Mechanisms of Hyperglycaemia-Induced Vascular Damage

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Coronary artery disease (CAD) remains one of the most important causes of morbidity and mortality worldwide, and revascularization through percutaneous coronary interventions (PCI) significantly improves survival. In this setting, poor glycaemic control, regardless of diabetes, has been associated with increased incidence of peri-procedural and long-term complications and worse prognosis. Novel antidiabetic agents have represented a paradigm shift in managing patients with diabetes and cardiovascular diseases.

diabetes mellitus coronary artery disease percutaneous coronary intervention

1. Increased Oxidative Stress and PKC-Mediated Pathway

Chronic hyperglycaemia and even more glycaemic variability (GV) are associated with increased production of reactive oxygen species (ROS), including free radicals such as superoxide anion (O^{2-}), lipid radicals (ROO^{-}), hydroxyl radical (HO^{-}), and not free radicals such as hydrogen peroxide (H_2O_2), hypochlorous acid (HClO) and peroxynitrite ($ONOO^{-}$) [1]. In humans, ROS are mainly produced in the mitochondrial respiratory chain by several enzymes, including xanthine-oxidase (XO), NADPH-oxidase (NOX), and uncoupled nitric oxide synthase (NOS) [2]. Glucose fluctuations have been reported to influence these enzymes inducing an increased ROS production through the activation of different pathways: protein kinase C (PKC), protein kinase B (PKB or AKT), mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [3]. Among these, the activation of PKC has emerged as a crucial mechanism. Interestingly, different molecular pathways can induce PKC activation. In hyperglycaemic conditions, glucose is converted to polyalcohol sorbitol through the polyol pathway, resulting in an increased intracellular NADH/NAD+ ratio and an enhanced formation of diacylglycerol (DAG). As a result, increased DAG levels provoke PKC activation. Furthermore, PKC's domain also binds Ca^{2+}; thus, the G-protein coupled receptor (GPCR)-mediated cleavage of the phosphatidylinositol 4,5-biphosphate (PIP2) in inositol-1,4,5-triphosphate (IP3) and Ca^{2+}, activates IP3 receptors on the smooth endoplasmic reticulum (ER) and facilitates the release of intracellular calcium stores with subsequent activation of PKC [4]. PKC is also directly activated by intracellular ROS, such as by O^{2-}, overproduced in hyperglycaemic conditions [5]. Interestingly, hyperglycaemia-induced PKC activation has been reported to have significant intracellular and intercellular consequences, affecting endothelial permeability, vasoconstriction, extracellular matrix synthesis/turnover, cell growth, cytokine activation and leukocyte adhesion, thus emerging as a potential

therapeutic target to prevent diabetic vascular complications [6]. Furthermore, high glucose levels induce the activation of the hexosamine pathway. The resulting formation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) leads to the glycosylation of several intracellular proteins that regulate pro-inflammatory and pro-thrombotic genes [7]. Hyperglycaemia also stimulates the formation of advanced glycation end products (AGEs), which linking to their receptors (RAGE), induce the generation of intracellular ROS and the subsequent activation of the redox-sensitive transcription factor NF-kB, which modulates the expression of a variety of genes associated with inflammation and atherosclerosis [7]. On the other hand, hyperglycaemia is also characterized by an abnormal imbalance of antioxidant defences. In this regard, the antioxidant enzyme superoxide dismutase (SOD) concentration, which usually helps to maintain ROS levels under a certain threshold, is reduced in hyperglycaemic conditions [6][7]. Among all responsible mechanisms for this latter pathophysiological mechanism, miRNA-21 induced dysregulation of Krev/Rap1 interaction trapped-1 (KRIT1), extracellular signal-regulated kinase (ERK) and nuclear erythroid 2 related factor-2 (NFE2L2 or NRF2) signalling has been recently investigated [8].

2. Endothelial Function

Endothelial cells play a central role in the pathogenesis of atherosclerosis and are strongly influenced by hyperglycaemia and glucose fluctuations [9]. Quagliaro et al. demonstrated that exposure to intermittent high glucose levels in human umbilical vein endothelial cells (HUVEC) produces endothelial cell dysfunction, apoptosis, and ROS production [10]. Glucose variations have also been demonstrated to influence the production of nitric oxide (NO) by endothelial cells and subsequent angiogenesis [11]. Therefore, Biscetti et al. demonstrated that GV in diabetic mice inhibits vascular endothelial growth factor (VEGF), endothelial NOS and AKT after ischemic injury [12]. The consequence of e-NOS downregulation is a reduction of NO synthesis and impaired endothelial-dependent vasodilation. Additionally, lower VEGF levels reduce angiogenesis by inhibiting angiogenic sprouting after ischemia [13].

Moreover, in hyperglycaemic conditions, the short NO remainder reacts with O^{2-} to form ONOO-, a strong cytotoxic oxidant. This latter compound has a double effect: direct damage to protein, lipids, DNA, and e-NOS enzyme uncoupling through oxidation of tetrahydrobiopterin [14][15]. Whether coupled e-NOS uses L-arginine to produce L-citrulline and NO, favouring cyclic guanosine monophosphate (cGMP) synthesis in vascular smooth muscle cells (VSMCs) and vasodilation, uncoupled e-NOS enhances O^{2-} rather than NO with subsequent cellular damage [16].

In turn, O^{2-} also stimulates the formation of AGEs [17]. AGEs, molecules generated by the non-enzymatic reaction between proteins, lipids or nucleic acids with the aldehydic group of sugars, cause vascular damage and accelerated atherosclerotic plaque formation through RAGE binding [18][19].

In endothelial cells, PKC βI and βII isoform activation induced by intermittent high glucose can also increase adhesion molecule expression. HUVECs exposed to stable and intermittent high glucose conditions show an increased expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [20]. This event may promote monocyte adhesion to endothelium, their migration in sub-endothelial space and consequent differentiation in foam cells [21].

Finally, hyperglycaemia and GV can induce apoptosis and autophagy in endothelial cells. HUVECs exposed to intermittent high glucose show elevated levels of p53 with consequent p21, p53 upregulated mediator of apoptosis (PUMA), phosphatase and tensin homologue (PTEN), TP53-induced glycolysis and apoptosis regulator (TIGAR) overexpression. These proteins are involved in cell growth arrest and apoptosis [22]. These fluctuations increase miR-1273g-3p levels and subsequent autophagy in the same cell line [23].

3. Vascular Smooth Muscle Cells

Glucose fluctuations significantly influence the proliferation and migration of VSMCs, which play a central role in atherosclerosis progression and in-stent restenosis (ISR). Indeed, GV promotes lipid-rich plaques with thin fibrous caps and neointimal thickening independently of dyslipidaemia control [24][25]. These data were confirmed by a recent metanalysis that underlines how reducing glucose fluctuations correlates with improved intimal-media thickness [26].

Hyperglycaemia influences VSMCs migration and proliferation through different molecular pathways. Sung Hoon Yu et al. showed that intermittent hyperglycaemia results in the accumulation of VSMCs mediated by MAPK, big mitogen-activated protein kinase 1 (BMK1), phosphoinositide 3-kinases (PI3K), and NF-κB [27]. This process is also driven by miRNA21, miRNA146a, matrix metalloprotease-2 (MMP-2) and osteopontin (OPN) [28][29]. Moreover, high glucose levels have been demonstrated to downregulate the insulin receptor substrate-1 (IRS-1), thus decreasing the p53/Krüppel-like factor 4 (KLF-4) association and enhancing VSMCs dedifferentiation and proliferation [30]. Concordantly, the VSMCs expression of genes participating in ERK mitogenic response is activated in the setting of hyperglycaemia, which furtherly stimulates cell proliferation [30]. Hyperglycaemia-induced ROS production also favours lipid peroxidation, affecting ion transport across cell membranes; among channels and pump altered, an abnormal function of the sarcoplasmic/endoplasmic reticulum ATPase (SERCA) results in modified intracellular Ca^{2+} signalling in VSMCs, enhancing their migration [31]. On the other side, hyperglycaemia inhibits apoptosis of VSMCs by upregulation of several anti-apoptotic proteins such as Bcl2, Bcl-xl and Bfl-1/A1 [32].

4. Inflammation

Atherosclerotic plaque formation and progression are favoured by monocyte adhesion to vascular endothelium and their subsequent migration in the sub-intimal layer. CD14+ and CD16+ sub-groups are the most represented in patients with CAD and peripheral artery disease. A recent virtual histology study showed that CD14+ and CD16+ monocyte accumulation correlates with plaque instability; most importantly, GV seems to increase their expression leading to accelerated atherosclerosis [33]. Consistently, monocytes exposed to an acute glucose load show a significant and rapid increase (within 120 min) of the adhesion molecule Mac-1 (CD11b), which interacts with endothelial ICAM-1 and with non-endothelial matrix ligands favouring sub-endothelial cellular migration [34]. Mac-1 also functions as a link between cellular adhesion and thrombosis via the activation of factor X and the coagulant cascade [35]. Other hyperglycaemia-stimulated receptors involved in monocyte adhesion are leukocyte function antigen-1 (LFA-1 or CD11a) and ICAM-1 [34].

Furthermore, an acute increase in blood glucose concentrations causes a rapid rising in several cytokine levels, such as interleukin 6 (IL-6), interleukin 18 (IL-18) and tumour necrosis factor-alpha (TNF-alpha), contributing to creating a pro-inflammatory environment [36]. Hyperglycaemia also induces the inactivation of CD59, an extracellular cell-membrane regulatory protein that inhibits the assembly of the membrane attack complex (MAC). The CD59 inactivation and the following increase in MAC deposition have been demonstrated to increase the release of pro-thrombotic cytokines [37]. Finally, the inhibition of CD59 induces the increased production of monocyte chemoattract protein-1 (MCP-1) with consequent monocyte activation and migration in the sub-endothelial layer [38].

5. Platelets

Chronic hyperglycaemia and GV have been reported to promote platelet activation and aggregation [39]. Firstly, hyperglycaemia is associated with a significant reduction in endothelial NO production. The underlying mechanisms have been previously reported; thus, hyperglycaemia-induced superoxide overproduction inhibits eNOS and activates PKC and NF-kB with subsequent ROS production. NO is fundamental to reduce platelet aggregation and stimulate preformed platelet aggregates' disaggregation [40].

Furthermore, the activation of transcription factors such as NF-kB results in increased production of inflammatory chemokines, thus increasing the exposure of endothelial adhesion molecules that favour platelet adherence and aggregation [41]. Increased oxidative stress also activates platelets through augmented response to agonists mediated by increased F2-isoprostane production and decreased prostacyclin levels [42]. Thus, low levels of prostacyclin have been associated with decreased aspirin effectiveness [43][44]. Finally, high blood glucose levels stimulate the expression of tissue factor (TF) by endothelial cells and monocytes.

Glycaemic levels also significantly influence the activity of several platelet surface glycoprotein (GP) receptors. Therefore, increases in GPIa/IIa (collagen receptor), GPIIb/IIIa (fibrinogen receptor), and GPIb-IX (von Willebrand factor receptor) have been reported in the setting of hyperglycaemia [45]. Furthermore, glucose variations stimulate in vivo and in vitro P-selectin (CD62p) production, a lectin family member that mediates platelets rolling on endothelial cells and stabilizes initial aggregates induced by GP IIb-IIIa and fibrinogen (40,41). Platelets of diabetic patients also show increased arachidonic acid-thromboxane (TxA2) production and CD-40 ligand (CD40L) expression, which enhances the production and release of pro-inflammatory cytokines and favours the development of platelet-rich thrombi [45]. Furthermore, platelet Ca^{2+} ATPase activity and intracellular Ca^{2+} signalling are abnormal in hyperglycaemic conditions, increasing platelet reactivity [46].

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