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Food Science and Human Wellness 5 (2016) 1–7
Food Science and Human Wellness
www.elsevier.com/locate/fshw

Bioactive peptides on endothelial function

Subhadeep Chakrabarti, Jianping Wu *

Department of Agricultural, Food & Nutritional Science and the Cardiovascular Research Centre, University of Alberta, Edmonton, AB, Canada

Received 8 November 2015; accepted 30 November 2015
Available online 29 December 2015

Abstract

Cardiovascular diseases (CVD) such as myocardial infarction and stroke are a major cause of morbidity and mortality worldwide. Impairment of the normal vasorelaxant functions of the vascular endothelium, termed endothelial dysfunction; appear to underlie the pathogenesis of CVD. Endothelial dysfunction is often secondary to abnormal increases in oxidative stress, inflammation and overactivity of the renin–angiotensin system (RAS), which makes these pathways attractive targets for therapeutic interventions. Given the side-effects associated with synthetic pharmaceutical agents, there is growing interest in using natural products such as bioactive peptides for treating chronic diseases like CVD. In this review, we discuss the potential for bioactive peptides with antioxidant, anti-inflammatory and RAS modulating properties for treating endothelial dysfunction and preventing CVD.

Keywords: Bioactive peptide; Endothelial dysfunction; Oxidative stress; Inflammation; RAS

1. Introduction

Cardiovascular diseases such as myocardial infarction and stroke are leading causes of morbidity and mortality [1]. Taken together, these two conditions caused 249.7 deaths/100,000 persons in 2013 and contributed to 28.2% of all deaths worldwide [2]. The key underlying pathology in cardiovascular disorders is atherosclerosis, the inflammatory thickening of the blood vessel wall [3]. Additional vascular factors predisposing to atherosclerosis include hypertension [4], the persistent elevation of blood pressure above 140/90 mmHg [5]. Both atherosclerosis and hypertension originate from impaired functioning of the endothelium, the monolayer of cells that line the lumen of blood vessels [6,7]. Thus, the endothelium is a key factor for maintaining vascular health and prevention of cardiovascular diseases.

While a number of pharmacological agents are widely used for prevention, treatment and long-term management of vascular diseases, these drugs are not without the risk of significant side-effects [8,9]. Not surprisingly, there has been an increased interest in developing alternative therapies from natural sources, which are commonly perceived to be safer than synthetic drugs. Naturally occurring proteins and their constituent peptides are an attractive source for novel natural compounds with various biological activities [10]. Bioactive peptides are defined as relatively short peptides (typically containing 2–20 amino acids) derived from their parent proteins (by enzymes, heat, chemical treatments or microbial fermentation) that demonstrate additional biological activities over and above their expected nutritional value [11,12]. Recent years have seen much interest in using bioactive peptides (and peptide-rich protein hydrolysates) from food sources as safe and natural alternatives for promoting and enhancing health [13–15]. This review will provide an overview of the potential roles of bioactive peptides in maintaining endothelial functions and/or preventing endothelial dysfunction through modulation of different physiological pathways.

* Corresponding author at: 4-10 Ag/For Centre, Department of Agricultural, Food & Nutritional Science, University of Alberta, Edmonton, AB T6G 2P5, Canada. Tel.: +1 780 492 6885; fax: +1 780 492 4265.
E-mail address: jianping.wu@ualberta.ca (J. Wu).
Peer review under responsibility of Beijing Academy of Food Sciences.

2. Endothelial functions and dysfunction

Over the past few decades, the roles of the endothelium in vascular physiology have become better understood. While

http://dx.doi.org/10.1016/j.fshw.2015.11.004

originally it was believed to be simply an inert layer of cells separating blood from the structural tissues, it is now well known for its critical roles in regulating vascular tone. Research from the last 20 years has defined many crucial roles for the endothelium in the regulation of vascular tone, modulation of inflammation, promotion or inhibition of vascular growth and of platelet aggregation and coagulation, and in the development of atherosclerosis [16].

The vascular endothelium is considered to be the largest endocrine organ in the body. Endothelial cells secrete various vasoactive agents, such as the vasodilatory nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), as well as the vasoconstrictory endothelin I, angiotensin II (Ang II) and thromboxane [17,18]. Endothelial dysfunction is a broad term that implies diminished production or availability of NO and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors [19]. Endothelial dysfunction has been shown in the elderly, in patients with hypertension, diabetes and hypercholesterolemia as well as in those subjected to air pollution or smoking [16,20,21]. Such dysfunction is involved in the pathophysiology of metabolic syndrome and cardiovascular diseases such as atherosclerosis, hypertension and heart failure [22,23]. Reduced bioavailability of endothelium-derived NO is the key for endothelial dysfunction. NO relaxes blood vessels (vasodilation), prevents thrombus formation, suppresses smooth muscle proliferation, and inhibits the leukocyte attachment to the activated endothelium [16,24]. Loss of endothelial NO bioavailability, a key manifestation of endothelial dysfunction, is increasingly accepted as a common trait of essentially all cardiovascular risk factors, showing profound prognostic implications in prediction of adverse cardiovascular events and long-term outcomes [25]. A number of pathological mechanisms appear to mediate endothelial dysfunction in general, including oxidative stress, dysregulated inflammation and overactivity of the renin–angiotensin system (RAS) all of which are potential targets for modulation by bioactive peptides. The key endothelial functions and their altered dysfunctional counterparts are summarized in Fig. 1.

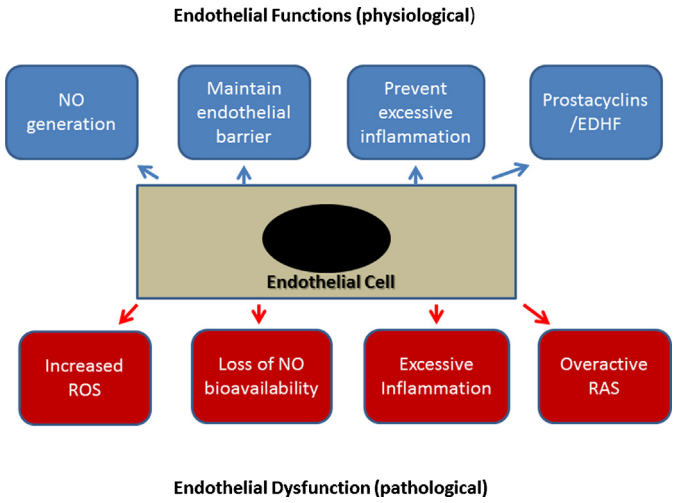

Fig. 1. Endothelial functions under normal (physiological) and abnormal (pathological) conditions.

3. Bioactive peptides on NO bioavailability and endothelial function

3.1. Oxidative stress, NO and endothelial dysfunction

Oxidative stress, *i.e.* the excessive and/or dysregulated generation of reactive oxygen species (ROS) such as superoxide and hydrogen peroxide, is a major contributor to disease pathologies. In the vascular endothelium, an excess of superoxide leads to its reaction with NO to generate peroxynitrite ($ONOO^-$), a highly reactive and toxic molecule that causes nitration at the tyrosine residues of various proteins. Not only does peroxynitrite formation reduce NO bioavailability (and hence contributes to endothelial dysfunction), tyrosine nitration can also adversely affect physiological functions of many cellular proteins, predisposing the endothelial cells toward inflammation and cell death [26,27]. In addition, high ROS levels also induce uncoupling of the NO generating enzyme endothelial nitric oxide synthase (eNOS), further jeopardizing the vascular functions [28]. Given the critical roles played by NO and its alterations observed under oxidative stress, regulation of ROS levels is a key area for enhancing or maintaining normal endothelial functions.

3.2. Antioxidant bioactive peptides

Recently, antioxidant peptides derived from hydrolysis of food proteins such as those from milk, egg, meat, wheat and soy have been reported [29–34]. Most peptides were characterized based on either radical-scavenging activity or metal-chelating activity; however, all these chemical assays are performed under cell-free *in vitro* conditions, making it impossible to extrapolate the results to *in vivo* situations [35]. Hence it is of great importance to evaluate the bioactivity of antioxidant peptides under physiological conditions to establish their protective roles in diseases. To date, only a limited number of studies have evaluated the role of antioxidant peptides under physiologically relevant conditions.

For example, glutathione (GSSH), was found to reverse the impaired relaxation of aortas from spontaneously hypertensive rats (SHR) to acetylcholine; an effect which was of comparable magnitude to other antioxidants such as aminotriazole and ascorbic acid, when given intraperitoneally at the same dose [36]. The effect of GSSH was also observed in human subjects, particular with vascular dysfunction [37,38]. Data from our laboratory have shown antioxidant properties of egg derived peptides Ile-Arg-Trp and Ile-Gln-Trp which may contribute toward their anti-hypertensive and vasorelaxant effects observed in animal studies as described later [39,40]. Milk derived peptides with antioxidant activity can improve vascular function and reduce blood pressure although additional mechanisms such as modulation of vasoactive factors are likely to contribute toward the observed beneficial effects [29].