



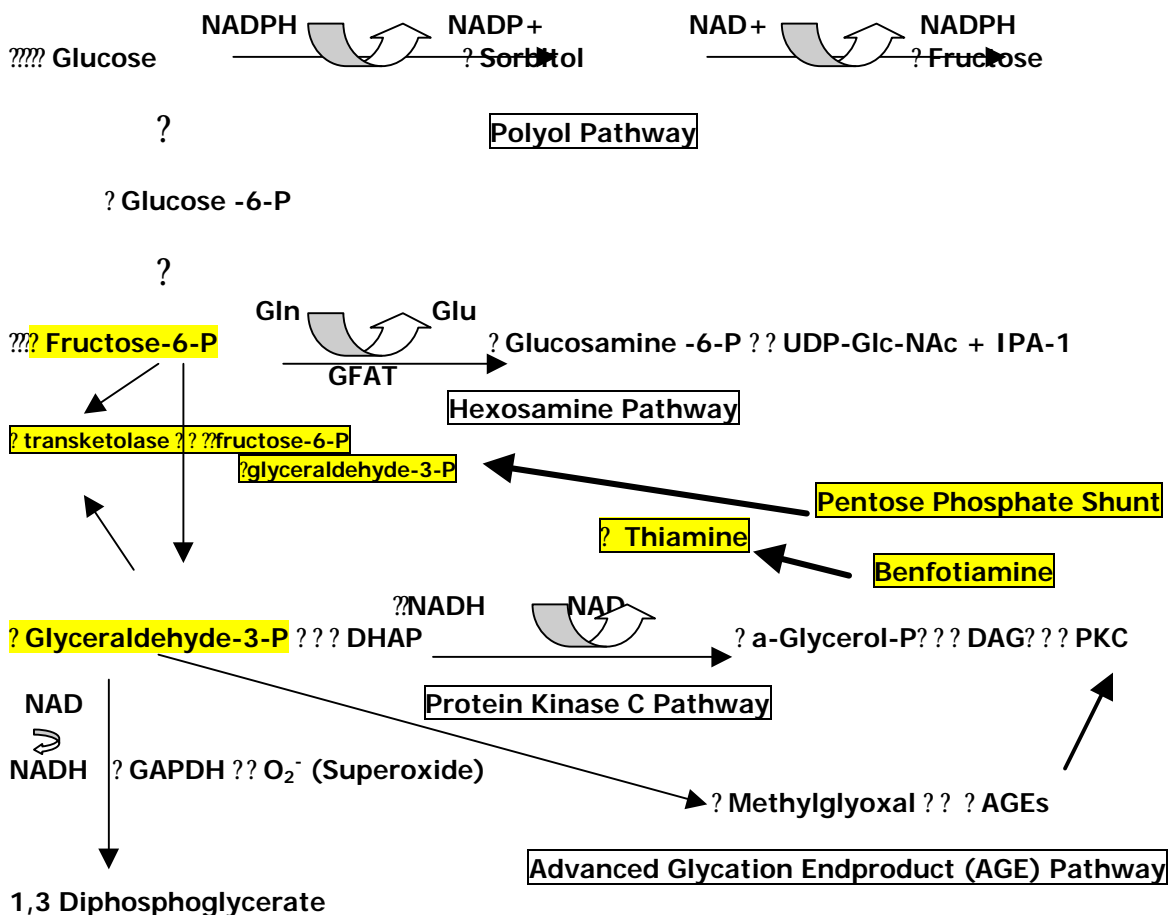
# Benfotiamine and Diabetic Eye Disease: A Biochemical Rationale for Prevention

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Type 1 diabetic since 1968

Last year, a great deal of excitement was generated by published findings demonstrating the prevention of diabetic retinopathy (DRT) in rats administered the lipid-soluble thiamine analog, benfotiamine (Hammes et al., 2003). As a doctor of optometry specializing in the eye complications of diabetes and diabetes education, and a Type 1 patient of 35 years, it caught my attention, as well. Here, it is my aim to lay out more clearly how and why benfotiamine might prevent DRT, and draw attention to some recent research suggesting that these same biochemical pathways may prevent or mitigate other eye complications of diabetes including: premature loss of near focusing ability, cataract, glaucoma, corneal disease and premature degeneration of the vitreous humor.

In the most recent study, benfotiamine was shown to block at least 3 pathways of hyperglycemia mediated vascular damage (hexosamine pathway, protein kinase C pathway, and the advanced glycation endproduct pathway.) Diagrammatically, the mechanism looks like this:

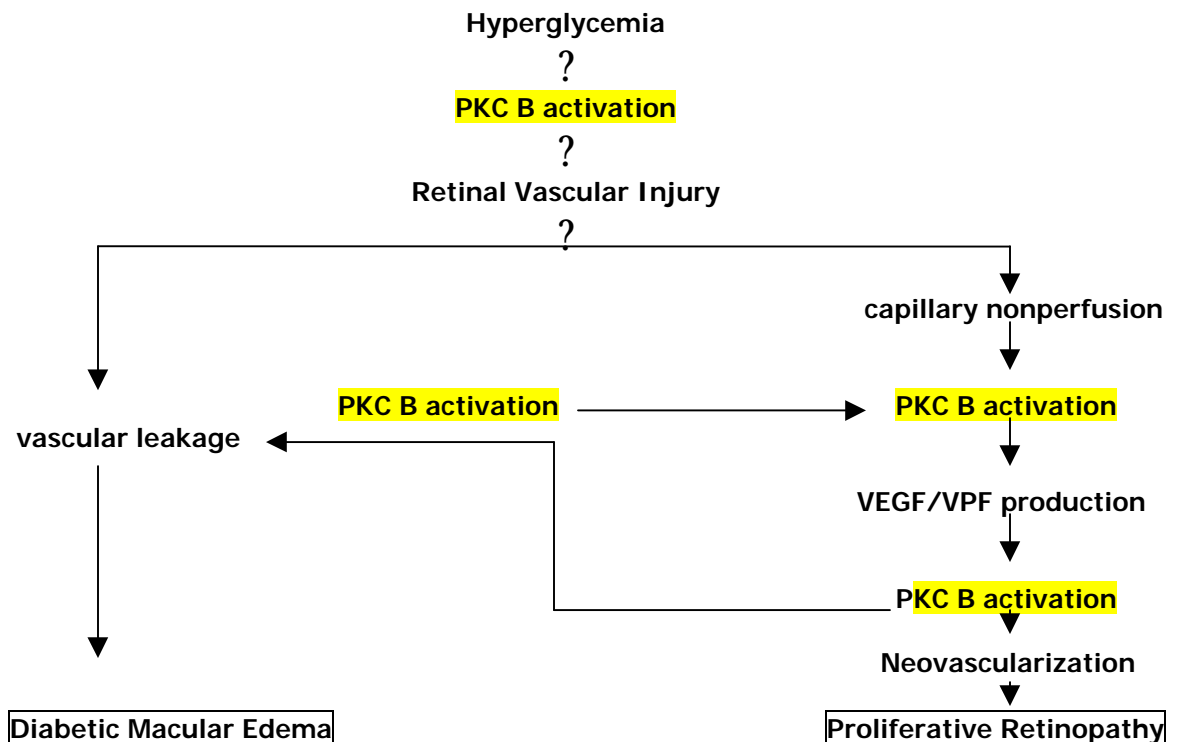
## Four Pathways of Hyperglycemic Damage



The enzyme transketalose provides a mechanism for cells to use up the injurious glucose metabolites, fructose-6-phosphate and glyceraldehyde-3-phosphate (via the pentose phosphate shunt). Transketalose activity depends on intracellular thiamine, which is often reduced in diabetes due to oxidative stress and malabsorption (Brownlee, 2001) Whereas ordinary thiamine requires active transport across the cell membrane, benfotiamine is lipophilic allowing easy diffusion and high intracellular concentrations, ramping up transketalose activity by 300-400% and reducing the harmful by-products of F-6-P and G-3-P (AGEs, PKC and inflammatory cytokines like IPA-1).

In terms of diabetic eye disease, let's focus on PKC and AGEs. In particular, PKC-B causes damage to retinal microvasculature, resulting in capillary leakage (left branch) and capillary closure (right branch).

### Protein Kinase C Beta in Diabetic Retinopathy



In turn, PKC-B triggers release of vascular endothelial growth factor (VEGF) and other vascular permeability factors (VPF) necessary for the development of neovascularization and proliferative diabetic retinopathy. Additional PKC-B release is initiated and a vicious cycle is created leading to the two most serious forms of DRT.

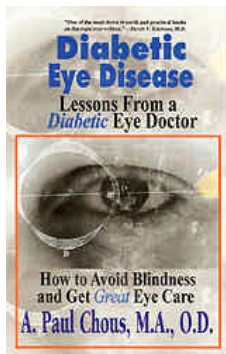
Advanced glycation end products describe a heterogeneous group of compounds resulting from the non-enzymatic glycation of proteins (exactly analogous to the process of caramelization). AGEs have been implicated in a host of age and diabetes related pathologies, including atherosclerosis, Alzheimer's disease, pulmonary fibrosis and erectile dysfunction (Brownlee, 2001). As for eye disease: (1) AGEs have been found at high levels in the optic nerves of both diabetics and those with primary open angle glaucoma (POAG), causing stiffening of the

collagenous “cribriform plates” that provide structural support for optic nerve axons as they exit the back of the eye. This may partially explain why diabetics have a 2 to 4 time relative risk for POAG (Amano et al., 2001; Albon et al., 1995); (2) Increased

AGEs have been demonstrated just below the corneal epithelium (Bowman’s layer), and have been implicated in weakened attachments between the epithelium and its underlying basement membrane, resulting in “recurrent corneal erosion syndrome” (RCE), a not uncommon finding in diabetic patients (Kaji et al., 2000); markedly increased AGEs in diabetic lenses leads to loss of elasticity in lens crystallins that allow for near focusing ability (“accommodation”) and generation of free radicals that lead to lens opacity (cataract) – this on top of increased osmotic pressure on the lens induced by sorbitol via the polyol pathway (the putative cause of “classic” diabetic cataract).

The identical AGE mechanism occurs in smokers, who have a much higher risk of premature cataract compared to non-smokers (Saxeena et al., 2000); premature, AGE-mediated liquefaction (loss of gel structure) occurs in the vitreous humor of diabetic eyes, increasing symptomatic “floaters” and possibly exacerbating vitreous traction in patients more prone to retinal detachment (Stitt et al., 1998; Sebag et al.2001); increased AGEs in retinal vascular endothelial cells contribute to pericyte destruction (Yamagishi et al., 1999), breakdown of the blood-retina barrier and release of PKC (Stitt et al.,1997), providing an important link between the PKC and AGE pathways in the development of retinopathy, and further demonstrating the complexity of these biochemical interactions.

Benfotiamine has a good track record, it seems, in terms of safety and efficacy in European studies for the treatment of diabetic neuropathy. In theory, at least, benfotiamine should block not only multiple pathways of hyperglycemia-induced damage, but multiple complications of diabetes, including several of the diabetic eye diseases. Will it do so? Will unknown side effects or specific contraindications to its use emerge? Only time and trials will tell.



Lessons from a Diabetic Eye Doctor: How to Avoid Blindness and Get Great Eye

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Dr. Paul Chous received his undergraduate education at *Brown University* and the *University of California at Irvine*, where he was elected to *Phi Beta Kappa* in 1985. He received his Masters Degree in 1986 and his Doctorate of Optometry in 1991, both with highest honors from the *University of California at Berkeley*. Dr. Chous was selected as the *Outstanding Graduating Optometrist* in 1991. He has practiced in Renton, Kent, Auburn and Tacoma, Washington for the last 12 years, emphasizing diabetic eye disease and diabetes education. Dr. Chous has been a Type 1 diabetic since 1968. He lives in Maple Valley, Washington with his wife and son.

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