Symposium on Treatment of Diabetic Complications*

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1. Retinopathy

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Diabetic retinopathy is one of the most important complications of diabetes mellitus because its progression can lead to blindness (1, 2). However, there is no effective medical therapy available for the prevention of vision-threatening retinopathy.

This review presents a description of the prevalence and progression of diabetic retinopathy, then briefly considers selected pathogenetic concepts, and concludes with a discussion of current and future treatments, including our data on the effects of the drugs for electroretinogram (ERG) in diabetic animals.

Clinical course and pathogenesis of diabetic retinopathy

Prevalence and progression of diabetic retinopathy

Recently, the stage of diabetic retinopathy is grouped into back ground (non-proliferative) retinopathy, pre-proliferative retinopathy, and proliferative retinopathy. When new vessels appear on the surface of the retina or optic disc, diabetic retinopathy is said to have entered the proliferative state, leading to the development of vision-threatening retinopathy.

Diabetic retinopathy is more common in the older-onset individuals with diabetes of <5-year known duration, and prevalence rose less rapidly with increasing duration, both in the insulin taking group (a mixture of insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus) and

in the non-insulin taking (non-insulin-dependent diabetes mellitus) group (3).

Pathogenesis of diabetic retinopathy

Several factors are important in the evolution of diabetic retinopathy, including metabolic, vascular and endocrine ones (1, 2). These factors are not independent but tend to interact. The key factor is hyperglycemia, which triggers and maintains all the other abnormalities. With regard to metabolic factor, it has long been considered that hyperglycemia-induced polyol pathway hyperactivity may play an important role in the genesis of diabetic microangiopathy leading to retinopathy and neuropathy (4–6). The demonstration that pericytes of retinal capillary contain aldose reductase, an enzyme of the polyol pathway (7), and that the inhibition of this enzyme activity by aldose reductase inhibitor leads to reduce pericyte loss in diabetic rats (8) and galactosemic dog (9) has strongly supported the suggestion that polyol pathway hyperactivity may be a fundamental mechanism underlying diabetic retinopathy. Another possible mechanism by which elevated blood glucose might damage retinal vascular and other cells is nonenzymatic glycation of proteins, a reaction occurring between glucose and amino acids groups of proteins and leading to cross-linking between proteins and modification of their function (10). An

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inhibitor of this process, aminoguanidine, is under study.

Diabetic retinopathy also seems to be related to focal retinal ischemia (1, 2). Abnormalities of blood rheological properties in diabetes include decreased erythrocyte deformability, increased platelet aggregation, and increased plasma viscosity, and these changes may play an important role in the development of microvascular abnormalities. It is strongly suggested that these abnormalities are partially related to hyperglycemia-induced polyol pathway hyperactivity (6). From the view of vascular factor, the pathogenesis of diabetic retinopathy can be explained as shown in Fig. 1 (2).

Prevention and treatment of diabetic retinopathy

Electroretinogram and diabetes mellitus

It is well accepted that the ERG specifically indicates retinal function and also provides an early warning of retinal abnormalities before ophthalmoscopically visible alterations are detectable in diabetes (11). Müller (glial) cells of the retina show damage due to diabetes mellitus earlier than the retinal blood vessels, and the b-wave of the ERG is known to be related to Müller cell function (12). Among the alterations of the b-wave, the latency shows more significant changes than the amplitude in rats with early diabetes (13).

In our study, streptozotocin-induced diabetic rats were given aldose reductase inhibitors (TAT (14), SNK-860 (15)) or vasodilatory and anticoagulant drugs (beraprost sodium (16)), and the changes in b-wave latency as well as the retinal sorbitol content were determined to investigate the pathogenesis of diabetic retinopathy and the mechanism of the preventive effect of these drugs. Either aldose reductase inhibitors or vasodilatory

and anticoagulant drug prevented ERG abnormalities in rats with streptozotocin-induced diabetes. Although the improvement by aldose reductase inhibitors in ERG abnormalities in diabetic rats was accompanied by reduction of elevated sorbitol levels in the retina, beraprost sodium had no effect on the sorbitol contents of the retina.

As shown in Fig. 2, the effect of beraprost sodium, a prostacyclin analog, on ERG abnormalities was accompanied by a significant increase of nerve conduction velocity and sciatic nerve blood flow (16). Although we do not show any data of cilostazol, an anticoagulant and vasodilatory drug, this drug also has the similar effect as beraprost sodium does. These findings suggest that both aldose reductase inhibitor and anticoagulant drug may have a therapeutic value for treatment and prevention of diabetic retinopathy.

Treatment of diabetic retinopathy

It is well recognized that high glucose is the hallmark of diabetic retinopathy and good control of it is very important for the prevention of diabetic retinopathy (1, 2).

Recently, the Diabetes Control and Complications Trial Study Group reported that the rigid control of blood glucose using intensified treatment with insulin significantly reduced the incidence of diabetic retinopathy and also reduced the progression of retinopathy from background to the proliferative form in patients of insulin-dependent diabetes mellitus (17). No such dramatic effect was not observed. Thus, it is clear that good control of blood glucose is very important as a fundamental treatment in diabetes mellitus, resulting in the prevention against the progress of diabetic retinopathy. In

Figure 1. Role of hyperglycemia in evolution of diabetic retinopathy.

Figure 2. Effects of beraprost sodium and insulin on the electroretinogram, nerve conduction, and nerve blood flow in rats with streptozotocin-induced diabetes. Values are means $\pm$ SEM for 10–11 rats. NC: Normal control rats, DC: Diabetic control rats, NB: Normal beraprost sodium-treated rats, DB: Diabetic beraprost sodium-treated rats, DI: Diabetic insulin-treated rats. * $p < 0.05$ vs. NC, NB, DB and DI.

addition to keeping good control of blood glucose, it is also important that risk factors for the development of diabetic retinopathy are reduced.

It is regrettable that only effective treatment of diabetic retinopathy is photocoagulation in the present time (1, 2). However, as seen in our animal studies (5, 6, 8, 14–16), it is suggested that some drugs may be useful for the reduction of the incidence of diabetic retinopathy and its prevention. If there were any chances, the following drugs may be valuable to keep in mind; aldose reductase inhibitor (1, 4–6, 8, 14, 15), anticoagulant and vasodilatory drug (1, 2, 16), and lipid-lowering agent (18). Our experimental and clinical data from pathological and physiological investigations strongly suggest that aldose reductase inhibitor can prevent the development of diabetic retinopathy, and underline the importance of the polyol pathway in its development (8).

It is concluded that good control of blood glucose and early adequate treatment may prevent the development of diabetic retinopathy, resulting to reduce blindness related to diabetes mellitus.

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