Peptides 67 (2015) 64–73

Contents lists available at ScienceDirect

Peptides

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

Review

Soluble elastin peptides in cardiovascular homeostasis: Foe or ally

Zhenyu Qin*

Division of Vascular Surgery, Department of Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

ARTICLE INFO

Article history:
Received 24 February 2015
Received in revised form 4 March 2015
Accepted 9 March 2015
Available online 17 March 2015

Keywords:
Elastin
Peptide
Cardiovascular diseases

ABSTRACT

Elastin peptides, also known as elastin-derived peptides or elastokines, are soluble polypeptides in blood and tissue. The blood levels of elastin peptides are usually low but can increase during cardiovascular diseases, such as atherosclerosis, aortic aneurysm and diabetes with vascular complications. Generally, elastin peptides are derived from the degradation of insoluble elastic polymers. The biological activities of elastin peptides are bidirectional, e.g., a pro-inflammatory effect on monocyte migration induction vs. a protective effect on vasodilation promotion. However, recent in vivo studies have demonstrated that elastin peptides promote the formation of atherosclerotic plaques in hypercholesterolemic mice and induce hyperglycemia and elevations in plasma lipid levels in fasted mice. More important, the detrimental effects induced by elastin peptides can be largely inhibited by genetic or pharmacological blockade of the elastin receptor complex or by neutralization of an antibody against elastin peptides. These studies indicate new therapeutic strategies for the treatment of cardiovascular diseases by targeting elastin peptide metabolism. Therefore, the goal of this review is to summarize current knowledge about elastin peptides relevant to cardiovascular pathologies to further delineate their potential application in cardiovascular disease.

Contents

Abbreviations: α-EPs, alpha-elastin peptides; κ-EPs, kappa-elastin peptides; CS, chondroitin sulfate; DANA, 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid; EBP, elastin binding protein; EPs, elastin peptides; MMP, matrix metalloprotease; TIMP, tissue inhibitors of matrix metalloproteinase; VSMCs, vascular smooth muscle cells.

* Correspondence to: Department of Surgery, Vascular Surgery Division, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, United States. Tel.: +1 210 567 5741; fax: +1 210 567 1762.
E-mail address: qinz@uthscsa.edu

http://dx.doi.org/10.1016/j.peptides.2015.03.006
0196-9781/

Introduction

Elastin is a highly polymerized insoluble protein in the extracellular matrix, and elastic laminae are major structures of the blood vessels that confer elasticity to the extracellular matrix. Elastic laminae are composed of insoluble polymers; the polymer precursor, tropoelastin, is a 72-kDa hydrophobic protein that is soluble in salt solutions. Tropoelastin proteins bind to each other via covalent cross-linking beginning with the oxidative deamination of lysine residues by lysyl oxidase. Subsequently, specific cross-links, including desmosine and isodesmosine, develop via a spontaneous condensation reaction between four lysine/allysine residues. Elastin contains two types of sequence: alanine (Ala)-lysine (Lys)-rich regions (cross-link region) and glycine (Gly)-valine (Val)-proline (Pro)-rich regions (hydrophobic region). In addition, fibrillins, fibulins and microfibril-associated glycoproteins are structurally associated with and may communicate with elastic laminae. Overall, hydrophobicity and cross-linking contribute to the long-lasting property of elastic laminae, which exhibit minimal discernible degradation in healthy adult vessels, with an estimated biological half-life of 70 years [93,94].

The degradation of elastic laminae leads to the release of elastin peptides (EPs), which are a group of soluble elastic polypeptides in blood and tissue. EPs are also called elastin-derived peptides or elastokines. This review will not discuss the preparation and pharmacological properties of EPs because Robert and Labat-Robert elegantly provided this information in their recent focus on kappa EPs (κ-EPs) [82]. Additionally, basic information on the immunity of EPs during aging is not included because it is available in a comprehensive review by Fulop et al. [27]. Rather, we focus on the metabolism (generation and maintenance), biological activities and pathogenesis of EPs and the concept of an elastin receptor complex, with special emphasis on factors that are relevant to cardiovascular homeostasis. For this task, a representative, although not exhaustive, review of the literature was conducted to illustrate a conceptual framework of EPs to facilitate more advanced investigation.

Generation of EPs

Insoluble elastin can be digested by a subset of proteases that contain elastolytic activity, known as elastases. Elastases from the serine protease, cysteine protease and metalloprotease families have profound implications on cardiovascular homeostasis and will be discussed in this section.

Serine proteases

Serine proteases utilize serine as the nucleophilic amino acid at their active site and comprise two superfamilies, chymotrypsin (trypsin) and subtilisin. Neutrophil elastase (also called leukocyte elastase), cathepsin G and proteinase 3 are members of the chymotrypsin superfamily; these proteases represent the three major serine elastases with cleavage site specificities of Ala, Gly and Val at P_1 [35] and have a similar ability to release bioactive EPs [35]. All three are stored in cytoplasmic azurophilic granules of neutrophils and act either intracellularly within phagolysosomes to digest phagocytized microbes or extracellularly to hydrolyze a group of matrix components, including elastin. These proteases are also expressed in monocytes and mast cells. Moreover, their activities are regulated by endogenous inhibitors in the serpin, chelonianin and microglobulin families [52]. One recent study by Wagsater et al. demonstrated that the overexpression of serpinA3 in transgenic mice reduced the activity of cathepsin G and neutrophil elastase but did not influence the development of atherosclerosis or calcium chloride-induced aneurysm formation [106].

An intriguing question is whether different elastases contribute equally to elastolysis [90]. Using a well-defined procedure to isolate the pure and intact elastin from human skin, Schmelzer et al. [90] revealed that neutrophil elastase was unable to degrade intact elastin fibers but hydrolyzed elastin from the aged skin, whereas cathepsin G cleaved all elastin samples, including those from younger skin. Thus, neutrophil elastase appears dispensable for elastolysis but promotes further breakdown of elastic fibers after the initial action of other elastases, such as cathepsin G [90]. A similar mechanism likely applies to the elastin from aorta or lungs.

Cysteine proteases

Cysteine proteases utilize a nucleophilic cysteine thiol in a catalytic triad. Cathepsins K, L, S and V are potent elastases [22,80,109]. These cathepsins are primarily located in lysosomes in reducing and slightly acidic environments and may also be released into the cytosol or secreted into the extracellular milieu [22]. Endogenous inhibitors for cysteine proteases include stefins, cystatin and kininogens, serpins and α2 macroglobulin [22]. Studies have revealed two steps in the kinetics of cathepsin binding to insoluble elastin: an initial non-catalytic adsorption on the elastin surface followed by rearrangement to form a catalytically competent complex [72]; thus, cathepsins may use certain non-catalytic surface structures to facilitate substrate binding, such as two