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Diabetic Retinopathy

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1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglicemia resulting from peripheral resistance to insulin, reduction of pancreatic secretion of such substance and increase of glycosis hepatic production, causing, after a long time, a series of complications (1).

Clinical diabetes complications may affect the great and medium arteries - causing coronary artery disease and peripheral artery disease - or the little arteries, causing diabetic microangiopathy – retinopathy, nephropathy and neuropathy (2,3).

2. Pathophisiology

Elevated glycemia induces a series of bichemical and cellular abnormalities which may cause vascular alterations found in diabetic retinopathy (4,5,6). Mechanisms induced by hyperglycemia which can cause endothelial cells dysfunction include increase of polyol pathway flux, accelerated and non-enzimatic formation of advanced glycation end-products (AGES), increase in diacylglycerol formation (with consequent activation of protein kinase C – PKC), increase of hexosamine pathway flux and a disturbed oxi-reduction status (4,5,6,7). All these mechanisms may contribute to the known phisiological characteristics of diabetic complications through increase of cytokines and growing factors regulation, and through formation of oxygen and nitrogen derived free radicals (8).

2.1 Free radicals

A free radical can be defined as a chemical species that has a non-paired electron (9). It may be also considered as a fragment of a molecule (10). Thus, free radicals can be formed in three ways:

- By cliving a covalent link of a normal molecule, with each of the fragments retainning one of the paired electrons (10);
- When a normal molecule lose one electron (10) and
- When a normal molecule receives one electron (10).

The most relevant free radicals in biological systems are those derived from oxygen (9,10,11).

3. Oxidative stress

It is said that a cell suffers oxidative stress when formation of free radicals overcomes hability of cellular antioxidant system (12). That may happen when a lot of free radicals is formed, when endogenous antioxidant defenses are diminished or, more commonly, when both events occur (12). Excessive free radical production may damage any cellular structure, including membrane (lipid peroxidation), proteins (anomalous polimerization) and nucleus (desoxirribonucleic acid – DNA - lesion) (12).

In diabetes, free radical formation, together with antioxidant deficiency, increases with time and may have an important role in retinopathy development (13,14).

Retina is known as an important target of diabete mellitus (1). Because of its high oxygen requirement and due to its unsaturated lipid content, retina may be a selective site for free radical production and for lipid peroxidation (1).

In endothelial cells, intracellular hyperglycemia promotes an increase in superoxide radical production at mitochondrial level (10). It is thought that such increase of superoxide production is the activator process of all pathways enrolled in diabetic complications pathogenesis (10). It is also seen an increase in nitric oxide production (NO) that is particularly damaging because it reacts with oxygen and produces peroxynitrite, a powerful oxidant (10). Peroxynitrite is cytotoxic because it inhibits mitochondrial transportation of electrons, oxidizes sulphidril groups in proteins, begins lipid peroxidation without the necessity of transition metals and nitrates aminoacids (such as tyrosine), what affects many signal transduction pathways (10). Chronic hyperglycemia promotes non-enzimatic glycation of proteins and glycated proteins may increase oxidant generation by activating fagocytes or by releasing superoxide and hydrogen peroxyde directly (10). Besides, AGEs estimulate oxidant production through specific interactions with receptors that are present in vascular cells (10).

4. Alterations of blood flux regulation

Endothelins are the main endothelial vasoconstrictors (12). In endothelial cells of retinal vessels, main endothelin is the subtype ET-1, that is synthethized and released by the action of several factors (growth factors, cytokines and insulin, among others) and is negativelly controlled by prostaciclin, nitric oxide and heparin, among other substances (12). ET-1 interacts with specific membrane receptors that are present in vascular smooth muscle fibers (ETA and ETB) and it triggers a vasoconstrictor effect (12). In diabetic animals retina, synthesis and activity of ET-1 and ET-3 are increased and factors which inhibit such actions are decreased; thus, endothelins are considered one of the factors that contribute to a reduction of retinal blood flux and to endothelial capillary proliferation (12).

Among the vasodilating factors those which deserve a greater attention are prostaciclin and nitric oxide (12). Prostaciclin is formed from arachidonic acid through participation of cycloxigenase, to form ciclic endoperoxides, as it occurs in platelets (12). Main difference between prostaciclin synthesis in platelets and in endothelium is that the first involves thomboxane synthetase that produces thromboxane A2 (TxA2, a powerful vasoconstrictor and platelet agregant) while the last one involves prostaciclin synthetase (a powerful vasodilating and platelet disagregant) (12). Due to shared biochemical origin but opposed

effects of both prostanoids, it is accepted that a proper balance between platelet thromboxane and vascular prostaciclin be fundamental to physiological interaction between platelets and vessel walls (12).

5. Vascular nitric oxide defficiency origin in diabete

In diabete, hyperglycemia may actvate PKC isoform bII in endothelial cells, what reduces calcium ingress in cells and, consequently, nitric oxide synthesis (15). Besides, PKC promotes superoxide generation in endothelial cells and it quenches in a reaction that produces the toxic radical peroxynitrite (15). This way, overactivation of PKC mediated by hyperglycemia may reduce the synthesis or accelerate the loss of nitric oxide (15).

Hyperglycemia also provides a substrate increase for endothelial aldose reductase (15). Such enzyme generates sorbitol from glucose in a reaction that oxidizes NADPH – and, this way, decreases disponibility of reducing co-factor for NO sintase (16).

Glycated tissue proteins (whose levels increase as a consequence of hyperglycemia) may generate superoxide in a non-enzymatic reaction that needs transition metal catalysis; such factor also contributes to NO deficiency associated to hyperglycemia (15). Besides, AGEs may also extinguish NO directly (15).

6. Pathogenic implications of NO deficiency

Vascular deficiency of NO may be critical for pathogenesis of micro and macrovascular complications of non-controlled diabetes mellitus (15). This may be appreciated in the light of physiological importance of basal activity of NO in maintaining an appropriate arteriolar vasodilation, stabilizing platelets and preventing excessive activation and circulating leucocyte adhesion (15). Loss of such activity may clearly promote ischaemia by inducing arteriolar vasoconstriction and microvascular occlusion by activated adhering leucocytes and thrombosis (15). Besides, NO increases sodium-potassium pump activity in arterial wall and in axons of peripheral nerve (15). Reduction of sodium-potassium pump activity in endothelial capillary cells exposed to hyperglycemia could, in the same way, be attributed to a lesser production of NO (15).

In diabetes, vasoconstrictor impact of NO deficiency is exacerbated by stimilus of PKC over endothelin production (15). There is also evidence that endothelial synthesis of PGI 1 (prostaciclin) tends to be subnormal in diabetics (15). Once prostaciclin, as well as protaglandin E1 (PGE1), present many physiological effects that are complementary to those of NO – including vasodilation – it is probable that an impairment in its production amplifies the pathogenic impact of NO deficiency (15).

In diabetes, NO deficiency and excessive activation of endothelial PKC cause an increased synthesis of Platelet Activating Factor (PAF) (15). Endothelial PAF, confined to luminal endothelial membrane, stimulates receptors in marginated leucocytes that circulate along post-capillary venules, inducing activation of these leucocytes and taking them to express β2-integrins (15). Such phenomenon possibilitates leucocytes to adhere tightly to endothelial surface (15). One of the main endothelial targets to which such endothelins adhere – ICAM-1 – is also estimulated by PKC activity (15).

Activated leucocytes also synthethize leucotrien B4 (LTB4), what also increases PKC activity more yet by estimulating phospholipase C-b (15).

Leucocytes are greater and more viscous than erithrocytes and the activation process increases their polymerization because of its action over actin (15). Thus, under conditions in which pressure gradient through capillaries is reduced – as in vascular beds supplied by estenotic arteries or in constricted arterioles – activated leucocytes become edged in capillaries, preventing vascular flux (15).

In diabetics, blood viscosity increases due to greater fibrinogen plasmatic levels and it may damage microcirculatory flux more yet (15). This way, these factors promote retinal hypoxia, which causes angiogenic factors release – more notably, vascular endothelial growth factors – which induce neovascularization (15).

7. Alterations of control mechanisms of growth factors

Among all growth factors, VEGF is the innermost factor related to retinal neovascularization because it takes part in formation of new vessels which appear after retinal ischaemia (12). VEGF is member of a great family of proteins with angiogenic and mitogenic capabilities (12). It is produced in retina in pigmented epitelium, in neurosensorial retina, in pericytes and in vascular smooth muscle layer (12). Even in the earliest stages of retinopathy (early or backgraund retinopathy) it is already observed an increased expression of (VEGF) messenger ribonucleic acid (mRNA) in retinal pigmented epitelium (12).

Studies about induction of permeability in retinal endothelial cells in culture showed that VEGF induces transitory and transcellular hyperpermeability, which involves nitric oxide synthase activation and nitric oxide formation (17). It is believed that such phase is followed by a sustained increase of paracellular permeability due to a reduction of ocludin protein of tight junctions and it involves urokinase receptor expression (uPAR), what may deflagrate plasmin formation and matrix metaproteinase activation (17).

VEGF, in turn, still promotes ICAM-1 expression by endothelial cell, what causes leucocyte activation and cytokine release leading to an amplification of inflammatory response (12,18).

8. Pigmented Epitelium Derived Factor (PEDF)

Besides causing vascular lesion, diabetes also presents an adverse and early impact over neural retina (2,12,18). Studies with diabetic patients showed early alterations in visual function, including damage of colored vision and contrast sensibility, and reduction of electroretinogram oscilatory potentials (2,12,18). Such alterations frequently precede microvascular lesions establishment and predict retinopathy worsening in a better way than clinical characteristics, suggesting that neurodegeneration, as well as vascular dysfunction, be an important characteristic of diabetic retinopathy (2,12,18). It was suggested that metabolic factors that cause such phenomenon include loss of trophic support mediated by insulin or a lesion due to excessive accumulation of hexosamine, α-Tumoral Necrosis Factor or glutamate (2,12,18). Data that show reduced levels of Pigmented Epitelium Derived Factor (PEDF) in ocular fluids and vitrectomy species of patients with diabetic retinopathy suggest that loss of PEDF contributes to neuroglial cells toxicity induced by diabetes (2,12,18).

PEDF occurs naturally in eye and it is expressed in multiple retinal cells, including retinal pigmented epithelial cells, glial cells, vascular endothelial cells and neurons (17). It was demonstrated that treatment with PEDF prevents retinal neovascularization in a model of ischaemic retinopathy (17). Recently it was verified that PEDF blocks the increase in vascular retinal permeability induced by ocular injections of VEGF (17). PEDF may also function as an antioxidant once it supresses reactive species generation mediated by NAD(P)H oxidase and blocks increase of expression of VEGF induced by oxidative stress (17). Studies of ocular fluids of patients with active neovascularization show an inverse correlation between VEGF levels (increased) and PEDF ones (decreased), suggesting that a change in balance between PEDF and VEGF levels may contribute to development of retinal neovascular disease (17).

Reductions of mRNA PEDF levels were related in endothelial cells in culture and in pericytes exposed to oxidative stress conditions, as well as in endothelial cells treated with TNF-α (17). Studies with cells in culture indicate that hypoxia and VEGF inhibit PEDF levels by increasing matrix metalloproteinases that degrade and inactivate PEDF (17).

9. Poly (ADP-ribose) polymerase and diabetic vascular disfunction

Poly(ADP-ribose)polymerase (PARP), also known as poly(ADP-ribose)synthase (PARS), is a nuclear enzyme abundant in eukaryotic cells that takes part in DNA repair in answer to genotoxic stress (19).

Compulsory trigger to PARP activation is DNA breakdown, which can be induced by a variety of environmental stimulations and free / oxidizing radicals, more notably hydroxil and peroxynitrite radicals (8,20).

When activated by DNA breakdown, PARP begins a cicle that consumes energy by transfering ADP ribose units from NAD+ to nuclear proteins (8,19). Such process results in a rapid depletion of intracellular supplies of NAD+ and ATP, reducing glycolisis tax (and mitochondrial respiration), as well as NADP levels (a co-factor for pentose way and of bio-reducing synthetic ways, involved in maintaning reduced glutatione pools), causing cellular dysfunction and death (8,19). It was showed that PARP activation occurs in a great variety of pathological states, including reperfusion lesion of colon, kidney, skeletal muscle and myocardium, inflammatory diseases such as colitis, diabetes and arthritis, septic and haemorragic shocks (8,19). It was demonstrated that PARP activation has also a central role in cardiovascular diseases, including encephalic vascular accident (EVA), atherosclerosis, cardiac ischaemic disease, doxorrubicin toxicity and diabetic cardiovascular disfunction (8).

PARP activation in answer to elevated glucose levels can be attenuated by SOD (8).

PARP activation may be relevant in endothelial cells dysfunction induced by hyperglycemia (8). Endothelial cells exposed to hyperglycemia during 1-2 days present an intense suppression of high energy phosphate cell levels, as well as NAD+ and NADPH levels (8). Since constitutive NO-sintetase (ec-NOS) is a NADPH-dependent enzyme, it is conceivable that NADPH cellular depletion in cells exposed to hyperglycemia be directly responsible for ec-NOS activity suppression and for reduction of endothelium dependent relaxing capacity of diabetic vessels (8). In diabetic patients, hyperglycemia effects over NADPH levels may be exacerbated by aldose redutase increased activity, which also depletes NADPH as well as generates reactive oxidants (8).

PARP activation in endothelial cells exposed to hyperglycemia may be a common factor among three of major hypotheses by which hyperglycemia causes diabetic complications: activation of PKC isoforms, increased flux of hesosamine pathway and AGEs increased formation (8,21). Each of these pathways may be activated by superoxide overproduction from mitochondrial electron transport chain and it is induced by hyperglycemia (8,21). Superoxide overproduction in endothelial cells exposed to hyperglycemia results from inhibition of activity of glyceraldeid-3-phosphate dehydrogense (GAPDH) enzyme, being PARP the mediator of such effect (8). Inhibition of GAPDH activity also activates pro-inflammatory transcription factor NF-κβ that is PKC-dependent in endothelial cells (8). Inhibition of GAPDH activity is a result of poly(ADP-ribosyl)ation of enzyme by PARP and can be reversed by inhibiting PARP (8). GAPDH is a multifunctional enzyme that presents effects as much in cytoplasm as in nucleus and it has been implicated not only in normal physiology (exportation of nuclear RNA, DNA replication, DNA repair, exocitotoxic membrane fusion, cytoskeletal organization and phosphotransferase activity), but also in pathological states, such as, neurodegenerative diseases (Parkinson's disease), cancer (prostate) and in viral pathogenesis, where it was demonstrated that GAPDH presents a role in apoptotic cellular death (8). It has been demonstrated that GAPDH is the link between PARP activation and endothelial cells diabetic dysfunction (8).

10. Vitamin C

10.1 Introduction

Vitamin C (ascorbic acid) is an essential micronutrient for normal body metabolism and it is present in fresh fruits, particularly in citrus ones, and in vegetables (15). Its deficiency causes scurvy (22).

Minimum necessary requirement of vitamin C is 60 mg/day for health and non-smoker people (22).

Vitamin C is a co-factor of several enzymes:

1. Pro-collagen-proline dehidrogenase (proline dehidrogenase) and procollagen lisine 5-dehidrogenase (lysine desidrogenase), involved in pro-collagen synthesis (22). Thus, vitamin C deficiency causes teeth losses, joint pains, bone and conective tissues disorders, and a deficient wound scar, all of which are characteristics of scurvy (22);
2. Deoxigenases, involved in carnitine biosynthesis, essential substance for long chain fat acids transportation to the interior of mitochondria (22). Thus, vitamin C deficiency results in fatigue and letargy, initial symptoms of scurvy (22);
3. Dopamine-monoxigenase, that catalyses conversion of dopamine into norepinephrine (22). Thus, norepinephrine deficiency must be related with depression, hipochondria and humor alterations that occur in scurvy (22).

Vitamin C was also implicated in cholesterol and biliary acids metabolism, through cholesterol 7α-monoxigense, and in adrenal steroid metabolism (22).

Other acitivties of vitamin C include thiol enzymes maintenance in a reduced state, and a saving effect of glutatione (an important intracellular antioxidant) and tetrahidrofolate (co-factor for cathecolamine synthesis) (22).

10.2 Antioxidant effect

According to the Panel on Dietary Antioxidants and Related Compounds of the Food and Nutrition Board, an antioxidant may be defined as a substance that reduces significantly the adverse effects of free radicals over normal physiological function (22).

Vitamin C (or L-ascorbic acid) is called electron donnor antioxidant due to its hability to prevent oxidation of other compounds by linking to their electrons (23). While ascorbic acid is oxidized in a stable and non-reactive form, free radicals are reduced to water and do not cause cellular lesion any longer (23).

Vitamin C scavenges superoxide and hydroperoxyl, watery peroxyl, oxygen singlet, ozone, peroxynitrite and nitrogen dioxide, nitroxide radicals and hypoclorous acid, protecting, this way, other substrates from oxidative lesion (16,22).

Besides, vitamin C regenerates α-tocopherol (vitamin E) from α-tocopheril radical (22). That is particularly important because α-tocopherol may act as a pro-oxidant in absence of co-oxidants like vitamin C (22).

10.3 Effects over coagulation, platelets and vessels

Studies showed an inverse association between vitamin C plasmatic concentrations and coagulation factors (22,24).

10.4 Effects over platelets

In vitro studies showed that physiological concentrations of vitamin C may increase PGE1 and PGI1 production, resulting in a reduction of platelet aggregation and thrombus formation (22). Besides, low concentrations of vitamin C are also associated to greater levels of Plasminogen Activating Inhibitor 1, a protein that inhibits fibrinolysis (22).

10.5 Vitamin C and nitric oxide

Other studies demonstrated that vitamin C restores endothelium depending vasodilation in diabetic type 1 patients and in acute hyperglycemia in health humans, while studies realized with type 2 diabetics showed varied results (24). Several mechanisms may be responsible for such effects and, probably, they are related to vitamin C antioxidant activity (22).

NO presents an important role in vasodilation and it also inhibits platelet aggregation and lecocyte adhesion (22). Studies showed that NO concentrations are reduced through its reaction with superoxide radicals and because of its release by oxidized LDL (22). This way, vitamin C may prevent NO breakdown by scavenging superoxide radicals or by preventing oxidized LDL formation (16,22,23).

10.6 Effects over capillary fragility

Vitamin C deficiency promotes the following alterations over vascular tissues: inner and basal membrane thickening, extra-cellular matrix accumulation due to a reduced sulfatation, endothelium tight junctions loss (with consequent increase of transcapilar escape tax – TET) and capillary fragility (24). Such findings are also met in diabetic microangiopathy (24).

10.7 Effects over diabetic complications

A recent report showed that all alterations induced by hyperglycemia – including aldose redutase, PKC and AGEs increases – are reversed by inhibiting free radicals production induced by glucose (25). Such fact gives the possibility that, by blocking glucose induced oxidative stress, it may also be possible to prevent lesions caused by other pathways (25).

Vitamin C presents a central role in antioxidant defense system and may help to mitigate oxidative stress associated to diabetic complications (22). In fact, there are reports that high dose vitamin C diets are associated to reversion of early signs of retinopathy and to normalization of capillary resistance in diabetes mellitus, confirming its antioxidant protector role in blood vessels lesion (9,26).

10.8 Intracellular transportantion of vitamin C

It is known the existence of two distict mechanisms of vitamin C transportation into the cells (25):

1. A sodium-dependent mechanism that is mediated by a pair of ascorbate carriers, which is predominant in hemato-encephalic barrier, osteoblasts, muscles, placenta, intestine walls, brush border kidney cells, liver, brain and in the majority of endocrine and neuroendocrine systems, and it is not affected by glucose plasmatic levels (25);
2. An extremely sensible mechanism to glucose blood levels and dependent of some members of glucose transporters family (GLUT) (25).

There are also some cellular types, as linfocytes and red blood cells, that use both ascorbate captation mechanisms (25).

Once dehidroascorbate (DHA) enters cells, it is converted into ascorbic acid and stored (25).

Glucose and DHA co-transportation by GLUT's in certain cellular types suggests a new causative mechanism of disease in these particular cellular types (25). Studies show an increase in free radicals production induced by hyperglycemia in target-organs affected by diabetes mellitus (25). Thus, it is suggested that free radicals production is the main causative pathway of diabetic complications (25).

Ascorbic acid functions as an important component of cellular defense against oxygen toxicity and lipid peroxidation caused by free radicals (13,26). Reduced ascorbic acid levels have been observed in diabetic patients, mainly in those with microangiopathy (13,26).

Ascorbic acid caption by cell is mediated by a process related to glucose transportation and it was demonstrated that a high glucose extracellular concentration in diabetics may damage such caption and accentuate problems related to deficiency of such vitamin (13,26).

That phenomenon would deprive cells of central antioidant and could cause accumulation of free radicals followed by activation of PKC and aldose redutase pathways and by AGEs production in diabetes (25).

Such effects are limited to certain specific cellular types that depend on glucose and DHA co-transportation by GLUT (25).

Since DHA and glucose compete for GLUT carriers, each of them can inhibit transportation of the other (25,26). Basal blood glucose in non-controlled diabetes is tipycally elevated and,

during hiperglycemic episodes, it increases still more (25,26). Besides, ascorbate levels tend to be significantly reduced in non-controlled diabetes, even in diabetics who eat diets rich in such substance (25,26). It seems that ascorbate loss is due to its excretion (together with glucose) by the kidneys, to a blockade of its recaption due to a greater glucose concentration and to its reduced absorption by kidney tubules (due to osmotic diuresis and glucosuria) (25).

It is verified, in average, a reduction between 30 and 80% of normal taxes of entrance of DHA into cells (25). Thus, DHA transportation into nerves, retina, kidney and other tissues that are unique or mainly GLUT –dependent, will be intense and chronically reduced (25).

This way, it is probable that hyperglycemia results in a vitamin C deficiency in certain types of cells (such as peripheral neurons, pigmented cells and retinal vascular endothelial cells) which depend mainly or exclusively on GLUT carriers for vitamin C caption (25).

11. Preventing and treating diabetic complications

Thus, it is believed that ascorbic acid may prevent or even treat complications associated to diabetes by affecting proteic glycosilation (25,27), sensibility to insulin, retinal blood flux and oxidative stress (25,28).

11.1 Adverse effects of vitamin C

Adverse effects from excess of vitamin C are hemochromatosis or iron overload, an increase of uric acid and oxalate excretion (with consequent development of kidney stones), nausea, vomiting and diarrhea (29).

12. Superoxide dismutase

12.1 Physiopathology of diabetes chronic complications

According to what has already been said, diabetes chronic complications occur as a consequence of persistent hyperglycemia (7). Hyperglycemia, in turn, promotes glucose auto-oxidation, AGEs formation and its interaction with RAGEs, activation of several isoformes of PKC, induction of poliol pathway and an increase of flux of hexosamine pathway (7).

Recently, it was made a hypothesis according to which all these processes would be a consequence of an increase of superoxide production by respiratory mitochondrial chain during hyperglycemia (7,30).

Mitochondrial role in retinopathy pathogenesis is supported by reports which show that retinal mitochondria presents a dysfunction in diabetes (30,31). Eight-month diabetic rats (a duration in which capillary cell apoptosis is seen in retina) present an increase of citocrome c release in citosol and of Bax pro-apoptotic protein in mitochondria (30,31). Besides, incubation of retinal capillary cells in a hyperglycemic environment results in these precise abnormalities, which are accompanied by increased cellular apoptosis (30).

Retinal capillary cells apoptosis is an early event in diabetic retinopathy pathogenesis, and oxidative stress is linked to accelerated apoptosis of retinal capillary cells (30). Because it was demonstrated that retinal capillary cells are lost through apoptosis before other hystopathological alteration is detectable and because treatments that inhibit retinopathy

development also inhibit apoptosis and caspase-3 activation, it is suggested that superoxide presents an important role in diabetic retinopathy pathogenesis (30).

This way, reduction in superoxide production by mitochondria or an increase in its tax of decomposition by antioxidants could block many of hyperglycemia pathological consequences (7).

13. SOD history

In 1938, Mann and Keilin described a blue-greened protein containing copper (hemocupprein), which they have isolated from ox blood (9,32). In 1953, a similar protein was isolated from horses' liver and it was called hepatocuprein (9).

In 1969, McCord and Fridovich related that an erithrocitic protein was capable of removing catalitically superoxide radical, that is, it functioned as a superoxide dismutase enzyme (SOD) (9,33). Posteriorly, it was demonstrated that SOD is identical to human erithrocuprein and to bovine hemocupprein described previously (31,33).

Soon, SODs were isolated from a variety of eucharyotes and prokaryotes (33). All eucharyotic SODs had copper and zinc (CuZnSOD), while procharyotic ones had manganese (MnSOD) (33). While he worked with chicken livers, Fridovich perceived that it contained two types of SOD, one localized in mitochondria and another one localized in cytosol (33). Surprisingly, mitochondrial SOD had manganese (33).

Similarity between mitochondrial and bacterial SODs suggests that mitochondria has evolved from an endocellular symbiotic relation with procharyotes (33).

Together with Fred Yost, Fridovich also isolated a SOD which contains iron (33).

Howard M. Steinman and cols. determined the complete sequence of aminoacids of CuZnSOD (33). Steinman and Robert L. Hill determined the sequence of the first 29 residues of ending amino of mitochondrial Mn dismutase, of bacterial Manganese dismutase and of bacterial Iron dismutase (33). Elevated degree of similarity of identity between bacterial and mitochondrial dismutases gave an additional support to endosymbiotic origin of mitochondria (33).

13.1 SOD actions

SOD constitutes primary defense against superoxide radicals and its reaction with such free radicals results in hydrogen peroxide formation (16).

Due to its mitochondrial localization, MnSOD is considered the first line of defense against oxidative stress (30).

It was demonstrated that there is less mitochondrial SOD activity in retina during capillary cells apoptosis and during the appearance of diabetic retinopathy hystopathological characteristics (30).

In vivo and in vitro studies suggest that MnSOD presents a protecting role against development of diabetic retinopathy because an increase in its expression in isolated retinal endothelial cells protects retinal capillary cells from oxidative stress induced by glucose and from capillary cells apoptosis (30).

13.2 Effect of MnSOD over "hiperglycemic memory"

A paradox in diabetes is called "hiperglycemic memory" and refers to a persistent progression of microvascular alterations induced by hyperglycemia during subsequent periods of normal glycemic homeostasis (34). That outstanding phenomenon occurred in eyes of diabetic dogs during a post-hyperglycemic period of euglycemia (34). Eyes were hystologically normal during 2,5 years before exposition to elevated and sustained glycemia (34). But, after a subsequent period of 2,5 years of normal glycemia, eyes developed severe retinopathy (34). Worsening of retinopathy, in spite of sustained normoglycemia, was also related in rats with streptozocin induced diabetes implicating that an isolated good glycemic control does not stop diabetic microangiopathy progression in its late stage (34).

Results from Epidemiology of Diabetes Interventions and Complications Study indicate that hiperglycemic memory also occurs in human patients (34). It was demonstrated that the effects of conventional and intensive treatments over occurrence and severity of post-study diabetic retinopathy and nephropathy persist until 4 years after Diabetes Control and Complications Trial, in spite of almost identical glycosilated hemoglobin values during the 4-year follow-up period (34). It is interesting that obtaining normoglycemia through pancreatic transplantation is not effective yet in reducing diabetic retinopathy progression (34). Other studies demonstrate that previous glycemic exposure and glycemic level at first visit also have influence over diabetic retinopathy development (34). The lesson from those studies is that achieving the best glycemic control when diabetes is diagnosed seems to be of outstanding importance once HbA1c levels already during the first year of disease are related to posterior development of diabetic retinopathy (34).

As it was suggested by Brownlee and cols., superoxide mitochondrial production induced by hyperglycemia (oxidative stress) may provide an explanation for development of complications during post-hyperglycemia normal glycemia periods (30,34).

Treatments that inhibit activation of apoptosis promoting enzyme and, consequently, diabetic retinopathy development, reduce oxidative stress in retina (30). Thus, it was observed that increases in MnSOD expression prevents oxidative stress induced by glucose in retinal endothelial cells (30). This way, MnSOD could be used in treatment of "hiperglycemic memory".

14. Adverse effects

Superoxide dismutase does not present known adverse effects (9).

15. Conclusion

There are evidences of a key-role of free radicals in diabetic retinopathy pathogenesis. Retina is rich in polyunsaturated fat acids and presents glucose oxidation and oxygen caption taxes greater than any other tissue, being, this way, extremely susceptible to increased oxidative stress. Alterations of enzyme activity of antioxidant system (such as superoxide dismutase) seem to be one of the possible sources of oxidative stress in diabetes. Recent evidences also point to a participation of oxygen reactive species in mithogenic cascade began by tyrosine kinase receptors of several growth factors, including Vascular Endothelial Growth Factor (VEGF). Antioxidants, at least, inhibit some metabolic

abnormalities and pathological alterations induced by hyperglycemia. Therefore, it is reasonable to postulate that an antioxidant treatment may be useful to prevent diabetic retinopathy progression and that medication combinations could be necessary to prevent visual loss in diabetic patients. Ascorbic acid is present in great amounts in human eyes and its hability of scavenging oxygen reactive species may have importance in the treatment of diabetic retinopathy. Biological role of superoxide dimutase is scavenging superoxide, which is generated in vivo after exposition to oxygen. Retinal Pigmented Epithelium (RPE) has elevated levels of Manganese-Superoxide Dismutase and a reduction of its levels may be related to retinal lesion. Antioxidants, such as vitamin C and superoxide dismutase, may provide aditional beneficial effects to patients with diabetic retinopathy. Thus, vitamin C and superoxide dismutase present the potential of influencing positively ocular disease.

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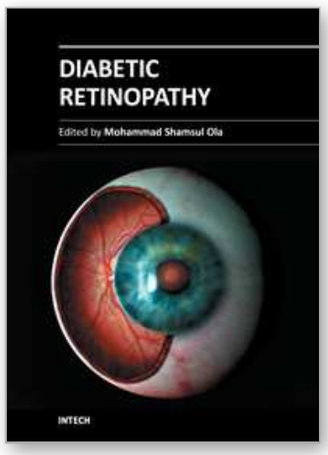
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The aim of this book is to provide a comprehensive overview of current concepts in pathogenesis, diagnosis and treatments of diabetic retinopathy. It provides a collection of topics written by excellent authors, covering discussions on advances in understanding of pathophysiology, immunological factors and emerging concepts, relating to clinical aspects and treatment strategies. The contents of the book will not only provide a resource for our knowledge but also improve diagnosis and treatment options for those patients who suffer vision loss due to diabetic retinopathy.

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