Targeting the elabela/apelin–apelin receptor axis as a novel therapeutic approach for hypertension

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Abstract
Hypertension is the leading risk factor for global mortality and morbidity and those with hypertension are more likely to develop severe symptoms in cardiovascular and cerebrovascular system, which is closely related to abnormal renin–angiotensin system and elabela/apelin–apelin receptor (APJ) axis. The elabela/apelin–APJ axis exerts essential roles in regulating blood pressure levels, vascular tone, and cardiovascular dysfunction in hypertension by counterbalancing the action of the angiotensin II/angiotensin II type 1 receptor axis and enhancing the endothelial nitric oxide (NO) synthase/NO signaling. Furthermore, the elabela/apelin–APJ axis demonstrates beneficial effects in cardiovascular physiology and pathophysiology, including angiogenesis, cellular proliferation, fibrosis, apoptosis, oxidative stress, and cardiovascular remodeling and dysfunction during hypertension. More importantly, effects of the elabela/apelin–APJ axis on vascular tone may depend upon blood vessel type or various pathological conditions. Intriguingly, the broad distribution of elabela/apelin and alternative isoforms implicated its distinct functions in diverse cardiac and vascular cells and tissues. Finally, both loss-of-function and gain-of-function approaches have defined critical roles of the elabela/apelin–APJ axis in reducing the development and severity of hypertensive diseases. Thus, targeting the elabela/apelin–APJ axis has emerged as a pre-warning biomarker and a novel therapeutic approach against progression of hypertension, and an increased understanding of cardiovascular actions of the elabela/apelin–APJ axis will help to develop effective interventions for hypertension. In this review, we focus on the physiology and biochemistry, diverse actions, and underlying mechanisms of the elabela/apelin–APJ axis, highlighting its role in hypertension and hypertensive cardiovascular injury and dysfunction, with a view to provide a prospective strategy for hypertensive disease therapy.

Keywords: Elabela; Apelin; APJ; Hypertension; Renin–angiotensin system

Introduction
Hypertension, a clinical syndrome characterized by increased systemic arterial blood pressure, has a severe impact on population health.¹ Hypertension is the primary risk factor for cardiovascular diseases, such as heart failure, atrial fibrillation, chronic kidney disease, and peripheral vascular disease.¹⁰ Numerious studies that focused on the pathogenesis and clinical treatment of hypertension have been conducted recently. The apelin receptor (APJ) is involved in numerous processes within the cardiovascular system. Its agonists are considered as therapeutic agents to modulate cardiovascular homeostasis.¹¹ Previously, apelin was believed to be the only ligand for APJ, while a newly discovered endogenous peptide ligand called elabela has been expected to become a biomarker and drug for cardiovascular disease.¹² Elabela, apelin, and APJ are widely expressed in human and rat cardiovascular system. The elabela/apelin–APJ axis exerts various important functions, including vascular tone regulation, heart contraction, angiogenesis, endoderm differentiation, and heart morphogenesis.¹³ Therefore, a comprehensive understanding of the effects of elabela/apelin–APJ axis on development and diseases of the cardiovascular system is critical. This review outlines recent advances with respect to the roles of elabela/apelin–APJ axis in the physiology and pathology of the cardiovascular system, as well as its possible functional mechanisms.

Physiology and biochemistry of the elabela/apelin–APJ axis
APJ, a G-protein coupled receptor composed of an APLNR gene, was first discovered in 1993⁴ and conserved in various species such as humans, monkeys,
chimpanzees, rats, and mice.\cite{5} APJ was initially conceived to be an orphan receptor, and does not bind to angiotensin II (Ang II), although it has 31% homology with angiotensin II type 1 receptor (AT1R). Apelin, a secreted protein extracted from a bovine stomach in 1998 and mapped to band q25–26.1 of chromosome X, was the first identified ligand for APJ. The apelin gene encodes a precursor peptide of 77 amino acids, which is cleaved into active fragments of 12–36 amino acids,\cite{6} such as apelin-36, apelin-17, apelin-13, and pyroglutamate (pyr)-apelin-13 [Table 1].\cite{6} All of the active fragments possess similar functions but display different tissue distribution, potency, and receptor binding affinity. Pyr1-apelin 13, with cyclized glutamine at the N-terminal residues and a longer half-period than apelin-13, is the predominant isoform in plasma and heart and functions as a potent cardiovascular protective factor.\cite{8}

Interestingly, investigators found differences in growth, development, and cardiac phenotypes between apelin knockout (KO) and APJ KO mice, implying that the existence of another endogenous ligand for APJ with biological action was earlier than that of apelin. Subsequently, two independent research teams identified a short-secreted peptide that binds to APJ and named it elabela/Toddler.\cite{9,10} The gene AK092578, which encodes the elabela protein, is a non-coding RNA located on chromosome 4.\cite{4} The precursor peptide of elabela consists of 54 amino acids and is highly conserved in mammals. Elabela-54 is cleaved to generate a mature elabela-32 peptide with two conserved di-arginine motifs, resulting in further processing into elabela-21 or elabela-11 by furin-like endopeptidase [Table 1].\cite{10} Different elabela isoforms may have different functions, of which elabela-32 is the most studied at present.

However, evidences indicate that apelin and elabela may not bind to APJ in the same way. Structure–activity relationship studies revealed that C-terminal moiety (Arg28, Val29, Pro30, Phe31, and Pro32) and His26 residues of elabela were most important for receptor binding,\cite{11} whereas the key pharmacophores (Arg2, Pro3, Arg4, and Leu5) of apelin-13 are primarily located at the N-terminal. A regulatory role for elabela/apelin–APJ axis has been shown in cardiovascular physiology and pathophysiology, thus making it a potential target for cardiovascular drug discovery.

### The elabela/apelin–APJ axis and blood pressure regulation

To gain further insight into the relevance of elabela/apelin–APJ axis in blood pressure regulation, investigators have examined the expression of the axis in both patients with hypertension and animal models of hypertension. The results point to a critical role of elabela/apelin–APJ axis in regulating vascular tone during the development of hypertension, indicating predictive and therapeutic value of elabela/apelin–APJ axis in hypertension. Notably, a marked decrease in circulating elabela and apelin levels were observed in patients with essential hypertension and general hypertension [Table 2].\cite{12,13} In addition, elabela has been demonstrated to cause vasodilation in coronary arteries\cite{14} to reverse vasopressor responses during pulmonary arterial hypertension and Ang II-induced hypertension [Table 2].\cite{15,16} Moreover, continued elabela treatment and elabela gene therapy effectively delayed elevation of blood pressure levels in hypertensive rats [Table 2].\cite{17} Mechanistically, elabela-induced relaxation in isolated mouse aorta could not be abolished in the presence of nitric oxide (NO) synthase inhibitor (ng-nitro-l-arginine methyl ester [L-NAME]), suggesting a NO-independent mechanism in the relaxation response to elabela.\cite{18} As a result, the specific mechanisms following elabela activation warrant detailed investigation in future studies in the context of hypertension.

### Table 1: Amino acid sequence and distribution of apelin and elabela isoforms.

<table>
<thead>
<tr>
<th>Identity</th>
<th>Amino acid sequence</th>
<th>Expressed tissue</th>
</tr>
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<tbody>
<tr>
<td>Apelin-77</td>
<td>MNLRLCQVQALLLLLWLSLTAVCGGSLMPLPDGNGLEDGNNLVRQGRNRPGPWQGRRKFRRQRPRLSHKGPMF</td>
<td>Vascular endothelial; Central nervous system</td>
</tr>
<tr>
<td>Apelin-36</td>
<td>LVQPRGSRNPGPWQGRRKFRRQRPRLSHKGPMF</td>
<td>Mammary gland</td>
</tr>
<tr>
<td>Apelin-17</td>
<td>FRRQPRLSHKGPMF</td>
<td>Heart; Lung; Kidney</td>
</tr>
<tr>
<td>Pyr-apelin-13</td>
<td>̂ERPRLSHKGPMF</td>
<td>Limbs; Retina; Liver; Skin</td>
</tr>
<tr>
<td>Apelin-13</td>
<td>RPRLSHKGPMF</td>
<td></td>
</tr>
<tr>
<td>Elabela-54</td>
<td>MRFQQLFAFFFFMSSLLISSGQPRVNPRTLTMRRKLKHNCLRCCNLQRRCMPLHSRVPFP</td>
<td>Pluripotent stem cells</td>
</tr>
<tr>
<td>Elabela-32</td>
<td>QRPVNLTMRRKLKHNCLRQRCMPLHSRVPFP</td>
<td>Heart; Lung</td>
</tr>
<tr>
<td>Elabela-21</td>
<td>RKHNCLRQRCMPLHSRVPFP</td>
<td>Placenta; Kidney</td>
</tr>
<tr>
<td>Elabela-11</td>
<td>MPLHSRVPFP</td>
<td></td>
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*E represents pyroglutamate (Pyr).*
Intraperitoneal injection of apelin has been implicated in downregulation of both systolic and diastolic pressure levels in anesthetized normotensive animals [Table 2].\[19\] Shortly thereafter, intravenous administration of apelin was shown to cause hypotensive effects\[20\] and venodilation.\[21\] Apelin administration increased NO production in hypertensive mice and rats. \[22,23\] The blood pressure-lowering effects of apelin were blocked by L-NAME. The studies revealed that apelin inhibited the calcification of vascular smooth muscle cells (VSMCs)\[24,25\] and abrogated abnormal Ang II-induced contractile in intra-renal arteries from diabetic mice through increasing phosphorylation of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/endothelial nitric oxide synthase (eNOS) signaling [Figure 1 and Table 2].\[25\] These findings suggested that apelin promotes vasodilation via a NO-dependent mechanism. Moreover, apelin promotes vasodilation via a prostanoid-dependent mechanism, as apelin administration promotes vasodilation in human mammary arteries, and this vasodilation can be abolished by cyclooxygenase inhibitor.\[26,27\]

<table>
<thead>
<tr>
<th>Experimental model/population</th>
<th>Experimental intervention</th>
<th>Effects</th>
<th>References</th>
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<tbody>
<tr>
<td>Patients with essential hypertension</td>
<td>–</td>
<td>↓Circulating elabela levels</td>
<td>[12]</td>
</tr>
<tr>
<td>Ang II-induced hypertensive mice</td>
<td>Elabela</td>
<td>↓Blood pressure levels</td>
<td>[16]</td>
</tr>
<tr>
<td>High-salt diet-induced hypertensive rats</td>
<td>Elabela</td>
<td>↓Blood pressure levels</td>
<td>[17]</td>
</tr>
<tr>
<td>Anesthetized normotensive animals</td>
<td>Apelin</td>
<td>↓Blood pressure levels</td>
<td>[19]</td>
</tr>
<tr>
<td>Diabetic mice</td>
<td>Apelin</td>
<td>↓Intrarenal arteries constriction</td>
<td>[24,25]</td>
</tr>
<tr>
<td>Hypertensive rats</td>
<td>Elabela-32</td>
<td>↓Blood pressure levels</td>
<td>[28]</td>
</tr>
<tr>
<td>Hypertensive rats</td>
<td>–</td>
<td>↓AP[3,23] mRNA and protein</td>
<td>[32,33]</td>
</tr>
<tr>
<td>Conscious sheep</td>
<td>Apelin</td>
<td>↑Blood pressure levels</td>
<td>[38]</td>
</tr>
<tr>
<td>Conscious rats</td>
<td>Apelin</td>
<td>↑Peripheral vascular resistance</td>
<td>[49]</td>
</tr>
<tr>
<td>Hypertensive rats with ADMA-damaged endothelial barrier</td>
<td>Apelin 13</td>
<td>↑Vasoconstriction</td>
<td>[39,40]</td>
</tr>
<tr>
<td>ICR mice</td>
<td>Apelin</td>
<td>↑Blood pressure levels</td>
<td>[41]</td>
</tr>
<tr>
<td>Normotensive rats</td>
<td>Apelin</td>
<td>↑Blood pressure levels</td>
<td>[45,46]</td>
</tr>
<tr>
<td>Rats’ aortic adventitial fibroblasts</td>
<td>Elabela</td>
<td>↓Apoptosis</td>
<td>[51]</td>
</tr>
<tr>
<td>Rats with pulmonary hypertension</td>
<td>Elabela</td>
<td>↓Right ventricular systolic pressure levels</td>
<td>[52]</td>
</tr>
<tr>
<td>Elabela KO mice</td>
<td>Elabela</td>
<td>↓Blood pressure levels</td>
<td>[54]</td>
</tr>
<tr>
<td>Patients with essential hypertension</td>
<td>–</td>
<td>↓Circulating apelin levels</td>
<td>[55]</td>
</tr>
<tr>
<td>Patients with aortic valve stenosis</td>
<td>–</td>
<td>↓Apelin</td>
<td>[56]</td>
</tr>
<tr>
<td>Patients with end-stage heart failure</td>
<td>Apelin-13</td>
<td>Improvement of cardiac dysfunction</td>
<td>[57]</td>
</tr>
<tr>
<td>VSMCs</td>
<td>Apelin-13</td>
<td>↑VSMC cell cycle</td>
<td>[60,61]</td>
</tr>
<tr>
<td>PASMCs</td>
<td>Apelin</td>
<td>↑VSMC proliferation</td>
<td>[62]</td>
</tr>
<tr>
<td>ApoE KO mice</td>
<td>Apelin</td>
<td>↑Jagged-1/Notch3</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑Pro-BNP</td>
<td>[56]</td>
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<td></td>
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<td>↑Pro-BNP</td>
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</tbody>
</table>
| ADMA: Asymmetric dimethylarginine; AKT: Protein kinase B; Ang II: Angiotensin II; APJ: Apelin receptor; ERK: Extracellular signal-regulated kinase; ICR: Institute of Cancer Research; KO: Knock out; mTOR: Mammalian target of rapamycin; NO: Nitric oxide; PASMCs: Pulmonary arterial smooth muscle cells; PI3K: Phosphatidylinositol 3-kinase; Pro-BNP: Pro-brain natriuretic peptide; RAS: Renin-angiotensin system; VSMCs: Vascular smooth muscle cells.

The renin–angiotensin system (RAS) is a key pathway in the development and progression of hypertension. It has been reported that administration of exogenous elabela-32 significantly lowered systolic blood pressure levels in hypertensive rats, accompanied with a reduction of Ang II and prorenin/renin excretion, supporting the antagonistic interaction between elabela and intra-renal RAS [Table 2 and Figure 2].\[28\] Apelin-induced vasodilation and depressor responses are preserved during RAS activation both in healthy humans and in patients with heart failure.\[3\]
Furthermore, activation of the elabela/apelin–APJ axis has an antagonistic effect toward AT1R-mediated responses, either by forming heterodimers with the receptor or by increasing NO-dependent signaling [Figure 2]. APJ is often co-expressed with AT1R and functions as an endogenous counter-regulator in the blood vessel wall. Both mRNA and protein levels of APJ were reduced in heart, kidney, and aorta of hypertensive rats [Table 2]. APJ can form heterodimers with bradykinin receptors, neurotensin receptor-1, and κ-opioid receptors, all of which are involved in cardiovascular regulation and all of whose ligands are sensitive to angiotensin-converting enzyme 2 (ACE2) proteolysis, implying that homodimers–oligomers of APJ could possibly mediate different signaling events in comparison to APJ monomers.

Most available evidences indicate that apelin plays a significant role in lowering blood pressure in hypertensive animal models. Nonetheless, several studies have reported the effect of systemic administration of apelin on blood pressure elevation. For instance, a brief initial decrease in arterial pressure was observed after intravenous administration of apelin in conscious sheep, followed by increased arterial pressure and peripheral vascular resistance [Table 2]. The biphasic hemodynamic response is possibly related to the use of high-dose apelin, and to the compensatory response caused by the rapid decrease in blood pressure. Apelin may also cause concentration-dependent vasoconstriction in isolated caudal arteries when endothelial cells are damaged by asymmetric dimethylarginine [Table 2]. In L-NAME-treated mice, apelin has been found to induce elevated levels of systolic blood pressure by activating APJ on VSMCs, while endothelial cells are dysfunctional. Based on the vascular bed and underlying conditions, apelin may cause either vasodilation or vasoconstriction. These dual actions of apelin are attributed to the presence of APJ in both the endothelial and smooth muscle cell layers of blood vessel walls and the integrity of endothelial cells. Notably, apelin-mediated vasoconstriction was significantly elevated in the presence of an α1-adrenergic receptor (α1-AR) agonist while it was significantly decreased in APJ-overexpression but α1-AR-deficient mice. These results indicate that the interaction between APJ and α1-AR is an important and complex mechanism contributing to vasoconstriction. However, the molecular mechanisms underlying apelin-induced vasoconstriction are poorly understood, and the downstream signaling of heterodimerization between APJ and α1-AR merits further investigation.

In addition, apelin may act on the central nervous system to regulate peripheral vascular function. The increased expression of apelin gene was found in rostral ventrolateral medulla of spontaneously hypertensive rats. Overexpression of apelin in rostral ventrolateral medulla of normotensive rats was demonstrated to increase mean arterial blood pressure through nicotinamide adenine dinucleotide phosphate oxidase-dependent superoxide formation [Table 2]. Central apelin promotes vasoconstriction through increasing myosin light chain phosphorylation via Go/o-dependent activation of protein kinase C and Na+-Ca2+ exchange-dependent pathways.
Vasopressor responses to apelin have been observed following injection of the peptide into cardiovascular regulatory regions of the brain. Intracerebroventricular and intravenous administration of apelin caused a dose-dependent increase in mean arterial pressure, but the peripheral effects of apelin were relatively weak compared to its central effects, and central regulatory mechanisms of blood pressure are mainly related to the neurohormonal mechanism and sympathetic nervous system. The reason for these discrepancies of apelin in blood pressure regulation is unclear. However, possible explanations are as follows. The pressor response to intravenous injection of apelin may be related to the direct effect of apelin on the heart or peripheral sympathetic nervous system. Another possible explanation may be related to experiment conditions – as the injection is implemented in the context of no anesthesia, the blood pressure levels of rats will definitely increase under stress.

In addition, apelin inhibits NO-induced activation of large-conductance Ca²⁺-activated K⁺ channel (BKCa) channels in cerebral artery smooth muscle cells, which may be another mechanism leading to vasoconstriction. In intracerebroventricular administration, elabela binds and activates APJ, resulting in arginine vasopressin release and enhanced PI3K/AKT phosphorylation, consequently raising blood pressure, which may further cause cardiovascular remodeling.

The elabela/apelin–APJ axis and hypertensive cardiovascular injury

Consistent with its critical roles in blood pressure regulation, the elabela/apelin–APJ axis exhibits potent effects in the improvement of the development and severity of hypertensive diseases. Endogenous elabela levels were reduced in hypertensive patients associated with hypertension-related vascular damage. Intriguingly, in our previously published works, we revealed the Ang II-mediated apoptosis and autophagy imbalance in rat aortic adventitial fibroblasts, leading to vascular injury and remodeling, which could be dramatically reversed by pretreatment with elabela. We also found that higher plasma elabela levels had a better major adverse cardiac event-free survival of hypertensive patients with heart failure than those with lower plasma elabela levels, implying that decreased plasma elabela levels in hypertensive patients were closely associated with left ventricular systolic dysfunction. In a rat model of pulmonary hypertension, administration of exogenous elabela improves right ventricular systolic pressure levels and pulmonary vascular remodeling. Elabela deficiency promotes pre-eclampsia and cardiovascular malformations while exogenous elabela alleviates pre-eclampsia symptoms in elabela-deficient mice.

The role of apelin in the pathophysiology of hypertensive disease has also received considerable attention. Circulating apelin levels are reduced in essential hypertensive patients, and decreased apelin levels are independently associated with more profound cardiac dysfunction. Meanwhile, apelin levels were downregulated in patients with aortic valve stenosis in comparison to controls. Apelin has been revealed to restore declining heart function, which is consistent with the beneficial therapeutic effects of apelin.

In addition to causing a depressor response during renovascular hypertension via APJ-kappa-opioid receptor heterodimers, apelin-13 also remarkably accelerated the transition from G0/G1 to S phase during mitosis and stimulated VSMC proliferation via PI3K/AKT/extracellular signal-regulated kinase and Jagged-1/Notch3 signaling pathways. In contrast, apelin treatment reduces pulmonary VSMCs proliferation in hypoxic conditions via PI3K/AKT/mammalian target of rapamycin signaling pathways. Likewise, downregulation of apelin signaling during pulmonary hypertension is correlated with hyper-proliferation of pulmonary endothelial cells and smooth muscle cells. Apelin attenuated Ang II-induced contractions in pulmonary arteries from normoxic animals, but not in arteries from animals exposed to chronic hypoxia, implying the changes of the APJ in the signal transduction downstream.

Of note, apelin increases NO formation to quench superoxide-induced changes in the vascular wall, which eliminate Ang II-induced atherosclerosis in ApoE KO mice. The apelin–APJ axis increased ACE2 promoter activity in vitro and upregulated ACE2 expression in failing hearts in vivo, which could increase conversion of Ang II to Angiotensin I–7. In contrast to apelin, the elabela–APJ axis protects from pressure-overload–induced heart failure, possibly by suppressing ACE rather than ACE2.

Activation of the elabela/apelin–APJ axis exhibited beneficial effects in the context of endothelial dysfunction such as end-stage heart failure, atherosclerosis, and obesity. The elabela/apelin–APJ axis may be a mediator for atherosclerosis, as the apelin gene was upregulated in atherosclerosis plaques. Collectively, the elabela/apelin–APJ axis has multiple protective functions in hypertensive conditions through its involvement in regulation of VSMCs and endothelial cells; the regulation is complex and might change during different pathologic conditions. Therefore, the means to precisely modulate the axis so as to develop it in a beneficial direction needs to be determined.

Conclusion and perspective

Hypertension has been recognized as a main risk factor for worldwide mortality. There is a continuing need for potent medications to reduce mortality and improve patients’ adherence to the hypertension treatment. Administration of apelin or elabela typically results in marked reductions in systolic/diastolic blood pressure levels and increases in blood flow. The elabela/apelin–APJ axis exerts essential roles in regulating vascular tone by counterbalancing the action of the Ang II/AT1R axis and activating the eNOS/NO signaling. Furthermore, The elabela/apelin–APJ axis demonstrates beneficial effects in vascular physiology and pathophysiology, such as angiogenesis, cellular prolifera-
tion, fibrosis, apoptosis, oxidative stress, and cardiovascular remodeling and dysfunction. Intriguingly, the effects of the elabela/apelin–APJ axis on vascular tone may depend upon blood vessel type or various pathological conditions. More importantly, the broad distribution of elabela/apelin and alternative isoforms implicated its distinct functions in diverse cardiac and vascular cells and tissue types.

Although elabela/apelin–APJ axis plays critical roles in blood pressure regulation, the underlying mechanisms have not been fully elucidated. A growing number of studies are devoted to shed new light on the regulatory roles of the elabela/apelin–APJ axis in vascular physiology and pathophysiology. At present, many clinical trials are evaluating the potential benefits of elabela/apelin analogs and novel APJ agonists in treating various cardiovascular disorders. Therefore, novel and innovative pharmacological approaches and anti-hypertensive drugs are expected to be developed to achieve long-term blood pressure reduction, improve hypertensive organ damage in people with hypertension, and thus increase mortality and health care costs worldwide. Thus, targeting the elabela/apelin–APJ axis has emerged as a promising approach against progression of hypertension and hypertensive cardiovascular dysfunction.

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Conflicts of interest
None.

References


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