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Review

Diabetes, oxidative stress and therapeutic strategies

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ABSTRACT

Background: Diabetes has emerged as a major threat to health worldwide.
Scope of Review: The exact mechanisms underlying the disease are unknown; however, there is growing evidence that excess generation of reactive oxygen species (ROS), largely due to hyperglycemia, causes oxidative stress in a variety of tissues. Oxidative stress results from either an increase in free radical production, or a decrease in endogenous antioxidant defenses, or both. ROS and reactive nitrogen species (RNS) are products of cellular metabolism and are well recognized for their dual role as both deleterious and beneficial species. In type 2 diabetic patients, oxidative stress is closely associated with chronic inflammation. Multiple signaling pathways contribute to the adverse effects of glucotoxicity on cellular functions. There are many endogenous factors (antioxidants, vitamins, antioxidant enzymes, metal ion chelators) that can serve as endogenous modulators of the production and action of ROS. Clinical trials that investigated the effect of antioxidant vitamins on the progression of diabetic complications gave negative or inconclusive results. This lack of efficacy might also result from the fact that they were administered at a time when irreversible alterations in the redox status are already under way. Another strategy to modulate oxidative stress is to exploit the pleiotropic properties of drugs directed primarily at other targets and thus acting as indirect antioxidants.
Major Conclusions: It appears important to develop new compounds that target key vascular ROS producing enzymes and mimic endogenous antioxidants.
General significance: This strategy might prove clinically relevant in preventing the development and/or retarding the progression of diabetes associated with vascular diseases.

1. Introduction

Diabetes mellitus is a chronic disease characterized by elevated blood sugar levels resulting from either a lack of insulin production or resistance to insulin. About 230 million people worldwide had diabetes in 2010. The global figure of people with diabetes is projected to increase to 333 million in 2025, and 430 million in 2030 [1]. As the prevalence of diabetes has risen to epidemic proportions worldwide, the vascular complications of diabetes have now become one of the most challenging health problems. A relatively small proportion (10%) of patients suffering from diabetes mellitus has type 1 or insulin-dependent diabetes. However, the majority of diabetes patients are not insulin-dependent and able, at least initially, to produce the hormone. This type of diabetes mellitus (DM) is termed type 2 diabetes. Insulin resistance (IR) is a fundamental aspect of the etiology of type 2 diabetes. Irrespective of the etiology, subjects with diabetes have an increased risk of ischemic heart disease, atherosclerosis and nephropathy [2]. (See Table 1.)

Obesity, which is a major public health concern worldwide, increases the risk of type-2 diabetes [3]. Early in the development of type-2 diabetes, IR requires the production of extra insulin to maintain normal blood glucose levels. In the majority of obese individuals, hyperinsulinemia can occur with an increase in beta-cell mass, which facilitates the increased production of insulin. As a result, these individuals do not develop diabetes. However, approximately one third of obese individuals exhibit a decrease in beta-cell mass caused by beta-cell apoptosis, which renders these individuals unable to compensate for their IR-state and the resulting hyperglycemia, leading to a diagnosis of type 2 diabetes. Thus, type 2 diabetes is caused by a combination of IR coupled with insufficient production of insulin to overcome the IR [4].

Endothelial dysfunction underlies both micro- and macrovascular complications of diabetes. Microvascular disease leads to diabetic retinopathy, nephropathy and neuropathy. Oxidative stress plays a key role in the pathogenesis of micro- and macrovascular diabetic complications. The increased oxidative stress in subjects with type 2 diabetes is a consequence of several abnormalities, including hyperglycemia, IR, inflammation and dyslipidemia [5]. Endothelial function is important for the homeostasis of the body and its dysfunction is associated with several pathophysiological conditions, including atherosclerosis, hypertension and diabetes. Patients with diabetes invariably show an impairment of endothelium-dependent vasodilation [6]. These dysfunctions contribute to mitochondrial superoxide overproduction in endothelial cells. The

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Table 1
Antioxidant strategies to control oxidative stress in diabetes.

Enzymatic antioxidants
SOD/Catalases/GXP mimetics
SOD mimetics: metaloporphyrins, tempol
Cationic meso Mn(III)-N-substituted pyridylporphyrins, N,N′-disubstituted imidazolylporphyrins (MnPs)
Mito Q10
Catalases mimetics
Salen–manganese complex
GXP mimetics:
Ebselen: 2-phenyl-1,2-benzisoselenazol-3(2H)-one
Diphenyl diselenide (DPDS)
Antioxidant vitamins
Vitamin C (ascorbic acid)
Vitamin E (tocopherols), trolox (an analog of alpha-tocopherol)
Folic acid (vitamin B9)
Non-vitamin antioxidants
N-acetylcysteine
Lipoic acid: alpha-lipoic acid
Coenzyme Q10
Mitochondria-targeted antioxidants: MitoQ, XJB-5-131, SS31
Sequestration of ions: Lazaroids: 21-aminosteroids, U75412E, tirilazad mesylate
Xanthine oxido-reductase inhibitors: allopurinol and its metabolite: oxypurinol
Drugs with antioxidant properties
Classical agents
Metformin: 1,1-Dimethylbiguanide
Glibenclamide: 1-[4-[2-(5-Chloro-2-methoxybenzamido)ethyl]phenylsulfonyl]-3-cyclohexylurea
Therapeutic approaches with new agents
Edaravone: 3-Methyl-1-phenyl-2-pyrazolin-5-one
Benfotiamine: S-[2-{[(4-amino-2-methylpyrimidin-5-yl)methyl] (formyl)amino}-5-(phosphonooxy)pent-2-en-3-yl] benzenecarbothioate
Poly(ADP-ribose) polymerase inhibitors (PARP inhibitors)
Classical PARP inhibitors: nicotinamide and its 5-methyl derivates; benzamide (3-aminobenzamide: 3-AB; 3-methoxybenzamide)
Newer PARP inhibitors: dihydroisoquinolinones, isoquinolinones, Zinc finger PARP inhibitors: 6-nitroso 1,2-benzopyrone,3,3-nitrosobenzamide and iodo-nitro-benzamide (INO2BA)
Peroxynitrite decomposition catalysts
FP-15: FeIIItetrakis-2-(triethylene glycol monomethyl ether)pyridyl porphyrin
FeTTPS, FeTMPs
Other pharmacological approaches
Angiotensin-converting enzyme inhibitors (ACEI)
Peroxisome proliferator-activated receptors (PPARs):
Thiazolidinediones (glitazones): troglitazone, pioglitazone, rosiglitazone
Promizing new clinical agents
FGF21: fibroblast growth factor 21
Epoxide hydrolase inhibitors: sorafenib (N-[4-Chloro-3-(trifluoromethyl)phenyl]-N′-[4-[2-(N-methylcarbamoyl)-4-pyridyloxy]phenyl]urea) and derivates
Incretin mimetics and inhibitors of their metabolism
Glucagon-like peptide-1 (GLP-1) receptors agonists: exenatide, exendin-4, liraglutide,
Dipeptidyl Peptidase-4 (DPP-4) inhibitors: sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin
Inhibitors of ceramide synthesis or activators of ceramide degradation and sphingosine modulators
S1P1,3,4,5 R agonist: Fingolimod (2-amino-2-2-(4-octylphenyl)ethyl) propane-1,3-diol hydrochloride) (FTY720)
S1P1R-specific agonist: (2-amino-2-{3-[4-(3-benzyloxy-phenylsulfanyl)-2-chloro-phenyl]-ethyl}-propan-1,3 diol hydrochloride): KRP203:

purpose of the present review is to consider the opportunities presented by currently used therapeutic agents which possess antioxidant properties, as well as those offered by new potential antioxidant substances.

Diabetes impact on the different steps in the pathogenesis of cardiovascular diseases (CVD) [7–9]. Obesity and IR in patients suffering from diabetes are associated with a chronic systemic inflammation, characterized by an increased expression of inflammatory markers. Multiple stimuli are among the most common causes of myocardial inflammation in cardiomyopathies in diabetic patients [10–12]. Diabetes is an established major factor of poor prognosis after an acute coronary syndrome (ACS). Abnormal glycemic regulation is more common than normal regulation in patients presenting with acute coronary syndrome. High blood glucose at admission, whether fasting or not, is associated with worse outcome [increased mortality and development of severe heart failure] in patients with acute coronary syndrome. The prognostic value of glycemia applies to both short and long term outcomes. However, fasting glycemia is a more powerful predictor than glucose levels upon admission for short term outcome after myocardial infarction. The mechanisms by which hyperglycemia worsens cardiovascular prognosis, in particular as regards left ventricular dysfunction and acute coronary syndrome, are not fully understood. Such patients are predisposed to a proinflammatory, prothrombotic state, which may lead to plaque rupture. Stress hyperglycemia may be a marker of extensive cardiac damage, reflecting a surge of stress hormones such as catecholamines and cortisol that contribute to IR and affect fatty acid and glucose homeostasis [13]. Intravenous insulin therapy is used in diabetic patients at the acute phase of coronary syndrome. Hyperglycemia in diabetic patients is a powerful predictive factor for patient outcome as it is associated with a doubling of in-hospital mortality and poor long-term prognosis. In non-diabetic patients, even mild hyperglycemia in the setting of ACS is also a predictive factor of in-hospital mortality. Moreover, impaired fasting glucose is not only an independent factor of mortality for coronary patients, but is associated with a doubling of the risk of in-hospital mortality in the setting of ACS [14,15]. After myocardial infarction, diabetic patients have a significantly higher risk of heart failure and cardiogenic shock. Circulating B-type natriuretic peptide (BNP) and its prohormone (NT-proBNP) levels are used for screening, diagnosis, and prognostic assessment of patients with acute decompensated heart failure and correlate with left ventricular dilatation, remodeling, and dysfunction. The median plasma NT-pro-BNP is increased in diabetic patients without overt cardiovascular disease, suggesting a higher prevalence of asymptomatic left ventricular dysfunction. In a large population of patients hospitalized for acute MI diabetes was a strong and independent factor for increased plasma NT-pro-BNP levels. The latter were associated with the increased incidence of in-hospital mortality and cardiogenic shock observed in diabetic patients after myocardial infarction, indicating that plasma NT-proBNP provides relevant prognostic information on in-hospital outcome in this population [16]. In a cross-sectional sample of type 1 diabetic patients an association between NT-proBNP and vascular complications depended on circulating levels of the inflammatory cytokine tumor necrosis factor: TNF-α [17]. TNF-α has pleiotropic effects in cytokine-mediated inflammation underlying vascular disease and the link between type 1 diabetes, TNF-α and vascular disease is well established [18]. However, the relationship between TNF-α and oxidative stress is not clear in a dose- and time-dependent manner, a dual role of TNF-α being observed. After TNF-α perfusion in isolated heart, an increase of catalase activity were observed while the superoxide dismutase activity remained unchanged. Other studies conducted in the heart have reported an oxidative stress with an activation of catalase and no change in superoxide dismutase. An explanation for this observation may be a difference in the dynamic and the spatial distribution between these two enzymes. [19–21].

2. Free radicals and antioxidants (Fig. 1)

Radicals derived from oxygen (ROS) and nitrogen (RNS: derived from nitric oxide: NO) are the largest class of radical species generated in living systems. ROS and RNS are products of normal cell metabolism and have either beneficial or deleterious effects, depending on the concentration reached in the tissues [22,23]. Free radicals can be defined as molecules or molecular fragments containing one or more unpaired