

PKC Inhibition in Diabetic Microvascular Complications

PKC-beta inhibition is a potential treatment for diabetic peripheral neuropathy, retinopathy and macular edema.

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While the full understanding of what causes nerve damage in diabetes is incomplete, many models have been developed to try to explain the process.

One of the models is that of a metabolic imbalance that consists of persistently elevated glucose. This state leads to an accumulation of sugar alcohol, such as sorbitol, and the accumulation of advanced glycation end products. Through either osmolar damage or glycation damage, nerves are compromised and a progressive decline in function follows.

The second possibility is that of microvascular dysfunction preceding the development of neurovascular dysfunction. In this microvascular hypothesis there is impairment of blood flow to the small blood vessels that feed the nerves. Many years ago this hypothesis was based on the notion that the small blood vessels became occluded, causing ischemic infarcts. However this theory has not stood the test of time.

What has emerged to be true is that these blood vessels are functionally deranged, such that they do not perfuse the nerves as well as they should, causing damage to the endothelial lining. There is an imbalance between the forces

that cause constriction and the forces that cause dilatation of the vessels, so that the delivery of fuel and nutrients to the nerve is compromised.

The forerunner to all this used to be believed to be hyperglycemia. It was thought that hyperglycemia mediated its damage through oxidative stress — or more recently nitrosative stress as well. So that either free oxygen radicals, hydroxyl radicals, or in the case of nitrosative stress, peroxynitrate, was the cause of damage generated by persistent hyperglycemia or elevations in free fatty acids.

Now we know that with oxidative stress comes the activation of the beta-2 form of protein kinase C (PKC). We have also found that a major stimulus is diacylglycerol. So now we recognize that damage cannot only be done from hyperglycemia, but it can also be from disturbed lipid metabolism and through the fatty acid diacylglycerol pathway that is activating PKC.

PKC overactivity has been shown in animal models to increase the leakiness of blood vessels and compromise their function in relationship to providing nutrients to nerves.

What makes the PKC model attractive is that in the nerve if there is overactivity of PKC, it may be possible to inhibit it

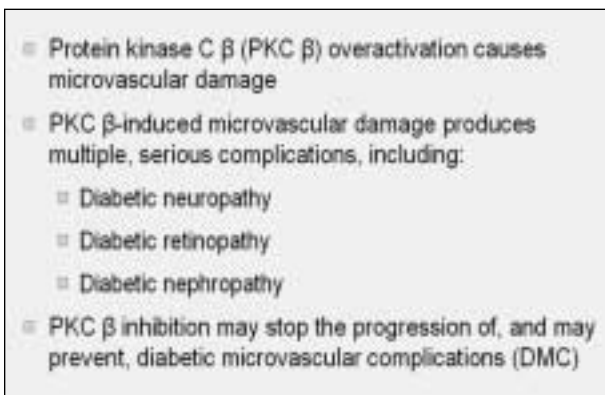


Figure 1. The role of PKC beta in diabetic microvascular complications.

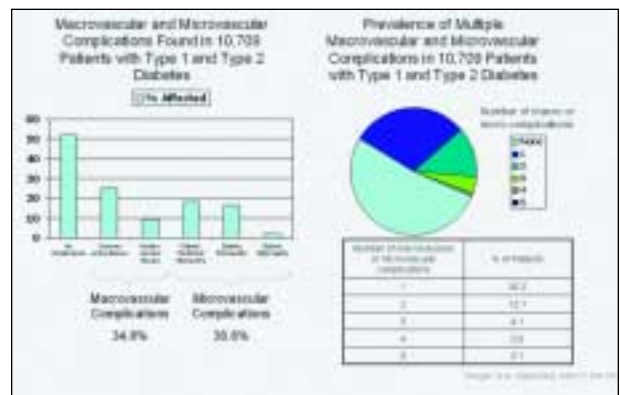


Figure 2. Prevalence of multiple diabetic complications in general practice shown.

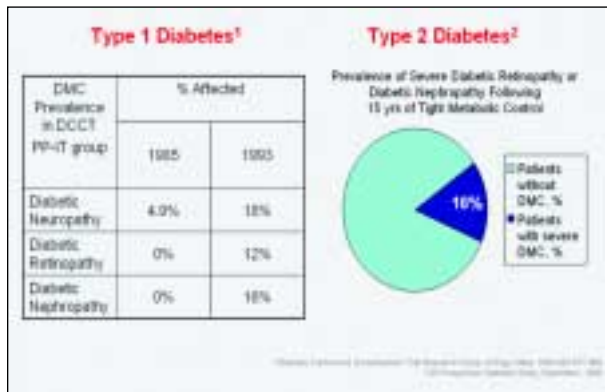


Figure 3. Prevalence of diabetic microvascular complications with tightly controlled diabetes.

distally in the pathway. Hyperglycemia and fat break down are proximal in the pathway, going through either direct activation of PKC or through the oxidative/nitrosative stress pathway and they have to funnel through PKC. So if PKC is blocked, irrespective of what happens proximally, you can effectively abrogate this predisposition to impairment of blood flow to nerves.

THE EYE

If there is impairment of blood flow to the eye, this causes leaky blood vessels and hemorrhages in the exudates. This is a clear parallel between the microvascular insufficiency in the eye and in the nerve, but it is mediated very differently.

In the eye, the moment there is PKC activation it stimulates the production of VEGF. VEGF itself stimulates the proliferation of new blood vessels in the eye. But if PKC could be blocked, VEGF would not be produced and there would be improvement in the eye.

The kidney is different. In the early phases of the development of kidney dysfunction there is an increase in glomerular filtration. This increase is due to an increase in capillary glomerular pressure. It is not that the afferent arteriole but the efferent arteriole that is regulated by substances such as angiotensin and renin which constrict the artery, which is why we have always thought they were central to the development of kidney disease in diabetes.

The similarities between activation of angiotensin and PKC are remarkable. In both instances you get constriction of the efferent arteriole, increase in intercapillary glomerular pressure and initial hyperfiltration. As the disorder progresses, hypofiltration with diabetic glomerulosclerosis occurs, as mesangial cells proliferate and hyaline is deposited in the glomeruli.

Mediation in the kidney is entirely different from mediation in the eye. TGF-beta is responsible for the

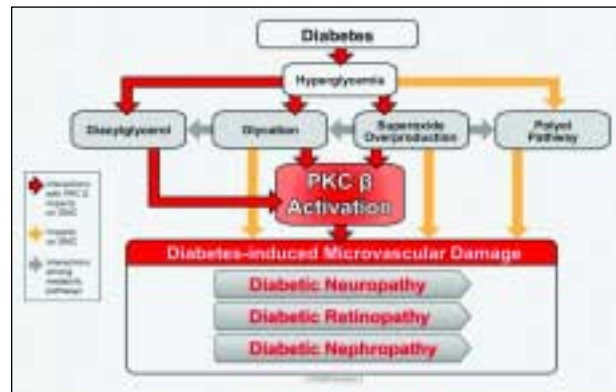


Figure 4. Numerous metabolic pathways lead to diabetic microvascular complications.

proliferation of mesangial cells in the glomerulus and the sclerotic kidney.

PERIPHERAL NERVES

In the nerve, VEGF may have exactly the opposite effect. Studies have shown that if the VEGF gene is implanted in muscle, it stimulates nerve growth. VEGF and TGF mechanisms cannot be impugned. The major players with regard to the nerves, from the growth factor point of view, are nerve growth factor and neurotrophin-3, and to some extent CNTF, BDNF, IGF, IGF-2 and C-peptide.

The data on those with regard to PKC is not strong. We know that PKC hyperactivity compromises endothelial function in the nerve; in the eye it is through VEGF, in the kidneys it is through TGF-beta; and in the nerves it may be through a variety of these mechanisms, but we are unsure.

We are excited about the fact that, in rat studies, PKC inhibition improves nerve function, decreases retinal vessel leakage and improves glomerular filtration. In humans, studies of the experimental PKC-beta inhibitor ruboxistaurin (Eli Lilly and Company) have shown that it is not only safe, but there is a strong trend toward efficacy in the nervous system.

A PKC-beta inhibitor may be a new treatment for diabetic peripheral neuropathy, as well as retinopathy and macular edema. Studies are being done on larger groups of patients over longer duration to support the early efficacy data and to ensure safety. ■

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