Vascular Pharmacology 54 (2011) 68–74

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Cellular and molecular mechanisms of vascular injury in diabetes — Part I: Pathways of vascular disease in diabetes

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ARTICLE INFO

Article history:
Received 6 March 2011
Accepted 19 March 2011

Keywords:
Diabetes
Hyperglycemia
Glucotoxicity
Insulin resistance
Vascular damage
Atherosclerosis

ABSTRACT

Diabetes-induced micro- and macrovascular complications are the major causes of morbidity and mortality in diabetic patients. While hyperglycemia is a key factor for the pathogenesis of diabetic microvascular complications, it is only one of the multiple factors capable of increasing the risk of macrovascular complications. Hyperglycemia induces vascular damage probably through a single common pathway – increased intracellular oxidative stress – linking four major mechanisms, namely the polyol pathway, advanced glycation end-products (AGEs) formation, the protein kinase C (PKC)-diacylglycerol (DAG) and the hexosamine pathways. In addition, in conditions of insulin resistance, i.e., preceding the onset of type 2 diabetes, the phosphatidylinositol (PI) 3-kinase (PI3K)/Akt pathway is selectively inhibited, while the mitogen activated protein (MAP)-kinase pathway remains largely unaffected, thus allowing compensatory hyperinsulinemia to elicit pro-atherogenic events in vascular smooth muscle and endothelial cells, including increased cell proliferation, and the expression of plasminogen activator inhibitor-1, as well as of proinflammatory cytokines and endothelial adhesion molecules.

Contents

1. Introduction . . . 68
2. Glucose toxicity and cardiovascular disease . . . 69
   2.1. The polyol pathway . . . 70
   2.2. Advanced glycation end products . . . 70
   2.3. The protein kinase C pathway . . . 70
   2.4. The hexosamine pathway . . . 71
3. Insulin resistance, hyperinsulinemia and cardiovascular disease . . . 71
4. Conclusions . . . 72
Acknowledgements . . . 72
References . . . 73

1. Introduction

According to the International Diabetes Federation Atlas in 2009, the estimated worldwide prevalence of diabetes for 2010 has risen to 285 million, representing 6.6% of the world's adult population (Unwin et al., 2010). Diabetes-induced vascular complications are the major causes of morbidity and mortality in such a huge cohort of patients. Efforts in understanding the mechanisms underlying the development of vascular disease in diabetes therefore hold the promise of a major health impact, limiting the huge burden of this disease.

A thorough understanding of vascular complications in diabetes requires the distinction of two different types of disease, one affecting small resistance arteries, arterioles and capillaries (microvascular disease), and the other affecting large conductance vessels (macrovascular disease). Atherosclerosis occurs earlier in patients with diabetes, frequently with greater severity and more diffuse distribution, in the form of coronary artery disease, cerebrovascular disease

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1537-1891/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.vph.2011.03.005

and peripheral arterial disease (Beckman et al., 2002). Microvascular disease also however contributes importantly to morbidity and mortality: diabetic retinopathy is a leading cause of blindness, and diabetic nephropathy is currently the major cause of chronic renal failure (Merimee, 1990; Zatz and Brenner, 1986). Characteristically, microvascular disease is almost never found before the onset of diabetes (both type 1 and type 2), while macrovascular disease frequently precedes, sometimes by years, the onset of overt type 2 diabetes, within the context of the "metabolic syndrome" (Basta et al., 2002; Haffner et al., 1990).

Two large studies, The Diabetes Control and Complications Trial Research Group (DCCT) and the UK Prospective Diabetes Study (UKPDS), clearly showed that intensive treatment of hyperglycemia can reduce the progression of microvascular complications, including retinopathy, nephropathy and neuropathy (Ahern et al., 1993; UK Prospective Diabetes Study (UKPDS) Group, 1998a). Attempts at reducing consequences of macrovascular disease in diabetes have been much more frustrating. Only recently, the long-term follow-up studies of DCCT and UKPDS have shown that patients who received intensive blood glucose control had also, in the long-term, a decreased incidence of macrovascular complications (Cleary et al., 2006; Nathan et al., 2003, 2005; Ruiz et al., 2010). The magnitude of such beneficial changes has been in any case relatively minor. These clinical observations suggest that hyperglycemia is a major factor for the pathogenesis of diabetic microvascular disease, but only one of the many other factors increasing the risk of atherosclerosis in large conductance arteries (Nathan et al., 2003).

In addition, the growing list of newly identified CHD-risk loci and single nucleotide polymorphisms (SNPs) provided by genome-wide association studies (GWASs) (Hayes et al., 2007) (for which recent examples are triglyceride-related genotypes (Sarwar et al., 2010; Thompson et al., 2010) and genetic variants at chromosome 9p21 associated with enhanced cardiovascular risk in type 2 diabetes through interaction with poor glucose control (McPherson et al., 2007; Zhou et al., 2008)), provides compelling evidence for the key role of genetic susceptibility in the pathogenesis of vascular disease in diabetes.

2. Glucose toxicity and cardiovascular disease

Haist and Best, in 1940, first observed that high glucose exerts multiple pathological effects on pancreatic β-cells (Haist and Best, 1940). Subsequently, the term "glucose toxicity" or "glucotoxicity" was coined to describe the adverse effects of chronic exposure of pancreatic β-cells to high concentrations of glucose (DeFronzo, 1988). At present, it is well established that high glucose exerts multiple pathological effects on many other cells and tissues, including those of the cardiovascular system (Ahern et al., 1993; Klein et al., 1995; Lastra et al., 2006; Nathan et al., 2003; UK Prospective Diabetes Study (UKPDS) Group, 1998b).

Chronic hyperglycemia, as measured by fasting plasma glucose concentrations or glycated haemoglobin (HbA1c) (Uusitupa et al., 1993), is an independent risk factor for cardiovascular disease both in patients with type 1 and in those with type 2 diabetes (Standl et al., 1996; Stolar, 2010; UK Prospective Diabetes Study (UKPDS) Group, 1998b). Despite the strong biological plausibility and clinical studies supporting hyperglycemia as a risk factor for cardiovascular disease, three recent multicenter randomized prospective clinical trials designed to evaluate the effects of intense glycemic control on macrovascular outcomes in patients with type 2 diabetes considered to be at high cardiovascular risk have provided contrasting results. In the Action in Diabetes and Vascular Disease (ADVANCE) trial (2005) there was a 10% relative reduction in the primary composite outcome of major microvascular events, primarily as a consequence of a reduction in the progression of microalbuminuria in the intensive treatment group. No effects, however, were observed on macrovascular morbidity or mortality. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (Buse et al., 2007), the primary outcome (the first occurrence of non-fatal myocardial infarction or non-fatal stroke or death from cardiovascular diseases) failed to be significantly reduced in the intensive treatment group, which actually suffered a three-fold higher mortality probably due to higher rate of severe hypoglycemia. The results of the Veterans Administration researchers (VADT) study (Murata et al., 2005) did not show that achieving a target of HbA1c <7% had a statistically significant effect on reducing major cardiovascular events, death, or even microvascular complications, excluding the progression of microalbuminuria. The compelling message from these three major studies is that a tight glycemic control to near normal values (which implies an important reduction of glucose toxicity) does not have a major impact on cardiovascular events and may actually be harmful (as shown, at least in the ACCORD trial, by an increased risk of death (Buse et al., 2007; Glah, 2008)). Contrary to these data, in the UKPDS study the original intensive therapy group, re-examined in the post-trial follow-up conducted 10 years later, there was a reduction in the risk of myocardial infarction and death from any cause, as well as of microvascular complications and of any diabetes-related outcome. This delayed effect, apparent years after the conclusion of the randomized treatments, would demonstrate the cumulative effects of glucose toxicity on cardiovascular disease (Holman et al., 2008). Taken together, these data show that glucose toxicity exerts a major role in microvascular complications, which are more closely temporally related to the onset of hyperglycemia, than macrovascular ones (Lachin et al., 2008; Nathan et al., 2003; UK Prospective Diabetes Study (UKPDS) Group, 1998a). Macrovascular complications as a consequence of glucose toxicity appear later and are more difficult to detect. Therefore glucose toxicity is a major factor for microvascular disease, but only one of the contributing factors for macrovascular disease.

In cells where glucose transport is partly independent of insulin, e.g., vascular endothelial, renal and retinal cells, as well as in peripheral nerves (Kaiser et al., 1993), hyperglycemia raises the intracellular concentration of glucose and of many other glycolytic intermediates (Stevens et al., 1977) that are critical substrates for several important biochemical pathways (Williamson et al., 1991). In the presence of chronic hyperglycemia there is an inadequate downregulation of insulin-independent transporters, which exposes cells to the continuous influx of high amounts of glucose from the extracellular space into the cytosol. This results in the generation of excess intracellular reactive oxygen species (ROS) (Baynes, 1991; Brownlee, 2001; Giacco and Brownlee, 2010). ROS are the final effectors, but also initiating factors, of at least four interrelated hyperglycemia-driven pathways: (a) the polyol pathway, with associated changes in the redox state of nicotinamide adenine dinucleotide phosphate (NADP) and its reduced form NADPH (Giacco and Brownlee, 2010; Tilton et al., 1989); (b) covalent modification of intracellular constituents by reactive advanced glycation end-products (AGEs) (Basta et al., 2002; Farmer and Kennedy, 2009; Wendt et al., 2002; Yao and Brownlee, 2010); (c) the *de novo* synthesis of diacylglycerol (DAG), which leads to the activation of several protein kinase C (PKC) isoforms (Ishii et al., 1998; Srivastava, 2002; Thallas-Bonke et al., 2008; Williamson et al., 1990); (d) increased flux through the hexosamine pathway (Brownlee, 2001; Giacco and Brownlee, 2010). The activation of these pathways, at least in part mediated by glucose-related hyperosmolarity (Madonna et al., 2010), can explain why chronic elevation of glucose impacts the biochemical homeostasis of cardiovascular cells, ultimately leading to the development of diabetic vascular (mostly microvascular) complications (Setter et al., 2003). Indeed, each of the above four different pathways is activated by hyperglycemia-induced ROS formation, in the form of an overproduction of superoxide anion through the mitochondrial electron transport chain (Nishikawa et al., 2000), together with an overproduction of nitric oxide (NO) (Cosentino et al., 1997), which, together, prompts the