Elabela: novel perspectives on vascular physiology and disease

Hendrianus, Suko Adiarto, Radityo Prakoso

Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Indonesia, National Cardiovascular Center Harapan Kita, Jakarta, Indonesia

Abstract

Recently, a novel endogenous ligand of APJ called elabela has been identified to play an important role in cardiovascular development. Elabela and its G-protein-coupled receptor APJ are widely expressed throughout the human body. These have been identified to play a significant role in diverse biological processes, especially in the normal and pathological cardiovascular systems. In addition, increasing evidence indicates that elabela is also intimately associated with a large number of vascular physiological processes in adulthood, such as angiogenesis, vascular tone and atherosclerosis. However, a comprehensive summary of elabela in the vascular system has not been reported to date. In this review, we provide an overview of elabela in vascular physiology and diseases. Collectively, elabela, a potential biomarker and therapeutic peptide, exerts diverse biological vascular effects in adults.

Key words: elabela; APJ; vascular system; apelin

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Introduction

Elabela, also known as Toddler, is a newly discovered peptide hormone that had been detected in the vascular endothelium and plasma in adults [1, 2]. Elabela shares the same receptor (APJ) and displays a similar profile with apelin which has been confirmed to be associated with vascular physiology and diseases [3]. Previous studies have suggested that elabela has the potential to protect the human body against a wide range of cardiovascular diseases. However, the specific role and mechanism through which elabela regulates blood vessels are still being intensively investigated, with most researchers using previous studies made on Apelin for guidance. To the extent of currently available studies, in addition to heart disease, the elabela-APJ axis is also expected to become a promising biomarker and therapeutic avenue for vascular diseases [4]. Thus, a comprehensive understanding of the manner in which elabela affects the vascular system is necessary. This review outlines the present state of knowledge regarding the role of elabela and its interaction with APJ in physiology and the pathology of the vascular system.

APJ and apelin

APJ or angiotensin receptor-like 1, which shares 54% sequence similarity in its transmembrane domain to the angiotensin II type 1 receptor (AT1), was discovered in 1993 by O'Dowd et al. during a search conducted for vasopressin receptors [5]. APJ belongs to the class A G-protein-coupled re-

Address for correspondence: Hendrianus, MD, Department of Cardiology and Vascular Medicine, Faculty of Medicine Universitas Indonesia, National Cardiovascular Center Harapan Kita, Jakarta, Indonesia; email: hendrianusthe@yahoo.com

ceptor (GPCR) family. The APJ gene is located on chromosome 11, which encodes 377 amino acids [5]. Despite its similarities to AT1, APJ cannot be activated by angiotensin II, and it was thought to have no ligand to bind it until the discovery of apelin in 1998 by Tatemoto et al. [5, 6]. The discovered ligand was named, apelin, which is abbreviated from APj Endogenous LIgaNd. The apelin gene is located on chromosome 10 that encodes a 77-amino acid precursor peptide apelin, and the mature peptide consists of apelin-36, apelin-17, apelin-13, and apelin-12. Apelin-13 can undergo cyclization of the glutamine at its N terminus to produce pyroglutamyl-apelin-13 (pyr-apelin-13) [7]. Among these peptides, apelin-13 and [pyr]-apelin-13 are identified as the more predominant and potent isoforms in the human cardiovascular system and plasma [6, 8]. Both apelin and APJ are expressed in various tissues, such as the heart, vascular endothelium, central nervous system, kidney, liver, retina, skin, adipose tissue and mammary glands. The apelin-APJ signaling pathway carries out a wide range of functions in the cardiovascular system. The addition of an exogenous apelin has also shown beneficial cardiovascular effects in animal models with hypertension, pulmonary arterial hypertension (PAH), atherosclerosis, myocardial infarction and heart failure [9]. In addition, the apelin-APJ axis also induces an important vascular-specific physiological effect, including vasomotor tone such as vasodilatation and vasoconstriction, and vascular stabilization, such as angiogenesis, proliferation and permeability [3].

Discovery of elabela

Various studies display the possible existence of another ligand for APJ, owing to the discrepancies between apelin and APJ mutations. APJ is detected early during gastrulation and throughout the subsequent development stages [10]. On the other hand, apelin expression only initiates at the end of gastrulation [11]. More than half of the mice embryos lacking APJ died in the uterus due to cardiovascular developmental defects or growth retardation [12]. Nevertheless, there was no deficiency in the early embryonic development of mice-lacking apelin, which are alive with normal development [13, 14]. These studies indicated that APJ may have another unknown ligand, which is later identified by two different research groups as the new endogenous peptide ligand for APJ called elabela [1, 2]. The gene that is encoding the peptide was named APELA (apelin receptor early endogenous ligand) by the HUGO Gene Nomenclature Committee. The elabela gene contains three exons and is located on chromosome 4 that had been considered a non-coding RNA region until the open reading frame was identified in 2013 [1]. The human elabela is a peptide of 54 amino acid peptides consisting of the signal peptide and a 32-amino-acid mature peptide (elabela-32). Elabela may generate several fragments and can be further processed into elabela-22 or elabela-11 (Fig. 1). The mature elabela binds to the APJ to become biologically active [15]. Since elabela is a recent discovery, it was thought to be expressed exclusively

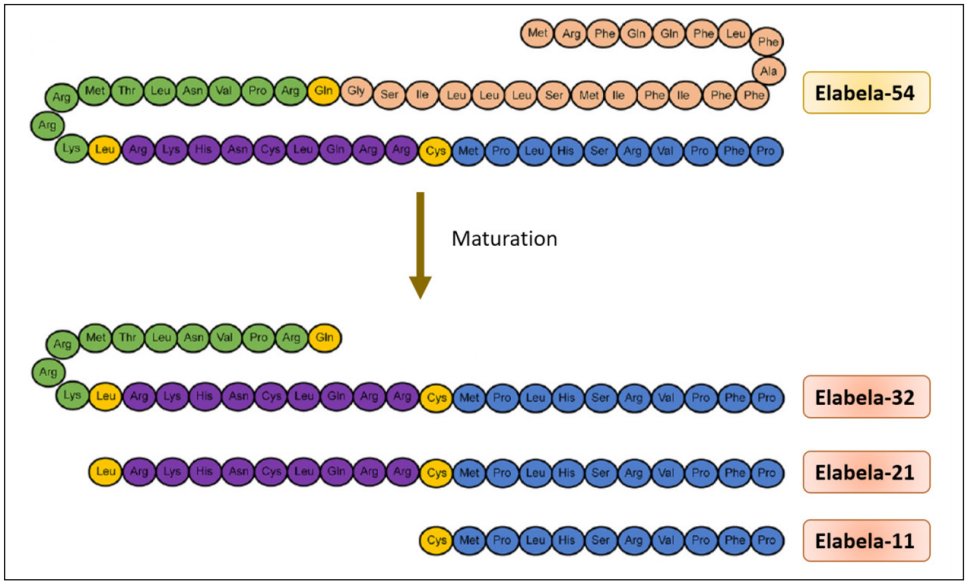

Figure 1. The amino acid sequence of different forms of elabela. The conserved C-terminal of elabela is important for signaling and binding. Those identical in all peptides are shown in blue

in the kidney, in contrast to the wide tissue distribution of Apelin and APJ [27, 32]. However, recent studies showed that the elabela expression was also detected in the cardiovascular system mainly localized to noncardiomyocytes, especially endothelial cells and fibroblasts [16]. In the vascular system, the expression of elabela in the arteries is higher than that in the veins [17]. Recent studies of elabela knockdown mice provide insight into the previously observed differences between the developmental phenotypes of the apelin and APJ null mice [12, 13]. Elabela is highly expressed during gastrulation and the phenotype of elabela knockdown in zebrafish is similar to the phenotype of APJ mutants [2, 18]. Furthermore, elabela is also substantially secreted by the human embryonic stem cells (hESCs) that do not express APJ, thereby indicating that APJ is not the only cell-surface receptor for elabela [19].

Elabela in blood vessel regulation

In addition to its presence in the mammalian cell types including human pluripotent stem cells, Wang et al. showed that elabela was able to perform functions in adult cell types and tissues [20], It is not only functional but also altered in the diseased state (Tab. 1). Elabela is expressed in the endothelial cells of the heart and various blood vessels and also circulates in the blood [16, 17]. Similar to apelin which exerts vasodilatory and hypotensive actions, elabela infusion also downregulates the blood pressure levels in mice [21]. A simultaneous addition of angiotensin II and elabela in rats can significantly suppress the effect of increasing angiotensin II, which controls arterial vasoconstriction and regulates the mean arterial blood pressure [22]. In addition, an overexpression of elabela in the heart of high-salt diet-feeding mice by a single intravenous injection of the adeno-associated virus serotype 9 (AAV9) vector can reduce the increase in blood pressure [23]. Elabela also possesses vasodilatory property, which effectively improves myocardial blood supply to mitigate the impairment due to myocardial ischemia [16]. In addition, elabela induces the relaxation of the aorta through the activation of APJ in mice [20]. In a case-control study conducted by Li et al., circulating elabela concentrations are reduced in patients with essential hypertension compared to normotensive subjects [11]. Consistent with this finding, the serum levels of elabela are significantly decreased in preeclamptic women. Elabela but not apelin knockout pregnant mice exhibit preeclampsia-like symptoms, including an elevated blood pressure that could be normalized by infusion of recombinant elabela [22]. The diastolic effect of elabela is independent of nitric oxide, which is in contrast to apelin [20]. The extracellular signal-regulated kinase (ERK) pathway, which causes excessive vasoconstriction, is enhanced in the cardiovascular system in various models of hypertension. Elabela can exert an antihypertensive effect by suppressing ERK activation [20].

PAH is a disease of the small pulmonary arteries characterized by vascular proliferation and remodeling. Consequently, the progressive increase in

Table 1. The regulatory roles of elabela in the vascular system

Reference	Experimental model	Experimental intervention	Effects
Deng et al. (2015) [27]	Rats	Elabela	↑ Diuresis and water intake
Santoso et al. (2015) [28]	Rats	Intracerebroventricular elabela injection	↑ Arginine vasopressin
Wang et al. (2015) [20]	Human umbilical vascular endothelial cells	Elabela	↑ Angiogenesis
	Mice	Elabela	↑ Aortic expansion
Schreiber et al. (2017) [23]	Rats with hypertension	AAV9 vector injection	↑ Elabela expression
Yang et al. (2017) [17]	Patients and rats with PAH	–	↓ Elabela expression
	Rats with PAH	Elabela	↓ Pulmonary artery remodeling
Sato et al. (2017) [22]	Mice	Elabela	↓ Angiotensin II ↓ Blood pressure
Li et al. (2019) [29]	Patients with essential hypertension	–	↓ Elabela
Yavuz et al. (2020) [30]	Patients with coronary artery disease	–	↓ Elabela
Kaplan et al. (2021) [31]	Patients with LEAD	–	↓ Elabela

AAV9 — adeno-associated virus serotype 9; LEAD — lower extremity arterial disease; PAH — pulmonary arterial hypertension

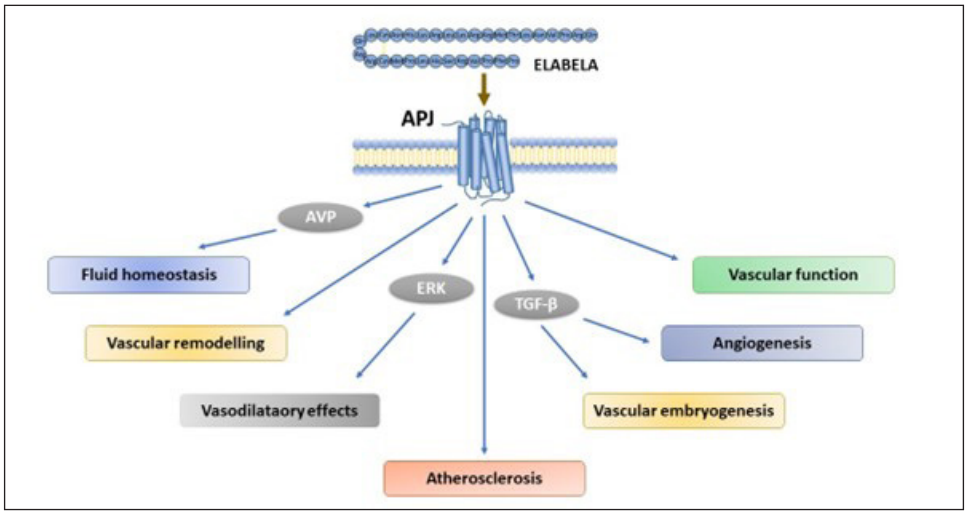

Figure 2. The elabela–APJ axis plays a variety of pathophysiological roles in the vascular system. AVP — arginine vasopressin; ERK — extracellular signal-regulated kinase; TGF-β — transforming growth factor beta

pulmonary vascular resistance induces right-sided heart failure [24]. It has been shown that patients with PAH have lower plasma apelin levels than controls [25]. Moreover, some researchers attribute PAH to the loss of apelin [26]. Similar to apelin, an elabela expression is also reduced in patients with PAH and rodent models of PAH [17]. Furthermore, an exogenous elabela infusion in mice can improve pulmonary vascular remodeling and right ventricular cardiomyocyte hypertrophy in PAH [17]. Future studies of the elabela agonist would provide novel evidence for an additional therapeutic regimen of PAH.

Elabela may also exert an antihypertension effect by affecting fluid homeostasis by increasing diuresis and water intake in adult rats [20]. Elabela regulates fluid homeostasis through a central mechanism in the brain seen with an intracerebroventricular injection of elabela that activates arginine vasopressin [27], as well as a peripheral mechanism in the kidney by binding to APJ to activate Gi signaling [28]. Recent *in vivo* studies also indicate that elabela affects vascular function and damage. Li et al. discovered that elabela is associated with the deterioration of endothelial function as assessed by flow-mediated dilation [29]. In a first study, which is currently under publication, we the authors and colleagues have found that low elabela concentrations are associated with subclinical atherosclerosis as characterized by increased carotid intima-media thickness. Elabela increases myocardial contractility and causes coronary vasodilation at the nanomolar level; it is more effective than Apelin at performing these functions [22]. In coronary artery disease, Yavuz et al. found that there was a decrease in elabela concentrations in patients with chronic total occlusion of the coronary arteries and those with poor collateral development [30]. In patients with a lower-extremity arterial disease, the serum elabela levels are positively correlated with WIfI (Wound, Ischemia, foot Infection) amputation risk score and negatively correlated with ankle-brachial index [31]. From what has been discussed above, it can be established that elabela is a promising peptide that mediates a wide range of physiological and pathological processes of the vascular system and should be examined in future research.

Conclusion

In summary, the newly identified ligand of APJ, elabela, plays a vital role in the regulation of the vascular system during adulthood, including blood pressure and vascular tone, vascular function and atherosclerosis (Fig. 2). The biological roles and mechanisms of elabela and APJ should be further explored, as it will lead to a promising novel therapeutic approach against vascular diseases and also provide a better understanding of the pathogenesis and pathophysiology of the diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical standards

The manuscript does not contain clinical studies or patient data.

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