Current Neuropharmacology, 2016, *14*, 792-804

REVIEW ARTICLE

Growth Factors in the Pathogenesis of Retinal Neurodegeneration in Diabetes Mellitus

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Abstract: Neurodegeneration is an initial process in the development of diabetic retinopathy (DR).

High quantities of glutamate, oxidative stress, induction of the renin-angiotensin system (RAS) and elevated levels of RAGE are crucial elements in the retinal neurodegeneration caused by diabetes mellitus. At least, there is emerging proof to indicate that the equilibrium between the neurotoxic and neuroprotective components will affect the state of the retinal neurons.

Somatostatin (SST), pigment epithelium-derived factor (PEDF), and erythropoietin (Epo) are endogenous neuroprotective peptides that are decreased in the eye of diabetic persons and play an essential role in retinal homeostasis. On the other hand, insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) are pivotal proteins which participate in the development of new capillaries and finally cause damage to the retinal neurons. During recent years, our knowledge about the function of growth factors in the pathogenesis of retinal neurodegeneration has increased. However, intensive investigations are needed to clarify the basic processes that contribute to retinal neurodegeneration and its association with damage to the capillary blood vessels. The objective of this review article is to show new insights on the role of neurotransmitters and growth factors in the pathogenesis of diabetic retinopathy. The information contained in this manuscript may provide the basis for novel strategies based on the factors of neurodegeneration to diagnose, prevent and treat DR in its earliest phases.

ARTICLE HISTORY

Received: October 20, 2015
Revised: November 12, 2015
Accepted: January 06, 2016

DOI: 10.2174/1570159X14666160813182009

Keywords: Diabetic retinopathy, growth factors, neurotransmitter, retinal neurodegeneration.

INTRODUCTION

1.1. Retinal Neurodegeneration Pathogenesis

Retinal neurodegeneration pathogenesis diabetic retinopathy (DR) is a microvascular disorder characterised by microaneurysms, capillary perfusion disorders, intraretinal haemorrhages, intraretinal microvascular abnormalities, and neovascularisation [1-3].

Neurodegeneration is the first phase in the development of DR.

Recent studies have identified neuroretinal abnormalities in diabetic patients, before the evidence of visible microvascular changes [4-7]. It has been shown in multicentre studies that over 80% of diabetic patients will develop DR within 20 years [8]. In these patients, reduced reactions in full-field and multifocal electroretinography, decreased blue-yellow colour sensitivity, and contrast sensitivity were usually observed before the occurrence of microvascular lesions [4-8].

Numerous neuronal cells are detected as damaged in the very early stage of the disease, while microvascular lesions are usually difficult to identify by fundus photography [9]. It is particularly interesting to assess abnormalities in the nerve fibre layer, ganglion cell density, photoreceptor pathological changes, retinal thickness, and evaluation of the extracellular space of the retina [10-12]. Retinal neurodegeneration has also been identified in diabetic rodent models as the very early phase of DR. Rats with streptozotocin-induced type 1 diabetes have exhibited the most accelerated loss of retinal ganglion cells at 8 months after the onset of diabetes [13]. The spontaneous development of diabetes in mice is also associated with changes in neurosensory retina, including apoptosis of retinal ganglion cells as well as marked changes in the pictures of surviving cells, reduction of cholinergic and dopaminergic amacrine cells, and a distinct thinning of the inner plexiform layer and inner nuclear layer [14, 15]. Furthermore, morphological alterations in astrocytes and microglial cells in the inner retina such as impaired glutamate metabolism by Müller cells have been found in rodents [16-18] and mice [19, 20]. Many growth factors participated in pathologic alterations of astrocytes and glial cells and are entailed in the evolution of vascular pathological changes in diabetic retinopathy: vascular

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1875-6190/16 $58.00+.00

endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), SDF-1, somatostatin, arginase, glutamate, NO, EPO, and others [21-26]. Neural apoptosis is attended by pathological processes in retinal glial cells (astrocytes and Müller cells) described as reactive gliosis.

Currently, it is not clear whether neural apoptosis or reactive gliosis is the initiator of the neurodegenerative changes developed in the retina of diabetic patients. The glial cells play a pivotal role in neuronal survival and normal metabolism. The suggestion that reactive gliosis precedes apoptosis in neural cells is based on the speculation that DR starts from neuronal injury. The biochemical and histo-pathological changes characterised for retinal neuro-degeneration have been noticed in diabetic patients without any pathologic microcirculatory changes in the retinas by ophthalmoscopic examinations [27-29]. The abnormal attitude between survival signalling and pro-apoptotic reactions in the retinas of subjects with diabetes in the initial phases of DR has been described [30]. The neural cells, glial cells, endothelial cells, and pericytes as well as several vasoactive mediators participate in neurovascular inter-actions [31-34]. Nitric oxide (NO) secreted from endothelial cells and neurocytes is involved in process of vasodilatation [32]. The block of NO synthase changes neurovascular complexes [35]. It has been shown that vasodilatation can be reduced by raising NO levels experimentally during suppression of the secretion of vasodilators by glial cells [32]. NO is qualified as a modulator process, rather than a direct mediator [33, 34]. In the literature, other mediators of vasodilatation in the retina have been described e.g. prostanoids, adenosine, ADP, ATP, lactate, glutamate, gamma-aminobutyric acid (GABA), taurine, adrenomedullin (AM), calcitonin gene-related peptide, atrial natriuretic peptide, brain-derived peptide, C-type natriuretic peptide, and retinal relaxing factor [35]. Glial cells play a key function in the haemodynamic processes by the secretion of vasoactive substances [33-39]. Interestingly, at low NO concentrations, glial-induced vasodilating prostanoids are active (i.e., epoxygenase metabolites), whereas vasoconstricting prostanoids (i.e., 20-hydroxyeicosatetraeonic acid) are activated by increased NO levels [35]. The second regulator is the local oxygen concentration; prostanoids can regulate blood flow in association with oxygen concentration, but the mechanism of this process has not been clarified to date [34]. In diabetes mellitus, without microvascular structural changes in the retina, abnormalities in retinal diameter have been reported [40-42]. These observations suggest that the neurovascular unit is damaged at the earliest phase of DR [43]. This problem required studies directed towards the signalling neural or glial cells and the relations between these cells. The mediators of retinal neurodegeneration include

- extracellular glutamate accumulation,
- oxidative stress,
- reduction of neuroprotective substances synthesised by the retina (Fig. **1**).

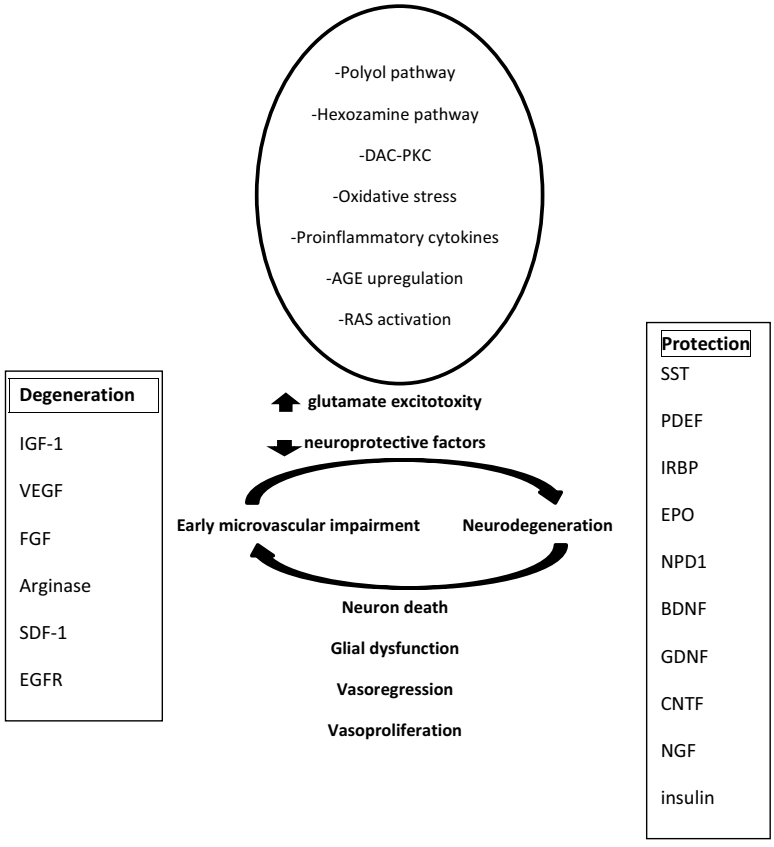

Fig. (1). Pathogenesis of diabetic retinopathy.

1.2. Diabetic Retinal Neovascularisation

2. GROWTH FACTORS AND NEUROTRANSMITTERS INVOLVED IN THE RETINAL NEURODEGENERATION

Diabetic retinal neovascularisation is considered a major consequence of retinal ischaemia caused by capillary occlusion similarly to other retinopathies; the mechanism of its development is not clear.

Diabetic retinopathy develops from soft non-proliferative changes, characterised by increased vascular permeability to moderate and severe non-proliferative diabetic retinopathy characterised by vascular obstruction. The next stage is proliferative diabetic retinopathy marked by the growth of new vascular vessels on the retina and posterior surface of the vitreous [10, 11]. Macular oedema defined by retinal thickening from leaky blood vessels can develop at any stage of retinopathy.

The new vascular vessels of DR and contracted concomitant connective tissues deformed the retina and can be cause of partial retinal separation, leading to severe and irreversible vision loss [12]. In DR, many mediators participate in the initial phases of eye complications. Overproduction of advanced glycation end-products through the pathogenesis of diabetes mellitus causes an overload of oxidative stress and activates inflammatory processes. Intensive production of oxygen-free radicals results in a decrease in the thickness of the vessel wall and diminished vascular permeability and elasticity. Inflammation is connected by an increased production of cytokines and is a secondary effect by hyperglycaemia [3-6, 9, 11]. The arterial wall damage in the peripheral and ocular vascular system is caused by chronic inflammation [3-6]. In this pathogenesis, an increase in permeability, leukocyte adhesion, and synthesis of the extracellular matrix is noticed. Inflammation processes lead to the development of retinopathy [3-6]. The prolonged hyperglycaemia causes apoptosis or death of the pericytes and malfunction of the vascular walls. Incompetent blood vessels in the retina characterised swelling. Disturbances of permeability results in the leaking of fluid or blood into the eye, connected with macular oedema or retinal haemorrhages. It is a cause of vision loss. In the late phase of DR, the deficit of oxygen in the retina is observed and stimulates the expression of VEGF and EPO. VEGF and EPO lead to the proliferation of blood vessels, stimulating the growth of new blood vessels on the surface of the retina. The new vessels are fragile, therefore, blood may leak from the ruptured vessels and cause scarring, which can damage eyesight, resulting in blindness [9-11].

2. GROWTH FACTORS AND NEUROTRANSMITTERS INVOLVED IN RETINAL NEURODEGENERATION

2.1. Glutamate

Glutamate is the main stimulating neurotransmitter for the photoreceptor-bipolar-ganglion cell in the retina. Increased glutamate concentration in the retina cause inordinate activation and are entailed in the so-called "excitotoxicity" leading to neurodegeneration [44-46]. The excitotoxicity of glutamate caused the over-activation of ionotropic glutamate receptors, which have been described in rats with streptozotocin-induced diabetes mellitus. 44, 46, 47]. The glutamate, oxidative stress [45-47], advanced glycation end-product receptor regulation [46-48], and renin-angiotensin system activation [44, 48] are pivotal processes in retinal neurodegeneration induced by diabetes mellitus. According to the last investigations, we can suspect that diabetes mellitus–induced down-regulation of neuroprotective factors synthesised by the retina participated in the neurodegenerative process of the DR [49, 50]. On these grounds, we can make the hypothesis that the prevention or arrest of DR development will involve methods based on neuroprotection.

2.2. Somatostatin (SST)

Somatostatin is an endogenous neuroprotective peptide and neurotransmitter that is decreased in the eye structures of diabetic patients [51]. Activation of the glial cells is a major cause of retinal neurodegeneration. Retinal astrocytes in healthy subjects express glial fibrillary acidic protein. In Müller cells, this expression is not noticed. In the course of diabetes mellitus, an abnormal expression of glial fibrillary acidic protein is observed in Müller cells [33]. Müller cells seem to play an important function in the development of diabetic retinal microangiopathy because these cells secrete substances that are capable of regulating blood flow, vascular permeability, and cell survival. Their processes fouled all of the blood vessels in the retina [33, 34]. The human retina secretes SST in significant amounts [52, 53]. The SST-receptors (SSTRs) are also presented in the retina, especially SSTR1 and SSTR2 [54]. SST is an important neuromodulator in the retina: this acts viaintracellular Ca^{2+}-signalling, nitric oxide function, and decreased glutamate secretion from the photoreceptors. SST is a powerful agent against angiogenesis and is involved in the regulation of ion transport and water transport systems [54]. It suspected that SST is crucial in the prevention of both proliferative DR (PDR) and diabetic macular oedema (DME). Eye drops with SST were capable of preventing glial cell activation [51]. Glial activation and apoptosis are the pivotal processes of retinal neurodegeneration [51]. Because SST receptors are expressed on the surface of endothelial cells, SST may directly inhibit angiogenesis [51, 52] and indirectly decrease the production of VEGF or suppress VEGF and other peptide growth factors e.g. IGF-1, epidermal growth factor, and platelet-derived growth factor post-receptor signalling pathways [51]. SST exhibits anti-angiogenic and neuroprotective properties as well, as in the case of PEDF [51, 55]. In PDR and DME the secretion of SST is decreased. In these diseases, low levels of intravitreal SST were noticed [51, 56]. The decrease of SST secretion by the human retina is observed in very early phases of DR and is strictly connected with retinal neurodegeneration [51, 56]. Cortistatin (CST) is a structural and functional neuropeptide that is similar to SST. CST is also decreased in DR [27, 28]. Treatment with SST eye drops has a strong effect in preventing ERG damage, glial cell activation, apoptosis, and abnormal proportions between pro-apoptotic and survival signalling described in rats with STZ-DM. The next observations indicated that SST

eye drops decreased glutamate accumulation in the retina inhibited glutamate transporter induction characterised by diabetes mellitus [51]. Topical therapies revolutionised the care of diabetic patients. The phase II-III randomised controlled clinical trial (EUROCONDOR-278040) assessed the efficacy of SST and brimonidine administered topically to prevent or arrest DR [56, 57].

2.3. PEDF-pigment-epithelial-derived Factor

The retinal production of pigment epithelial-derived factor (PEDF), is decreased in the retina of diabetic patients in comparison with non-diabetic subjects.

PDEF production probably has a neuroprotective effect and acts against neurotoxic factors caused by neurodegeneration. The retinal pigment epithelium (RPE) is the main source of PEDF in eye. This peptide is absolutely crucial in retinal homeostasis due to anti-angiogenic and neuroprotective properties. PEDF decreased oxidative stress and glutamate excitotoxicity [7, 57]. In diabetic patients, PEDF down-regulation is observed in the retina; it seems that the factor causes neurodegeneration and could also mediate early microvascular damage [57].

2.4. IRBP-interphotoreceptor retinoid-binding Protein

IRBP is a glycoprotein produced by photoreceptors and extruded into the interphotoreceptor matrix filling the subretinal space [58]. Besides participation in the visual cycle, IRBP is essential in fatty acid transport and plays a very important role in the care of photoreceptors [57-59]. Significantly decreased levels of IRBP have been noticed in the retinas of diabetic patients at the introduction phase of DR, and retinal neurodegeneration is strictly connected with IRBP down-regulation [56, 57].

2.5. EPO-erythropoietin

EPO and its receptor (Epo-R) are both produced by the human retina (especially in retinal pigment epithelium) [60]. In the vitreous fluid of diabetic eyes, a significant amount of EPO was found and its neuroprotective action was observed [60]. EPO is a strong natural stimulator for mobilisation of endothelial progenitor cells (EPCs) and migration to damaged retinal sites. These cells play an important role in the remodelling of injured retinas [60-64]. The elevated levels of VEGF and EPO are connected with the decreased secretion of neuroprotective substances. On the other hand, in advanced stages of DR, overexpression of VEGF or EPO causes neovascularisation. This process is involved in PDR development [61-63].

EPO raises the influence of VEGF. It is described that the high activity of VEGF and EPO might play a role as protective (in the initial phase DR) and degenerative (in advanced phase DR) substations.

2.6. Other Contributing Factors

Other neuroprotective factors e.g. insulin [64,65], neuroprotectin D1 (NPD1) [66], brain-derived neurotrophic factor (BDNF) [67], glial cell line derived neurotrophic factor (GDNF) [68], ciliary neurotrophic factor (CNTF) [69], nerve growth factor (NGF) [70], and adrenomedullin [71] might contribute to the pathogenesis of neurodegenerative processes in DR.

3. LINKS OF RETINAL NEURODEGENERATION WITH MICROVASCULAR ABNORMALITIES

3.1. Inflammation

A newly created aim in DR investigations is a problem with the connection between the activation of subclinical inflammation and neurodegeneration. It has been described that Müller cells indicate inflammation-linked reactions in diabetic patients [72-75]. It has recently been demonstrated that up-regulation of the receptor for AGEs (RAGE - receptor for advanced glycation end-products) is very important in the activation of Müller glia cells and cytokine production induced by hyperglycaemia in DR [73]. The mechanism of action of cytokines is not clearly explained. This cytokine probably participates in neural apoptosis and may contribute to the induction of excitotoxicity, oxidative stress, or mitochondrial dysfunction [75]. Previous investigations indicate that activation of the renin–angiotensin system (RAS) may be crucial in the retinal neurodegeneration developed in diabetic milieu [76-78].

3.2. IGF1-Insulin-like Growth Factor 1

IGF-1 is secreted by numerous cells of the retina: vascular endothelial cells, pericytes, glial cells, retinal ganglion cells, and retinal pigment epithelium [79-81]. IGF-1R (IGF-1 receptor) is expressed in retinal pigment epithelium cells and retinal endothelial cells. Activation of IGF-1R by IGF-1 stimulates the hypoxia-inducible factor 1a protein synthesis and increases the expression of VEGF. The IGF-1 participated in the activation of VEGF in human RPE cells [80, 81]. VEGF is a significant agent contributing to the formation of a novel capillary vessel. IGF-1 is involved in the regulation, growth, maturation and functioning of blood vessels [80, 81]. IGF-1 is a polypeptide hormone that is produced and secreted in the liver and fibroblasts and chondrocytes; it has a similar structure and function to insulin. Insulin increased the secretion of IGF-1 [79]. In healthy subjects, insulin is the main hormone regulating the level of glucose in the blood, and IGF-1 has a subsidiary function.

In diabetic patients, treatment with insulin or oral hypoglycaemic drugs should be a classical treatment for control of blood glucose levels. There were experimental therapies in which IGF-1 was applied in the case of extreme insulin resistance or insensitivity. It was hoped that recombinant IGF-1 treatment might be other method lead to decrease glycaemia and may prevent acute complications of diabetes [80-82]. Unfortunately, treatment with IGF-1 has significant complications: swelling of the optic nerve behind the eye and headaches. The observation of side effects prevent treatment with IGF-1 [81, 82]. The second cause of very careful treatment with IGF-1 and limitation of this is the mitogenic effect. Investigations have shown numerous incidences of proliferative DR as a result of treatment with IGF-1. Nowadays, it has been explained that IGF-1 has an important function in the pathogenesis of DR. IGF-1 during

long-term treatment may exacerbate retinal deterioration by promotion of the proliferation of retinal endothelial cells. IGF-1 increased the secretion and action of vascular endothelial growth factor and erythropoietin.

By coupling IGF-1 with IGF-1 receptors, various signalling pathways associated with DR are activated - the phosphatidylinositol 3-kinase/protein kinase B pathway, mitogen-activated protein kinase pathway, and nuclear factor-κB signalling pathway [83]. In animals, the administration of IGF-1 through intravitreal or intracorneal injections accelerates neovascular changes in the retina and cornea. In diabetic subjects with DR, increased levels of IGF-1 have been noticed in the vitreous fluid [84]. These investigations have shown the detrimental activity of IGF-1.

According to our knowledge, in the eye, IGF-1 receptors are found in numerous cells, and treatment with an IGF-1 receptor antagonist [81, 82], with blockade of the action of IGF-1, impedes the development of microvascular changes in the retina [83-89]. Like the effect of IGF-1 on VEGF, IGF-1 induces hypoxia-inducible factor-1, resulting in elevated mRNA levels and the overproduction of EPO [90]. This process probably participates in the development of new blood vessels. The biological function of IGF-1 is to act on IGF-1R and activation of PI3K and several intracellular kinases. PI3K plays an important function in the induction of growth and proliferation of vascular smooth muscle cells. The inhibition of PI3K is caused by wortmannin. This process was observed by a reduction of the early replication of vascular smooth muscle cells (VSMCs) in rats [91]. In normal endothelial cells, IGF-1 might also be efficient in the prevention of apoptosis before new and abnormal capillary vessels are formed.

The mitotic effect of IGF-1 is the main cause of the growth and proliferation of vascular endothelial cells. In this situation, the use of recombinant IGF-1 as a therapeutic agent may cause complications of DM with DR [83]. IGF1 and IGF1R are involved in the pathogenesis or progression of proliferative vitreoretinal disorders [92].

3.3. VEGF-Vascular Endothelial Growth Factor

VEGF is necessary for physiological vascular development and has an important function in maintaining the integrity of endothelial cells, because it is involved in anti-apoptotic signalling. It is a main pathogenic factor for DME and PDR. Moreover, VEGF may have neuroprotective effects. In recent research, following the injection of an antibody that blocks all VEGF isoforms in rats, a dose-dependent decrease in ganglion cells has been reported [93-98]. Other authors of experimental studies have not described any significant neural damage in VEGF knockout mice after blocking the phosphorylation of VEGF receptors in transgenic mice with the sustained expression of VEGF in the photoreceptors [98, 99]. The influence of VEGF on retinal neuroprotection should be clarified in further investigations. Angiogenesis, a process of the development of new capillary networks from pre-existing vessels is a characteristic process of proliferative diabetic retinopathy [94]. Numerous investigations show that vasculogenesis, i.e. *de novo* formation of blood vessels from circulating bone marrow-derived endothelial progenitor cells (EPCs), can participate in neovascularisation [94, 95]. The circulating bone marrow-derived EPCs that migrate to the ischaemic region differentiate into mature endothelial cells *in situ,* leading to neovascularisation [93]. In many investigations, it was shown that bone marrow-derived CD133 EPCs are involved in new vessel formation in PDR fibrovascular epiretinal membranes [94, 95]. In angiogenesis and vasculogenesis, several cytokines/chemokines and their associated tyrosine kinase receptors contribute. A pivotal factor in both of these processes is VEGF [96, 97].

VEGF binds with high affinity and activates two tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR in humans/Flk-1 in mice) [98]. These receptors participate in the regulation of physiological and pathological angiogenesis. VEGFR-2 is expressed mainly on vascular endothelial cells [98]. VEGFR-2 is also expressed by bone marrow-derived circulating EPCs. VEGFR-2 has intensive tyrosine kinase activity and is the main positive signal transducer for pathological angiogenesis in neoplasm and DR [98]. Activation of VEGFR-2 stimulates endothelial cell proliferation, migration and survival, angiogenesis and microvascular permeability [98]. VEGFR-2 has a short soluble form (sVEGFR-2) that has been reported in mouse and human plasma [99, 100]. Recent evidence shows that the decrease of VEGF, sVEGFR-2, and SCF concentration in the vitreous fluid from patients with PDR are associated with angiogenesis and vasculogenesis in DR [101].

3.4. Fibroblasts Growth Factor (FGF)

The fibroblast growth factor in normal tissue is detected in basement membranes and in the subendothelial extracellular matrix of blood vessels [102]. It is suspected that the action of heparan sulphate-degrading enzymes activates bFGF, and inducing the formation of new blood vessels (angiogenesis) may have an important role in wound healing of normal tissues and during tumour development [102, 103]. FGF is produced by human adipocytes and a correlation between the levels of bFGF and BMI was observed in blood samples. Moreover, bFGF also contributed to the proliferation of preosteoblasts [102, 103]. The fibroblast growth factor family consists of 22 members with a wide range of biological functions in organisms, such as cell growth, development, angiogenesis, and wound healing [104] FGF21 is a member of the endocrine FGF subfamily, which is expressed predominantly in the liver and stimulates glucose uptake through the induction of GLUT1 in adipocytes [105]. The application of FGF21 leads to decreased glucose levels and modulates lipid metabolism in both murine and nonhuman primate models of diabetes and obesity [106]. These investigations have shown that FGF21 has an essential function in the regulation of glucose and lipid metabolism. FGF21 may be used for the effective treatment of diabetes and obesity in the future. Latest investigations have indicated increased serum concentrations of FGF21 in obese subjects and patients with metabolic syndrome and type 2 diabetes mellitus [107, 108]. FGF21 is probably involved in the pathogenesis of retinopathy in diabetic patients but its role is unclear. In patients with type 2 diabetes, increased serum FGF21 levels were noticed,

which are higher in patients with diabetic retinopathy than in those without it and connected with the development of diabetes and DR. The prospective studies with greater numbers of patients can explain the relationship between serum FGF21 concentrations and the severity of vascular complications [109, 110].

3.5. Arginase

Vascular epithelial cells contain endothelial nitric oxide synthase (eNOS), an enzyme that hydrolyses L-arginine to form L-citrulline and NO [111]. NO contributes to healthy vascular function as a main signalling molecule [111]. NO induces blood flow by activating guanylyl cyclase within the vascular smooth muscle cells, which leads to the dilation of vessels [112]. The normal production of NO by eNOS is required for the metabolism of healthy vessels, proper blood flow, prevention of leucocyte adhesion and platelet aggregation, and control of smooth muscle cell growth [112]. A decrease in bioavailable NO is a major factor of endothelial cell dysfunction and its implications are shown in diabetic vascular disease [112]. NOS produces NO from its substrate L-arginine. If the level of L-arginine is insufficient, uncoupling of the NOS homodimer can stimulate it to produce superoxide [113]. Superoxide can react with NO to form peroxynitrite, thus reducing levels of NO and increasing oxidative stress [114].

Two isoforms have been described: arginase I is localised in the cytosol and arginase II exists in the mitochondria. Arginase is expressed in epithelial cells. The increase of arginase protein levels and/or activity influenced vascular dysfunction in hypertension, ischaemia reperfusion, ageing, and diabetes [115]. The function of arginase in the DR pathway has not been investigated. Excessive arginase activity has been found to reduce NO production by reducing the L-arginine supply for eNOS [116-118]. Ornithine is a metabolite of arginase activity. It can be further metabolised into polyamines and proline, which are necessary for cell proliferation and collagen synthesis, respectively. Increases in their levels have been connected with vascular remodelling and stiffness [119, 120].

The most recognised feature of retinopathy is retinal neovascularisation, but neuronal dysfunction is also observed. Alterations in polyamine metabolism are involved in neurodegeneration in various diseases. Polyamines participate in the pathogenesis of ischaemic brain damage [121-123]. Arginase activity is increased in various pathologies characterised by vascular dysfunction: diabetes, hypertension and ischaemia-reperfusion injury [122, 123]. High arginase activity and polyamine overproduction have been connected to retinal ganglion cell death due to excessive activation of excitotoxic NMDA receptors and hyperoxia-mediated neuronal death [124-130]. The deletion of arginase strongly reduces retinal degeneration and improves retinal function following hyperoxia treatment in the mouse model of oxygen retinopathy [131]. The mechanism of this neuroprotective effect has been described: deletion of arginase II reduces neuro-glial damage and significantly improves retinal function [131, 132]. Arginase I is a potential therapeutic target for the treatment of DR using arginase inhibitors [133]. Arginase has been linked to DR and is the enzyme with increasing interest in endothelial dysfunction [133].

3.6. SDF-1-Stromal Cell-derived Factor-1

Stromal cell-derived factor-1 (SDF-1) is a CXC-chemokine which participates in haematopoiesis. Mice lacking SDF-1 or its receptor CXCR4 die in the foetal period, after developing defects in various organs including the heart, brain, large vessels, and bone marrow. In bone marrow, endothelial cells and stromal cells showed the expression of SDF-1. This protein recruits hematopoietic stem cells to the bone marrow niche, but also supports their survival and proliferation [134, 135]. SDF-1 and the receptor CXCR4 stimulate bone marrow-derived cells to neovascularisation and regeneration sites in the heart, liver and eye [136, 137]. SDF-1 levels are increased in the vitreous in ischaemic ocular diseases, such as proliferative diabetic retinopathy (PDR) and retinopathy of prematurity, retinal vein occlusion [138, 139]. This factor induces the expression of VCAM-1 adhesion molecules in the eye epithelial cells and reduces expression of intramembrane occludin proteins. The level of SDF-1 and its receptor CXCR4 is regulated by VEGF [140]. SDF-1/CXCR4 contributed to the ocular inflammation process by enrolling CD4 T-cells, and is potentially engaged in the formation of proliferative membranes in patients with proliferative vitreoretinopathy [141]. SDF-1 has both beneficial and adverse effects in DR, such as neuro-protection or inflammatory cell accumulation, respectively. Endogenous SDF-1 is a tissue-protective role in RD. Elucidation of the mechanisms underlying the role of SDF-1 in neural protection will support the development of safe and effective treatments [142].

3.7. EGFR-Epidermal Growth Factor Receptor

Inactivation of A disintegrin and metalloproteinase 17 (ADAM17), a membrane-anchored metalloproteinase, which is involved in cleaving ligands of the epidermal growth factor receptor (EGFR) and regulating EGFR signalling, reduces neovascularisation [143-145]. The tissue inhibitor of metalloproteinases-3 (TIMP3) acts as a natural inhibitor of ADAM17 [146-149] and inhibits the release of ligands of EGFR [146-149]. TIMP3 belongs to the family of tissue inhibitors of matrix metalloproteinases (TIMPs) and can be immobiliszed in the extracellular matrix [150]. Mice lacking TIMP3 develop pathologies that can be explained by an increase in the activity of ADAM17, e.g. an enhanced inflammatory response with increased TNFα activity [150, 151]. TIMP3 with ADAM17 regulates angiogenesis in three-dimensional tissue culture assays [151]. The inactivation of ADAM17 in endothelial cells prevents pathological retinal neovascularisation and the growth of heterotopically-injected tumours in mice [152, 153]. The investigations with Timp3−/− mice have demonstrated that TIMP3 regulates choroidal neovascularisation, as well as VEGF-induced corneal neovascularisation and laser-induced choroidal neovascularisation. In these mice, the delivery of TIMP3 by adeno-associated viral vectors has been shown to ameliorate ischaemia-induced neovascularisation [152-154]. In addition,

TIMP3 may regulate angiogenesis by binding directly to the VEGF receptor 2 (VEGFR2) [152-154]. Moreover, the impact of intravitreal injection of the EGFR inhibitor erlotinib on neovascularisation in the OIR model in wild-type mice has been described [154, 155]. The intravitreally injected TIMP3 probably blocked tuft formation by reducing ADAM17 activity [152-155]. VEGF-A has a very intensive effect in mouse OIR, [156-160] and investigations have shown that VEGF-A/VEGFR2 signalling activates ADAM17 to induce EGFR and stimulate the migration of endothelial cells [154, 155]. Since the injection of TIMP3 might also affect the binding of VEGF-A to VEGFR2, the injection of IMP3 treats pathological neovascularisation by the inhibition of two pivotal components of this pathway: binding of VEGF-A to VEGFR2 and the activation of ADAM17 [161, 162].

4. THERAPY STRATEGIES

A classical treatment method in diabetes retinopathy is laser therapy. Immunotherapy targeting VEGF was revolutionary in the treatment of DR. Trials of these immunotherapies documented that intraocular injections of anti-VEGF agents are better than laser therapy in preserving and improving vision in DME patients [57]. The anti-VEGF agents ranibizumab, bevacizumab, pegaptanib, and aflibercept have recently been used. Both laser treatment and anti-VEGF antibodies-intraocular injections could be aggregated. In patients receiving combined ranibizumab and laser therapy, the best long-term visual improvement could be achieved with the initiation of injections followed by laser therapy [57]. Currently, nationwide studies by groups such as the Diabetic Retinopathy Clinical Research Network (DRCRnet) explained the role of ocular anti-VEGF therapy for PDR. Intravitreous injections of anti-VEGF agents is an invasive procedure and could even have harmful effects on healthy retina. Besides local side effects, anti-VEGF agents can produce systemic complications due to their capacity to pass into systemic circulation [57].

Neuroprotective factors such as PEDF, SST, NGF, BDNF, and EPO have been applied in experimental DR. Intraocular gene transfer of PEDF significantly increases neuroretinal cell survival after ischaemia-reperfusion injury [163]. In early DR, intravitreal injections of PEDF prevent neuronal derangements and vascular hyperpermeability [164]. SST and SST analogues administered intravitreally protect the retina from AMPA-induced neurotoxicity [165]. Treatment of diabetic rats with NGF prevented apoptosis of ganglion cells and Müller cells [166]. Probably, growth factors can be involved in the regeneration of ganglion cells from stem cells [170].

These results suggest that the increased expression and function of neuroprotective factors synthesised by the retina could be a therapeutic target in DR. Intravitreal or intraperitoneal administration of exogenous EPO and EPO-derived peptides acts against neuroglial and vascular degeneration in diabetic rats [167-169]. EPO or EpoR agonists used in the treatment of DR have neuroprotective properties, cause vessel stability, and increase in tissue repair by the recruitment of EPCs toward the pathological area [168-169]. Nevertheless, in advanced stages, the elevated levels of Epo EPO could enhance the effects of VEGF, thus contributing to neovascularisation and PDR worsening [114, 115]. Probably the next step in this field is the active prevention of neurodegeneration in patients before clinical symptoms. At present, we can diagnose retinal neuro-degeneration in a very early stage in children with diabetes [171].

5. CONCLUSIONS

For patients with the early identification of neuro-degeneration, implementing an early treatment based on drugs with a neuroprotective effect will be pivotal. The possibility of using biological treatment against neuro-degenerative factors and special therapy for the activation of neuroprotective growth agents is based on a new and safe strategy for treatment of the early stages of diabetic retinopathy. Therefore, investigations into growth factors in the process of retinal neurodegeneration have important practical aspects. The explanation of the important role of neurodegeneration in the pathogenesis of DR is the basis for new treatment methods. Neuroprotection is an effective method for treating, preventing or arresting DR.

LIST OF ABBREVIATIONS

ADAM17	=	metallopeptidase domain 17 also called TACE (tumour necrosis factor-α-converting enzyme)
AM	=	adrenomedullin
AMPA	=	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid is a compound that is a specific agonist for the AMPA receptor, where it mimics the effects of the neuro-transmitter glutamate
BDNF	=	brain-derived neurotrophic factor
CNTF	=	ciliary neurotrophic factor
DAG-PKC	=	diacylglycerol- protein kinase C
DR	=	diabetic retinopathy
EGFR	=	epidermal growth factor receptor
EPO	=	erythropoietin,
EPO-R	=	receptor of erythropoietin
FGF	=	fibroblast growth factor
GABA	=	gamma-aminobutyric acid
GDNF	=	glial cell line derived neurotrophic factor
IGF 1	=	insulin-like growth factor 1
IRBP	=	interphotoreceptor retinoid-binding protein
NGF	=	nerve growth factor
NO	=	nitric oxide,
NPD1	=	neuroprotectin D1
PDGF	=	platelet-derived growth factor
PEDF	=	pigment-epithelial-derived factor,

SDF-1 = stromal cell-derived factor-1

SST = somatostatin,

VEGF = vascular endothelial growth factor

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Source of funding for the study: Grant of Medical University of Lublin Poland: PW 415/2015.

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