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Review

Current development of nanocarrier delivery systems for Parkinson's disease pharmacotherapy

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder second only to Alzheimer's disease in seriousness and tends to worsen with aging. Several drugs and genes have been developed and identified to treat PD. However, their activity against PD as solo agents has been hindered by their inability to permeate the blood–brain barrier (BBB), and also that they have a short half-life. Drug delivery systems (DDS) play a vital role in drug transport to specific tissue sites in the central nervous system by overcoming the hurdle presented by the BBB. A variety of DDS, including nanosized polymers, liposomes, solid lipid nanoparticles and exosomes, have been introduced to improve the capability of drug/gene. The DDS surface has been modified with active components, such as lactoferrin, transferrin, wheat germ agglutinin, Angiopep, Trojan horse and antibody OX26, to facilitate BBB permeation. Of the DDS, exosomes, a natural vehicle, is exposed to a limited extent and may be an efficacious carrier system in the near future. Though there is still a lack of clinical trials investigating DDS for PD management, DDS have assisted in improving therapeutic efficiency in animal models. This review is focused on an overview of DDS established to enhance the efficacy of drug/gene in PD treatment.

Contents

1. Introduction

People are exposed to an immense variety of new diseases in day-to-day life, and a number of novel drugs have been developed to treat them. The efficacy of these drugs is dependent on their ability to directly interact with definite cells and on their biodistribution [1,2]. Drugs have an optimal concentration range of therapeutic activity – when they are above that range, they may induce toxicity, and below that range, they may be ineffective, in general. Thus, drugs should maintain an ideal level in the circulatory system to fulfill the purpose of treatment [3,4]. In fact, drug concentration in the blood through oral or intravenous (i.v.) injection initially reaches a supraoptimal level, and then decreases to a suboptimal level due to metabolic reactions. Therefore, different types of drug delivery systems (DDS) have been fabricated to promote pharmaceutical function and reduce adverse responses. DDS assist

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in carrying drugs with the advantages of easy transport, including a controlled manner of drug release, a diminished time restriction in the blood and an active tissue targeting by changing drug distribution in the body. In simplified explanation, drug carriers modify pharmacokinetics (drug absorption, distribution, metabolism (biotransformation) and elimination), medicinal effect and toxicity [5–7]. Nanocarrier delivery systems, including nanosized polymers, liposomes (LIP), solid lipid nanoparticles (SLNs) and exosomes, are the most widely used DDS [8]. The carrier surface modified with active ligands can enter easily into an organ by preventing reticuloendothelial system (RES) elimination. In addition, nanocarriers provide prolonged duration for drugs in the circulatory system, which allows them having a high chance of delivering to injured tissue [9]. Furthermore, in addition to the hydrocarbon chains as the main structure, other functional groups, such as amine and carboxyl, are utilized as reactive sites for chemical modification [10]. Therefore, DDS have a fascinating future in treating several incurable and deadly diseases.

Parkinson's disease (PD), a neurodegenerative disorder causing cognitive decline, second only to Alzheimer's disease, affects 1–2% of elderly people and results mainly from a dopamine deficit due to the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [11–13]. At present, a clear etiology of PD remains elusive; however, current researches show that oxidative stress, mitochondrial dysfunction and genetic factor may be the causative elements [14,15]. Oxidative stress results from an imbalance between antioxidant activity and production of reactive oxygen species (ROS) from enzymes such as tyrosine hydroxylase (TH) and monoamine oxidase [16]. The heroin analog, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is metabolized into 1-methyl-4-phenylpyridinium (MPP^+), which is taken up by dopaminergic neurons that inhibit the mitochondrial respiratory chain and lead to excess production of superoxide. Thus, the overwhelming reduction in antioxidant capacity of dopaminergic neurons causes their death [17]. Six genes (α-synuclein, LRRK2, VPS35, Parkin, PINK1 and DJ-1) have been identified to be in association with an autosomal-dominant or recessive PD mode of inheritance [18]. PD currently is treated through either surgical management or drug supplement, and PD treatment with drugs is considered to be the most common therapeutic approach. L-3,4-dihydroxyphenylalanine (levodopa; L-Dopa), a dopamine precursor, is known as the gold standard in treating PD, but its long-term use may cause complications and also, achieving only a palliative effect requires increasing the dosage [19,20]. Further, permeating the blood–brain barrier (BBB) (Fig. 1), as part of the central nervous system (CNS), remains a great challenge to drug delivery into the brain because the BBB inhibits the passage of almost all macromolecular drugs and of >98% of small drugs [21]. DDS with active biomolecules can penetrate the BBB, target particular disease, and maintain drug concentration in the human body for a prolonged period, thereby enhancing drug activity in the CNS. Hence, this article deals with DDS used to deliver drugs for PD pharmacotherapy in recent years. To the best of our knowledge, this is the first paper reviewing a detailed feature of DDS in PD treatment.

2. Drug for Parkinson's disease pharmacotherapy

A few drugs (Fig. 2) have been developed – mostly dopamine agonists – to treat PD, and it is suggested that they be utilized based on different stages of PD symptoms. PD can be categorized into motor and non-motor symptoms. Motor symptoms, such as rigidity, bradykinesia and tremor, result from the loss of dopaminergic neurons, and are considered to indicate a progressively worst stage of PD [22,23]. Non-motor symptoms, such as olfactory problem, constipation, depression and rapid eye movement disorder, occur in the early stage of PD. Non-motor symptoms can be used to identify PD in its initial stage [24,25]. Motor symptoms are generally treated with L-Dopa, dopamine agonists (pramipexole, ropinirole, rotigotine, cabergoline and pergolide), monoamine oxidase B inhibitors (selegiline and rasagiline) and catechol-O-methyltransferase inhibitors (entacapone and tolcapone). This could be sufficient to treat the patients during the first year after identifying PD. Patients will require increased doses and numbers of L-Dopa administration due to the appearance of motor fluctuation and dyskinesia [26,27]. Non-motor symptoms are treated with paroxetine, citalopram, sertraline, fluoxetine, atomoxetine, nefazodone, pergolide, Ω-3 fatty acids for depression, methylphenidate and modafinil for fatigue, amantadine for pathological gambling; donepezil, galantamine and memantin for dementia, quetiapine for psychosis, fludrocortisone and domperidone for orthostatic hypotension, sildenafil for erectile dysfunction, ipratropium bromide spray for sialorrhea, and L-Dopa/carbidopa, pergolide, eszopiclone and melatonin for insomnia [25]. Mitochondrial dysfunction and oxidative stress also play a crucial role in the PD pathogenesis. Oxidative stress results from the reactive metabolites of dopamine, and changes in the concentration of iron and glutathione in the SNpc leads to mitochondrial dysfunction [28]. Mitochondria-associated oxidative stress in PD is treated with paroxetine [29], mitoquinone [30], lycopene [31], hesperidin [32], resveratrol [33], gastrodin [34], DL-3-n-butylphthalide [35], rapamycin [36], rutin [37], silymarin [38], acetyl-L-carnitine and α-lipoic acid [39]. In familial or sporadic PD, genetic factors, such as mutations in α-synuclein, LRRK2, PARK7, PINK1 and PRKN, require another pathological hallmark strategy. Misfolded and aggregated α-synuclein is a major neurotoxic substance on Lewy bodies, and Lewy neurites is critical in PD [40–42]. The formation of aggregated α-synuclein has been prevented using drugs, including melatonin [43], curcumin [44,45], curcumin pyrazole, N-(3-Nitrophenylpyrazole) curcumin [46], selegiline [47], bafilomycin A_1 [48], entacapone, tolcapone [49], (2S)-1-[[(2S)-1-(1-oxo-4-phenylbutyl)-2-pyrrolidinyl]carbonyl]-2-pyrrolidinecarbonitrile [50], baicalein [51], theaflavins [52], epigallocatechin gallate [53], quercetin [54] and acetylcorynoline [55].

3. Drug delivery system for PD pharmacotherapy

The particle size of materials is an essential criterion for the use with DDS. A large specific surface area of DDS assists in achieving fine control over drug release rate. Further, nanosized materials have the ability to circulate long term in the body after being injected, and provide potentiality for drugs to target the site of diseases [56]. Some of the high-ranking DDS in current practice are natural polymers, synthetic polymers, LIP, SLNs and exosomes (Fig. 3). DDS are a proper vehicle for drugs to attack the zone of interest, increase drug bioavailability, prevent deleterious side effects, and minimize drug degradation and loss [57]. Several physicochemical factors of nanocarrier delivery systems affect their behavior and efficacy such as circulation half-life, cellular internalization, biodistribution and uptake by organs. These factors include particle size, surface charge, morphology, chemical composition and targeting functionalization. Pharmacological performance of DDS also depends on their cellular uptake and intracellular trafficking [58–60]. The surface charge of DDS plays a pivotal role in electrostatic interactions between carriers and charged components in the outer plasma membrane of cells. In addition, nanocarriers may be internalized through clathrin-mediated or caveolae-mediated endocytotic pathway, and can be helpful to target monocytes and macrophages [61]. Further, the effectiveness of DDS is considerably influenced by the loading efficiency of drug/gene and their releasing rate [62]. Moreover, DDS modified with bioactive molecules improve the efficiency of metabolized drugs for CNS-based diseases during con-

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