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REVIEW ARTICLE

Nanotechnology in Parkinson's Disease - A Review

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ABSTRACT:
Parkinson's Disease is considered as a neurodegenerative disorder and is identified by the deterioration of the motor functions due to loss of the dopamine releasing neurons. Due to this dementia occurs which is characterised by forgetfulness and impairment in cognitive abilities. The effectiveness, cellular penetration and transport of drugs to the target organs, tissues or cells is the main hindrance in the diagnosis and the treatment of this disorder. The main obstacle in the drug delivery system is the presence of blood brain barrier which checks the penetration of drugs and causes side effects. Nanoparticle eases the drug delivery to the central nervous system via blood brain barrier against the conventional drug delivery. Nanotechnology interact at a molecular level with the biological system and revolutionize the treatment by stimulating, responding to, and interacting with target sites to induce physiological responses while minimizing side effects. This review focuses on current applications of nanomaterials in the therapy and diagnosis of the most common neurodegenerative disorder and highlights the future nanotechnological approaches.

KEYWORDS: Neurodegenerative disorder, Blood Brain Barrier, Nanoparticles, Nanotechnology.

INTRODUCTION:

Parkinson's disease (PD) is considered to be the second most common neurodegenerative disease. This is a movement disorder which follows Alzheimers disease which affects 1-3% of people over 80 years and 0.5-1% of people aged 65-69 years. The features of this disease was first described by James Parkinson in his monograph "Essay on shaking palsy". There is an increase in age related neurodegenerative disorders in the countries that has an existence of population aged above 65 years. According to a survey, the population of elderly Indians has increased from 5.6% to 7.1% in the year 1961-2001. This review will focus on ayurvedic, medical, surgical treatment and how nanotechnology will have a great impact in the treatment of PD[1][2] . Parkinson's disease is a complex condition and has a wide range of symptoms[3]. It is considered to be caused by genetic and environmental factors[4].

The micro-architecture of the substantia nigra was studied in control cases of varying age and patients with Parkinsonism[5]. Dopamine is responsible for the smooth and coordinated movement of the muscles[6]. It is caused due to the reduction of neurons in the substantia nigra pars compacta. Parkinson disease is characterized by deterioration of motor functions due to loss of dopamine releasing neurons. During this, Dementia occurs which results into awareness impairment and forgetfulness. Recently, it has been reported that nanoparticles as compared to conventional drug delivery systems have an easy drug delivery through blood brain barrier into the central nervous system. Present studies have been attempted to clarify the alpha synuclein activity, major factor causing PD, in presence of cerium oxide (its inhibitor) nanoparticle via computational biology approach. An analysis was conducted with biocompatible metal NPs such as Gold NPs and SPIONs for the alpha synuclein activity to scrutinize the efficacy and degree of inhibition induced by CeO_2.According to the results CeO_2 NP fits best in the active site of alpha synuclein, potentially inhibiting the PD against L-DOPA drug selected as the positive control in the PD biochemical pathway. Therefore, CeO_2 has been used as the potential inhibitor of alpha synuclein and can be employed as nano drug against PD[7]. At times it is genetic but in most of the cases it is not. Chemicals in

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the environment these days is also considered a major factor for developing this disease. Symptoms are often seen on one side of the body but later it affects both the sides which includes: trembling of face, jaw, arms and legs, stiffness of the trunk, legs and arms, slow movement, poor coordination and balance.

In the later stages people may have trouble in doing simple tasks such as walking and talking. They may also suffer from speaking, swallowing, depression and sleep[8]. Hyposmia or Olfactory dysfunction (loss of smell) is also a common symptom[9].

THE BLOOD BRAIN BARRIER (BBB):

The transport mechanisms at the BBB can be manipulated for cerebral drug targeting. Studies of the kinetic flux have revealed a unidirectional, concentration-dependent movement of compounds across the BBB. The direction of flow is considered to be from the plasma to the brain, or visa versa. Small lipophilic molecules can pass easily from blood capillaries. The hydrophilic or the charge bearing large molecules require gated channels, ATP, proteins, and/or receptors to facilitate passage across the BBB. Evasion of the BBB can be achieved through the systemic administration or implantation of nano-enabled drug delivery systems that have the ability to control and target the release of various bioactive agents used in the treatment of PD[10].

THE DOPAMINE REPLACEMENT:

Dopamine deficiency is the key neurochemical abnormality in early-stage PD. Levodopa replacement remains the standard clinical treatment for PD. Levodopa has a relatively short half-life in plasma, which results in the need for frequent levodopa administration over the long term to maintain its therapeutic effect and can cause fluctuating plasma levodopa and striatal DA levels. Fluctuation of the levodopa concentration in plasma levels causes nonphysiological pulsatile stimulation of striatal DA receptors, consequently inducing response failures and motor complications such as dyskinesia. NPs have been engineered to control levodopa release and have a longer half-life, thereby reducing drug dose and the risk of levodopa-induced dyskinesias. Zn/Al-layered double hydroxides is a layered organic–inorganic nanocomposite material which was synthesized to incorporate levodopa[11].

UNDERSTANDING THE AYURVEDIC APPROACH:

In Ayurveda this disease is known as “Kampavata”. Famous physician Galen gave one of the first descriptions of this condition under the name “Shaking Palsy”. This disease was named after James Parkinson after he published a very detailed description of the condition in 1817.

AYURVEDIC ETIOLOGY AND PATHOLOGY (Nidana and Samprapti):

As we age, apana vayu accumulates and may become aggrevated (prakopa) which leads to constipation in the elderly. When apana vayu is combined with vata increasing lifestyle, the stage gets set for vata to overflow into circulation. Dryness of the membranes of the body occurs as the systematic signs of vata disturbance. Vata relocates dhatus that are weak. When a weakness already exists in the tissue of the brain, we have a condition of vata in the majja dhatu, damaging portions of the brain stem which alters coordination and tremors. Pitta plays an important role in pathology (samprapti) as its heat burns out the cellular structure. Therefore, personalities based on fear and intensity are most exposed to this condition, and those with kapha nature are the most naturally protected.

NIDANAM (Diagnosis):

Diagnosis is particularly based on signs and symptoms. Rigidity, loss of facial expression or gait abnormalities suggests the disease. Only 70% of the patients exhibit tremors and the rest 30% are more difficult to diagnose.

AYURVEDIC TREATMENT (Chikitsa):

According to the journal Movement Disorders by Bala V. in 1990, Mucuna pruriens contains levopoda (or) L-DOPA within its seeds. It is considered to be as the precursor of dopamine, the neurotransmitter responsible for Parkinson disease. A trial using Mucuna pruriens called HP 200 was used in effective treatment of Parkinson disease. Ayurveda is a holistic treatment offering the greatest chance of success with Parkinson patients.[12]

PRESENT TREATMENT OPTIONS:

DRUG TREATMENT:

Current treatment of PD is focused on alleviating the impaired movement, but there is no therapy that slows down PD progression[13].Introduction of levodopa (dihydroxyphenylalanine) for the treatment of PD was a major scientific and clinical breakthrough in the treatment of this disease. It has two aspects. First is the enormous benefit to patients. Second is the realization that an understanding of biochemical deficits can provide a clue as to how replacement therapy could be successfully employed in neurodegenerative diseases, providing significant sympomatic benefit, if not a cure. Dopa is considered to have an impact on attempts to treat other neurodegenerative disorders, particularly AD. Later it became clear that dopa does not slow the neurodegenerative process and its effects are purely symptomatic. The dopa does required to control the

motor manifestations must be increased as the disease progresses. Out of the two dopa isomers only the levorotatory stereoisomer, levodopa, produced therapeutic benefits, and chemical means to separate the two isomers were developed[14] .

SURGERY:

Surgery is considered as an option for some people with Parkinson's disease to treat the symptoms. There is no assurance to cure PD; however surgical techniques may relieve symptoms from PD in some patients. Surgery is often considered after medication have been exhausted. It generally works to improve the motor symptoms of PD that have previously improved on levopoda therapy.

Surgical procedures for people with PD aims to destroy specific parts of the brain to relieve symptoms. This includes Pallidotomy, thalamotomy and subthalamotomy. These procedures have significant risks, including possibility of death. Deep brain stimulation is the most common surgery for PD[15].

NANOTECHNOLOGY AS VIABLE ALTERNATIVE:

Nanotechnology and nanoscience, are the two interdisciplinary areas that are directed toward manipulation of materials at atomic or subatomic levels whose properties differ significantly from those of bulk matter. Nanotechnology exploits manipulated materials for designing, characterizing, and production of improved structure, devices and systems with controlled size and shape (1-100 nm) for various applications. Nanostructures have been applied for diagnosis of diseases, imaging, for tissue regeneration as well as for drug delivery and therapeutics. Nanotechnology involves the manipulation of various systems at the nanoscale that can have potential in the management of Parkinson's disease. Nanotechnology helps in the development of sensors that are able to sense various biomarkers at low concentrations in the presence of other analytes and help in the development of affordable and cheap diagnostic devices. Nanotechnology-based drug delivery plays an important role to achieve better therapeutic efficacy and enhance bioavailability across BBB for the treatment of CNS disorders. Are the few of the approaches that can improve the treatment of PD. Nanotechnology also improves neural prosthetic devices for deep brain stimulation with better contact with the brain. Nanotechnology helps improve precision in neurosurgery through nano-level precision of Laser axotomies. Nanotechnology may be employed to develop platforms for effective stem cell therapy through various tissue engineering approaches.[16]

RECENT NANOTECHNOLOGICAL: DEVELOPMENTS IN DIAGNOSIS OF DISEASE:

In parkinson's disease, sustained and safe delivery of dopamine across the blood brain barrier (BBB) is a major hurdle for successful therapy. Therefore, in the present study neurotransmitter dopamine-loaded PLGA nanoparticles (DA NPs) to deliver dopamine to the brain have been designed. These nanoparticles slowly and at a constant rate release dopamine. These were internalized in dopaminergic SH-SY5Y cells and dopaminergic neurons in the substantia nigra and striatum, regions affected in PD. Treatment with the dopamine nanoparticles did not cause reduction in cell viability and morphological deterioration in SH-SY5Y, as compared to bulk dopamine-treated cells, which showed reduced viability. These nanoparticless were able to cross the BBB and capillary endothelium in the striatum and substantia nigra in a 6-hydroxydopamine (6-OHDA)-induced rat model of PD. The systemic intravenous administration of dopamine nanoparticles has led to the increase in significant levels of dopamine and its metabolites and reduced dopamine-D2 receptor supersensitivity in the striatum of parkinsonian rats. Furthermore, DA NPs significantly recovered neurobehavioral abnormalities in 6-OHDA-induced parkinsonian rats. Dopamine transporting through these nanoparticles did not cause extra generation of ROS, dopaminergic neuron degeneration, and ultrastructural changes in the striatum and substantia nigra as compared to 6-OHDA-lesioned rats. These results shows that NPs delivered dopamine into the brain, reduces dopamine autoxidation-mediated toxicity, and ultimately reversed neurochemical and neurobehavioral deficits in parkinsonian rats.[17]

DRUG DELIVERY FOR PD:

An unique drug delivery system has been developed for ropinirole (RP) for the treatment of Parkinson's disease (PD) consisting of biodegradable poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles (NPs). The formulation selected is prepared with 8 mg RP and 50 mg PLGA 502[18]. Ropinirole is used to treat restless leg syndrome and is taken orally.

TRANSPORT EFFICIENCY OF NANOMATERIALS IN NOSE TO BRAIN DRUG DELIVERY:

Nanoparticles can offer an improvement in nose to brain drug delivery since they are able to protect the encapsulated drug from biological or chemical degradation and extracellular transport by P-glycoprotein efflux. This increases the availability of CNS of drugs. Studies are still going on the nanotechnology based nose to brain drug delivery[19]

NEUROPROTECTIVE EFFECTS OF GOLD NANOPARTICLES COMPOSITES:

For these patients, over-expression of α-synuclein (SNCA) leads to the death of dopaminergic neurons. This can be prevented by suppressing SNCA over-expression through RNA interference. These gold nanoparticles (GNP) composites are successfully synthesized via the combination of electrostatic adsorption and photochemical immobilization, which could load plasmid DNA (pDNA) and target specific cell types. The GNP was transfected into cells via endocytosis to inhibiting the apoptosis of PC12 cells and dopaminergic neurons. Along with this, GNP composites are also used in PD models in vivo, and it can successfully cross the blood-brain barrier by contents of GNP in the mice brain. All these works demonstrated that GNP composites have good therapeutic effects for PD models in vitro and in vivo[20]

USE OF CERIUM OXIDE NANOPARTICLES:

The surface of these nanoparticles can contain small markers that allow them to pass through the blood-brain barrier and gain access to the central nervous system, specifically anchoring to the target cells and releasing their active pharmacological agent.

Researchers compared three different nanoparticles: gold nanoparticles which have been shown to prevent alpha-synuclein aggregation; graphene and superparamagnetic iron-oxide nanoparticles that have also been reported to prevent fibrils formation; and the cerium oxide nanoparticles that have been shown to have neuroprotective activity due to their antioxidant and anti-apoptotic effects.

This analysis was build on compiled information about drug design and effects, disease diagnosis and features, and also molecular target interactions and systems biology data. The cerium oxide nanoparticles had a greater affinity toward alpha-synuclein, while sustaining good stability and overall response.

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This analysis showed that cerium oxide could prevent the aggregation of alpha-synuclein, and promote the activation of dopamine receptors and the regulation of signaling pathways and genes important in Parkinson's disease.

As per the preclinical results, the researchers proposed cerium oxide nanoparticles "as a potential inhibitor of alpha-synuclein" that might "be employed as a nano-drug against Parkinson's disease."[21]

USE OF SILICA NANOPARTICLES:

Organically modified silica nanoparticles (ORMOSIL) are used for the in vivo gene delivery. They are non viral vector, highly monodispersed, stable aqueous suspension of nanoparticles. The ORMOSIL mediated transfections are also used to manipulate the biology of the neural stem/progenitor cells in vivo.[22]

NANOTECHNOLOGY AS A POTENTIAL TOOL FOR siRNA DELIVERY IN PARKINSON'S DISEASE TREATMENT:

siRNA-based approach provides an interesting option for designing new strategies for treating PD through the silencing of genes, whose abnormal expressions contribute to the pathophysiology of the disease; however, the siRNA delivery to brain is a key issue that remains unsolved to date. The Current research efforts are focused on designing vectors that effectively transport and protect siRNAs. For this, nanoparticles are being developed as carriers for siRNAs with controlled delivery efficiency and low toxicity profiles, and these represent an alternative to common vectors.[23]

TREATMENT FOR PD USING GENE THERAPY:

Gene therapy for PD involves the incorporation of standard healthy genes into a parkinsonian patient with defective faulty genes with aim to trigger the cells within these genes to begin producing dopamine. It is expected that the healthy genes begin to adapt the malfunctioning cells by making alterations to them that trigger the production of dopamine within them to resume. If this process is achieved effectively with little or no complications, then this treatment could be a valid way of controlling or ceasing the symptoms of Parkinson's disease.[24]

ZnO NANOWIRES ARRAYS:

ZnO nanowire arrays are fabricated on 3D graphene foam and is used to selectively detect uric acid (UA), dopamine (DA) and ascorbic acid (AA). The optimized ZnO nanowire /graphene foam electrode provided a high surface area and high selectivity with a detection limit of 1nm for UA and DA. This high selectivity in the oxidation potential is explained by the gap difference between the lowest unoccupied and highest occupied molecular orbitals of a biomolecule for a set of given electrode. This method is further used to detect UA levels in the serum of patients with PD. The PD patients have 25% lower UA level than healthy individuals. This strongly implies that UA can be used as a biomarker for PD.[25]

CONCLUSION:

Nanotechnology can resolve many underlying problems in today's medicine and improve a great number of current methods regarding diagnosis, prevention and treatment. Regarding Parkinson's disease, carbon nanotubes and other nanostructures are used for the drug delivery such as levodopa and dopamine agonists. If

ethical guidelines are made then it would allow nanotechnology to be used within medicine safely and people could benefit from its attributes. In the coming future, if these guidelines are resolved and nanomedicine is explored further, it could have a profound impact on the management of Parkinson's disease, and the future of medicine itself.

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