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Research Progress in the Neurovascular Unit Impairment and Treatment of Diabetic Retinopathy

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Abstract: ***Diabetic retinopathy (DR) is one of the common complications of diabetes and is a leading cause of blindness. Traditionally, DR was considered primarily a microvascular disease. However, with the progress of research, it is now believed that damage to the neurovascular unit plays a key role in the early stages of DR. An updated understanding of neurovascular unit damage facilitates early intervention of retinal function and control of DR progression. This article summarizes the latest understanding of neurovascular unit damage in DR and the latest methods for treating DR, and looks forward to more new treatment strategies in the future.***

Keywords: Neurovascular unit impairment, Treatment, Diabetic retinopathy.

1. Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes mellitus and one of the major blinding eye diseases, which seriously affects the quality of life of patients. The World Health Organisation reported the latest global diabetic population is as many as 422 million, which is expected to reach 642 million by 2040, and the number of diabetic patients in China will be the first in the world [1]. With the rapid increase in the prevalence of diabetes mellitus year by year, the incidence and blindness rate of DR have gradually increased. Studies on the exact pathogenesis and pathways of diabetic retinopathy are not well developed. In early DR, oxidative stress, inflammation, and mitochondrial damage lead to dysfunction of the retinal neurovascular unit (NVU), which further leads to alterations such as haemorrhage, exudation, neovascularization, and fibrous tissue proliferation. Currently, the main treatments for DR aimed at controlling microvascular complications, including laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs or anti-inflammatory drugs, and vitreoretinal surgery, are short-lasting, invasive, or associated with significant side effects and are used to prevent severe visual impairment and blindness in advanced stages of the disease [2]. In recent years, in order to slow down the clinical progression of DR or to reverse retinal damage, national and international experts have worked to develop standardised therapies for earlier stages of DR. This article discusses the latest understanding of retinal neurovascular unit damage and the latest treatment progress of DR.

2. Neurovascular Unit Damage

Microvascular changes have long been considered central to the pathogenesis of DR. However, in recent years, a growing number of studies have shown that under hyperglycaemic pathological conditions, neurological damage may be the origin, followed by vascular lesions, blood flow changes and alterations in the secretion of matrix molecules [3]. In early DR, the normal regulatory mechanisms of the retinal neurovascular complex have been impaired and do not result from damage to vascular or neural tissue alone. Vascular abnormalities can lead to an imbalance between blood supply to the inner retina and retinal nerve cell metabolism, causing neuronal apoptosis and glial cell dysfunction. Nerve cell damage in turn leads to a decrease in vasodilatory factors released by nerve cells, inhibiting microvascular dilation [4].

2.1 Retinal Neurovascular Unit

Functionally coupled and interdependent between neurons, glial cells and the highly differentiated central nervous system, and vascular system, in the retina, the NVU serves as the basic structural and functional unit regulating its normal physiological activities. The NVU consists of neurons (ganglion cells, glioblasts without long synapses, horizontal and bipolar cells), glia (Müller cells and astrocytes), vascular cells (endothelial cells and pericytes), immune cells (microglia and macrophages), basement membranes, and extracellular matrix [5]. Neurons are the ultimate effectors of the nervous system, receiving nutrients and eliminating metabolic wastes by regulating vascular activity. Glial cells play a synergistic vascular role to meet the metabolic needs of neurons, eliminate metabolites, deliver neurotransmitters, and maintain homeostasis of the internal environment as well as signal transduction [6-7]. Endothelial and pericytes constitute the retinal microvasculature, and intercellular communication between the two through gap junctions plays a crucial role in maintaining intravascular homeostasis in the retina [8]. Microglia act as immune cells, monitoring and removing functionally declining cells in their normal state [9]. NVU dysfunction has been found to play a key role in the development of DR.

2.2 Retinal Neurodegeneration and Microangiopathy

Retinal neurodegeneration is a thinning of the nerve fibre and ganglion cell layer of the retina in patients with DR [2], which mainly consists of apoptosis of neurons and proliferation of glial cells [10]. The mechanisms of retinal neurodegeneration are intricate and include inflammation, oxidative stress, glutamate accumulation, autophagy, downregulation of neurotrophic factors and apoptosis [11]. In DR, increased excitotoxic metabolites, increased oxidative stress, decreased synthesis of neurotrophic factors and neuroinflammation occur, ultimately leading to neuronal apoptosis [5]. Neurological stress and apoptosis prompt reactive activation

and proliferation of glial cells, and activated glial cells and microglia phagocytose apoptotic cells, remove cellular debris and toxins, and secrete neurotrophic factors to act as neuroprotective agents. However, sustained glial activation is detrimental to retinal vessels and neurons [12]. The continuous secretion of inflammatory cytokines, cytotoxic molecules, and vascular growth factors by hyperproliferative glial cells leads to increasing microvascular dysfunction and nerve damage. In addition to this, microglia are induced to a pro-inflammatory phenotype when activated by chronic hyperglycaemia, retinal ischemia and hypoxia and endoplasmic reticulum stress with rapid activation and accompanying transcriptional adaptive functional changes. Such activated microglia show alterations in the intracellular metabolic microenvironment, especially upregulation of glycolysis, which is the main source of retinal pro-inflammatory cytokines in early DR, inducing retinal neuroinflammation and neovascularisation [13].

In the hyperglycaemic state, pericytes detach from the vascular endothelium, and without the structural support of pericytes, retinal capillaries become fragile, leading to microaneurysms. In addition, inflammatory factors secreted by neighbouring neurons and glial cells may lead to endothelial cell death [14]. Endothelial cell injury produces more vasoconstrictors such as endothelin and thromboxane A2 to promote microvessel constriction, which further leads to hypoxia and the formation of large areas of capillary nonperfusion. Endothelial cells, pericytes, and retinal pigment epithelial cells release more VEGF, and VEGF and erythropoietin act synergistically with each other to promote microvessel generation, and due to the fragile structure of neovasculature that is easy to rupture and haemorrhage, patients with DR are susceptible to retinal haemorrhage, and if neovasculature grows into the vitreous body, vitreous haematochezia may occur [15]. In addition, the gap junction protein between endothelial cells and pericytes consists of two half-channels docked together and is expressed from the mitochondrial connexin 43 (MtCx43) gene. Hyperglycaemia inhibits MtCx43 gene expression, which breaks the structure and activity of gap junctions, further affecting intercellular communication and increasing vascular permeability leading to leakage [16].

3. The Latest Treatment Progress of DR

3.1 Regulation of Neurotrophic Factors

Neurotrophic factors include pigment epithelium-derived factor (PEDF), brain-derived neurotrophic factor (BDNF) and erythropoietin (EPO). Imbalance of neurotrophic factor production in the retina promotes retinal NVU damage, and appropriate neurotrophic factor supplementation can improve DR.

PEDF can exert its protective effects in DR through various pathways such as anti-vascular permeability, protection of neurons, and inhibition of apoptosis [17]. In the early stage of DR patients, intravenous injection of PEDF can ameliorate retinal neuronal damage and reduce the expression of VEGF [18]. After intravitreal injection of PEDF gene-modified human umbilical cord MSCs in diabetic rats, PEDF-MSCs were found to significantly reduce retinal ganglion cell apoptosis and protect and repair retinal damage [19]. BDNF is secreted by Müller cells and ganglion cells to maintain normal retinal ganglion and longissimus dorsi cell survival. Studies have shown that downregulation of BDNF may be an important cause of diabetic optic nerve degeneration [20]. Quercetin, a type of flavonoid with potent antioxidant effects, may protect diabetic retinal neurons by up-regulating the levels of neurotrophic factors, such as BDNF, and inhibiting neuronal apoptosis in DR rats [21]. EPO is a glycoprotein hormone with anti-apoptotic, neuroprotective, and neurotrophic effects [22]. Intravitreal injection of EPO can effectively protect many types of cells in the retina (e.g., various types of neurons, vascular constituent cells, glial cells, RPE cells, etc.) against diabetic damage, which provides a theoretical basis for EPO intervention in the treatment of early DR.

3.2 Anti-apoptosis and Anti-autophagy

Methyl CpG-binding domain protein 2 (Mbd2) is an important protein in the process of DNA methylation, which is associated with retinal cell death. Mbd2 was significantly upregulated after high glucose treatment of RGCs, and Mbd2 overexpression led to retinal neuronal cell apoptosis partly through the miR-345-5p/Atf1 axis. Therefore, targeting Mbd2 may be a novel therapeutic strategy for the treatment of early DRN [11]. Prolonged hyperglycaemia leads to mammalian target of rapamycin (mTOR) inhibition, resulting in dysregulation of autophagy, which in turn leads to DRN. the use of an mTOR activator restores glucose transporter protein expression, which in turn increases glucose uptake and mTOR complex 1 signalling activity as a means to reduce dysregulation of autophagy and serve as a protective agent for ganglion cells. Inhibition of short hairpin RNA by intravitreal injection of adeno-associated virus (AAV2) vector-delivered mTOR in an early DR mouse model reduces neuronal cell loss, improves vascular permeability and retinal thinning [23].

3.3 Increase in Vascular Endothelial Progenitor Cells

Damage to the retinal vasculature in the diabetic state requires continuous proliferation of vascular endothelial cells for repair. Vascular endothelial progenitor cells (EPCs) belong to the somatic stem cells, which have the ability to self-renew and differentiate into more than one cell type, and are regulated by the stromal cell-derived factor 1 (SDF-1) and its receptor CXCR4 signalling pathway. Expression of SDF-1 leads to a failure of EPCs to differentiate and repair damaged microvessels, and an increase in the proliferation and migration of EC, which can lead to pathologic neovascularization [1]. Currently, the main focus is to increase the number and function of EPCs to counteract diabetic inhibition. Therapies based on granulocyte colony-stimulating factor, erythropoietin or CXCR-4 antagonists have been developed and have demonstrated that increasing natural EPCs alone may be beneficial.

3.4 Protection of Vascular Microcirculation

Calcium hydroxybenzenesulfonate is a kind of vascular microcirculation protection agent commonly used in clinical practice, which can have an inhibitory effect on vasoactive substances such as 5-hydroxytryptamine, histamine and other

vasoactive substances leading to elevated vascular permeability, thus reducing intima-media damage, and improving the permeability of the vascular wall, blood flow rate and microcirculation [24]. Calcium hydroxybenzenesulfonate can inhibit reductase and reduce sorbitol production, which can reduce blood viscosity, inhibit thrombosis, and promote ocular circulation; and calcium hydroxybenzenesulfonate also has an antioxidant effect, which can elevate the activity of nitric oxide synthase, increase endothelium-dependent diastole, and ultimately improve the local microcirculation [25]. Wang Chunyan et al [26] treated patients with diabetic retinopathy with calcium hydroxybenzenesulfonate after fundus laser treatment, which resulted in greater improvement in visual acuity levels, as well as a reduction in macular thickness, haemorrhagic spot area, and vascular tumour volume of the patient's retina. Another study showed that the combination of calcium hydroxybenzenesulfonate capsule and VEGF antagonist in the treatment of diabetic retinopathy could further improve visual acuity and fundus microcirculation in patients [27]. As a vasodilator, pancreatic kininogenase has the effect of dilating small blood vessels and capillaries, improving vascular permeability and blood flow, and studies have shown that pancreatic kininogenase can significantly improve best-corrected visual acuity, increase choroidal blood flow, and significantly reduce the thickness of the choroid in the sub-central concavity [28].

3.5 Retinal Laser Treatment

Retinal laser photocoagulation is still the classical treatment for proliferative DR. Studies have shown that its mechanism for treating DR is to stop disease progression by improving retinal oxygenation and inhibiting retinal VEGF production [29]. In this regard, there are two ways to improve oxygenation: (1) Laser burns cause the retina to thin, bringing the choroidal capillaries physically closer to the inner layers, thus increasing the oxygen supply to the inner retina. (2) Using the thermal effect of laser, i.e., by increasing the local tissue temperature to coagulate proteins, the highly metabolically active photoreceptor complex is eliminated, which reduces the overall oxygen demand of the retina, decreases the expression of VEGF, and finally achieves the goal of effectively inhibiting retinal neovascularisation [30]. There are a large number of clinical studies confirming the efficacy and safety of laser photocoagulation therapy, but side effects such as decreased peripheral vision, reduced visual field, and decreased contrast sensitivity may also occur. Laser technology, which has been improved and developed over the past decades, can be adjusted to minimise adjacent tissue damage, complications and patient discomfort by adjusting the parameters of the laser [31]. In addition, selective photocoagulation of eyes with proliferative DR based on the no-perfusion zone shown by FFA can reduce the risk of laser-related complications as well as achieve the goal of slowing down the progression of the disease [32].

3.6 Anti-VEGF Therapy

VEGF is a key cytokine leading to vascular leakage and macular leakage, and intravitreal VEGF-A levels are closely associated with the progression of DR and DME. Currently, drug therapy represented by anti-VEGF agents has become the first-line therapy for DR, which can dry the retina and reduce vascular leakage and neovascularisation by resisting VEGF [33], effectively reducing the thickness of the central concavity and improving the visual function of patients. Clinically, the more frequently used anti-VEGF drugs include bevacizumab, ranibizumab, abciximab, and compeximab. Bevacizumab antagonises all VEGF-A isoforms and may be a useful adjunct to DR vitrectomy for retinal detachment. Ranibizumab, the first anti-VEGF agent internationally available and specifically designed for ophthalmic diseases [34], binds to all isoforms of VEGF-A. It has a high affinity, good retinal penetration, low molecular weight, and high efficacy and safety [35], but has a relatively short half-life. Abciximab also binds all isoforms of VEGF-A with more than 100 times the affinity of ranibizumab [36]. In addition, it can bind to placental growth factor receptor and modulate a range of neural, glial and vascular cellular responses distinct from VEGF, thereby affecting pathological angiogenesis [37]. Compazine was independently developed in China and initially used for the treatment of wet age-related macular degeneration, and later expanded for the treatment of diabetic macular edema (DME). It has strong affinity and multi-targeting properties, can reach the target concentration in a short period of time [38], and has a long half-life and price advantage. All existing anti-VEGF drugs require repeated injections over a certain period of time, and the development of new drugs targeting VEGF with high efficiency and long duration of action has been a hot research topic.

Farecilizumab is a novel bispecific anti-angiopoietin 2 and VEGF antibody, which, through dual inhibition of angiopoietin 2 and VEGF-A, reduces vascular permeability and suppresses inflammatory responses, thereby inhibiting pathological angiogenesis and restoring vascular stability. This dual inhibition may be more effective and durable than targeting VEGF therapy alone [39]. KSI-301 is also a novel anti-VEGF drug consisting of two components: a specific anti-VEGF antibody and a biopolymer. The biopolymer is an optically clear, high molecular weight choline phosphate polymer that prolongs the duration of action of the anti-VEGF antibody in the eye, but the efficacy and safety of this biopolymer has yet to be further confirmed in larger clinical trials. In addition, gene therapy has emerged as a powerful strategy for the treatment of ocular diseases, offering another possibility for prolonging the duration of action of anti-VEGF therapy. For example, intravitreal injections using the lipopolymer complex LPP delivered HuR siRNA for the treatment of DR. human antigen R (HuR) is an RNA-binding protein that can have a role in regulating VEGF protein expression by binding to mRNA encoding VEGF. Down-regulation of HuR with small interfering RNA (siRNA) can prevent VEGF protein overexpression in DR. Cationic polymers and lipid nanoparticles (liposomes) were co-formulated with siRNA to form LPP to deliver HuR siRNA to the cytoplasm [40].

3.7 Anti-inflammatory Drugs

Inflammation occurs throughout the development of DR, and the activation of inflammatory cells and the expression of inflammatory factors not only lead to the disruption of the blood-retinal barrier (BRB) and the death of retinal neurons, but also exacerbate the onset and progression of DR.

Glucocorticoids modulate the inflammatory response and are used in the treatment of DR including drugs such as triamcinolone acetonide, dexamethasone, and fludrocortisone acetate. Triamcinolone acetonide is a synthetic glucocorticoid, which can be administered by intravitreal injection or subcapsular injection via Tenon's capsule for DME, both of which have significant efficacy [41], but can lead to increased intraocular pressure (IOP) and accelerated cataract progression. Dexamethasone, also known as Aldisil, is a degradable intraocular implant that was approved by the State Drug Administration of China in 2021 for the treatment of DME due to its long-lasting and stable efficacy as well as good safety profile. Dexamethasone has been shown to be a treatment with fewer side effects in routine clinical practice, with elevated intraocular pressure (IOP) being the most common side effect, but it generally does not require surgical intervention and can be medically controlled or self-recovery [42]. Fludrocortisone acetate is a non-biodegradable vitreous implant that significantly improves vision in patients with DME and has shown a favourable safety profile. The device provides continuous release of fludioxonil into the vitreous for 36 months and its therapeutic effect can last up to 3 years [43].

NSAIDs inhibit the cyclooxygenase system, an important mediator of ocular inflammation, by modulating prostaglandin-dependent pathways [44]. These drugs include bromfenac, diclofenac, flurbiprofen, ketorolac, and nepafenac. Studies have shown that topical bromfenac eye drops may play a role in reducing DME [45]. Topical NSAID therapy has shown some degree of efficacy in DR, but there is a lack of reliable high-level evidence to support the use of NSAIDs in the treatment of DR. Therefore, larger clinical trials are still needed to validate their efficacy.

3.8 Gene Therapy

The research and application of gene therapy in inherited retinal diseases has matured, which provides a theoretical and technological basis for gene therapy in DR. Strategies of gene therapy include gene supplementation, gene editing and gene silencing [46]. Most of the current clinical trials of gene therapy for fundus vascular diseases have adopted the strategy of adeno-associated virus (AAV)-mediated gene supplementation with anti-VEGF-related molecules. For example, the adeno-associated virus vector ADVM-022 can induce long-term endogenous production of abciximab by intravitreal injection, while inhibiting neovascularisation [39]. A phase II clinical trial of ADVM-022 in patients with DME is currently underway [47]. Whereas gene editing technology involves knocking out/knocking down signalling molecules in the angiogenic pathway, gene silencing involves introducing antisense nucleic acids (e. g. , siRNA, shRNA, antisense RNA, antisense DNA, etc.) and ribozymes etc. into the cell to block the abnormal expression of specific genes at the transcriptional and translational levels, or to disrupt the structure of a particular gene so that it is not expressed, so as to achieve the therapeutic goal.

4. Summary

More and more studies have shown that DR is not just a simple stage of microvascular disease, but an intricate neurovascular complication. Most treatments are still focused on proliferative DR and macular oedema, but suffer from short duration and IOP-causing deficiencies, so many new therapeutic strategies have been proposed, including neuroprotective drugs, drugs that modulate angiogenesis, protection of the vascular microcirculation, and gene therapy. The goal of these new therapeutic approaches is to intervene in the developmental process of DR at multiple levels in order to improve therapeutic outcomes. In-depth exploration of the pathogenesis of retinal NVU in DR, searching for new therapeutic strategies, guiding the development of related drugs, and intervening and modulating the function of retinal NVU at an early stage are expected to inhibit the occurrence and development of DR.

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