Mechanisms of glucose toxicity. New hope for prevention of diabetic complications?

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Long-standing diabetes mellitus is characterized by the development of widespread micro- and macroangiopathy. The goal of the treatment of diabetes mellitus is to prevent both acute and long-term complications. It has been thought for a long time that the occurrence of diabetic complications depends on glycaemic control as well as genetic factors. It has now clearly been proved by the Diabetes Control and Complications Trial that hyperglycaemia is a major factor in the development of diabetes complications; intensive treatment can significantly delay the development and slow the progression of microvascular complications (1). Understanding the mechanism of glucose-induced diabetes complications is necessary to try to prevent or stop glucose toxicity. Multiple biochemical alterations have been reported in diabetes, and several metabolic pathways seem to be involved in glucose toxicity with a possible redundancy in their mechanisms: (i) insulin deficiency and hyperglycaemia enhance glucose metabolism through the polyol pathway via aldose reductase. In turn, the increased aldose reductase activity reduces nitric oxide synthetase activity and induces sorbitol accumulation, which leads to myoinositol depletion. This myoinositol depletion ultimately results in a decrease in Na⁺,K⁺ ATPase activity. (ii) Simultaneously, hyperglycaemia enhances non-enzymatic glycosylation of circulating and membrane-bound proteins, leading to the accumulation of advanced glycosylation end products (AGE) associated with the activation of AGE receptors (2). (iii) Finally, hyperglycaemia enhances the oxidative pathway, with an increased production of oxygen-free radicals (O₂, H₂O₂, OH) which are very unstable products participating in protein and DNA alteration. Interventional studies with aldose reductase inhibitors or with aminoguanidine to inhibit glycation have not brought evidence of more alterations or primary pathogenic mechanisms in humans.

Recently, Ishii et al. (3) provided new evidence that the abnormal activation of protein kinase C (PKC) induced by hyperglycaemia underlies some of the vascular complications of diabetes. Indeed, they showed that orally administered LY333531, a specific inhibitor of PKC b, improved vascular dysfunctions in diabetic rats.

PKC is a ubiquitous family of phospholipid-dependent serine threonine protein kinases which take part in cellular responses to various substances including hormones, neurotransmitters and growth factors. PKC is relatively abundant in vascular tissue and plays an important role in the regulation of the growth and contraction of vascular smooth muscle cells. PKC is activated by an increased amount of diacylglycerol (DAG) resulting from agonist-induced hydrolysis of inositol phospholipids. In diabetic animals, increased DAG levels and PKC activity have been reported for many tissues such as the heart, aorta, renal glomeruli, retina, and granulation tissue. The high level of DAG is probably related to an increased flux of glucose metabolites, leading to an accelerated production of DAG de novo. In cultured vascular smooth muscle cells, PKC activity responded rapidly to variations in extracellular glucose concentration. Moreover, the vitral injection of phorbol dibutyrate which activates PKC and especially its b2 isoform reproduces the vascular dysfunction observed in diabetic rats. Furthermore, PKC b2 seems to be preferentially activated in the membranous fraction from glomeruli of diabetic rats.

To specify further the importance of PKC b2 activation in the pathogenesis of diabetic vascular complications, Ishii et al. (3) synthesized a new PKC b1b2 selective inhibitor, LY333531, with a half-maximal inhibitory constant (IC₅₀) of 5 nM. In contrast, the IC₅₀ for other PKC isoenzymes was 250 nM. In rat aortic smooth muscle expressing high levels of PKC b2 after treatment with phorbol 12-myristate 13 acetate, LY333531 inhibited the activation of PKC b2 by up to 70%. Its action was also effective in vivo when orally administered to streptozotocin-induced diabetic rats. Two weeks of LY333531 treatment at three oral doses (0.1, 1 or 10 mg/kg) showed no apparent toxicity, and no effect on body weight and blood glucose in controls and in diabetic rats. Low dose treatment (0.1 mg/kg) was sufficient to return PKC activity in the retina to normal in diabetic rats and had no effect in the non-diabetic animals. Concomitantly, it induced a significant (70%) decrease in retinal mean circulation time. In the renal glomeruli, PKC was significantly reduced only with high doses of LY333531. This high dose treatment could also normalize the renal glomerular filtration rate, one of the earliest abnormalities of renal dysfunction. After 8 weeks of treatment, albumin excretion rate was also significantly lowered.
These new results hold promise in that they suggest that LY333531 can prevent some of the vascular abnormalities of diabetics. They call for clinical trials in order to assess if such a treatment could slow the progression of diabetic complications in humans. Nevertheless, we are aware that it is far from being a proven effective treatment; the beneficial effect might vary with the patient’s genetic background. In any single patient, one or more of the mechanisms of glucose toxicity may play either a major or a minor role.

References