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Pharmacological approaches to coronary microvascular dysfunction

Giacinta Guarini, Alda Huqi, Doralisa Morrone, Paola Capozza, Giancarlo Todiere, Mario Marzilli *

Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, University of Pisa, Italy

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ABSTRACT

In recent decades coronary microvascular dysfunction has been increasingly identified as a relevant contributor to several cardiovascular conditions. Indeed, coronary microvascular abnormalities have been recognized in patients suffering acute myocardial infarction, chronic stable angina and cardiomyopathies, and also in patients with hypertension, obesity and diabetes. In this review, we will examine pathophysiological information needed to understand pharmacological approaches to coronary microvascular dysfunction in these different clinical contexts. Well-established drugs and new pharmacological agents, including those for which only preclinical data are available, will be covered in detail.

Contents

1. Introduction

Hypertension, obesity, diabetes, acute myocardial infarction, chronic stable angina and cardiomyopathies share a common pathophysiological denominator: coronary microvascular dysfunction. Impairment of myocardial perfusion appears to be a relevant feature for disease progression and prognosis in all these clinical settings. This is because the coronary microvascular bed is the site where myocardial blood flow is tightly adjusted to meet myocardial metabolic needs. In this review, pathophysiological changes occurring at coronary microvascular level associated with diabetes, acute myocardial infarction, chronic stable angina and cardiomyopathies will be explored. Subsequently, pharmacological approaches including well-established drugs and new agents not currently used in the clinical arena, specifically designed to treat coronary microvascular dysfunction in each of these clinical scenario, will be covered in detail.

* Corresponding author at: Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, Via Paradisa 2, 56124 Pisa (Pi). Tel.: +39 050996751.
E-mail address: mario.marzilli@med.unipi.it (M. Marzilli).

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2. Diabetes

2.1. Pathophysiology of diabetes related coronary microvascular dysfunction

Structural and functional coronary microvascular abnormalities at the level of the coronary microcirculation have been described in type 1 and 2 diabetes. Morphological changes include thickening of the arterial wall (Strauer et al., 1997) and of the capillary basement membrane, periodic acid-Schiff positive deposits in the vessel wall of small arteries (Ledet, 1976), microaneurysms, perivascular and interstitial fibrosis, and fibrosis in the wall of small coronary arteries (Fein et al., 1984). Moreover, studies in small arteries and arterioles of diabetic subjects have demonstrated that vasomotor dysfunction in microvessels precedes the appearance of morphological changes, affecting both smooth muscle- and endothelium-mediated regulatory mechanisms (De Vriese et al., 2000; Erdos et al., 2002). In humans, impaired coronary vasodilation was demonstrated after pharmacological [mainly acetylcholine (ACh)] or mechanical (cold test) stimuli; these vasomotor abnormalities were apparent in large vessels even in the absence of coronary stenosis, and were independent of other cardiovascular risk factors (Nitenberg et al., 1998). Bagi et al. found that both arteriolar

responses to myogenic and adenosine stimulation were unaffected by diabetes, whereas dilations in response to cumulative concentrations of ACh and a nitric oxide (NO) donor (NONOate) were significantly decreased in db/db mice, compared to control vessels (Bagi et al., 2003). Furthermore, arterioles of diabetic mice exhibited greatly reduced dilations to flow that were unaffected by an NO inhibitor. In carotid arteries of diabetic mice these investigators also demonstrated enhanced superoxide production (Bagi et al., 2003). Correspondingly, intraluminal administration of superoxide dismutase (SOD) significantly augmented flow-, ACh-, and NONOate-induced dilations of diabetic arterioles. Conversely, flow- and ACh-induced responses could be inhibited by L-NAME. Collectively, these findings suggested that NO mediation of agonist- and flow-induced dilations of coronary arterioles is reduced due to an enhanced superoxide production in type 2 diabetes. Furthermore, in the same year Miura et al. confirmed the impairment of coronary microvascular function (reduced vasodilation to hypoxia) in human coronary arterioles isolated from patients affected by type 1 and type 2 diabetes mellitus which was attributed, at least in part, to a decreased activity of ATP-sensitive potassium channels (Miura et al., 2003). Lately, Guarini et al. (2012) reported corruption of transient receptor potential vanilloid 1 channels- (TRPV1 channels) mediated coronary microvascular dilatation, in mice with type 2 diabetes. TRPV1 channels are involved in pathways that mediate the metabolic regulation of coronary blood flow acting via nitric oxide and BK channels. Moreover, impairment in coronary metabolic dilatation, due to enhanced ROS production, and mitochondrial DNA (mt-DNA) fragmentation, was demonstrated in diabetic rats (Guarini et al., 2010). Similar results were reproduced in lean rat in which mitochondrial dysfunction was selectively induced through mt-DNA damage, in the absence of coronary atherosclerosis and other risk factors (Guarini et al., 2011). In addition, abrogated ischemia-induced coronary collateral growth, i.e. reduced capacity to produce collaterals after brief repetitive episodes of ischemia, has been described in obese/diabetic rats (Hattan et al., 2007).

The metabolic disturbances of diabetes, like hyperglycemia, hyperlipidemia, and hyper-insulinemia act as "triggers" eventually causing endothelial dysfunction through the influence of different "mediator" molecules. Several lines of evidence point to "oxidative stress" as key player in endothelial dysfunction. Similar alterations in endothelial function have been described in obese patients (Perticone et al., 2001) without overt diabetes. High circulating levels of free fatty acids and pro-inflammatory adipokines likely contribute to endothelial dysfunction early in the course of insulin resistance. Free fatty acids induce endothelial dysfunction, whereas several adipokines promote both inflammatory responses and insulin resistance (Steinberg et al., 1997). In this sense, a critical role has been established for tumor necrosis factor (TNF), leptin, and adiponectin in vascular inflammation and modulation; notably, obesity and diabetes modify plasma levels and expression of these cytokines (Ouchi et al., 2003; Yang et al., 2009).

There are multiple sources of ROS in diabetes, including mitochondrial and non-mitochondrial origins. ROS are involved in several important molecular pathways of hyperglycemia-induced oxidative tissue damage. At present, four pathways are known, including: activation of protein kinase C, increased hexosamine pathway flux, increased advanced glycation end-product (AGE), and increased polyol pathway flux. This increased production of free radicals overwhelms the capacity of scavenger enzymes to neutralize ROS. Activated PKC has a number of effects on gene expression, such as decreased expression of endothelial nitric oxide synthase (eNOS), increased expressions of endothelin, vascular endothelial growth factor (VEGF), plasminogen activator inhibitor-1 (PAI-1), transforming growth factor-beta(TGF-β), nicotinamide adenine dinucleotide phosphate- [NAD (P) H] oxidases, and nuclear factor κB (NF-κB). All these in turn activate many pro-inflammatory genes in the vasculature. The activation of the AGE pathway can damage cells by three mechanisms: first, these compounds modify intracellular proteins, especially those involved in the regulation of gene transcription; second, these compound can diffuse to the extracellular space and modify extracellular proteins such as laminin and fibronectin to disturb signaling between the matrix and the cells; and finally, these compounds modify blood proteins such as albumin, causing them to bind to AGE receptors on macrophages/mesangial cells and increase the production of growth factors and pro-inflammatory cytokines. In line with this, AGE/RAGE system has been shown to be directly involved in the development of endothelial dysfunction in coronary arterioles isolated from diabetic mice (Gao et al., 2008).

Apart from the increased pool of mitochondrial and non-mitochondrial reactive oxygen species, patients with diabetes exhibit reduced antioxidant capability. Studies assessing the level of antioxidant defenses in diabetes have clearly shown that antioxidant capacity is compromised. Consistently with this, lower antioxidant activity – and specifically SOD1 activity – has been associated with both type 1 and 2 diabetes (Maxwell et al., 1997; Uchimura et al., 1999) and with endothelial dysfunction in children with Type 1 diabetes (Suys et al., 2007). This was further confirmed in human endothelial cells exposed to high glucose for 7 and 14 days. In this experiment, increased SOD1 and SOD2 protein levels were associated with reduced SOD activity, highlighting dysfunctional enzyme activity in conditions of high oxidative stress (Ceriello et al., 1996). As for the coronary microvessels, exposure of retinal endothelial cells to high glucose concentration has been proven to induce cells and mitochondrial DNA damage. Moreover, gene expression of mitochondrial-encoded proteins of the electron transport chain complexes is decreased. Other reports have demonstrated altered plasma/serum total antioxidant status or reduced free radical scavenging activity and increased plasma oxidability in type 2 diabetes, together with reduced levels of specific antioxidants such as ascorbic acid and vitamin E. In addition, the activities of antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and aldehyde dehydrogenase have been described as reduced in diabetics (Traverso et al., 2002; Lashin et al., 2006).

Altogether, it appears that a pivotal role in diabetic microvascular dysfunction is played by oxidative stress, which causes unbalance between vasodilator and vasoconstrictor factors (Bagi et al., 2005), causing ultimately damage to the arterial wall. Loss of function/regulation of the endothelium (i.e. endothelial dysfunction) may be a critical and initiating factor in the development of diabetic micro- and macrovascular disease (Basha et al., 2012). Fig. 1 summarizes main mechanisms involved in diabetes related coronary microvascular dysfunction. Given the relevancy of mitochondrial ROS-induced vasculature damage, strategies to target mitochondria, ROS and manipulation of cardiac metabolism in diabetes are under investigation.

2.2. Pharmacological approaches to diabetes related coronary microvascular dysfunction

2.2.1. Mitochondria manipulation

Only few preclinical data are available at the moment regarding pharmacological approaches to manipulate mitochondrial function. Although yet unsolved, mitochondrial uncoupling may provide beneficial effect by the means of reducing ROS generation. In this sense interestingly, a recent study has proposed that Silybin and dehydrosilybin (Tong et al., 2011) exert their protective role on cardiomyocytes from ROS by means of mitochondrial uncoupling properties (Gabrielova et al., 2010). This may open the way to further investigation in using mild/modified mitochondrial uncouplers to prevent endothelial and coronary microvascular dysfunction (Modriansky & Gabrielova, 2009). Recently, using a pharmacological approach to selectively repair mt-DNA fragmentation, coronary metabolic dilation was partially restored in diabetic rats (Guarini et al., 2011). These results may provide strength for new research.

2.2.2. Controlling reactive oxygen species production and oxidative damage

Several vitamins and chemical compounds with antioxidant properties and effect on mitochondria have been tested in attempt to control