· Review Article ·

Advances in new hypoglycemic drugs for diabetic retinopathy

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糖尿病视网膜病变的新型降糖药物研究进展

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摘要

糖尿病视网膜病变(DR)是糖尿病(DM)患者中常见的并发症,视力受到严重影响的同时,生活质量也将随之降低。最新研究表明,降糖治疗不仅能改善血糖控制,还可能对DM相关的眼部并发症产生保护作用。尽管初步临床数据支持这一观点,但仍需进一步深入探索以阐明这些药物在DR中的具体作用机制及疗效。目前相关研究仍处于发展阶段,尚存某些未解决的科学问题和临床挑战。本叙述性综述总结了新型降糖药物在DR中的应用及最新进展,尤其关注的是胰高血糖素样肽-1受体激动剂(GLP-1RA)、钠-葡萄糖协同转运蛋白2抑制剂(SGLT2i)以及二肽基肽酶-4抑制剂(DPP-4i),重点阐述其作用机制证据、现有临床发现及未来研究方向,为DR的管理提供参考。

关键词:糖尿病视网膜病变;新型降糖药物;胰高血糖素样肽-1受体激动剂;钠-葡萄糖协同转运蛋白2抑制剂;二肽基肽酶-4抑制剂

Abstract

• Diabetic retinopathy (DR) is a common complication in patients with diabetes mellitus(DM) that seriously affects the vision and quality of life. Ongoing research suggests that glucose-lowering therapies not only improve glycemic control but may also exert protective effects on DM related ocular complications. Although preliminary clinical data support this viewpoint, further in-depth exploration is warranted to investigate the specific mechanisms and efficacy of these drugs in DR. Currently, relevant research is still in the developmental stage and certain unresolved scientific questions and clinical challenges still exist. This narrative review summarizes the applications and recent advances of new hypoglycemic drugs in DR, with a focus on glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and dipeptidyl peptidase-4 inhibitors (DPP-4i), highlighting mechanistic evidence, available clinical findings, and future research directions to provide insights for DR management.

• KEYWORDS: diabetic retinopathy; new hypoglycemic drugs; glucagon-like peptide-1 receptor agonists; sodium-glucose cotransporter-2 inhibitors; dipeptidyl peptidase-4 inhibitors

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INTRODUCTION

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus (DM) that can lead to blindness in severe cases. With the increasing number of people with DM worldwide, the incidence of DR is also increasing and becoming an important public health challenge. Research has shown that the occurrence of DR is closely related to the duration of diabetes, degree of blood glucose control, and other metabolic factors[1]. In DM, good blood glucose control is considered a key factor in preventing DR, whereas poor blood glucose control significantly increases the risk of retinopathy[2]. Traditional hypoglycemic drugs, such as

metformin, sulfonylureas, and insulin, mainly exert their effects by directly regulating the blood glucose levels, whereas new hypoglycemic drugs such as sodium - glucose cotransporter-2 inhibitors (SGLT2i), glucagon - like peptide-1 receptor agonist (GLP - 1RA), and dipeptidyl peptidase-4 inhibitors (DPP-4i) achieve broader metabolic regulation through multi-target mechanisms. In recent years, with the development of new hypoglycemic drugs, treatment options for diabetes have increased considerably. Notably, these new drugs not only improve blood glucose control, but may also exert indirect protective effects on the retina by improving cardiovascular health and reducing renal burden[3]. Although emerging evidence suggests potential benefits of new hypoglycemic drugs in the context of DR, direct clinical evidence evaluating their effects on DR - specific outcomes remains limited, and further well - designed clinical studies are warranted to verify their long - term effectiveness and safety. Most currently available studies are derived from mechanistic investigations, *in vitro* experiments, or animal models, whereas clinical studies specifically evaluating DR outcomes remain relatively scarce. The efficacy of these drugs may vary, especially in different types of DM; therefore, the development of personalized treatment plans is particularly important[4]. Further investigation into the underlying mechanisms of DR may facilitate the development of targeted therapeutic approaches and provide additional insights for the management of diabetes-related retinal complications[5].

LITERATURE SEARCH STRATEGY

This narrative review was conducted based on a comprehensive literature search of PubMed, Web of Science, and Embase databases. Relevant articles published up to December 2024 were identified using combinations of keywords related to DR and new hypoglycemic drugs, including "diabetic retinopathy", "diabetes mellitus", "hypoglycemic drugs", "glucose - lowering agents", "GLP - 1 receptor agonists", "SGLT2 inhibitors", and "DPP - 4 inhibitors". Studies investigating the mechanisms of DR, retinal microvascular injury, oxidative stress, inflammation, neurodegeneration, as well as the potential retinal effects of novel hypoglycemic agents were considered. Additional relevant publications were identified through manual screening of reference lists of selected articles. Studies were included if they provided experimental, mechanistic, or clinical evidence related to retinal structure, vascular function, inflammatory responses, oxidative stress, or neuroprotection in the context of diabetes or DR. Articles unrelated to retinal outcomes, non - English publications, conference abstracts, and duplicate reports were excluded. As this is a narrative review, no formal systematic quality assessment or meta-analysis was performed.

MECHANISM OF DR OCCURRENCE

DR is one of the most common complications of DM and the leading cause of blindness in adults. Its pathological and physiological mechanisms are complex, involving structural changes in the retinal blood vessels, effects of hyperglycemia on the retina, and role of pro - inflammatory and oxidative stress responses.

Structural Changes in the Retinal Blood Vessels Microvascular injury is the hallmark of DR. This type of injury can cause small protrusions in the blood vessel walls, leading to the formation of microaneurysms. This rupture can cause retinal hemorrhage. As the disease progresses, the reduction in the number and diameter of retinal capillaries affects the overall perfusion and exacerbates the hypoxic state of the retina, leading to degeneration and functional impairment of the retinal neurons[6], particularly damage to the ganglion and Müller cells, which play an important role in the pathogenesis of retinal ischemia and hypoxia, resulting in a vicious cycle[7]. At the same time, hypoxia can promote the production and release of vascular endothelial growth factor (VEGF), leading to abnormal neovascularization[8-9], which is more likely to cause bleeding and more serious complications, such as tractional retinal detachment. In addition, studies have shown that compared to healthy participants, patients with DR often exhibit dilation and degeneration of the retinal arteries and veins, resulting in hemodynamic changes[10]. This change in the vascular diameter correlates with the severity of retinal lesions and is considered a manifestation of ischemia and neurodegeneration within the retina. In the context of DR, the increase in the retinal vessel diameter is also considered to be associated with poor long - term blood glucose control and ischemic factors[11-12]. Retinal vessel whitening indicates vascular wall damage and is another manifestation of retinal ischemia. These changes are particularly evident in the later stages of DR and can serve as prognostic indicators for disease progression and potential visual outcomes in patients[13].

Hyperglycemia Some of the main pathways affected by hyperglycemia include the formation of advanced glycation end products (AGEs), the polyol pathway, and the activation of the protein kinase C and hexosamine pathways. Research has revealed that hyperglycemia can lead to excessive production of reactive oxygen species (ROS), which can damage cell membranes, proteins, and mitochondria, causing apoptosis and necrosis[14-15], ultimately leading to the development of DR. In addition, inflammatory activation and damage under hyperglycemia conditions as well as damage to the retinal neurons contribute to a decline in retinal function and visual ability[16]. Notably, oxidative stress increases the inflammatory cytokines levels, which in turn increases ROS production to reproduce oxidative stress, creating a vicious cycle.

Oxidative Stress Free radicals are crucial for key redox signaling pathways; however, metabolic disorders can alter the balance between free radicals and antioxidants, thereby damaging the retina, which is exposed to both cytoplasmic and mitochondrial ROS. In DM, the oxidation of pyruvate

increases the flux of the electron transport chain and the voltage gradient in the mitochondrial membrane. Electron transfer within complex III will be hindered upon reaching the critical threshold, leading to a further increase in superoxide production. During the pathogenesis of DR, a vicious cycle is formed between mitochondrial damage and cytoplasmic ROS generation, leading to damage to various systems, including the inhibition of mitochondrial superoxide scavenging enzymes, reduction of antioxidants, transcription of antioxidant enzymes regulating antioxidant responses, and decreased transcriptional activity of major transcription factors. Thus, oxidative stress plays a major role in the pathogenesis of DR[17].

Inflammatory Response DM increases the expression of many inflammatory molecules in the retina, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, whose activation further promotes the release of inflammatory factors[18]. The significant increase of inflammatory factors, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, directly promotes the inflammatory response of the retina in patients with DM[19]. Studies have reported elevated levels of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in patients with DR[20]. Compared with patients with non-proliferative DR, patients with proliferative DR exhibit significantly increased expression levels of inflammatory mediators (IL-8, IL-11, and TNF-α) in the vitreous fluid. In addition, growth factors [platelet-derived growth factor AA (PDGF-AA), glial cell line-derived neurotrophic factor (GDNF), and vascular endothelial growth factor A (VEGFA)] and cytokines [C-X-C motif chemokine ligand 10 (CXCL10), interferon-gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF)] in the vitreous fluid are also elevated. The results of this comprehensive analysis suggest that a combination of therapeutic strategies based on anti-VEGF therapy may improve the progression of DR. These results indicate that inflammatory response plays an important role in the occurrence and development of DR.

Genetic Factors The role of epigenetics in DR is still in the early stages of development. Studies have reported that patients with type 2 DM (T2DM) with retinal lesions exhibit significantly higher overall DNA methylation levels than those without retinal lesions[20], and several non-coding RNAs, including miRNAs and long non-coding RNAs (LncRNA), are associated with oxidative stress in DM. miR-145 and miR-383 can also inhibit the apoptosis of retinal endothelial cells[21]. Another study demonstrated that LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) regulates antioxidant defense in DR through Kelch-like ECH-associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (Nrf2). Inhibition of LncRNA MALAT1 may protect the retina from oxidative damage, and upregulation of LncMALAT1 inhibits the transcriptional activity of Nrf2, thereby impairing the transcription of antioxidant defense genes, such as *HO*-1 and *Sod*2, and preventing or slowing down DR[22]. Therefore, both DNA methylation and epigenetic modifications of non-coding RNA play an important role in the pathogenesis of DR.

CLASSIFICATION AND MECHANISMS OF NOVEL HYPOGLYCEMIC DRUGS

Mechanism of Action of New Hypoglycemic Drugs

Compared with traditional hypoglycemic drugs, such as metformin and sulfonylureas, the research and development of new hypoglycemic drugs provide multiple new treatment options for patients with DM. These drugs can not only effectively control the blood glucose levels but also exert additional biological effects, especially in the prevention and treatment of diabetes-related complications. Based on their mechanism of action, new hypoglycemic drugs can be divided into various categories, including GLP-1RA, SGLT2i, and other types of hypoglycemic drugs.

GLP-1RA GLP-1RA primarily enhances insulin secretion in the pancreatic beta cells through glucose dependent mechanisms. The stimulation of insulin release during elevated blood glucose levels can minimize the risk of hypoglycemia[23]. It can also inhibit glucagon secretion, thereby reducing hepatic glucose production and lowering blood glucose levels. The dual effect of enhancing insulin while inhibiting glucagon is crucial for regulating the overall blood glucose levels[24]. In addition, GLP-1RA can delay gastric emptying, which not only helps in better postprandial blood glucose control, but also enhances satiety, thereby contributing to weight management. Research has shown that GLP-1RA may regulate appetite and energy expenditure through signaling pathways in the brain, thereby positively affecting lipid metabolism and promoting weight loss[25]. In addition to these metabolic effects, recent studies have also reported on the anti-inflammatory properties of GLP-1RA. Chronic inflammation is a common in T2DM that promotes disease progression and complications, including cardiovascular disease. The anti-inflammatory effect of GLP-1RA may help alleviate these risks while providing cardiovascular protection for blood glucose management. Existing studies have shown that GLP-1RA reduces the incidence of major adverse cardiovascular events in high-risk patients with T2DM by improving hypertension and high cholesterol levels[26-28]. These drugs can reduce the triglyceride levels and improve liver function, which is particularly important considering the high prevalence of nonalcoholic fatty liver diseasein patients with obesity and diabetes[29].

SGLT2i SGLT2i reduces the blood glucose levels in patients with T2DM by inhibiting renal glucose reabsorption and increasing glucose excretion in urine. Recent studies on SGLT2 inhibitors have demonstrated that these drugs not only

comprehensively control the blood glucose levels but also improve postprandial blood glucose control by targeting SGLT2, which reabsorbs residual glucose in the intestine. This dual effect is crucial for optimizing the treatment of T2DM, and the hypoglycemic efficacy of such drugs may be further improved. In addition to controlling the blood glucose, it improves cardiovascular and renal health and aids in weight loss, resulting in favorable metabolic changes[30-31]. For example, SGLT2i can reduce sympathetic nervous system activity, which is also associated with a reduction in cardiovascular events in patients with T2DM[32-33]. This autonomic nervous system regulation by SGLT2i helps in reducing the hospitalization and cardiovascular mortality rates for heart failure[34-35], thus reducing the risk of major adverse cardiovascular events[36]. Moreover, SGLT2i helps in regulating weight and components of the metabolic syndrome, including increased urinary glucose excretion and associated calorie loss. Meanwhile, appetite regulation can influence dietary behavior associated with brain mechanisms, such as the hypothalamic circuit activity, which may be altered by the pharmacological effects of SGLT2i[33].

DPP-4i DPP-4i specifically blocks the activity of DPP-4 enzyme, which is responsible for degrading intestinal insulinotropic hormones, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), by inhibiting its activity. By inhibiting this enzyme, DPP-4i increases the concentration of these hormones in the blood and prolongs the half-life of GLP-1 and GIP; thus, DPP-4i has many similarities with GLP-1RA, including enhancing insulin secretion, inhibiting glucagon release and secretion, slowing gastric emptying, reducing appetite, and improving beta cell function. It also exerts positive effects on cardiovascular and kidney health. Thus, these mechanisms contribute to better blood glucose control in patients with T2DM, thereby reducing the risk of complications associated with uncontrolled blood glucose levels.

Mechanism of Action of New Hypoglycemic Drugs in DR Management Current evidence regarding the retinal effects of novel hypoglycemic drugs mainly originates from experimental studies, animal models, and mechanistic investigations, while direct clinical evidence evaluating DR-specific outcomes remains relatively limited.

Protective effect on the retinal blood vessels

GLP-1RA GLP-1 receptors are present in the retinal capillary endothelial cells, and exendin-4 effectively regulates the retinal capillary diameter through the GLP-1 receptor-phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt, also known as PI3K/PKB) endothelial nitric oxide synthase (eNOS)/nitric oxide (NO) cyclic guanosine monophosphate (cGMP) pathway. In addition, under ischaemia-reperfusion(I/R) conditions, local administration of exendin-4 improves retinal endothelial function, and GLP-1RA has been reported to protect endothelial connections by inhibiting stimulator of interferon genes(STING) signaling[37]. In addition, GLP-1RA may reduce pathological angiogenesis in the retina by inhibiting VEGF expression, thereby further protecting the integrity of retinal blood vessels[38]. Liraglutide protects retinal blood vessels and nerve function, and enhances the function of neurovascular units in the retina[39]. Liraglutide reportedly inhibits the activation of the NLRP3 inflammasome and reduces the proinflammatory reaction of microglia, thus indirectly maintaining the integrity of the blood-brain barrier and enhancing pericellular coverage, which is essential for maintaining vascular stability[40], improving the disorder of angiogenesis attributed to diabetes and normalizing it, thus helping regulate vascular coverage and improve retinal function.

SGLT2i It may protect retinal microvessels by improving endothelial function and reducing the vascular inflammatory response. SGLT2i can significantly reduce retinal vascular permeability in DM mouse models while alleviating retinal inflammation and vascular damage[41]. The protective effect of SGLT2i on retinal microvessels may be closely related to their unique metabolic regulatory properties. For example, SGLT2i can improve the energy metabolism status of cells by restoring autophagy function, thus promoting the clearance and renewal of damaged mitochondria[42-43]. It may also directly act on the nutrient-sensing pathway, modulating mechanistic target of rapamycin (mTOR) signaling and activating the AMPK pathway to alleviate endothelial cell damage attributed to high glucose levels[44]. In addition, SGLT2i also reduces periretinal cell swelling, improves microcirculation regulation, and inhibits excessive production of type IV collagen, thus maintaining the integrity of the retinal blood retinal barrier[45-46].

DPP-4i Sitagliptin has been reported to exert protective effects against retinal degeneration, which is closely related to the improvement of endothelial function regulated by DPP-4i. Maintaining retinal vascular integrity is crucial[47]. High-quality endothelium can regulate blood flow and nutrient delivery to the retina, thereby reducing the risk of DR. The mechanism of action of DPP-4i may involve the expression of VEGF, release of pro-inflammatory factors such as IL-6 and TNF-α, and inhibition of high glucose induced increased vascular permeability and pathological neovascularization[48]. In addition, the regulation of VEGF signaling by DPP-4i may also play an important role in preventing the progression of retinal vascular changes associated with DM. Thus, although DPP-4i reportedly may have beneficial effects on the progression of DR through its anti-inflammatory and vascular protective properties, further research is warranted to establish a direct link between DPP-4i and retinal progression in DR.

Reduction of oxidative stress and inflammatory response

GLP-1RA Exenatide reduces the oxidative stress markers MDA and oxidized low-density lipoprotein(oxLDL). It also reverses the downregulation of Sirtuin 1(SIRT1) and prevents increased ROS production, decreased mitochondrial

membrane potential, and mitochondrial cell apoptosis[49]. Dulaglutide not only improves inflammation by restoring mitochondrial membrane potential, superoxide and hydrogen peroxide levels, NOX4 expression, and glutathione (GSH) levels in TNF-α treated human fibroblast like synovial cells[50]. Moreover, improving mitochondrial fragmentation can potentially restore mitochondrial morphology and function[51]. Both semaglutide and liraglutide increased the superoxide dismutase (SOD) levels and exerted anti-inflammatory effects. Liraglutide can also reduce oxidative stress by increasing the serum SOD levels and lowering the expression of serum MCP-1 and NF-κB to inhibit internal inflammatory reactions[52]. In addition, it can also induce SIRT1 mediated mitochondrial improvement, reduce ROS production to stabilize the mitochondrial membrane potential, increase adenosine triphosphate levels, and enhance the activity of mitochondrial complex-I[53]. Studies have shown that inflammation (IL-6 and inducible NOS) and oxidative stress (3-nitrotyrosine) markers normalize after treatment with liraglutide[54], and serum HO-1 concentration also increases, which may indicate an increase in the antioxidant capacity.

SGLT2i Canagliflozin acts through pathways involving AMPK, Akt, eNOS, and Nrf2, to attenuate pro-oxidative, pro-inflammatory, and pro-apoptotic signaling[55]. In addition, it improves mitochondrial homeostasis. Dapagliflozin can reduce macrophage infiltration and the expression of inflammatory cytokines and oxidative stress-related genes, such as NOX4, MCP-1, and osteopontin[56]. Several studies on the treatment of dapagliflozin and empagliflozin alone or in combination have also shown that they can reduce IL-1β levels to weaken NLRP3 inflammasome activation. More diverse studies exist on the SGLT2i class of empagliflozin, such as its significant reduction of mitochondrial Ca^{2+} in human endothelial cells by empagliflozin, which triggers overload and superoxide production[57]. Reducing high glucose levels induces apoptosis and improves mitochondrial function by restoring mitochondrial ROS, matrix metalloproteinase (MMP), and ATP production[58]. It can also reverse mitochondrial dynamics and autophagy[59]. Empagliflozin also has a protective effect against high glucose-induced epithelial-mesenchymal transition (EMT) inhibits oxidative stress (MDA levels, SOD, and GSH Px activity) in the peritoneal mesothelial cells (PMCs) by activating the Nrf2/HO-1 signaling pathway[60]. Empagliflozin improves blood glucose regulation and endothelial function, reduces several oxidative stress parameters, such as whole blood oxidative burst and aortic and endothelial ROS formation (measured by dehydroergosterol under a microscope), and regulates the epigenetic regulation of AGE/receptor for advanced glycation end products (RAGE) signaling to prevent inflammation and glucose toxicity[61].

DPP-4i Sitagliptin can inhibit NF-κB activation and inflammatory cytokine expression in rat insulinoma cells, suggesting a direct anti-inflammatory effect of DPP4i in pancreatic beta cells[62]. Inhibition of DPP4 by agliptin is manifested in TLR4 mediated extracellular regulated protein kinase (ERK) activation and ERK-dependent MMP expression in U937 cells, indicating that DPP-4 may play an important role in macrophage-mediated inflammation and tissue remodeling in U937 cells[63]. The DPP-4 inhibitor des-fluoro-sitagliptin (DFS) significantly increases GLP-1 induced cyclic adenosine monophosphate cytoplasmic levels, leading to inhibition of c-jun N-terminal kinase and extracellular signal regulated kinase 1/2, as well as phosphorylation of NF-κB p65 through the cyclic adenosine monophosphate/protein kinase A pathway for nuclear translocation, and inhibition of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and monocyte chemoattractant protein 1 production of lipopolysaccharides. Compared to GLP-1 alone, DFS enhances GLP-1 activity, maintains eNOS phosphorylation, and reduces endothelial cell aging and apoptosis[64].

Protective effect on the retinal nerves GLP-1RA: Local application of GLP-1RA in DM mice can improve retinal blood flow and reduce apoptosis of retinal ganglion cells (RGCs). Besides neuroprotection[65], it has also been reported to promote retinal regeneration in experimental models[41]. This means that it likely reverses the neurovascular damage attributed to long-term diabetes. GLP-1RA treatment can also reduce reactive gliosis and vascular leakage, and prevent cell apoptosis and retinal dysfunction. Prevention of DNA/RNA damage, increase in DNA repair, and enhancement of cell proliferation following GLP-1RA treatment confirms that GLP-1RA may promote retinal neurogenesis in experimental studies. Thus, GLP-1RA may exert protective effects against retinal neurodegeneration. In another study evaluating the effect of GLP-1RA on the nerves in various neurodegenerative diseases[65], the results revealed that GLP-1RA can reduce neuroinflammation and provide protection to RGCs. A retrospective clinical analysis found that the use of GLP-1RA in patients with DM can reduce the risk of developing glaucoma by 44%; this protective effect was independent of the hypoglycemic effect[66-67]. These findings suggest that GLP-1RA may have potential benefits in retinal neurodegenerative conditions, although further clinical studies are required to confirm these effects. This shift in our understanding highlights the potential of GLP-1RA to address multiple aspects of DR, suggesting promising outcomes with their use in early intervention strategies.

SGLT2i: From a molecular perspective, the protective effect of SGLT2i on retinal nerves may be associated with the dual regulation of retinal microvessels and neurons. Its intervention in the pathological process of DR includes but is not limited to improving microcirculation disorders, reducing oxidative stress, and inhibiting neuroinflammatory responses, thereby delaying the degenerative changes of RGCs[65,68-69]. In the DM

animal model, it was found that not only can tofogliflozin inhibit VEGF production, but empagliflozin can also downregulate VEGF expression[70-71]. These findings suggest that SGLT2i may indirectly protect neurons from high glucose toxicity damage by regulating the function of retinal pericytes [such as inhibiting pericyte swelling and normalizing glucose uptake) and maintaining the integrity of the blood-retinal barrier[69,72]. However, despite the existing evidence supporting the neuroprotective potential of SGLT2i, its specific targets and long-term efficacy need to be validated through well-designed randomized controlled trials.

DPP-4i Sitagliptin (eye drops) can prevent the downregulation of presynaptic proteins [such as synaptophysin and synaptosome-associated protein 25 kDa (SNAP-25)] in retinal neurons in db/db mouse models, improve synaptic dysfunction and neuronal damage, and maintain synaptic plasticity and neuronal signal transmission integrity[73-74]. It exhibits significant neuroprotective potential through a multitarget mechanism. This discovery has important clinical significance, as traditional hypoglycemic drugs often cannot directly act on the pathological changes in retinal neurons, and this neuroprotective effect is related to the improvement in retinal function, as evaluated by electroretinography. The American Diabetes Association recently redefined DR as a neurovascular rather than microvascular disease, emphasizing the importance of neurodegeneration in its pathogenesis.

It should be noted that most of the evidence discussed above is derived from experimental studies, animal models, or mechanistic investigations. Althoughthese findings suggest that GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors may influence pathways involved in the development of DR, direct clinical evidence demonstrating their efficacy on DR-specific endpoints are still limited. Therefore, the potential retinal benefits of these agents should be interpreted with caution.

Comparative Perspectives Among GLP-1RA, SGLT2i, and DPP-4i Although GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors differ in their primary mechanisms of glucose regulation, accumulating evidence suggests that these agents may exert overlapping protective effects on retinal tissues. Proposed mechanisms include anti-inflammatory actions, reduction of oxidative stress, protection of retinal microvascular integrity, and potential neuroprotective effects on retinal neurons. However, the strength and type of supporting evidence vary among these drug classes. For GLP-1 receptor agonists, several experimental and animal studies have suggested potential neuroprotective and vascular protective effects in the retina, and a limited number of clinical observations have also been reported. SGLT2 inhibitors appear to exert indirect retinal benefits mainly through improvements in metabolic status, reduction of oxidative stress, and modulation of inflammatory pathways, although most current evidence is derived from experimental and preclinical studies. In contrast, evidence regarding the retinal effects of DPP-4 inhibitors is relatively limited and is primarily based on mechanistic or experimental investigations. Overall, while these novel hypoglycemic agents may influence multiple pathways involved in the pathogenesis of DR, robust clinical evidence directly evaluating their impact on DR progression remains limited. A summary of the proposed retinal protective mechanisms and the types of supporting evidence for these drug classes is presented in Table 1.

RESEARCH DIRECTIONS AND CLINICAL APPLICATIONS OF FUTURE NEW HYPOGLYCEMIC DRUGS IN DR

Despite the promising mechanistic and preclinical findings summarized in this review, several limitations should be acknowledged. Most available studies do not directly evaluate DR as a defined clinical endpoint, and evidence from large-scale randomized controlled trials specifically targeting DR outcomes is scarce. In addition, heterogeneity in study design, disease stage, and patient populations may contribute to inconsistent findings. Future well-designed clinical studies are therefore required to clarify the role of new hypoglycemic drugs in the prevention and progression of DR.

Table 1 Proposed retinal protective mechanisms and supporting evidence for novel hypoglycemic drugs in DR

Drug class	Proposedretinal protective mechanisms	Type of supporting evidence	Representative references
GLP-1RA	Anti-inflammatory effects, reduction of oxidative stress, protection of retinal microvascular endothelial cells, inhibition of pathological angiogenesis, andpotential neuroprotective effects on retinal ganglion cells	Mainly experimental studies and animal models; limited clinical observations	[37-39,65-67]
SGLT2i	Improvement of endothelial function, reduction of vascular permeability, attenuation of oxidative stress and inflammatory responses, improvement of mitochondrial function, and indirect retinal protection through metabolic regulation	Experimental studies, animal models, and some observational clinical studies	[41-46,55-61,68]
DPP-4i	Anti-inflammatoryeffects, regulation of VEGF signaling, protection of endothelial function, and potential neuroprotective effects on retinal neurons	Primarily experimental and mechanistic studies; clinical evidence remains limited	[47-48,62-64,73-74]

DR: Diabetic retinopathy; GLP-1RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; DPP-4i: Dipeptidyl peptidase-4 inhibitor; VEGF: Vascular endothelial growth factor.

Future Research Directions In the future, research on new hypoglycemic drugs for DR should mainly focus on improving microvascular dysfunction, inhibiting inflammatory responses, improving retinal nerve function, and exploring multi-target combination therapies. Exploring multi-target combination therapies is an important direction for future DR research. In summary, the pathological mechanism underlying DR is complex and involves multiple molecular pathways, and the therapeutic effect of a single target is often limited. Therefore, the direction of research and development is gradually shifting towards combination and multitarget therapies. Evidence has demonstrated that the combination of SGLT2i with GLP-1RA or DPP-4i may have a synergistic protective effect against DR and more effectively delay its progression. The combined use of insulin and GLP-1RA can not only improve blood glucose control, but also delay the progression of DR by regulating inflammation and angiogenesis pathways.

Another study has shown that DR10627, a novel GLP-1/GIP dual target agonist, has demonstrated significant hypoglycemic and weight control effects in preclinical studies and may have a positive impact on DR by improving the metabolic inflammatory status[75]. Although multitarget hypoglycemic drugs have demonstrated broad application prospects in DR treatment, their research and clinical applications still face many challenges. In the future, the clinical efficacy and long-term safety of these combination therapy regimens in DR should be further validated to provide new treatment methods for the early intervention and prevention of DR, thereby improving patients' quality of life and visual prognosis.

Development and Application of Personalized Therapy

Based on the diverse pathological mechanisms underlying DR, modern medicine can optimize the treatment outcomes by combining genetic and lifestyle data for developing personalized treatments. The application of machine learning and big data analysis technologies can play an important role in developing personalized treatment plans. Predictive models can be constructed by integrating patient genomic data, clinical features, and metabolic indicators to identify subgroups of patients who respond well to specific drugs. In addition, the combination of continuous blood glucose monitoring and artificial intelligence technology can evaluate blood glucose fluctuations and drug efficacy in real-time, providing a basis for the dynamic adjustment of the treatment process. The application of these technologies not only improves the precision of treatment but also promotes early intervention in DR. However, owing to the high cost of precision medicine technology, its widespread application in clinical settings may be limited. In addition, patient compliance and data privacy issues need to be fully considered, and personalized treatment plans for DR require validation through large-scale clinical trials to ensure safety and effectiveness.

CONCLUSION

In recent years, the development of novel hypoglycemic drugs has provided new hope for the prevention and treatment of DR. These drugs are not only effective in controlling blood glucose, but also have the potential to protect the retina. Although preliminary studies have confirmed the protective effects of new hypoglycemic drugs on the retina, more large-scale randomized controlled trials and long-term studies are warranted to verify their efficacy and safety. Some studies have emphasized the advantages of specific novel hypoglycemic drugs in slowing the progression of retinopathy, whereas other studies have not replicated the same results. This underscores the need for a scientific and cautious approach when interpreting the research results, especially when applying these findings to clinical practice. At the same time, considering the complexity of DM, researchers should also consider multidimensional factors to provide patients with more comprehensive treatment plans. Systematic research and individualized treatment can truly aid in the effective prevention and treatment of DR, thereby improving the quality of life and visual health of patients.

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