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## Electroretinogram Alterations in Diabetes?

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### 1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterized by hyperglycemia resulting from defective insulin secretion (type 1), resistance to insulin action (type 2), or both. It is often associated with complications, such as cardiovascular disease, kidney failure, retinopathy, as well as peripheral and autonomic neuropathies. Retinopathy is the most common microvascular complication of diabetes, and it remains a major cause of visual impairment worldwide. Vascular lesions in the early stages of diabetic retinopathy are characterized by the presence of capillary microaneurysms, pericyte deficient capillaries, and obliterated and degenerated capillaries. Proliferative diabetic retinopathy is the more advanced form of the disease, when circulation problems cause the retina to become oxygen deprived. As a result, new fragile blood vessels can begin to grow in the retina and into the vitreous. Therefore, diabetic retinopathy has long been recognized as a vascular disease. However, it is becoming increasingly clear that neuronal cells of the retina are also affected by diabetes. Electroretinogram (ERG) is the neurophysiological test used in order to measure electric changes that happen in the retina after a light stimulus. Changes in the ERG may be due to an impairment of any of the retinal cell types: photoreceptors (a-wave ERG), and amacrine, bipolar, and, mainly, Müller cells (b-wave ERG). Moreover, oscillatory potentials are likely to be due to inner retinal neurotransmission. Though it may seem that diverse studies have presented contradictory results, it is important to point that most of the studies in diabetic experimental animals point to a very early alteration in the b-wave amplitude and reductions in oscillatory potentials. The nervous potential originated in the retina after a light stimulus is transmitted to the visual cortex via the optic nerve. Retinal ganglion cells (RGCs), which form this optic nerve, are the best studied of the retinal neurons with respect to the effect of diabetes. The aim of this work is to summarize recent clinical and laboratory findings about several experimental therapies that have been used to minimize neural changes in retina of different animal models of diabetes.

### 2. Diabetic retinopathy: a microvascular or a neuronal disease?

The prevalence of diabetes mellitus (DM) worldwide is increasing rapidly in association with the increase of obesity. Complications are a major fear of patients with diabetes. Retinopathy is the most feared complication of diabetes, compromising quality of life in

most sufferers. Almost all patients with type 1 diabetes will develop retinopathy over a 15- to 20-year period, and approximately 20-30% will advance to the blinding stage of the disease. More than 60% of patients with type 2 diabetes will have retinopathy. However, current therapeutic options for the treatment of diabetic retinopathy (DR) such as photocoagulation and vitrectomy are limited by their considerable side effects and far from satisfactory.

Retinal changes in diabetes are thought to be initiated by sustained hyperglycemia leading to biochemical abnormalities, that include alterations of various vasoactive and growth factors (Brownlee, 2001), nonenzymatic glycation (Bierhaus et al., 1998), increase in the polyol pathway and redox imbalance (Engerman et al., 1993; Ido et al., 1997), oxidative stress (Arnal et al., 2009; Johnsen-Soriano et al., 2008; Miranda et al., 2006), and activation of protein kinase C (PKC) (Koya & King, 1998).

In addition, DR has long been recognized as a vascular disease, but it is becoming increasingly clear that neuronal cells of the retina are also affected by diabetes.

Diabetic retinopathy is classified into an early, nonproliferative stage, and a latter, proliferative stage. Histologically, vascular lesions in the early stages of diabetic retinopathy in man and animals are characterized by the presence of capillary microaneurysms, pericyte deficient capillaries, and obliterated and degenerated capillaries.

Non-proliferative diabetic retinopathy (NPDR) is the early stage of the disease in which symptoms will be mild or non-existent. NPDR is characterized by the presence of: (i) microaneurysms, (ii) intraretinal hemorrhages, (iii) exudates, (iv) intraretinal vascular abnormalities (IRMA), (v) vascular changes of veins, (vi) alterations in the foveal avascular zone (FAZ), (vii) macular edema.

Approximately 50% of patients with very severe NPDR progress to PDR within 1 year. Proliferative diabetic retinopathy (PDR) is the more advanced form of the disease. At this stage, circulation problems cause the retina to become oxygen deprived. As a result new fragile blood vessels can begin to grow in the retina and into the vitreous. New vessels may proliferate on the optic nerve head and along the course of the major vascular arcades. The new vessels mostly grow along the posterior hyaloid and sudden vitreous contraction may result in rupture of these fragile vessels. When the vitreous detachment occurs, the new vessels are pulled anteriorly along with the underlying retina, resulting in tractional retinal detachment. On the other hand, vitreous might detach completely without any pull on the retina and the new vessels disappear. Diabetic macular edema is now the principal cause of vision loss in diabetes and involves leakage from a disrupted blood-retinal barrier. The intraretinal fluid comes from leaking microaneurysms or diffuses from capillary incompetent areas. In the clinical course of PDR, rubeosis may appear as a result of the progression of neovascularization in the front of the iris and the angle of the chamber, and finally result in neovascular glaucoma.

The final metabolic pathway causing diabetic retinopathy is not known. Numerous researchers have suggested that pathogenesis of diabetic retinopathy includes microvascular damage induced by glucose. Currently, there has been a great interest in vasoproliferative factors, which induce neovascularization. It has been shown that retinal ischemia stimulates a pathological neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in PDR. VEGFs are released by retinal pigment epithelium, pericytes and endothelial cells of the retina.

Evidence has begun to point to the fact that even before vascular complications begin to manifest, neuronal cell death and dysfunction have already begun.

Retinal ganglion cells (RGCs) are the best studied of the retinal neurons with respect to the effect of diabetes. Loss of ganglion cells has been detected in diabetic rats, mice and humans (Asnaghi et al., 2003; Barber et al., 1998; Martin et al., 2004). Barber et al. (1998) studied retinal sections from streptozotocin diabetic rats after 7.5 months of diabetes and identified 22% and 14% reductions in the thickness of the inner plexiform and inner nuclear layers, respectively, and a 10% reduction in the number of surviving ganglion cells. An increase in the frequency of retinal apoptosis was also observed in whole-mounted rat retinas after 1, 3, 6, and 12 months of diabetes and TUNEL-positive cells were not associated with blood vessels. Some researchers suggest that this "retinal neuropathy" require severe hyperglycemia and high activity of aldose reductase (Asnaghi et al., 2003).

Consistent with a possible role of apoptosis in the death of retinal neurons, numerous initiator and effector caspases have been found to become activated in retinas of both patients and diabetic animals. Upregulation of Bax, caspase-9 and -3 expression in the ganglion cell layer has been associated with neuronal degeneration in human diabetic retinopathy (Oshitari et al., 2008), suggesting that RGCs undergo apoptosis in diabetic patients leading to a reduction in the thickness of the nerve fibre layer (Kern et al., 2008). In streptozotocin (STZ) diabetic rats an increase in TUNEL-positive and caspase 3-positive cells have been observed in the ganglion cell layer (Arnal et al., 2009), and this was accompanied by a reduction in the thickness of all the layers of the retina. The mitochondria- and caspase-dependent cell-death pathway may be, in part, associated with neuronal degeneration in diabetic retinas.

Kern (Kern et al., 2010) induced diabetes in three different strains of rats with streptozotocin: Sprague Dawley, Lewis, and Wistar rats. After 8 months a significant loss of cells in the GCL occurred only in diabetic Lewis rats, whereas Wistar and Sprague Dawley rats showed little change, though all type of rats showed alterations in the electroretinogram.

Although RGC are the best studied, other neuronal cells can be damaged by diabetes, like horizontal cells, amacrine cells and photoreceptors (Park et al., 2003; Kusner et al., 2004; Seki, et al., 2004). In this sense, apoptosis has been observed in a few photoreceptor cells 4 weeks after the induction of diabetes in rats, and the number of apoptotic photoreceptors increased thereafter (Park et al., 2003). Others (Zhang et al., 2008) observed an increase in the number of TUNEL-positive cells especially in the outer nuclear layer (ONL) 1 week after diabetes onset and reached a peak at 4 to 6 weeks, at the same time retinal ONL thickness was reduced significantly. With regard to photoreceptor function in diabetes, decreased amplitudes of the photoreceptor response 12 weeks after diabetes induction in rats and significantly faster dark adaptation than controls have been observed (Lieth et al, 2008); this faster relative recovery found in diabetes after bleach, in the presence of normal pigment dynamics, may reflect a decrease in outer segment lengths. Animal studies also show glial activation (Lieth et al., 2008), impaired glial cell metabolism (Li et al., 2002), and microglial cell activation (Layton et al., 2005).

### **3. Electroretinogram (ERG) and diabetic retinopathy.**

The onset of vision loss is insidious in diabetes. While clinical diagnosis of diabetic retinopathy requires detection of vascular pathology, diabetes also induces changes in retinal function; indeed, functional changes occur in the retina prior to clinical symptoms of the disease.

Electrophysiological studies of humans with diabetes could be used to assess alterations such as dysfunction of ganglion cells and loss of colour and contrast sensitivity (Roy et al., 1986; Ghirlanda et al., 1991), moreover alterations in oscillatory potentials have been shown to predict the onset of proliferative retinopathy better than vascular lesions seen on fundus photographs (Bresnick & Palta, 1987). Recently Luu (Luu et al., 2010) performed full-field electroretinograms in subjects with nonproliferative diabetic retinopathy, diabetic subjects without retinopathy, and normal control subjects and found that all the oscillatory potential (OP) components (OP1-OP4) were significantly reduced in amplitude and increased in implicit time in the no-DR and NPDR groups. OP4 amplitude correlated significantly with the retinal arteriolar caliber suggesting a correlation between retinal neuronal dysfunction and microvasculature changes. Interestingly, one study has assessed the effect of short-term strict glycemic control on OP amplitude (Frost-Larsen et al., 1983) and reported that OP amplitudes, which were initially abnormal in a group of retinopathic subjects with IDDM, were normalized after 11 days of strict glycemic control.

Other studies have concluded that neuroretinal function is affected before the onset of vascular lesions in humans. The amplitude of the b-wave of the scotopic full-field (flash) ERG, reflecting largely the activity of the bipolar cells are abnormal in diabetes in the absence of visible fundus signs of retinopathy (Coupland, 1987; Hardy et al., 1995). Although functional changes can occur in the absence of retinopathy, this does not mean that function is not related to retinopathy, it is more a sign of the retinopathy severity and the magnitude of the functional loss.

The origin of the electroretinogram anomalies is not known, though it can be related to apoptosis of retinal ganglion cells (RGCs) and the morphological alterations in the surviving RGCs.

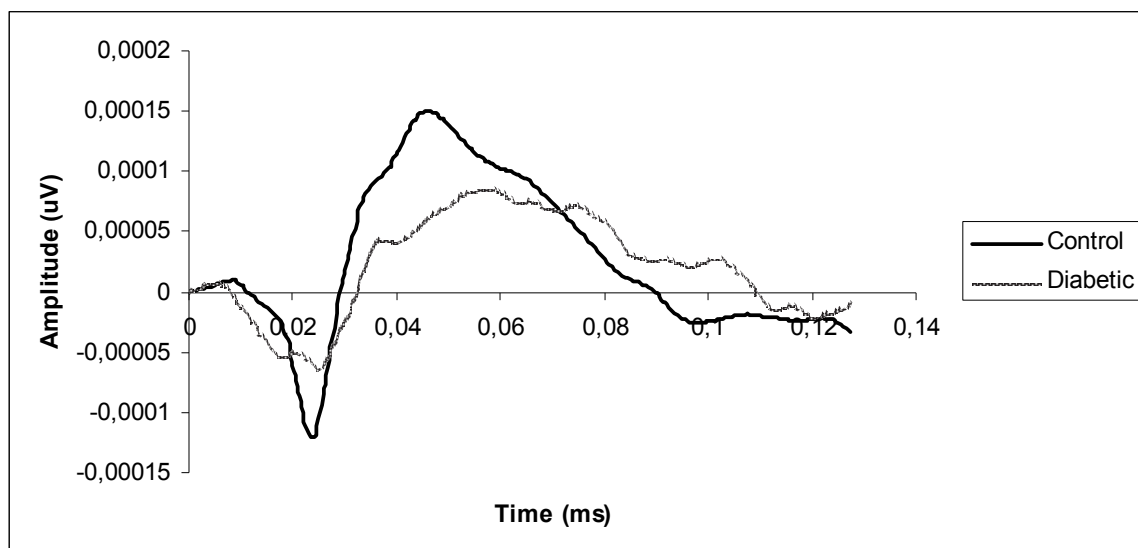


Fig. 1. Example of an electroretinogram in a control and streptozotocin-induced diabetic rat (12 weeks after the induction of diabetes).

ERG studies performed in diabetic rats have detected reduced ERG responses as early as 2 weeks after diabetes induction (Li, 2002). Experience in our lab suggest that the most consistent result is a decrease in b-wave amplitude after 1 month of streptozotocin-induced diabetes in Sprague Dawley rats and after only one week in alloxan-induced diabetic mice.

Kern et al., (2010) studied streptozotocin-induced diabetes in Lewis, Wistar and Sprague Dawley rats and observed that all strains tended to show diabetes-induced impairment of dark-adapted b-wave amplitude, but only Sprague Dawley and Lewis strains had a significant reduction in latency. The electroretinogram b-wave is generally believed to reflect mainly light-induced activity of ON-center bipolar cells and Muller cells. It has also been suggested that the b-wave of the electroretinogram is a particularly sensitive index of retinal ischemia and that, although the amount of reduction in b-wave amplitude during ischemia corresponds to the severity of the insult, the degree of recovery of the b-wave during reperfusion depends on the duration of ischemia. In this sense the b-wave of the ERG represents a functional measure for potential therapeutic efficacy of drugs interacting with these pathophysiological processes.

It is thought that the ERG a-wave originates from photoreceptors (rods and cones), and alterations have been observed in a-wave amplitude and/or latency in diabetic animals. Although it may seem that diverse studies have presented contradictory results, it is important to point that most of the studies in experimental animals show a very early alteration in the b-wave amplitude and reductions in oscillatory potentials and the differences observed in the different studies can be due to either the different models used or the different conditions of the ERG. Most interesting results of diabetes alterations in ERG from diabetic rats are summarized in Table 1

#### **4. Clinical and laboratory findings about experimental therapies**

The duration of diabetes and severity of hyperglycaemia are the major risk factors in diabetic retinopathy. Strict metabolic control and tight blood pressure control can significantly reduce the risk of developing retinopathy and its progression, but are difficult to achieve in clinical practice. Laser photocoagulation and vitrectomy are effective in preventing severe visual loss from sight-threatening diabetic retinopathy and its complications, but both modalities have potential side-effects. The use of pharmacological agents as monotherapy has allowed patients to recover vision faster than with previous treatment modalities, but these effects are frequently, but not always, short-lived. As sustained beneficial effects have been shown only in the treatment schedules which require frequent intravitreal injections, with the subsequent side-effects derived such as increase in intraocular pressure, develop of secondary glaucoma, retinal detachment, cataract formation and endophthalmitis. Due to the limitations of current treatment, new pharmacological therapies are being developed. The latter target underlying biochemical mechanisms that cause DR through involvement of protein kinase C (PKC) activation, oxidative stress, the angiogenesis pathway, and the glycation and sorbitol pathway. These treatments aim to prevent diabetes-induced damage to the retinal microvasculature.

Relatively new research on neurodegeneration is expanding our views of the pathogenesis of DR because it is becoming increasingly clear that neuronal cells of the retina are also affected by diabetes, resulting in dysfunction and even degeneration of some neuronal cells. Several experimental therapies have been used to minimize neural changes in retina of different animal models of diabetes (Table 2). Most of them have focused on the inhibition of RGC apoptosis though we do not know yet metabolic pathways causing this apoptotic response. Other agents like anti-inflammatory drugs, aldose reductase inhibitors, growth factors, erythropoietin, have also been tested with positive results.

Model	Duration	Observation	Reference
Male Sprague-Dawley STZ rats	3 months	Decreased a- and b-wave amplitudes	Ma et al., 2009
Sprague-Dawley STZ rats	1, 3 months	Reduced b-wave amplitudes and OPs with the progress of diabetes	Zhang et al., 2009
Alloxan Swiss mice	3 weeks	Reduced b-wave amplitude	Johnsen-Soriano et al., 2008
Sprague-Dawley STZ rats	4, 8 and 11 weeks	Unaffected a- and b-wave. Reduced OPs by 8 weeks.	Kohzaki et al., 2008
Male Wistar STZ rats	3, 6, 9 and 12 weeks	Reduction in the amplitude and increase in the peak time of all waves	Layton et al., 2007
Female Long Evans STZ rats	12 weeks	No differences in the amplitude of the a- or b-wave, differences in the pattern of OPs	Ramsey et al., 2006
Spontaneously Diabetic Torii rat	44 week	Prolongation of the peak latencies	Sasase et al., 2006
Sprague-Dawley STZ rats	12 weeks	Decreased amplitudes of the photoreceptor response	Phipps et al., 2006
Alloxan Swiss mice	1 week	Latency and implicit times were not affected	Miranda et al., 2006
Alloxan Swiss mice	1 week	Decreased b-wave amplitude	Miranda et al., 2004
Long-Evans male STZ rats	12 weeks	Small but significant delay in a-wave, no change in b-wave timing, sensitivity of b-wave reduced and a-wave not changed	Hancock et al., 2004
Brown-Norway STZ rats	1 month	Reduction in the amplitudes of a- and b-waves	Aizu et al., 2002
Male albino STZ rats	2 weeks	Reduced a- and b-amplitude, b-wave more affected than a-wave	Li et al., 2002
Male Wistar STZ rats	1, 2 months	Abnormal increase in latency and reduction of amplitude of ERG and VEP waves	Biró et al., 1998
Male Sprague-Dawley STZ rats	6 to 20 weeks	Reduced amplitudes of OP 1 and OP 2	Ishikawa et al., 1996
Male Sprague-Dawley STZ rats	1 month	Prolongation of the peak latency of oscillatory potentials in the b-wave of the erg	Hotta et al., 1995
Alloxan-induced diabetic rats	1, 2 months	After 1 month, 20% reduction in amplitudes, after 2 months this decrease was about 60%	Doly et al., 1992
Rats with STZ fructose-induced diabetes	4, 8 and 12 weeks	Prolonged peak latencies and intervals and reduced amplitudes	Funada et al., 1987
STZ pigmented rat	2, 4, and 19 weeks	No effect on the b-wave at 2- and 4-week; at 19 weeks reduced amplitude. c-wave reduced in amplitude at 2-week	Pautler et al., 1980

(STZ: streptozotocin, OP: oscillatory potentials, GC: ganglion cells, VEP: visual evoked potential)

Table 1. Changes in electroretinogram in different animal models of diabetes.

Drug	Type of drug	Model	Effect	Reference
Aminoguanidine	Aldose reductase inhibitor	Wistar albino STZ rats	Prevented the impairment in retrograde axonal transport and neuroaxonal changes	Zhang et al., 2008
Baicalein	Antiinflammatory	STZ rats	Reduced ganglion cell loss	Yang et al., 2009
Cannabidiol	Nonpsychotropic cannabinoid	Male Sprague-Dawley STZ rats	Reduced oxidative stress; decreased levels of TNF- $\alpha$ , VEGF, and ICAM-1; and prevented retinal cell death. Inhibited p38 MAP kinase	El-Remessy et al., 2006
des(1-3)IGF-1	Insulin-like growth factor (IGF)-1 analog	Male Sprague-Dawley STZ rats	Decreased IGF receptor protein phospho-Akt (Thr 308) immunoreactivity in GCL	Kummer et al., 2003
DHA	Omega-3 fatty acid	Male Wistar STZ rats	Decreased TUNEL and caspase-3 positive cells in GCL	Arnal et al., 2009
Erythropoietin	Hormone	Sprague-Dawley STZ rats	Improves abnormalities of ERG, GC with swollen mitochondria, increased retinal glutamate and EPO-R in the retinas	Zhu et al., 2008
FeTTPS	Peroxy-nitrite decomposition catalyst	Male Sprague-Dawley STZ rats	Prevented tyrosine nitration, restored NGF survival signal, and prevented neuronal death	Ali et al., 2008
Insulin-like growth factor (IGF-1)	Growth factor	Male Sprague-Dawley STZ rats	Reduced the number of TUNEL and p-Akt, Caspase-3 and BAD immunoreactive	Seigel et al., 2006
KIOM-79	Mixture of extracts obtained from <i>Puerariae lobata</i> , <i>Magnolia officinalis</i> , <i>Glycyrrhiza uralensis</i> and <i>Euphorbia pekinensis</i>	db/db mice	Prevented apoptotic cell death and AGEs accumulation	Sohn et al., 2009
Latanoprost	Prostaglandin F <sub>2</sub> alpha analogue	Male Sprague-Dawley STZ rats	Rescued retinal neuro-glial cells from apoptosis inhibiting caspase-3, increased phosphorylated to total protein ratio of p44/p42 MAPK, but not of Akt	Nakanishi et al., 2006
Lutein	Carotenoid	Male Wistar STZ rats	Decreased TUNEL and caspase-3 positive cells in GCL	Arnal et al., 2009



Drug	Type of drug	Model	Effect	Reference
Memantine	Glutamate NMDA receptor antagonist	STZ Brown Norway rats	Improved amplitudes of a- and b-waves GC loss	Kusari et al., 2007
Minocycline	Antiinflammatory	Sprague-Dawley STZ rats	Repressed cytokine production, reduced release of cytotoxins from activated microglia, and reduced caspase-3 activity	Krady et al., 2005
Nepafenac (topical)	Non-steroidal cyclooxygenase inhibitor	Male Lewis STZ rats	No effect on diabetes-induced loss of cells in GCL. Inhibited development of OP delays	Kern et al., 2007
Nerve growth factor	Growth factor	Male wistar STZ rats	Prevented both early PCD in RGC and Muller cells	Hammes et al., 1995
Nipradilol	Beta-adrenoceptor blocking agent	Male Sprague-Dawley STZ rats	Antiapoptotic, removal of the NO moiety from nipradilol blocked these effects	Tatsumi et al., 2008
(+)-pentazocine	Sigma receptor 1 ligand	Spontaneous diabetic Ins2(Akita/+)	Preservation of retinal architecture, reduced nitrotyrosine and HNE	Smith et al., 2008
Rottlerin	PKC delta inhibitor	Otsuka Long-Evans Tokushima fatty (OLETF)	Inhibit protein kinase C-delta and neuronal apoptosis	Kim et al., 2008
Salicylates (aspirin, sodium salicylate, sulfasalazine)	anti-inflammatory, unlike aspirin, sodium salicylate and sulfasalazine can not inhibit COX at therapeutic doses.	Male Lewis STZ rats	Inhibited translocation of NF-KB to the nucleus, prevented RGC loss	Zheng et al., 2007
Sorbinil	Aldose reductase inhibitors	Male Sprague-Dawley STZ rats	Regulated retinal homeostasis and protected neurons against damage	Asnaghi et al., 2003

(TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; ICAM-1: intercellular adhesion molecule-1; GCL: ganglion cell layer; DHA: docosahexaenoic acid; ONL: outer nuclear layer; ERG: electroretinogram; NGF: nerve growth factor; AGE: advanced glycation endproduct; OP: oscillatory potentials; PCD: programmed cell death; RGC: retinal ganglion cell; HNE: hidroxynonenal).

Table 2. Experimental therapies resulting in preservation of retinal neurons in diabetes.

We will focus on oxidative stress. It has been repeatedly suggested that oxidative stress is involved in the pathogenesis of late diabetes complications (Baynes & Thorpe, 1993), though it is not definitely demonstrated if this is the cause or the consequence of these complications. It is clear that the elevated glucose levels present in diabetes and the

existence of oxidative stress are inseparable. Hyperglycemia reduces antioxidant levels and concomitantly increases the production of free radicals. These effects contribute to tissue damage in diabetes mellitus, leading to alterations in the redox potential of the cell with subsequent activation of redox-sensitive genes (Bonnetfont-Rousselot, 2002). The retina is the neurosensorial tissue of the eye and is extremely rich in polyunsaturated lipid membranes. This feature makes it specially sensitive to oxygen- and/or nitrogen activated species and lipid peroxidation.

Oxidative stress is linked to early apoptosis in diabetic retinopathy both at the microvasculature and neuronal cells of the retina but oxidative stress appears to be highly interrelated with other biochemical imbalances that lead to structural and functional changes.

Among the proposed pathogenic mechanisms, the polyol pathway model has received the most scrutiny. Aldose reductase (AR) is the first enzyme in the polyol pathway, converting excess glucose to sorbitol, which is then metabolized to fructose by sorbitol dehydrogenase. According to several studies, AR is correlated with the early events in the pathogenesis of diabetic retinopathy, leading to a cascade of retinal lesions including blood retinal barrier breakdown, loss of pericytes, neuroretinal apoptosis, glial reactivation, and neovascularization. Increased AR activity has been shown to contribute to increased oxidative stress by promoting nonenzymatic glycation and the activation of PKC (Stitt and Curtis, 2005). It has been demonstrated that AR inhibition counteracts diabetes induced oxidative and nitrosative stress and prevents vascular endothelial growth factor (VEGF) overexpression, basal membrane thickening, pericyte loss, and microaneurysms in retinal capillaries (Obrosova et al., 2003). Increased expression of VEGF and apoptosis and proliferation of blood vessels have been shown to be less prominent in diabetes rats than in diabetic AR-deficient animals (Obrosova et al., 2005).

A recent clinical study has substantiated the concept of "hyperglycemic memory" in the pathogenesis of diabetic retinopathy. The Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications Research, has revealed that the reduction in the risk of progressive retinopathy resulting from intensive therapy in patients with type 1 diabetes persisted for at least several years after the DCCT trial, despite increasing hyperglycemia. The process of formation and accumulation of advanced glycation end products (AGEs) and their mode of action are most compatible with the "hyperglycemic memory" theory. Advanced glycation end products are formed by nonenzymatic reactions between reducing sugars and free amino groups of proteins or lipids. AGEs have been detected within retinal vasculature and neurosensory tissue of diabetic eyes. Multiple consequences of AGE accumulation in the retina have been demonstrated, including upregulation of VEGF, upregulation of NF- $\kappa$ B, and increased leukocyte adhesion in retinal microvascular endothelial cells (Moore et al., 2003). In a 5-year study in diabetic dogs, administration of aminoguanidine (an inhibitor of AGE formation) prevented retinopathy (Kern et al., 2001). AGEs exert cell-mediated effects via RAGE, a multiligand signal-transduction receptor of the immunoglobulin superfamily (Schmidt et al., 1992). Consequences of ligand-RAGE interaction include increased expression of vascular cell adhesion molecule (VCAM)-1, vascular enhanced permeability, enhanced thrombogenicity, induction of oxidant stress and abnormal expression of eNOS (Schmidt et al., 1995). Recently, it has been shown that after RAGE activation NADPH oxidase is activated by phospholipase C-mediated activation of Ca(2+)-dependent PKC and that this may lead to an increase in ROS that could be associated with the initial stages of macular

edema and diabetic retinopathy (Warboys et al., 2005). Studies in models of retinopathy show that increases in oxidative stress and signs of vascular inflammation are correlated with increases in arginase activity and arginase expression, and that decreasing arginase expression or inhibiting its activity blocks these effects, and that the induction of arginase during retinopathy is blocked by inhibiting NADPH oxidase activity (Caldwell et al., 2010). Finally it has been also demonstrated that AGEs can induce glial reaction and neuronal degeneration in retinal explants (Lecleire-Collet et al., 2005).

Different antioxidants (ebselen, lutein and DHA) have been used in our lab in different animal models of diabetes, and all of them have shown good results in improving the decrease of b-wave amplitude ERG observed in these animals.

Alterations associated with oxidative stress offer many potential therapeutic targets making this an area of great interest for the development of safe and effective treatments for diabetic retinopathy. Animal models of diabetic retinopathy have shown beneficial effects of antioxidants on the development of retinopathy, but clinical trials (though very limited in number) have provided somewhat ambiguous results. Although antioxidants are being used for other chronic diseases, controlled clinical trials are warranted to investigate potential beneficial effects of antioxidants in the development of retinopathy in diabetic patients.

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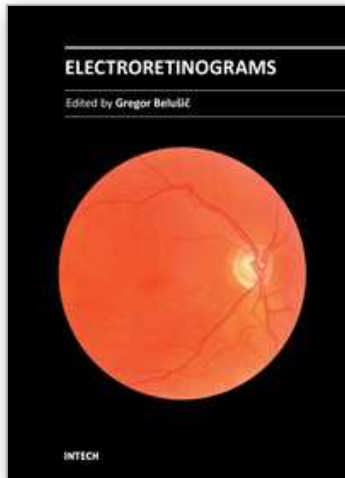
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