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Drug delivery devices for retinal diseases☆

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ABSTRACT

Retinal degenerative diseases are a leading cause of irreversible blindness and visual impairment, affecting millions of people worldwide. Although intravitreal injection can directly deliver drugs to the posterior segment of the eye, it is invasive and associated with serious side effects. The design of drug delivery systems targeting the posterior segment of the eye in a less invasive manner has still been challenging because of various anatomical and physiological barriers. In this review, we provide an overview of the current implant device-based approaches used for treating retinal degenerative diseases. We then offer our perspectives on future directions and challenges that remain for developing more effective device-based therapies for retinal diseases.

Contents

1. Introduction

Sensory functions including vision are necessary to maintain the quality of life, but those functions deteriorate due to diseases and aging. Because approximately 80% of all sensory input is received *via* the eyes, countermeasures against emerging visual dysfunctions should be developed, especially in super-aging countries such as Japan. Many irreversible blindness and visual impairments result from intractable disorders of the retina. The retina is a layered structure with several layers of neurons at the back of the eye, where visual processing begins. It is therefore crucial to establish an effective therapy for retinal degenerative diseases. Although there has been considerable progress in the development of clinical examination equipment, pathological analyses,

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and surgical procedures, it is still difficult to rescue abnormal retinal cells. A problem for drug treatment of retinal diseases is that it is difficult to permeate the retina [1–5]. The eyeball is covered by the cornea and the sclera and is isolated from the blood circulation by the blood-retinal barrier (BRB). Intravitreal injection of the drug, ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor, had a positive effect on some patients with age-related macular degeneration (AMD) accompanied by choroidal neovascularization (wet AMD) [6,7]. Currently, intravitreal injection of VEGF inhibitors (mainly ranibizumab, bevacizumab, or aflibercept) is the standard care for patients with wet AMD as well as additional retinal indications [8]. However, as most of the retinal diseases are chronic some issues remain, including the high cost of the drug and the need for frequent intraocular injections involving possible side effects. Also, considering the small size of the eye and its ocular barriers, standard delivery methods such as systemic administration and topical instillation are less desirable for the treatment of retinal diseases [1–5]. In order to sustainably administer drugs to the retina, various ophthalmological drug delivery systems (DDS) and devices have been devised [9–11]. However, to date, few have been widely used in clinical medicine due to the high invasiveness and complicated procedures for device implantation.

Pharmacological therapies based on nanometer-scale carriers (nanocarriers), such as lipids and polymers assembled with drugs (including small molecule drugs, peptides, proteins, and nucleic acids) [12–14], which were initially developed for cancer treatments, have been extensively investigated for treating ocular diseases, while most of them are still in preclinical phase. These approaches present several advantages, including increase of the stability of entrapped drugs and the drug half-life in the vitreous, reduction of the drug toxicity, the possibility of ligand attachment, and a reduction of the number of administrations, which could be complementary to those of device-based approaches mentioned in this review. Several comprehensive reviews are available describing ocular nanotherapy [15–20].

In this review, we focus on implant device-based approaches for locally delivering drugs to the posterior segment of the eye for treating retinal degenerative diseases. We first mention conventional treatments for retinal diseases and provide an overview of the current ophthalmological DDS devices. We also present our perspectives on future directions and challenges that remain for developing effective device-based therapies for retinal diseases.

2. Conventional treatments for retinal diseases

The leading causes of irreversible blindness and visual impairment are retinal degenerative diseases including glaucoma, diabetic retinopathy, retinitis pigmentosa, and AMD, which affect millions of people worldwide [21]. Although the biological basis of these diseases is not fully understood, the degeneration of the retina is caused by the progressive and eventual death of retinal cells [22]. Damage to any type of retinal cell results in irreversible changes, so therapeutic options that can reverse the degenerative processes are not available. Therefore, the fundamental therapy involves delaying the degeneration progress by use of drugs. The current conventional treatments for retinal degenerative diseases are topical instillation of intraocular pressure lowering agents and intraocular injection of anti-VEGF agents (Fig. 1).

2.1. Topical instillation

Topical instillation of eye drops is the most convenient and effective method for treating ocular surface and anterior eye diseases. Glaucoma is triggered by elevated intraocular pressure and its endpoint is the apoptosis of retinal neurons [21]. The biological basis of glaucoma is not fully understood, and the factors contributing to its progression are currently not well characterized. Still, lowering the intraocular pressure, the only proven treatable risk factor, is an effective initial approach for reducing the progression of the glaucoma, and there are five major classes of drugs used for lowering intraocular pressure, which are usually administered in combination as eye drops [8]. Poor patient compliance (*e.g.*, due to forgetfulness) has limited the improvement of the disease states; less than half of the patients with glaucoma are said to maintain

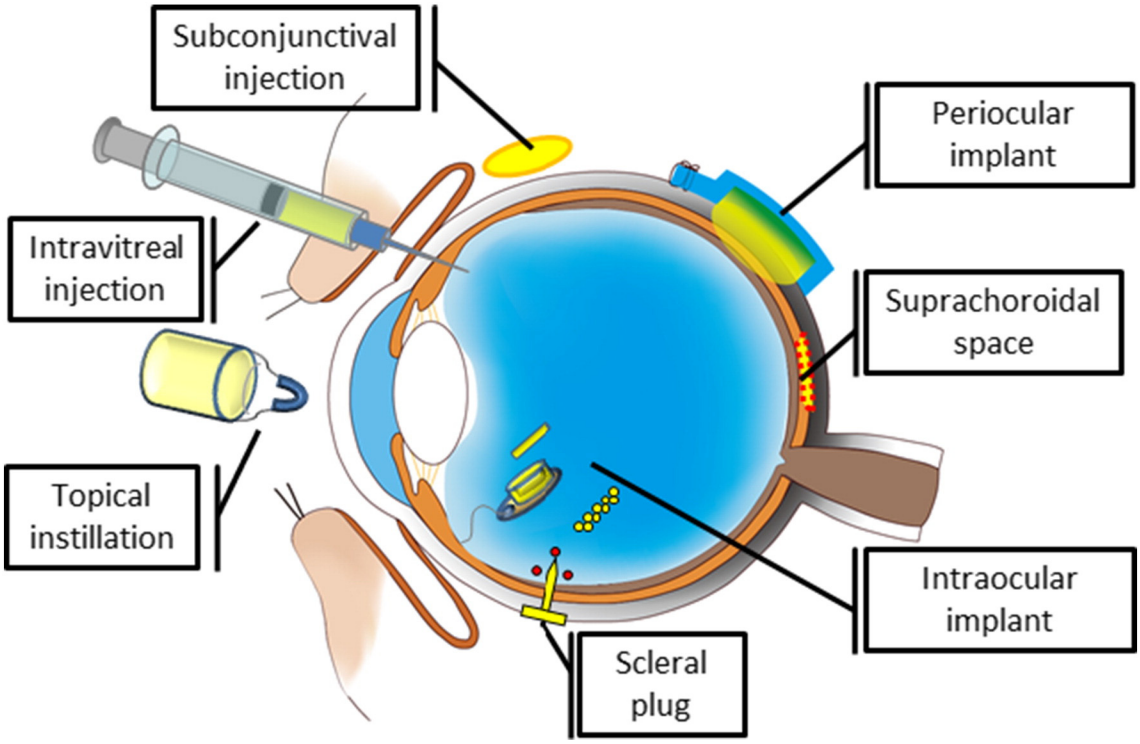

Fig. 1. Examples of drug delivery systems and devices for the posterior segment of the eye.