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The Trigger of Diabetic Complication

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Abstract

Hyperglycemia is a primary cause of endothelial dysfunction in diabetes. Modification of the cellular environment by carbonic anhydrate inhibitors favors generation of Nitric oxide, which causes relaxation of the vascular endothelium. Endothelial dysfunction contributes to the development of diabetes associated micro vascular and macro vascular complications, which are the main cause of morbidity and mortality.

Keywords: Diabetes Mellitus; Retinopathy; Dyslipidemia; Streptozotocin

Introduction

Diabetes can be defined as a complex metabolic condition characterized by impairment of glucose regulating pathways, resulting in sustained endogenous glucose production. Advances in understanding the vascular pathology of diabetes have made it clear that the pathogenesis of diabetic vascular complications is determined by a balance between molecular mechanisms of injury and endogenous protective factors [1].

Hyperglycemia has been reported to be a mediator of endothelial dysfunction and is involved in several intracellular pathways associated with vascular complications, which are the major cause of morbidity and mortality in diabetes mellitus [2].

The development of long-term complications in diabetes is influenced by hyperglycemia. Poor control of hyperglycemia accelerates its progression. The resulting chronic hyperglycemic condition in diabetes is associated with macro and micro vascular complications. Macro vascular complications are involved in the development of heart disease and cerebrovascular disease, which account for much of the reduction in life expectancy experienced by patients with diabetes mellitus. Micro vascular complications in patients with diabetes mellitus manifest as nephropathy, neuropathy and retinopathy, which also contribute to the morbidity burden [3]. Poor control of hyperglycemia is not the only risk factor for diabetic complications: genetic pre-disposition, dyslipidemia and hypertension are also important [4-6]. The alterations in cellular homeostasis and regulation of vascular physiology may lead to vascular complications.

Hyperglycemia contributes to the development of vascular complications through several mechanisms: activation of the polyol and hexosamine pathways, activation of diacylglycerol (DAG)-protein kinase C (PKC), increased oxidative stress, increased production of advanced glycation end-products, increased synthesis of growth factors, cytokines, and angiotensin II [7]. These factors can, in turn, induce a diffuse endothelial dysfunction and contribute to the progressive development of micro- and macrovascular complications and multiorgan damage [8]. Among the number of factors involved in maintaining proper vascular wall homeostasis is nitric oxide (NO) which is of pivotal relevance in guaranteeing physiological endothelial function [9]. In

fact, impaired NO synthesis and/or availability results in endothelial dysfunction [10], thus promoting the development of vascular damage. Although it has been demonstrated that diabetes is associated with endothelial dysfunction, and it is known that endothelium-dependent vasodilation is significantly impaired in diabetic patients.

It was reported that hyperglycemia significantly attenuated the production of NO in response to increasing glucose concentration. Likewise, insulin-stimulated NO production was greatly reduced in hyperglycemic conditions. Similar results were obtained using neurons from streptozotocin-induced diabetic rats and from non-diabetic rats cultured in hyperglycemic conditions, affirming that high glucose was responsible for the decreased production of NO, rather than other diabetes-associated pathologies [11]. The impairment has been linked to numerous circulatory derangements in diabetes, including increased capillary permeability [12], enhanced platelet aggregation [13], and accelerated progression of diabetic nephropathy [14]. Loss of endothelial-dependent vasodilator capacity is mediated to a great extent by nitric oxide (NO), which may cause excessive vasoconstriction in some vascular beds [15-18]. It was reported that in isolated blood vessels exposure to elevated glucose causes endothelial dysfunction [19,20].

The Role of Carbonic Anhydrase in Endothelial Dysfunction

Biological control of cellular and extracellular fluid pH is highly important for all aspects of metabolism and cellular activities. The organism's first line of defense against changes in internal pH is provided by buffer systems. Three important systems include the bicarbonate, phosphate, and ammonia buffer systems [21]. The hydration of carbon dioxide occurs too slowly without catalysis. Thus, the carbonic anhydrase enzyme family evolved to catalyze a reaction in which carbon dioxide is hydrated to form a proton and bicarbonate [21,22].

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

Multiple is forms have been discovered in plant and animal tissues where it is believed to facilitate the transport of carbon dioxide. Carbonic anhydrase II has the highest molecular turnover number of any known enzyme. One molecule of carbonic anhydrase can hydrate 36,000,000 molecules of carbon dioxide in a period of 60 seconds [23]. Carbonic anhydrase are involved in diverse physiological functions including pH regulation, ion transport, bone resorption and secretion of gastric, cerebrospinal fluid and pancreatic juices [24].

Carbonic anhydrase inhibitors (CAIs) have been shown to have a vasodilating effect on the blood vessels in the retina and the optic nerve from animals both in vitro [25] and in vivo [26], and in the human retina in vivo [27], an effect that has been shown to be independent of NO [28]. CA is expressed in a wide range of cell types, including capillary endothelial cells, glial cells, and erythrocytes, and is soluble, intracellular, extracellular, or membrane bound [29,30]. The most active iso form CAII has a wide tissue distribution and is also the second most abundant protein in red blood cells. Modin et al. [31] were the first to demonstrate in a seminal paper that physiological nitrite levels induce NO-dependent aortic vasodilation, particularly at acidic pH and independently of NOS activity. Aamand et al. [32] revealed a novel nitrous anhydrase enzymatic activity of CA that would function to link the in vivo main end products of energy metabolism (CO_2/H^+) to the generation of vasoactive NO, termed CA-mediated NO production. Having being one of the fastest enzymes known [33] CA in red blood cells is able to generate a local decrease in pH due to CO_2 hydration in the short transit time (<0.5 s) [34] of blood in the capillaries of active tissues. This local acidosis decreases the O_2 affinity of the hemoglobin through the Bohr effect, so that more O_2 is unloaded to active tissues at a constant O_2 tension [35-37]. This decrease in pH is what probably favours the production and diffusion of NO into tissues. Zweier et al. [38] earlier reported that NO may be produced non-enzymatically from nitrite at low pH (< pH 5). This further confirms the role of carbonic anhydrase in endothelial function.

Conclusion

It is clear that CA inhibitors play a very important role in endothelial dysfunction by creating local acidotic environment that favors generation of NO. The NO increase observed in the presence of carbonic anhydrase inhibitors may be particularly active in blood, and may participate in intrinsic mechanisms of nitrite-induced vasodilation. The present review shows the potential of therapeutic applications of carbonic anhydrase inhibitors in reversing the course of endothelial dysfunction.

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