Review Article

Liposomes: A Novel Carrier for Targeted Delivery of Active Agents against Schizophrenia

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ABSTRACT

Schizophrenia is a severe brain disorder in which people have abnormal perceptions of reality. Schizophrenia can cause hallucinations, delusions, and extremely disordered thinking and behavior. Schizophrenia, contrary to popular belief, is not a split or multiple personality disorder. The term "schizophrenia" literally means "split mind," but it refers to a disruption in the normal balance of thoughts. Clozapine is currently the only medication approved by the USFDA for the treatment of refractory schizophrenia. However, for patients who do not respond to clozapine or for whom clozapine therapy fails to treat refractory schizophrenia, a combination of antipsychotics is used. Overall, the focus of this article is to summaries the most recent findings and news concerning liposome technology in the treatment of neurodegenerative diseases, as well as to demonstrate the potential of this technology for the development of novel therapeutics and the potential applications of liposomes in the two most common Schizophrenia disorders.

Keywords: Liposomes, brain targeting, Schizophrenia.

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INTRODUCTION

Schizophrenia, a chronic psychiatric condition characterized by distortion of perception, thinking, behavior, and language; Hallucinations, that is, accepting situations, visualizing things and hearing voices that do not exist in reality, as well as delusions or false beliefs. The disease is unknown, but a variety of environmental factors and genetic changes are believed to be common causes of schizophrenia. Neuropathologically, the disease is characterized by impaired dopaminergic and glutamate neurotransmission, a synaptic deficit, and hypofrontality. Reddening of the skin after taking niacin has been linked[1]. Increased visibility of the nail fold nerve plexus and immune aberrations have also been reported[2, 3]. According to the 2018 WHO report, around 23 million people worldwide suffer from schizophrenia, although it is less common than other brain disorders and more common in men than women[4]. Patients with schizophrenia have shorter lifespan and higher mortality from accidental or suicidal death. The disease can be managed or managed with appropriate treatment and psychiatric counseling, support, and family care[5, 6]. However, as with other brain disorders, effective targeting of the brain by BBB is the main challenge in drug delivery. Therefore, several novel technologies have been introduced that improve bioavailability in the brain and reduce the peripheral side effects of antipsychotics and bioactive agents acting on the CNS[7].Most of the drugs ingested do not fully reach the brain and are instead metabolized in whole or in part by the liver. This ineffective use of the drug may require the ingestion of higher concentrations of the drug, which can cause toxic effects on the heart, liver, or kidney. In addition, many therapeutic agents are sparingly soluble or insoluble in aqueous solutions. These drugs present a challenge to oral or parental administration. However, these compounds can have significant benefits when formulated by other technologies such as liposomes. Various strategies have been developed to deliver drugs to the brain that would otherwise not be able to cross the BBB. Generally, an intraventricular catheter is surgically implanted to deliver a drug directly to the brain, although this is quite undesirable. New therapeutic drugs that cross the BBB are critical in the treatment of many brain diseases. Kinetics of BBB and drug release causing serious peripheral side effects. Contrary to popular belief, neurodegenerative and neurological diseases can be multi-system in nature, creating numerous difficulties for their possible treatment. For brain diseases, especially neurodegenerative diseases, where genetically modified cells can be used to deliver specific growth factors to target cells. However, clinical problems have limited this technique due to insufficient gene transfer, prolonged lack of gene expression, or immune rejection of producer cells. A promising technology is the development of new bio-material components with the ability to encase genetically engineered cells that produce and deliver drug therapy while isolating themselves from the immune system. This technology includes, but is not limited to, liposomes, which are a potential supply of the system with specific proteins and growth. Brain damage factors in which different producer cells can be isolated from micro environmental

factors[8].Liposomes are the foremost common and well-investigated nanocarriers for targeted drug delivery. They need improved therapies to expand drug applications by stabilizing therapeutic compounds, overcoming barriers to absorption by cells and tissue, and increasing the biodistribution of compounds to target sites in vivo. Double layers of concentric macromolecules that introduce separate spaces for lipid bi layers. The characteristic ability of liposomal systems to capture both lipophilic and hydrophilic compounds enables a wide variety of drugs to be encapsulated by these vesicles. Hydrophobic molecules insert themselves into the bilayer membrane and hydrophilic molecules become trapped in the aqueous center[9, 10, 11, and 12]. Liposomes have received considerable attention as drug delivery vehicles because of their biocompatibility and non-toxicity can deliver both hydrophilic and lipophilic drug molecules, protect their cargo from plasma enzyme degradation, and transport their cargo across biological membranes and the BBB[13, 14].

THE BLOOD–BRAIN BARRIER (BBB)

The blood-brain barrier (BBB) has a unique structure that separates extracellular fluid from neurons in the bloodstream[15-19]. The BBB acts as a barrier to the complete separation of the bloodstream from the fluid in the CNS and protects the nerve cells from damage from foreign substances and infections originating in the blood[20]. In addition, the BBB prevents water-soluble molecules, proteins, peptides, genes and antibiotics with a molecular weight greater than 500 Da from reaching the brain, although the nanoparticles of these molecular weights could get through the brain due to their aspect ratio and spatial geometry[21, 22]. This special barrier consists of different cell types; endothelial cells, pericytes, astrocytes and microglia are built into the 3D structure of the BBB[23]. Endothelial cells in the BBB structure have different properties than their peripheral counterparts, including high mitochondrial cell content and altered pinocytic activity. The close connections between neighboring endothelial cells are complex and consist of several transmembrane proteins. Pericytes are located on the inner membrane of the brain and are covered by the basal lamina and proteins. Astrocytes and their terminal legs have attached themselves to the capillary walls and help stabilize the capillary structure. The BBB is the main problem in treating CNS disorders[24, 25, and 26].

TYPES OF LIPOSOMAL DRUG DELIVERY PLATFORMS

1. Conventional liposomes

Conventional liposomal formulations reduced the toxicity of the compounds in vivo by modifying pharmacokinetics and biodistribution to improve drug delivery to diseased tissue compared to free drug; however, the delivery system tended to be rapidly cleared from the bloodstream, which limited its therapeutic effectiveness[27]. Conventional liposome formulations consist mainly of natural phospholipids or lipids such as 1, 2-distearyl-sn-glycero3-phosphatidylcholine (DSPC), sphingomyelin, egg phosphatidylcholine and monosialoganglioside. Faced many challenges; One of the main causes is plasma instability, which leads to a short half-life of the bloodstream[28, 29, 30, 31]

2. Stealth liposomes

Conventional liposomes of the first generation, based on phospholipids bilayer membranes, have shown poor stability and rapid clearance after injection, since the membranes of conventional liposomes are strongly influenced by physical interactions with proteins circulating in the blood (opsonization) and protein adsorption which lead to improvement from to contribute. Deficient, longer circulating liposomes were developed by modulating the composition, size, and charge of regular liposomes. It is important to note that longer circulation time is not always desirable, for example in applications where an encapsulated drug is required to reach the target site. As quickly as possible[32]. The PEG coating provides an extended circulation time and a protective hydrophilic layer, attempting to make "stealth" liposomes suitable delivery vehicles for active targeting on target cells. Active targeting ligands coupled to these supports include small molecule ligands, peptides, and monoclonal antibodies[33]. PEGylated liposomal doxorubicin (DOXIL / Caelyx) is an exceptional example of stealth liposome technology that has been approved by both the US Food and Drug Administration (FDA) and the Federation of Europe[34].

3. Targeted liposomes

While specific sub cellular targeting remains a major challenge, efforts to target drugs to lysosomes or mitochondria have been more successful. Most of these systems are still in the in vitro research phase. With various lysosomotropic ligands such as octadecyl-rhodamine B (RhB) were successfully delivered to the lysosomes. Elsewhere, mitochondrial targeting was achieved in vitro with the polymer (Rh123) -PEG-DOPE (rhodamine 123-polyethylene glycol-1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine) containing rhodamine mitochondrial dye[35]. Ligand-targeted liposomes provide huge potential for site-specific drug delivery to specific cells types or organs in vivo by selectively expressing or overexpressing certain ligands (e.g., receptors or cell adhesion molecules) at the disease site[36]. Hence, the new generation of liposomes uses the combination of the above design platforms to further improve liposome targeting and drug delivery associated therewith (discussed in Experimental Use of Liposomes for Biomedical Applications). PEG (generation of long circulating immunoliposomes) has significantly improved the pharmacokinetics of immunoliposomes[37]

4. Other types of liposomes

4.1. Virosomes and Stimuli-Responsive Liposomes

Liposome technologies, such as conventional liposomes, stealth liposomes and targeted liposomes, have been clinically approved. Next generation liposome types are

designed to increase the release of bioactive molecules to the cytoplasm by escaping the endosome[38, 39]. Virosomes are created by combining parts of the infectious agent with non-viral vectors or by exploiting pseudovirions without replicating the viral genome. Viruses like contagious disease virus, HVJ (Japanese haemagglutination virus; Sendai virus) and viral hepatitis virus have been utilized in the development of virosomes. The HVJ-derived vector is especially promising due to its extremely economical delivery of DNA, siRNA, proteins, and cancer drugs. In addition, the HVJ envelope vector exhibits intrinsic anti-tumor activities, as well as the activation of multiple anti-tumor immunities and therefore the induction of cancer-selective apoptosis[40].

4.2. Gene-Based Liposomes

Characterization of the human genome coupled with recombinant DNA technology has created opportunities for gene therapy that have never been seen before. Candidate diseases for such technology include cancer, atherosclerosis, cystic fibrosis, hemophilia, sickle cell anemia, and other genetic diseases. The gene of interest must lead to the expression of the therapeutic protein. However, one of the most difficult endeavors has been to deliver the large anionic bioactive DNA through the cell. DNA is easily broken down by circulating and intracellular deoxyribonucleases. Released intact to the nucleus through the cell and nucleolar membranes[41, 42, 43, 44]. Such liposomes are made from phospholipids with a hydrophilic amine head group. The amines can be quaternary, tertiary, secondary or primary ammonium, and liposomes produced in this way are commonly referred to as cationic liposomes because they have a positive surface charge at physiological pH.

LIPOSOMES AS NEUROPHARMACOLOGICAL AGENTS

Liposomes are of great importance as nanocarriers due to their relatively large loading capacity. They have long been used as a drug delivery system for the brain because the particles can trap the compounds and prevent their rapid clearance or deterioration. As well as promote penetration through the BBB, which in turn reduces the effective dose[45]. In addition, they do not induce negative biological reactions that generally occur when foreign material is introduced into the system. When properly pretreated and formulated in or near the brain, liposomes are non-toxic, non-immunogenic, non-carcinogenic, non-thrombogenic. And biodegradable[46].

LIPOSOMES IN SCHIZOPHRENIA DISORDER

Schizophrenia could be a neurological disease characterized by sudden disturbances in thought processes and poor emotional responses. Unlike other tissues, endothelial cells in the brain are more closely connected and prevent potentially toxic substances from entering the brain[47]. Various strategies have been used to use routes of drug delivery other than oral or parenteral, such as intranasal and olfactory routes, and they like to use drug nanocarriers to solve the problem of transport across the blood-brain barrier[48]. A recent review by Koola et al. It shows that oxidative stress in schizophrenic patients can lead to impairment and can be associated with positive and negative cognitive symptoms. Therefore, the antioxidant galantamine-memantine combination can be useful in the treatment of cognitive, positive and negative symptoms in schizophrenic patients[49]. Shuker and Ahmed developed amisulpride-cyclodextrin liposomes to treat schizophrenia. Singly and doubly charged liposomes were produced, singly charged liposomes consisted of amisulpride-hydroxylpropyl-β-cyclodextrin (HP-β-CD) in the aqueous phase, while the doubly charged liposomes consisted of amisulpride-HP-β-CD in the aqueous phase Phase and free drug in the lipid bilayer. Shows the mean plasma level of amisulpride after oral administration of conventional liposomes, doubly charged amisulpride liposomes with HP-β-CD and commercially available (Solian). The results showed that the maximum plasma concentration of doubly charged liposomes was 1, 55 and was 1.29 times greater than the commercially available tablet or the conventional liposomes. In addition, the AUC0 - ∞ of the doubly charged liposomes were 1.94 and 1.28 times higher than that of the commercial tablet and conventional liposomes[50] eight clinically used phenothiazinederived drugs: promazine, chlorpromazine, trifluprom azine, trifluoperazine, perphenazine, fluphenazine, prochlorperazine (stemetil) and thioridazine (Table 1)[51].

Table 1: Inhibition of phosphatidylserine liposome-stimulated dynamin I and II GTPase activity; and clathrin-mediated endocytosis by Antipsychotic drugs (APDs)

Compound	DynI IC_{50} (μM)	DynII IC_{50} (μM)	CME IC_{50} (μM)
Phenothiazine (parent compound)	>300[a]	Not active	Not active
Promazine (T)	11.5 ± 1.4	ND	44.1 ± 7.9
Chlorpromazine (T)	6.8 ± 1.5[b]	4.1 ± 2.5	17.4 ± 2.4[c]
Trifluprom azine (T)	4.0 ± 1.1[c]	7.4	13.5 ± 5.0[a]
Thioridazine (T)	4.7 ± 0.5[c]	6.8 ± 3.1	6.9 ± 1.3[c]
Trifluoperazine (T)	2.6 ± 0.7[b]	2.5	10.4 ± 1.7[a]
Perphenazine (T)	5.8 ± 1.2[c]	1.7	10.5 ± 0.9[a]
Fluphenazine (T)	6.8 ± 0.7[b]	3.1 ± 0.7	10.4 ± 1.1[b]
Prochlorperazine (Stemetil) (T)	7.0 ± 1.2	~3.9	5.8 ± 0.8[b]
Haloperidol (T)	19.0 ± 2.2[b]	6.5	54.5 ± 23[b]
Droperidol (T)	Not active	ND	Not active
Clozapine (A)	28.2 ± 1.2[a]	5.3	85.3 ±14[b]
Olanzapine (A)	209	ND	Not active
Risperidone (A)	Not active	ND	Not active
Calmidazolium (calmodulin antagonist)	2.7 ± 1.0	0.81± 0.5	ND

A series of APDs and related compounds were tested for the inhibition of dynamin I and II GTPase activity stimulated by phosphatidylserine liposomes. Illustrated is the structure of each compound and IC_{50} for dynamin I and II inhibition. All compounds were tested at 0.1, 0.4, 1, 4, 10, 40, 100, 300 µM in 3% and 1%final DMSO in GTPase and CME assay, respectively. Data were normalized against untreated control samples, which contained 1% DMSO.

Not active, not active upto 300 µM; ND, not determined; T, typical APD; A, atypical APD.

CONCLUSION

Current liposomal drugs develop from various plan systems for the improvement in biodistribution over free medications. Psychotic disorders have not before been beneficially treated by an oral classic therapy. The targeted drug delivery is an alternative drug supported new technologies can have a key role within the general application of the latest medicine, such as, growth factors, peptides or hormones. Now is not possible to treat properly several diseases principally for the localization of damaged tissue. The complexity of the illness and, many times, the localization of the tissue injury, troublesome the potential treatment, such as, the brain is isolated by the BBB. Liposomes are used clinically as delivery systems for targeted drug delivery of anti-tumor, antibiotics, antifungal and chemotherapeutic agents. This is often because liposomal preparations are shown to extend the margin of safety of the many drugs and also their efficacy. The current targeted drug delivery strategies for neurodegenerative and neurological diseases represent one of the biggest unmet medical needs today. The rapid development of liposome technology may provide a near solution to overcome these diagnostic and neurotherapeutic challenges to schizophrenia disorder.

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