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Research Paper

Current nanotechnology approaches for the treatment and management of diabetic retinopathy

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ABSTRACT

Diabetic retinopathy (DR) is a consequence of diabetes mellitus at the ocular level, leading to vision loss, and contributing to the decrease of patient's life quality. The biochemical and anatomic abnormalities that occur in DR are discussed in this review to better understand and manage the development of new therapeutic strategies. The use of new drug delivery systems based on nanoparticles (e.g. liposomes, dendrimers, cationic nanoemulsions, lipid and polymeric nanoparticles) is discussed along with the current traditional treatments, pointing out the advantages of the proposed nanomedicines to target this ocular disease. Despite the multifactorial nature of DR, which is not entirely understood, some strategies based on nanoparticles are being exploited for a more efficient drug delivery to the posterior segment of the eye. On the other hand, the use of some nanoparticles also seems to contribute to the development of DR symptoms (e.g. retinal neovascularization), which are also discussed in light of an efficient management of this ocular chronic disease.

1. Introduction

Diabetes mellitus is a chronic disease that affects billions of people all over the world, and results from the body's inability to either produce or use insulin. This disease is mainly associated with high levels of glucose in the blood, i.e. hyperglycemia. It can be classified into two chronic forms, namely: (i) Type 1, which is diagnosed earlier usually in children and youth and is characterized by the deficiency in the production of insulin. In this case, there is a destruction of islet beta cells mostly attributed to auto-immune etiology; (ii) Type 2, which has higher incidence (≈90–95% of the cases) and it is characterized by the reduced production of insulin and/or by insulin resistance, affecting mainly muscle, liver and adipose tissue, resulting in inappropriate levels of circulating glucose. There is a third form of diabetes, the gestational diabetes, which is observed during pregnancy in a small number of women caused by interference of placental hormones interference with insulin receptor resulting in inappropriate elevated glucose levels [1].

The inability of the body to use glucose resulting from the deficiency of the hormone responsible for its use (i.e. insulin), leads to constant hyperglycemia which results in many chronic effects, such as macro- and microvascular complications associated with

Abbreviations: ACE, angiotensin-I converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II type 1 receptor; AGEs, advanced glycation end-products; AMD, age-related macular degeneration; AR2, aldose reductase; ARPE, arising retinal pigment epithelia; BRB, blood–retinal barrier; CAT, catalase; DME, diabetic macular edema; DR, diabetic retinopathy; EPO, erythropoietin; FDA, Food and Drug Administration; GH, growth hormone; GHIH, growth hormone-inhibiting hormone; GLUT1, glucose transporter 1; GPx, glutathione peroxidase; GSH, reduced glutathione; GR, glutathione reductase; IGF-1, insulin-like growth factor 1; IOP, intraocular pressure; IRMA, intra-retinal microvascular abnormalities; K5, plasminogen kringle 5; mRNA, messenger ribonucleic acid; PAMAM, polyamidoamine; PDGFs, platelet-derived growth factors; PEDF, pigment epithelium derived factor; PEG-β-PCL, poly(ethylene glycol)-β-polycaprolactone; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PMMA, poly(methyl methacrylate); PVA, polyvinyl alcohol; PDR, proliferative diabetic retinopathy; PKC, protein kinase C; MnSOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; NISA, non-peptide imidazolidine-2,4-dione; NLC, nanostructured lipid carriers; NPDR, non-proliferative diabetic retinopathy; NOS2A, NOS3, nitric oxide synthases; o/w, oil-in-water; RAGEs, receptor for AGEs; RNS, reactive nitrogen species; ROS, reactive oxygen species; RVO, retinal vein occlusion; SI, silicate; SLN, solid lipid nanoparticles; SRIF, somatotropin release-inhibiting factor; SSTR, somatostatin receptor; STZ, streptozotocin; SOD, superoxide dismutase; TGFbeta, transforming growth factor beta; TiO_2, bare titanium dioxide; UDP, uridine diphosphate; VEGFs, vascular endothelial growth factors; w/o, water-in-oil.

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heart disease, stroke and peripheral arterial diseases. The constant hyperglycemia causes damage in the small blood vessels, which affects the ocular, nervous and renal system. That is why it is of utmost relevance to control diabetes and its consequences, to prevent retinopathy, neuropathy and nephropathy complications [1].

Diabetic retinopathy (DR) is one of the major consequences of diabetes and it is characterized by microvascular complications having a significant impact on patient's life quality, in particular, in visual acuity, eventually leading to blindness [2]. Diabetic patients, both Types 1 and 2, are regularly screened for retinopathy with an initial dilated and comprehensive eye examination by an ophthalmologist. Even patients with a very rigorous control of diabetes, are not free from developing DR [3].

In order to prevent and reverse diabetic side effects, such as retinopathy, several strategies have been used to prevent the chronic disease with modern and innovative systems based on nanoparticles which are addressed in this review. Nanoparticles may be applied for several clinical purposes. When applying this concept in medicine, it is called nanomedicine. In drug delivery, nanoparticles (1–1000 nm) are used for the treatment and/or prevention of diseases, with the final goal to spam patient's life-time. Regarding these goals, nanoparticles offer numerous advantages, compared to treatments with drugs alone or even with classic delivery systems. The majority of the drugs show problems including (i) low solubility in solvents; (ii) high toxicity; (iii) need of high doses to exhibit therapeutic effect; (iv) aggregation; (v) enzymatic and chemical degradation and (vi) reduced half-time. Thus, the loading of drugs into nanoparticles could overcome these limitations and additionally provide (i) sustained delivery; (ii) targeted delivery to specific cells or tissues; (iii) improved delivery of both water-insoluble drugs and large biomolecule drugs, and (iv) reduced side effects minimizing toxicological reactions [4,5].

This paper reviews the diabetes-induced mechanisms involved in the course of DR, a knowledge that is fundamental in the design of new therapeutic strategies. The contribution of nanomedicine to treat and manage DR and its microvascular changes is also discussed.

2. Diabetic retinopathy

2.1. Concepts

DR is potentially caused by sustained hyperglycemia and the consequences occurring in the minor vascular retinal vessels [6]. DR is also characterized by the abnormal growth of new blood vessels resulting from a hypoxic retina, in order to improve the supply of oxygen [7].

According to the international classification system, DR is divided into two broad categories, namely, the non-proliferative DR (NPDR) and the proliferative DR (PDR) [8]. NPDR is further subdivided into mild, moderate, and severe. This classification system considers the number and severity of anatomical abnormalities, which include: (i) microaneurysms; (ii) hemorrhages; (iii) venous beading, and (iv) intra-retinal microvascular abnormalities (IRMA), when attributing to the eyes a particular level of severity [9]. The international classification of DR is summarized in Table 1. An ophthalmologist could detect the DR by the analysis of these symptoms, in parallel with additional examinations, such as visual acuity test, dilated eye examination and tonometry, which measures the intraocular pressure (IOP) [2].

Retina is the anatomical structure of the eye affected in the DR. Physiologically it is the light-sensitive tissue located at the back of the eye, it is characterized by a thin transparent structure composed by several layers comprising the light-sensitive structures. It is enriched in polyunsaturated fatty acids and is metabolically very active having high glucose oxidation and oxygen uptake [10]. The schematic structure of the human eye and the ocular globe is shown in Fig. 1. The cells figuring in retina are divided into three major groups, namely, (i) the neuronal component, which includes photoreceptors, interneurons, and ganglion cells, responsible for retinal visual function which converts light into electrical signals; (ii) the glial components, Muller cells, astrocytes and resident macrophages (microglia), which are responsible for retina support (e.g., nutritional, regulatory); and (iii) the vascular components, which consist of the central retinal artery, supplying the inner and outer retina by diffusion from choroidal circulation. The retinal vessels are responsible for the maintenance of blood–retinal barrier (BRB) and are composed of endothelial cells with tight junctions between them [7,11]. Pericytes or mural cells are another type of contractible cells surrounding the capillaries endothelial cells. The main function of these cells is the regulation of retinal capillary perfusion and its loss is associated with DR. Diabetes will affect both neuronal and vascular components of the retina and will influence some cells and extracellular proteins [2,12].

Table 1
International clinical DR disease severity scale, adapted from [8].

Proposed disease severity level	Dilated ophthalmoscopy findings
No apparent retinopathy	No abnormalities
Mild non-proliferative DR	Microaneurysms only
Moderate non-proliferative DR	More than just microaneurysms, but less than severe NPDR
Severe non-proliferative DR	No signs of PDR, with any of the following: – More than 20 intra-retinal hemorrhages in each of four quadrants – Definite venous beading in two or more quadrants – Prominent intra-retinal microvascular anomalies in one or more quadrants
PDR	One or more of the following: – Neovascularization – Vitreous or pre-retinal hemorrhage

2.2. Pathophysiology

The major symptom in diabetes is hyperglycemia, which causes both acute and reversible changes in cellular metabolism and long-term irreversible changes in stable macromolecules. The metabolism of the cells starts to response to the hyperglycemic environment even before disease pathology is detectable [6,13].

In an advanced stage, the ischemia is the major factor responsible for the growth of abnormal retinal blood vessels (neovascularization) which grow in an attempt to supply oxygen to the hypoxic retina [2]. In addition, the loss of some retinal cells is also detected in DR patients [13]. In addition to hyperglycemia, there are other factors that contribute to the development of DR, such as hyperlipidemia and hypertension [14–17]. Despite the acknowledgment hyperglycemia consequences at the ocular level, the mechanisms causing the vascular disruption in retinopathy are not well known, and, not surprisingly, several pathways have been pointed out as being implicated. However, it is crucial to understandthe mechanism of capillary loss due to biochemical mechanisms to clarify the disease pathogenesis. Thus, good glycemic control is a very important strategy to inhibit/prevent the development of DR in addition to early intervention to prevent the progression of retinopathy in diabetes [2]. However, the challenging in maintaining good glycemic levels for this chronic disease could be a hard task, since other factors also contribute to the development of DR, including pregnancy, age and hypertension [1]. In order to find a