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THE ROLE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN THE PATHOGENESIS OF DIABETIC RETINOPATHY

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SUMMARY

Diabetic retinopathy is a common and progressive microangiopathic complication of diabetes mellitus, and a major cause of blindness in working age adults. Hypertension together with the duration of diabetes and hyperglycemia is considered as one of the substantial risk factors for the development of diabetic retinopathy. It is increasingly clear that anti-hypertensive therapy in conjunction with rigorous glycemic control may be effective in preventing the development and progression of diabetic retinopathy, but the mechanism of this protective influence is still insufficiently understood. It has been proposed that simple lowering of blood pressure is important and that any class of anti-hypertensive agents would be effective. Alternatively, it has been suggested that angiotensin-converting enzyme (ACE) inhibition may be particularly beneficial. There is evidence for the existence of independent renin-angiotensin system

(RAS) in the eye. Experimental and clinical studies imply that the RAS may have pathogenetic influence in the development of diabetic retinopathy and thus the blockade of the RAS by ACE inhibitors could provide protection from the development of this long term complication of diabetes.

INTRODUCTION

Diabetic retinopathy is a common and progressive microangiopathic complication of diabetes mellitus and a major cause of vision loss and blindness in working age adults worldwide. It is characterized by the loss of pericytes, hypertrophy of the basement membrane, microaneurysm formation, increased vascular permeability, capillary occlusions, neovascularization and fibrovascular proliferation. The predominant cause of visual loss in diabetic patients results primarily from intraocular angiogenesis (proliferative diabetic retinopathy, PDR) and leakage of retinal vessels (diabetic macular edema, DME). These intraocular lesions develop and progress despite advances in laser photocoagulation and vitrectomy and other accessible medical approaches including intensified glycemic control (1).

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THE INFLUENCE OF HYPERTENSION ON DIABETIC RETINOPATHY

Systemic diseases which accompany diabetes mellitus can have marked effects upon the development and progression of diabetic retinopathy. Together with the duration of diabetes and hyperglycemia, they are considered as substantial risk factors in the development of diabetic ocular microvascular complications (2). Diabetic patients commonly suffer from concomitant hypertension and evidence from cross-sectional and prospective epidemiological studies demonstrate that elevated blood pressure may have a detrimental effect on the development and progression of diabetic vasculopathy (2,3).

Diabetics with hypertension are more likely to develop diabetic retinopathy. They tend to display a more rapid progression (4,5) and have more severe levels of retinopathy (6) compared to diabetics without hypertension. In addition, diabetic patients with concomitant hypertension have been reported to be three times more likely to develop diffuse DME (7). This fact implies the importance of hypertension in vision loss in the diabetic population since 90% of them have type 2 diabetes in which DME is more common than PDR (1).

Several mechanisms have been proposed to account for the influence of hypertension in the development of diabetic ocular microvascular complication. The impairment of retinal vascular autoregulation in response to raised systemic blood pressure may play a role, since diabetic patients with high blood glucose do not autoregulate retinal blood flow at the levels of raised mean arterial pressure as compared with nondiabetics (8). Hypertension may additionally enhance endothelial damage of the retinal vasculature in patients with diabetes (9). Vascular stretch of the retinal endothelium has been shown to increase the expression of vascular endothelial growth factor (VEGF) and its receptors, which could account for both the progression of diabetic retinopathy and aspects of hypertensive retinopathy (10).

DIABETIC RETINOPATHY DEVELOPMENT AND ANTIHYPERTENSIVE TREATMENT

Until recently, the only systemic measure to prevent or slow down the progression of diabetic retinopathy was rigorous glycemic control, but it is now increasingly evident that antihypertensive therapy may also be effective (11). In the latter case, the mechanism of any protective influence still remains insufficiently understood. It has been hypothesized that simple lowering of blood pressure is important and that any class of antihypertensive agents could be effective (12). Alternatively, it has been suggested that angiotensin-converting enzyme (ACE) inhibition may be particularly beneficial, as a result of local or non-hemodynamic effects (13), as it is in diabetic nephropathy (14).

A relationship between diabetic retinopathy and hypertension is strongly suggested by the results of the United Kingdom Prospective Diabetes Study (UKPDS). It was a large randomized prospective clinical trial evaluating the effects of rigorous blood pressure control in addition to glycemic control on the prevention and slowing down the progression of diabetic vasculopathy in patients with type 2 diabetes mellitus (11). These beneficial effects of blood pressure control in retinopathy prevention were independent of glycemic control. The result of this study also implies that blood pressure control prevents the development of diabetic maculopathy, which is the main cause of visual impairment in type 2 diabetes (1). As diabetic maculopathy responds far less to laser retinal photocoagulation than PDR (15), reducing the risk of maculopathy by tight blood pressure control could provide a major clinical benefit in reducing the risk of visual loss and blindness in diabetic patients. This study shows that treatment including both an ACE inhibitor and β blocker aiming at blood pressure of <150/85 mm Hg substantially reduces the risk of death and complications due to diabetes, including the reduction of deterioration in visual acuity (11). This observation suggests that the lowering of blood pressure alone, rather than the inhibition of ACE, may be of principal importance, although this point is still being debated (12).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND DIABETIC RETINOPATHY

It is known that antihypertensive therapy, especially the use of ACE inhibitors, slows down the progression of diabetic nephropathy (14) but whether these agents have a beneficial effect on retinopathy is not as clear. The relationship between the renin-angiotensin system (RAS) and the progression of diabetic renal disease has been a major focus of investigation over the past 20 years. More recently, experimental and clinical studies have also suggested that the RAS may have a pathogenetic role at other sites of micro- and macrovascular injury in diabetes as well as in the eye (16). Better understanding of the relationship of ACE inhibitors and diabetic retinopathy is contributed by the knowledge of the existence of an independent RAS in the eye (17). Major components of the RAS including angiotensin type 1 and angiotensin type 2 receptors have been identified in ocular tissues. There is also evidence that ACE is produced locally by vascular endothelial cells (18) and may have direct detrimental effects on retinal flow and vascular structure, independent of changes in the systemic blood pressure (12). Activation of angiotensin II type 1 receptors expressed on retinal endothelial cells and pericytes has been implicated as contributing to the microvascular abnormalities found in diabetic retinopathy (19). This may therefore account for the beneficial effect of ACE inhibition on this ocular complication, however, the mechanism of their action is not yet fully understood. These observations imply that the use of ACE inhibitors may protect against the development and progression of diabetic retinopathy (20), yet the association between the RAS and the development and progression of diabetic retinopathy is not straightforward.

There is evidence supporting the relationship of serum concentrations of ACE inhibitor and the presence and degree of diabetic retinopathy (21). In addition, it has been shown that captopril, an ACE inhibitor, limits the abnormal leakage of fluorescein from retinal vessels, which is one of the elementary features of diabetic retinopathy (22). The Eurodiab Controlled Trial of Lisinopril in Insulin Dependent

Diabetes (EUCLID) study found that the use of lisinopril in normotensive type 1 diabetic patients decreased the progression of retinopathy and was associated with the reduction in PDR (13). However, some investigations showed non-significant benefits of other ACE inhibitors in subjects with type 1 (23) and type 2 diabetes (24).

Advanced diabetic retinopathy is characterized by neovascularization and enhanced vascular permeability. The vascular endothelial growth factor VEGF glycoprotein is a potent vessel angiogenic and vasopermeability factor, which plays a key role in the pathogenesis of retinopathy, particularly its proliferative form. VEGF expression is induced by hypoxia and is considered to be a stimulus for neovascularization. Intraocular levels of this glycoprotein positively correlate with the degree of diabetic retinopathy and their elevated concentrations precede the onset of the proliferative form of retinopathy. It has been shown that intraocular VEGF concentrations fall to near normal levels after photocoagulation (25). Inhibition of VEGF activity also suppresses the development of retinopathy (26). Angiotensin II enhances VEGF-mediated proliferation by inducing VEGF receptors in retinal endothelial cells (24), thus potentially accounting for the improvement in permeability of the blood-retinal barrier observed with captopril therapy and the beneficial effect of ACE inhibition on diabetic ocular microvascular complications (13).

The concentrations of both angiotensin II and VEGF in the vitreous fluid of patients with PDR were significantly higher than those in non-diabetic patients and diabetics without retinopathy. Vitreous fluid levels of angiotensin II were found to significantly correlate with those of VEGF. Moreover, the levels of both VEGF and angiotensin II were higher in active PDR than in quiescent PDR. These findings therefore suggest that angiotensin II contributes to the development and progression of PDR in combination with VEGF or *via* stimulation of VEGF (27).

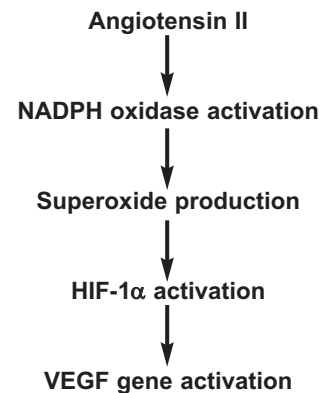
Macrogial Müller cells are the likely site for pathophysiological processes involving the retinal RAS. Retinal cells able to produce VEGF are Müller glial cells, pigment epithelial cells, vascular smooth

muscle cells and pericytes (28). One of the known factors implicated in the pathogenesis of diabetic retinopathy, which increases retinal VEGF production, is also angiotensin II (29). It is known that angiotensin II, the effector molecule of the RAS, has angiogenic activity (30) and may also induce neovascularization *via* paracrine effect on VEGF in diabetic patients with PDR (27). The induction of VEGF by angiotensin II requires hyperglycemic (31) or oxidative conditions (32) which accompany diabetes. If the RAS system plays a role in the VEGF overexpression found in PDR in humans, one would expect that the VEGF accumulation in the ocular fluid would be reduced upon medicinal intervention of angiotensin II-mediated processes. It is found that patients with PDR treated with an ACE inhibitor have relatively lower vitreous VEGF concentrations. Moreover, a strong negative correlation between vitreous VEGF concentration and the daily dose used was found in patients receiving an ACE inhibitor, enalapril (33). In animal studies, ACE-inhibitor treatment reduced the retinal overexpression of VEGF mRNA both in streptozotocin-induced diabetes (39) and in retinopathy of prematurity models (35). It is feasible that a reduction in retinal angiotensin II concentrations was involved in the lowering effect of ACE inhibition on the high vitreous VEGF concentrations in patients with PDR.

An intracellular signaling pathway that could mediate the angiotensin II-induced overexpression of VEGF in the retina involves the hypoxia-inducible factor-1 α (HIF-1 α). In addition to hypoxia, it has been shown that this transcription factor can be increased by various agonists of which angiotensin II is most potent. The mechanism of HIF-1 α induction by angiotensin II depends on the production of reactive oxygen species (32). The observation that hyperglycemia is required to detect angiotensin II-induced expression of VEGF in cultured smooth muscle cells (31) could be related to the formation of radicals, because of the fact that an altered cellular redox state is induced by hyperglycemia. These *in vitro* observations agree closely with earlier *in vivo* observations in rat aorta, namely, that infusion of angiotensin II increases the production of superoxide

anions by activation of NADPH oxidase. This effect could be completely blocked by losartan, an angiotensin type 1 receptor antagonist (36). From this data on smooth muscle cells, a sequence of events is suggested that connects cellular activation by angiotensin II *via* NADPH oxidase activation, superoxide production and HIF-1 α activation to the transcriptional activation of the VEGF gene (Fig. 1). Although such a mechanism has yet to be verified in the eye and the retina, the fact that angiotensin II also increases VEGF transcription and production in pericytes and mesangial cells points to a broader

Figure 1. **Possible signaling pathway of angiotensin II mediated VEGF overexpression**



implication of the suggested mechanism.

It has been observed that the use of ACE inhibitors decreases the incidence of diabetic complications based on microvascular dysfunction, i.e. nephropathy (14), neuropathy (37), and there is even more evidence pertaining to their beneficial effect on retinopathy (13,23). In diabetic patients, ACE-inhibition reduces microalbuminuria and normalizes the increase in skin capillary permeability (14), and also attenuates the increased retinal blood flow (36) which accompanies the progression of nonproliferative diabetic retinopathy (38). It has been considered that the beneficial effects of ACE-inhibition on diabetic microangiopathy could involve VEGF activity at various stages. High vitreous VEGF concentrations present in patients with PDR were found to be lower in those treated with an ACE inhibitor (33). According to recent accessible data it is clear that ACE-inhibitors

influence the role of VEGF in microangiopathy either by attenuating its overexpression (33) or by reducing the number of VEGF receptors (39), or both. Hence, it is suggested that interference with a retinal effect on one or more of the ACE-related agonists, angiotensin II is most likely involved in the observed association between ACE inhibiting therapy and lower vitreous VEGF concentrations in patients with PDR.

CONCLUSION

Hypertension has been identified as one of the major risk factors for the occurrence and development of diabetic retinopathy. The role of the RAS in its pathogenesis has been investigated and there is increasing evidence for the beneficial effects of ACE inhibition on diabetes induced abnormalities in retinal hemodynamics and vascular permeability (19). Therefore, a number of large clinical trials have examined whether blockade of the RAS might provide protection from the development of diabetic retinopathy. It has been proposed that angiotensin II, the effector molecule of RAS, possibly participates directly and/or indirectly in the occurrence and development of diabetic retinopathy *via* up-regulation of VEGF expression. According to the existing

investigations, early treatment with angiotensin-converting enzyme inhibitors could protect the retina and consequently improve diabetic retinopathy to some degree. While some controversy remains, in general, it is suggested that ACE inhibition reduces the development and progression of diabetic nephropathy, cardiovascular diseases and probably diabetic retinopathy. Diabetics with better glycemic control benefited most from ACE-inhibitors, thus the combination of rigorous glycemic control with ACE inhibitor therapy may prove to be the best therapeutic approach in these patients.

To confirm that ACE inhibitors have a beneficial role in the development of diabetic retinopathy, the Diabetic Retinopathy Candesartan Trial (DIRECT) is currently under way. The aim of this large randomized controlled clinical trial is to examine the efficacy of ACE inhibitors (and ACE receptor blockers) in preventing the incidence and progression of retinopathy in both type 1 and type 2 diabetic subjects (40). The results of this study will hopefully provide recommendations for the prevention and treatment of diabetic retinopathy, and thereby facilitate diabetic care and reduce visual impairment in these patients.

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