Vascular Pharmacology 57 (2012) 150–159

Contents lists available at SciVerse ScienceDirect

Vascular Pharmacology

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

Review

Oxidant stress and skeletal muscle microvasculopathy in the metabolic syndrome

Adam G. Goodwill [a,b], Jefferson C. Frisbee [a,b,*]

[a] Department of Physiology and Pharmacology, West Virginia University School of Medicine, Morgantown, WV 26506, United States
[b] Center for Cardiovascular and Respiratory Sciences, West Virginia University School of Medicine, Morgantown, WV 26506, United States

ARTICLE INFO

Article history:
Received 14 May 2012
Received in revised form 19 June 2012
Accepted 4 July 2012

Keywords:
Metabolic syndrome
Vasculopathy
Microcirculation
Oxidant stress

ABSTRACT

The evolution of the metabolic syndrome in afflicted individuals is, in part, characterized by the development of a severely pro-oxidant state within the vasculature. It has been previously demonstrated by many investigators that this increasingly pro-oxidant state can have severe negative implications for many relevant processes within the vasculature, including the coordination of dilator/constrictor tone or reactivity, the structural adaptations of the vascular wall or distal networks, as well as the integrated regulation of perfusion resistance across and throughout the vascular networks. The purpose of this review article is to present the different sources of oxidant stress within the setting of the metabolic syndrome, the available mechanism for attempts at regulation and the vascular outcomes associated with this condition. It is anticipated that this overview will help readers and investigators to more effectively design experiments and interpret their results within the extremely complicated setting of metabolic syndrome.

Contents

1. Introduction

Using body mass index as a criterion, the World Health Organization estimated that, as of 2005, as many as 1.6 billion individuals over the age of 15 could be classified as overweight (BMI: 25–29.99) with 400 million of those individuals classified as obese (BMI > 30) (World Health Organization, 2009). Projections from that same organization estimate that by the year 2015, there will be approximately 2.3 billion overweight individuals globally with over 700 million of those

* Corresponding author at: Center for Interdisciplinary Research in Cardiovascular Science, Department of Physiology and Pharmacology, Robert C. Byrd Health Sciences Center, PO Box 9105, West Virginia University School of Medicine, Morgantown, WV 26505, United States. Tel.: +1 304 293 6527; fax: +1 304 293 5513.
E-mail address: jfrisbee@hsc.wvu.edu (J.C. Frisbee).

1537-1891/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.vph.2012.07.002

individuals classified as obese. This rapid increase in the number of overweight and obese individuals has become particularly significant in the United States where the American Heart Association has demonstrated that 30.2% of male Americans could be classified as obese in 2004 whereas only 10.7% of the male population achieved that classification in 1962 (American Heart Association, 2009). Women have not been spared from this negative health trend as prevalence of obesity increased from 15.7% to 34% over an identical time period (American Heart Association, 2009). While there are socioeconomic and racial disparities regarding the prevalence of overweight/obese states, no individual population in the developed world has shown itself to be immune to the continual increases in non-lean body mass.

While obesity itself is a well-established risk factor for cardiovascular disease, type II diabetes mellitus (Mokdad et al., 2003; The American Heart Association, 2009) and cancer (Matsuo et al., 2012; Bracci, 2012; Faulds and hlman-Wright, 2012), the co-morbidities associated with negative vascular consequences have demonstrated such a degree of prevalence and correlative power with obesity that the myriad co-morbidities and obese state have been classified communally as the metabolic syndrome. Generally, the metabolic syndrome can be thought of as an increased risk for negative cardiovascular outcomes in obese individuals. The syndrome itself has been recognized as far back as the 1920s with the term gaining popularity in those years following the 1970s. In recent history, the American Heart Association has defined the metabolic syndrome as a group of metabolic risk factors in a single person including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, a pro-thrombotic state, and a pro-inflammatory state (The American Heart Association, 2009). According to the most recent data from the Centers for Disease Control, approximately 34% of American adults over the age of 20 meet the criteria for metabolic syndrome as defined above (Ervin, 2009). Given the well-documented and continuous global rise in the prevalence of obesity, the primary stimulus for metabolic syndrome, the burden of metabolic syndrome is expected to continue to increase in the coming years.

Type II diabetes mellitus, also known as non-insulin dependent diabetes mellitus or insulin resistant diabetes, is a condition defined by an inability of the body to properly handle glucose despite a hyperinsulinemic state. Unlike type I diabetes mellitus, prevalence of type II diabetes has long been correlated with increases in abdominal obesity. Of all the contributing pathologies comprising the foundations of the metabolic syndrome, type II diabetes may be the single most significant mechanistic link between obesity and one of the most significant negative health outcomes, peripheral vascular disease. This vasculopathy is most generally defined as an inappropriate response of the vasculature to normal stimulation and regulation. In the metabolic syndrome it is characterized by both microvascular rarefaction (a reduction in microvascular density) and endothelial dysfunction. Endothelial dysfunction, which can be defined as a diminished responsiveness of the vascular endothelium to vasodilator stimuli (primarily mediated through NO and prostacyclin) along with exaggerated responses to α-adrenergic stimuli, is not the only culprit in the complex peripheral vasculopathies which are characteristic of the metabolic syndrome. There are also significant changes to both the signaling mechanisms that control the vasculature, and the smooth muscle layers and connective tissues that form the vascular wall. In recent years, basic, clinical and translational research initiatives have found strong links between the oxidative stress stemming from the insulin resistant state found in metabolic syndrome and the development of peripheral vasculopathy. The purpose of this review is: 1) to discuss the sources of oxidative stress associated with the metabolic syndrome, 2) to summarize known altered relationships between the balance of pro- and anti-oxidant mechanisms within the vasculature, and 3) to present the general vascular consequences of the metabolic syndrome.

2. Disparities in the regulation of oxidant stress

Reactive oxygen species (ROS) are molecules that contain at least one or more oxygen atoms and generally have one or more unpaired electrons. These highly reactive compounds include the superoxide anion (O_2^-), the hydroxyl radical (OH^-) and the peroxynitrite radical ($OONO^-$) (Stephens et al., 2009). Although hydrogen peroxide (H_2O_2) is not a radical *per se*, due to its chemical structure and extremely reactive nature, it is commonly also included on the list of ROS (Stephens et al., 2009). As with most physiological systems, the regulation of levels of ROS does not occur at a single level. Rather, in addition to the biological machinery provided to generate ROS, there is additional biological machinery provided to degrade those species. A pro-oxidant environment is achieved when the pathways for generation of ROS outstrip the capabilities of those enzymes and biomolecules with anti-oxidant character. This is relevant to the metabolic syndrome as animal models of the disease have shown consistent elevations in oxidative stress as assayed through multiple markers (Phillips et al., 2005; Frisbee et al., 2009; Hopps et al., 2009; Isogawa et al., 2009). Additionally, human beings have been clearly shown to demonstrate elevations in oxidative stress as the "Framingham study", an extensive human population analysis, reported significant correlations between body mass index and diabetes with systemic oxidative stress as measured by urinary excretion of 8-epi-prostaglandin $F_{2\alpha}$ (Keaney et al., 2003).

Hyperglycemia, a hallmark of both type I and type II diabetes, has a well-documented association with increase in ROS through varying mechanisms (Baynes and Thorpe, 1999; Nishikawa et al., 2000; Oberley, 1988; Sakurai and Tsuchiya, 1988; van Dam et al., 1995). These mechanisms can be mediated through an active process such as increases in ROS production through the mitochondrial complex II or through passive processes such as glucose auto-oxidation and the formation of advanced glycation end products (AGEs). The passive processes, in addition to the directly oxidative nature of the compounds formed, have also been demonstrated to indirectly shift the pro-oxidant *vs.* anti-oxidant homeostasis by acting through cell surface receptors to downregulate production of antioxidants such as glutathione (Yan et al., 1994; Stern et al., 2002).

The specifics of the mechanisms regulating oxidant stress will not be covered in depth in this review as the research into the generation and degradation of reactive species is sufficiently extensive to merit a completely separate and suitably detailed body of work. In general, the primary sources of vascular oxidant stress known today are the NADPH oxidase family, xanthine/xanthine oxidase, uncoupled endothelial nitric oxide synthase (eNOS), cyclooxygenase, lipoxygenase, cytochrome P450 and deficiencies in the mitochondrial electron transport system. These various systems generate unstable oxygen radicals including superoxide radical ($^{\bullet}O_2^-$). If one considers anti-oxidants to be agents that are able to compete with oxidizable substances thereby delaying or inhibiting the oxidation of these substances, the primary anti-oxidant mechanisms in humans include the enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx), thioredoxin and catalase as well as nonenzymatic compounds including, but not limited to, α-tocopherol (vitamin E), ascorbate (vitamin C), glutathione and β-carotene (Bouanane et al., 2009; Kuzuya et al., 2008; Kaimul et al., 2007; Cardona et al., 2008; Jain et al., 2009; Gersch et al., 2008; Codoner-Franch et al., 2009).

3. Type II diabetes mellitus and inflammation

Previous studies have demonstrated elevations in both intracellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) in small resistance arteries of diabetic human subjects with further studies demonstrating a powerful correlation between these two inflammatory adhesion molecules and glycosylated hemoglobin levels (Schiffrin and Touyz, 2004). Additional studies have