Advances in Molecular Mechanisms and Pharmacology of Diabetic Complications

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Editor

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Preface

The term *diabetes* (Greek: διαβήτης, *diabētēs*) was coined as early as in the 1st century AD by Aretaeus of Cappadocia as the name for a disease involving the discharge of excessive amounts of urine. In 1675, Thomas Willis added the word *mellitus*, from Latin meaning "honey", a reference to the sweet taste of the urine.

Although diabetes has been recognized since antiquity, the pathogenesis of diabetes has only been understood experimentally since about 1900.

Diabetes mellitus exacts a huge toll in health care cost and human suffering. The diabetic individual is prone to late onset complications such as neuropathy, nephropathy, retinopathy, cataracts and accelerated atherosclerosis, which are largely responsible for the morbidity and mortality associated with the disease.

Links between chronic hyperglycemia and the development of long-term diabetes-specific complications have been proved. Nevertheless, little is known about the exact sequence of events leading to the pathogenesis and progression of complications since hyperglycemia can mediate its adverse effects through multiple pathways. Included are increased formation and accumulation of advanced glycation end products (AGEs), increased hexosamine pathway flux, imbalance in the generation and scavenging of reactive oxygen species followed by oxidative damage, enhanced polyol pathway activity, activation of protein kinase C.

It has been widely accepted that adequate metabolic control lies primarily in the prevention of diabetic complications. Thus, the major aims of conventional therapies are regulation of glycemia by affecting insulin sensitivity in peripheral tissues and insulin secretion, which should be accompanied by measures to improving the lipid profile and blood pressure levels.

Since lowering the blood glucose of patients with long-standing disease failed to be very effective, it is rather important to identify new pharmacological approaches. The understanding of mechanisms by which glucose exerts its toxicity is of utmost importance for rational pharmacological interventions. Drugs are designed to interact with biological targets whose structures and molecular mechanisms are known. The development of new drugs for the management of diabetic complications is an urgent therapeutic need, given the worldwide high prevalence of diabetes mellitus.

This book, written by scientists with relevant expertise, offers representative examples of the mechanisms involved in the etiology of diabetic complications. A major stress is also on recent achievements in pharmacology of diabetes-specific complications.

Various aspects of posttranslation modifications (PTMs) of proteins under conditions of hyperglycemia are covered by the first five chapters. Molecular mechanisms of the glycoxidation cascade leading to the generation of AGEs and related clinical consequences are subject of the first chapter (*Odetti et al.*). AGEs comprise a plethora of stable products still poorly characterized; advanced proteomic approaches to their characterization are covered by chapter 2 (*Lacinova et al.*). Chapter 3 (*Lapolla et al.*) reviews recent sophisticated mass spectrometric techniques able to give highly specific and reliable results in the proteome field. A comprehensive account of PTMs of eye lens crystallins in relation to diabetic cataract is given in chapter 4 (*Kyselova*). Chapter 5 (*Portero-Otin et al.*) summarizes the relationship between hyperglycemic disarrangement in diabetes and free-radical-mediated oxidation of amino acid residues in proteins.

Chapter 6 (*Waczulikova and Sikurova*) focuses on biophysical approaches to hyperglycemia-induced cell membrane changes in diabetes.

As stressed in the next two chapters, functional impairment of endothelial activity is the first step in the development of diabetic micro- and macro- vasculopathies, which represent major causes of disability and death in patients with diabetes mellitus. Chapter 7 (*Sotnikova and Bauer*) summarizes knowledge on NO regulatory mechanisms and their changes in diabetes. Based on the premise that oxidative stress is a key player in diabetes, therapeutic interventions with antioxidants to prevent endothelial dysfunction are discussed in chapter 8 (*Sena and Seica*) along with new therapeutic strategies involving drugs sharing both antioxidant and carbonyl scavenger activities.

Diabetes is intimately related with complications which are characterized by impaired cognitive function and structural and neurochemical abnormalities in the brain. Chapter 9 (*Moreira et al.*) reviews diabetes as a risk factor for several neurological disorders, including Alzheimer's, Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis and cerebral ischemic stroke; the existing therapeutic approaches aimed at counteracting diabetes-associated neurodegeneration are also covered.

It is well established that aldose reductase (ALR2, E.C. 1.1.1.21), the first enzyme of the polyol metabolic pathway, is implicated in the etiology of secondary complications of diabetes. Inhibition of the polyol pathway is therefore considered to be a promising approach to control diabetic complications. Chapter 10 (*Nicolaou et al*.) gives data supporting the notion that compounds which combine aldose reductase inhibitory activity and ability to prevent the glycation of proteins possess pharmacotherapeutic potential for the prevention and/or treatment of long-term complications of diabetes mellitus. 2,4-Thiazolidinedione and 2-thioxo-4-thiazolidinone derivatives are presented as active aldose reductase inhibitors (ARIs) in chapter 11 (*Maccari and Ottana*) and their structure-activity relationships, biological properties and therapeutic potential in the management of long-term diabetes complications are reviewed. Multiple ARIs have been designed and tested in animal models as promising agents to combat complications of diabetes. However due to lack of inhibitor specificity resulting from unwanted inhibition of the structurally-similar aldehyde reductase (ALR1), these drugs have not yet passed clinical trials. By articulating the mechanisms by which each enzyme binds identical ARIs within its active site, chapter 12 (*El-Kabbani et al.*) defines those interactions which may be of key importance for specific inhibition of ALR2.

As a result of the diabetic milieu, increased generation of reactive oxygen species and subsequent oxidative stress are thought to play a key role in the development of diabetes complications. Antioxidant treatment might therefore be an important therapeutic option for preventing complications in diabetes as reviewed in the next three chapters. Effects of pharmacological doses of melatonin, phosphatidylcholine and ursodeoxycholic acid in alloxan- and streptozotocin-induced diabetes in rats are reviewed in chapter 13 (*Zavodnik et al.*). Chapter 14 (*Stefek et al*.) introduces the pyridoindole antioxidant stobadine and its structural analogues as prospective agents with a therapeutic potential of preventing long-term diabetic complications. In addition, the chapter presents a structurally related group of carboxymethylated pyridoindoles possessing antioxidant and aldose reductase inhibitory activities as another example of potential multitarget pharmacology approach to the treatment of diabetic complications. Chapter 15 (*Karasu and Stefek*) reviews the links between oxidative stress and diabetes-induced cardiovascular abnormalities and the effects of various antioxidants altering the course of cardiovascular complications in diabetic animal models.

A growing body of evidence emphasizes the role of mitochondrial dysfunction in the development of chronic diabetic complications. Coenzyme Q (ubiquinone) is an essential part of the mitochondrial respiratory chain necessary for ATP synthesis. Moreover, it has antioxidant properties and in cooperation with α-tocopherol it is able to inhibit lipid peroxidation in mitochondrial membranes. Chapter 16 (*Kucharska*) summarizes the effects of coenzyme Q10 treatment investigated in experimental models of diabetes and in diabetic patients.

Milan Stefek

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"*When I first began doing research in the diabetes-related arena, diabetes was considered a premature aging process. But now with more aggressive management of diabetes and risk factors that relate to the complications of diabetes, we no longer consider diabetes as premature aging. I think the good news now is that patients with diabetes, whether type 1 from an early age on or type 2 developed during adulthood, can live as nearly as long, if not as long, as patients without diabetes*."

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