] of nanomaterials (nanoparticles) is more and more warranted to be researched. Toxicity of nanoparticles depend on physiochemical properties, therefore alterations in any parameters will have impact on toxicity[43,44]. Important toxicity seen in nanoparticles are: 1) biodegradation 2) bioaccumulation 3) genotoxicity 4) cytotoxicity and 5) ecotoxicity. To gain a fundamental understanding of the toxicity of nanomaterials on the environment and humans, there is a need to enhance to research activities in future.

DISCUSSION

Advances in nanotechnology propose effective, safe, diagnostic and therapeutic options for AD with far less adverse reactions. Nanotechnology has a safe and promising system of drug delivery with controlled release of drugs to disease sites. Nanotechnology also provides easy BBB penetration of drugs with enhancement of pharmacokinetic and pharmacodynamic, and reduces adverse reactions. Targeted delivery with increase viability-controlled release of drugs have become easier and therapeutic efficaciousness with nanotechnology. Future advances in nanoparticles will bring more therapeutic advantage and efficacy for medication in general. Prevention aspect can be worked and can be achieved by utilization of epigenesis of AD[2,3]. The applications of nanotechnology in medicine are multiple, easy for example, improving of diseases, improving of drug delivery, improving therapeutic efficacy, correction of defective DNA and genetic disorders, developing technology for neurosurgery and cancer management[1-3].

CONCLUSION

Because nanotechnology works in many areas of medicine, The National Institute of Health in the USA coined the word "nanoscience". The future hope of nanomedicine and nanotechnology is early diagnosis of AD and other diseases. For AD patients the earliest possible diagnosis and the therapeutic pathway described in this paper, will markedly change the treatment and prevention of AD.

REFERENCES

1. Singh, A. N. (2012). The importance of nanoscience, nanotechnology and nanomedicine for genetic research of medicine, psychiatry and psychosomatic medicine. *International Medical Journal*, 19(2), 92-92.
2. Singh, A. N. (2021). Role of Epigenesis in Alzheimer's Disease. *International Medical Journal*, 28(5).
3. Singh, A.N. (2012) Advances in Genetic Mystery of Psychosomatic Disorders by Epigenesis and Utilization of Nanoscience and Nanotechnology. Presented at the 99th India Science Congress, Bhubaneswar, India January 3-7, 2012.
4. Leighton, R. B., & Sands, M. (1965). *The Feynman lectures on physics*. Boston, MA, USA: Addison-Wesley.
5. Baranowska-Wójcik, E., & Szwajgier, D. (2020). Alzheimer's disease: Review of current nanotechnological therapeutic strategies. *Expert Review of Neurotherapeutics*, 20(3), 271-279.
6. Thoe, E. S., Fauzi, A., Tang, Y. Q., Chamyuang, S., & Chia, A. Y. Y. (2021). A review on advances of treatment modalities for Alzheimer's disease. *Life sciences*, 276, 119129.
7. Modi, G., Pillay, V., & Choonara, Y. E. (2010). Advances in the treatment of neurodegenerative disorders employing nanotechnology. *Annals of the New York Academy of Sciences*, 1184(1), 154-172.
8. Skaat, H., & Margel, S. (2013). Newly designed magnetic and non-magnetic nanoparticles for potential diagnostics and therapy of Alzheimer's disease. *J. Biotechnol*. Biomater, 3(2), 1000156.
9. Pansieri, J., Gerstenmayer, M., Lux, F., Mériaux, S., Tillement, O., Forge, V., ... & Marquette, C. (2018). Magnetic nanoparticles applications for amyloidosis study and detection: a review. *Nanomaterials*, 8(9), 740.
10. McCullough, B. J., Kolokythas, O., Maki, J. H., & Green, D. E. (2013). Ferumoxytol in clinical practice: implications for MRI. *Journal of Magnetic Resonance Imaging*, 37(6), 1476-1479.
11. Çetin, M., Aytekin, E., Yavuz, B., & Bozdağ-Pehlivan, S. (2017). Nanoscience in targeted brain drug delivery. In *Nanotechnology Methods for Neurological Diseases and Brain Tumors* (pp. 117-147). Academic Press.
12. Liu, G., Garrett, M. R., Men, P., Zhu, X., Perry, G., & Smith, M. A. (2005). Nanoparticle and other metal chelation therapeutics in Alzheimer disease. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1741(3), 246-252.
13. Kang, D. Y., Lee, J. H., Oh, B. K., & Choi, J. W. (2009). Ultra-sensitive immunosensor for β-amyloid (1-42) using scanning tunneling microscopy-based electrical detection. *Biosensors and Bioelectronics*, 24(5), 1431-1436.
14. Choi, J. S., Choi, H. J., Jung, D. C., Lee, J. H., & Cheon, J. (2008). Nanoparticle assisted magnetic resonance imaging of the early reversible stages of amyloid β self-assembly. *Chemical communications*, (19), 2197-2199.
15. Tiwari, S., Atluri, V., Kaushik, A., Yndart, A., & Nair, M. (2019). Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *International journal of nanomedicine*, 14, 5541.
16. Agarwal, M., Alam, M. R., Haider, M. K., Malik, M. Z., & Kim, D. K. (2020). Alzheimer's disease: An overview of major hypotheses and therapeutic options in nanotechnology. *Nanomaterials*, 11(1), 59.
17. Nguyen, T. T., Nguyen, T. T. D., Nguyen, T. K. O., & Vo, T. K. (2021). Advances in developing therapeutic strategies for Alzheimer's disease. *Biomedicine & Pharmacotherapy*, 139, 111623.
18. Tiwari, S. K., Agarwal, S., Seth, B., Yadav, A., Nair, S., Bhatnagar, P., ... & Gupta, K. C. (2014). Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway. *ACS nano*, 8(1), 76-103.
19. Taylor, M., Moore, S., Mourtas, S., Niarakis, A., Re, F., Zona, C., ... & Allsop, D. (2011). Effect of curcumin-associated and lipid ligand-functionalized nanoliposomes on aggregation of the Alzheimer'ss Aβ peptide. *Nanomedicine: Nanotechnology, Biology and Medicine*, 7(5), 541-550.
20. Zlokovic, B. V. (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience*, 12(12), 723-738.
21. Zhao, Z., Nelson, A. R., Betsholtz, C., & Zlokovic, B. V. (2015). Establishment and dysfunction of the blood-brain barrier. *Cell*, 163(5), 1064-1078.
22. Sood, S., Jain, K., & Gowthamarajan, K. (2014). Intranasal therapeutic strategies for management of Alzheimer's disease. *Journal of drug targeting*, 22(4), 279-294.
23. Z Ahmad, M., Ahmad, J., Amin, S., Rahman, M., Anwar, M., Mallick, N., ... & Akhter, S. (2014). Role of nanomedicines in delivery of anti-acetylcholinesterase compounds to the brain in Alzheimer's disease. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, 13(8), 1315-1324.
24. Kumar, N., & Kumar, R. (2013). *Nanotechnology and Nanomaterials in the Treatment of Life-threatening Diseases*. William Andrew.
25. Miyake, M. M., & Bleier, B. S. (2015). The blood-brain barrier and nasal drug delivery to the central nervous system. *American journal of rhinology & allergy*, 29(2), 124-

127.
26. Wong, Y. C., & Zuo, Z. (2010). Intranasal delivery─modification of drug metabolism and brain disposition. *Pharmaceutical research*, 27(7), 1208-1223.
27. C Ligade, P., R Jadhav, K., & J Kadam, V. (2010). Brain drug delivery system: an overview. *Current Drug Therapy*, 5(2), 105-110.
28. Mittal, D., Ali, A., Md, S., Baboota, S., Sahni, J. K., & Ali, J. (2014). Insights into direct nose to brain delivery: current status and future perspective. *Drug delivery*, 21(2), 75-86.
29. Alam, M. I., Beg, S., Samad, A., Baboota, S., Kohli, K., Ali, J., ... & Akbar, M. (2010). Strategy for effective brain drug delivery. *European journal of pharmaceutical sciences*, 40(5), 385-403.
30. Lajoie, J. M., & Shusta, E. V. (2015). Targeting receptor-mediated transport for delivery of biologics across the blood-brain barrier. *Annual review of pharmacology and toxicology*, 55, 613-631.
31. J Gaillard, P., C Visser, C., CM Appeldoorn, C., & Rip, J. (2012). Targeted blood-to-brain drug delivery─10 key development criteria. *Current Pharmaceutical Biotechnology*, 13(12), 2328-2339.
32. Thakur, G., Micic, M., Yang, Y., Li, W., Movia, D., Giordani, S., ... & Leblanc, R. M. (2011). Conjugated quantum dots inhibit the amyloid β (1─42) fibrillation process. *International Journal of Alzheimer's Disease*, 2011.
33. Quan, L., Wu, J., Lane, L. A., Wang, J., Lu, Q., Gu, Z., & Wang, Y. (2016). Enhanced detection specificity and sensitivity of Alzheimer's disease using amyloid-β-targeted quantum dots. *Bioconjugate Chemistry*, 27(3), 809-814.
34. Tokuraku, K., Marquardt, M., & Ikezu, T. (2009). Real-time imaging and quantification of amyloid-β peptide aggregates by novel quantum-dot nanoprobes. *PloS one*, 4(12), e8492.
35. Babazadeh, A., Vahed, F. M., & Jafari, S. M. (2020). Nanocarrier-mediated brain delivery of bioactives for treatment/prevention of neurodegenerative diseases. *Journal of Controlled Release*, 321, 211-221.
36. Howarth, M., Takao, K., Hayashi, Y., & Ting, A. Y. (2005). Targeting quantum dots to surface proteins in living cells with biotin ligase. *Proceedings of the National Academy of Sciences*, 102(21), 7583-7588.
37. Van Giau, V., An, S. S. A., & Hulme, J. P. (2018). Mitochondrial therapeutic interventions in Alzheimer's disease. *Journal of the neurological sciences*, 395, 62-70.
38. Hauptmann, S., Scherping, I., Dröse, S., Brandt, U., Schulz, K. L., Jendrach, M., ... & Müller, W. E. (2009). Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. *Neurobiology of aging*, 30(10), 1574-1586.
39. Liu, Y., Xu, L. P., Dai, W., Dong, H., Wen, Y., & Zhang, X. (2015). Graphene quantum dots for the inhibition of β amyloid aggregation. *Nanoscale*, 7(45), 19060-19065.
40. Han, Y., Chu, X., Cui, L., Fu, S., Gao, C., Li, Y., & Sun, B. (2020). Neuronal mitochondria-targeted therapy for Alzheimer's disease by systemic delivery of resveratrol using dual-modified novel biomimetic nanosystems. *Drug delivery*, 27(1), 502-518.
41. Lustbader, J. W., Cirilli, M., Lin, C., Xu, H. W., Takuma, K., Wang, N., ... & Wu, H. (2004). ABAD directly links Aβ to mitochondrial toxicity in Alzheimer's disease. *Science*, 304(5669), 448-452.
42. Kwon, H. J., Cha, M. Y., Kim, D., Kim, D. K., Soh, M., Shin, K., ... & Mook-Jung, I. (2016). Mitochondria-targeting ceria nanoparticles as antioxidants for Alzheimer's disease. *ACS nano*, 10(2), 2860-2870.
43. Sharifi, S., Behzadi, S., Laurent, S., Forrest, M. L., Stroeve, P., & Mahmoudi, M. (2012). Toxicity of nanomaterials. *Chemical Society Reviews*, 41(6), 2323-2343.
44. Ganguly, P., Breen, A., & Pillai, S. C. (2018). Toxicity of nanomaterials: exposure, pathways, assessment, and recent advances. *ACS Biomaterials Science & Engineering*, 4(7), 2237-2275.