DERLEME REVIEW

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Vascular Functional Effects of the Apelinergic System

Apelinerjik Sistemin Vasküler Fonksiyonel Etkileri

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ABSTRACT The apelinergic system consists of apelin, elabela, and their common receptor apelin receptor (APJ). APJ is a G protein-coupled receptor. Apelin is the first discovered endogenous APJ ligand. Later, elabela was discovered and added to the system. Apelinergic system components have a widespread expression in the human body. The apelinergic system which plays a role in many physiological processes such as body-fluid homeostasis, energy metabolism, and regulation of cardiac contractility participates in the regulation of vascular tone and blood pressure. Apelin and elabela, which have similar effects on vascular tone, differ in their effect mechanisms. APJ is expressed in both vascular endothelial cells and vascular smooth muscle cells. This situation is important because it mediates the opposite effects in vascular tension. Apelin usually has a vasodilator effect through the activation of the endothelial nitric oxide synthase/nitric oxide (NO) pathway in physiological conditions. However, in the absence of a functional endothelium, apelin causes vasoconstriction. Elabela has a vasodilator effect similar to apelin, but it is thought that NO has no role in the vasodilator effect of elabela. When apelin and elabela are administered peripherally, they usually lower blood pressure and exhibit an antihypertensive effect. Therefore, the apelinergic system has great potential to develop alternative agents for the treatment of hypertensive diseases such as essential hypertension and pulmonary hypertension. The half-lives of apelin and elabela are quite short, and current studies have focused on developing longer-acting apelinergic analogs. In this review, we focused on the vascular functional effects and effect mechanisms of the apelinergic system.

Keywords: Apelin; vasodilation; vasoconstriction; hypertension; elabela

ÖZET Apelinerjik sistem apelin, elabela ve bunların ortak reseptörü apelin reseptörü (APJ)'nden oluşur. APJ, G-proteini kenetli bir reseptördür. Apelin, ilk keşfedilen endojen APJ ligandıdır. Daha sonra ise elabela keşfedilerek sisteme eklenmiştir. Apelinerjik sistem elemanları insan vücudunda yaygın ekspresyona sahiptir. Vücut-sıvı homeostazı, enerji metabolizması ve kardiyak kontraktilitenin düzenlenmesi gibi birçok fizyolojik süreçte rolü olan apelinerjik sistem, damar tonusunun ve kan basıncının düzenlenmesine de katılır. Damar tonusu üzerine benzer etkileri olan apelin ve elabela, etki mekanizmasında farklılık gösterir. APJ, hem damar endotel hücrelerinde hem de damar düz kas hücrelerinde eksprese edilmektedir. Bu durum, damar geriminde karşıt etkilere aracılık etmesi nedeni ile önemlidir. Apelin, fizyolojik koşullarda genellikle endotelyal nitrik oksit sentaz/nitrik oksit (NO) yolağının aktivasyonu aracılığıyla vazodilatatör etki gösterir. Buna karşın apelin, fonksiyonel bir endotelin olmadığı durumlarda vazokonstriksiyona neden olmaktadır. Elabela da apeline benzer şekilde vazodilatatör etki gösterir fakat NO'nun, elabelanın vazodilatatör etkisinde hiçbir rolü olmadığı düşünülmektedir. Apelin ve elabela, periferik olarak uygulandıklarında, genellikle kan basıncını düşürür ve antihipertansif etki gösterirler. Bu nedenle apelinerjik sistem, esansiyel hipertansiyon ve pulmoner hipertansiyon gibi hipertansif hastalıkların tedavisi için alternatif ajanlar geliştirme konusunda büyük bir potansiyele sahiptir. Apelin ve elabelanın yarılanma ömürleri oldukça kısadır ve güncel çalışmalar, daha uzun etkili apelinerjik analoglar geliştirmeye odaklanmıştır. Bu derlemede, apelinerjik sistemin vasküler fonksiyonel etkileri ve etki mekanizmalarına odaklandık.

Anahtar Kelimeler: Apelin; vazodilatasyon; vazokonstriksiyon; hipertansiyon; elabela

The apelinergic system consists of apelin receptor (APJ) and endogenous APJ ligands. Two known endogenous APJ ligands are apelin and elabela. The apelinergic system is involved in various physiological processes such as cardiovascular regulation, energy metabolism, body-fluid homeostasis, angiogenesis, food intake, and neuroendocrine stress response.[1-8] The apelinergic system which has very important cardiovascular regulatory functions mediates positive inotropic and cardioprotective effects.[5,9] Furthermore, the apelinergic system is involved in the regulation of vascular contractility and arterial blood pressure.[10-12] Because of vasodilator and hypotensive effects of the apelinergic system, apelinergic analogs

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and APJ agonists may be a new treatment modality in common diseases such as essential hypertension and pulmonary hypertension. Therefore, understanding the vascular functional effects and mechanisms of action of the apelinergic system is very important.

APELIN RECEPTOR

APJ, a G protein-coupled receptor, was discovered in 1993.[13] Since its ligand was unknown, it was previously described as an orphan receptor. This situation continued until 1998 when apelin was found. APLNR gene encoding APJ is located on chromosome 11.[13] APJ, which consists of 380 amino acids, has 7 transmembrane regions. The amino acid sequence of APJ is well conserved in rats and humans.[14] APJ has significant sequence homology with angiotensin II (Ang II) type 1A (AT1A) receptor (31%), and this similarity is greater in the transmembrane region (54%).[15] Tissue distribution of these two receptors is also very similar. Despite that, APJ doesn't bind Ang II, and AT1A receptor doesn't bind apelin.[15] APJ expression is commonly observed in many different tissues. In the cardiovascular system, APJ is extensively expressed in cardiomyocytes, vascular endothelial cells, and vascular smooth muscle cells.[16] It is suggested that APJ exerts its effects through activation of various signaling pathways such as phosphatidylinositol 3-kinase (PI3K)/Akt/endothelial nitric oxide synthase (eNOS) and phospholipase C (PLC)/protein kinase C (PKC).[17] G proteins such as Gai/o, Gaq11, and Ga12/13 are related to these signaling pathways.[17] As a result of activation of these signaling pathways, effects such as suppression of cAMP production, stimulation of extracellular signal-regulated kinase (ERK) phosphorylation, activation of eNOS, and calcium mobilization occur.[17] PI3K/Akt/eNOS signaling pathway is responsible for vascular functional effects of apelin.[17,18]

APELIN AND VASCULAR FUNCTION

Apelin, the first endogenous APJ ligand, was isolated from the bovine stomach extracts in 1998.[19] APLN gene encoding apelin is located on band q25-26.1 of chromosome X.[10] There are various isoforms of apelin such as apelin-12, apelin-13, apelin-17, and apelin-36.[17] The isoforms of apelin are formed from the precursor protein preproapelin containing 77 amino acids.[17] [Pyr1]apelin-13 (pyroglutamyl-apelin-13) is produced from apelin 13 via posttranslational modification.[17] Among the isoforms of apelin, [Pyr1]apelin-13 is more stable and more resistant to enzymatic degradation.[17] Since the C-terminal 12 amino acids of apelin are required for binding to the receptor, fragments of apelin shorter than 12 amino acids are biologically inactive. Apelin is highly expressed in various tissues such as heart, brain, stomach, lung, liver, intestine, kidney, skeletal muscle, adipose tissue, and vascular endothelium.[15,17] Tissue distribution and potency differ between apelin isoforms. [Pyr1]apelin-13 is the dominant isoform of apelin in human plasma and cardiac tissue.[20,21] It has been determined that plasma concentration of [Pyr1]apelin-13 is 7.7-23.3 pg/mL.[20,21] Among the isoforms of apelin, apelin-13 and [Pyr1]apelin-13 have a more potent effect on the cardiovascular system.[19,21] It has been demonstrated that the plasma half-life of apelin is very short and does not exceed 8 minutes for apelin-13 and apelin-36.[11] Angiotensin-converting enzyme 2 (ACE2) and neprilysin are involved in the enzymatic degradation of apelin. Apelin is involved in the regulation of physiological processes such as blood pressure, cardiac contractility, angiogenesis, body-fluid homeostasis, gastrointestinal motility and secretion, and energy metabolism.[1-8,22] Furthermore, it has been suggested that apelin plays a role in various pathological processes such as heart failure, obesity, diabetes, and cancer, which are the most common causes of mortality and morbidity.[23]

Cardiovascular effects of apelin are very important and have been investigated in many aspects. Apelin, which has a potent positive inotropic effect, increases cardiac output, ejection fraction, and cardiac index.[24-26] Apelin has a curative and cardioprotective effect in conditions such as heart failure, myocardial infarction, and coronary artery disease.[27] Apelin has a curative and cardioprotective effect in conditions such as heart failure, myocardial infarction and coronary artery disease in the studies used different isoforms of apelin.[27] Besides the antihypertensive effect of apelin has been shown in various studies.[28] Moreover, it has been suggested that apelin can be used as a biomarker in cardiovascular dis-

eases, such as coronary artery disease, left ventricular hypertrophy, and left ventricular dysfunction.[23]

Apelin can cause both vasoconstriction and vasodilation. This is likely due to the presence of APJ in both vascular endothelial cells and vascular smooth muscle cells. The apelin-induced vasodilator effect has been demonstrated in many different vessels of various species (Table 1). Gurzu et al. reported that apelin-13 didn't affect the basal tone in the rat portal vein, but it prevented the Ang II-induced contraction via NO.[29] Salcedo et al. demonstrated that apelin-13 caused relaxation in human mesenteric and hepatic arteries pre-contracted with U46619 (Tromboxan A2 analog).[30] In that study, it has been shown that prostanoids have no role in the apelin-13-mediated vasodilator effect, but a NO-mediated mechanism contributes to the vasodilator effect of apelin-13 in the mesenteric artery.[30] In an in vivo study in humans, arterial vasodilation has been observed as a result of the infusion of [Pyr1]apelin-13 or apelin-36 into forearm resistance vessels, while no change in venous tone has been reported.[11] In that study, it has been demonstrated that NO plays a role in [Pyr1]apelin-13-induced vascular relaxation, but prostanoids do not play a role.[11] Maguire et al. reported that [Pyr1]apelin-13, apelin-13, and apelin-36 caused relaxation in the human internal thoracic artery pre-contracted with endothelin-1 (ET-1).[21] In that study, it has been shown that NO plays no role in the relaxation of the human internal thoracic artery, but this relaxation is mediated by an endothelium-dependent and prostanoid-mediated mechanism.[21] Andersen et al. demonstrated that apelin-13 inhibited ET-1 and Ang II-mediated vascular contraction in the pulmonary artery of normoxic rats.[31] In that study, it has been detected that the vasorelaxant effect of apelin is insufficient in chronic hypoxic rats.[31] Huang et al. reported that apelin induced endothelium-dependent and NO-mediated relaxation in the rat pulmonary artery pre-contracted with norepinephrine.[32] In that study, it has been shown that the vasorelaxant effect of apelin decreases in the pulmonary arterial rings from the hypoxic rats.[32] Wang et al. determined that apelin-13 induced endothelium-dependent relaxation in mouse aortic rings pre-contracted with U46619.[33] In that study, it has been observed that the apelin-13-mediated vasodilator effect significantly decreases in the endothelium-denuded vessels.[33] Mughal et al. demonstrated that apelin-13 inhibited serotonin-induced contraction in the rat coronary arteries through a mechanism associated with NO and large-conductance calcium-activated potassium channels (BK_{Ca}).[34]

It has been reported that apelin-induced vasodilation occurs through a NO-mediated and endothelium-dependent mechanism in many vascular beds in mice, rats, and humans. After the binding of apelin to the APJ receptor, PI3K/Akt activation mediates the stimulation of eNOS phosphorylation and endothelial NO is produced.[11,12,35] NO diffuses into the vascular smooth muscle cells and activates the cyclic GMP/protein kinase G (PKG) pathway. Activated PKG stimulates the pumping of cytoplasmic calcium back into the sarcoplasmic reticulum through sarcoplasmic reticulum Ca^{2+}-ATPase activation and increases dephosphorylation of myosin light chains. Thus, the number of the cross-bridges reduces and vasodilation occurs (Figure 1).[36-38] Fur-

TABLE 1: Vasodilator effect and effect mechanism of apelin.

Drug	Species	Vessel	Pre-contracted with	Mechanism	Reference
Apelin-13	Rat	Portal vein	Ang II	NO	Gurzu et al.[29]
Apelin-13	Human	Mesenteric artery, hepatic artery	U46619	NO (in only mesenteric artery)	Salcedo et al.[30]
[Pyr1]Apelin-13, Apelin-36	Human	Forearm resistance vessels	No precontraction applied	NO	Japp et al.[11]
Apelin-13, Apelin-36, [Pyr1]Apelin-13	Human	Internal thoracic artery	ET-1	Prostanoids	Maguire et al.[21]
Apelin-13	Rat	Pulmonary artery	ET-1, Ang II	Machanism not researched	Andersen et al.[31]
Apelin (Isoform not specified)	Rat	Pulmonary artery	NE	NO	Huang et al.[32]
Apelin-13	Mouse	Aorta	U46619	Machanism not researched	Wang et al.[33]
Apelin-13	Rat	Coronary artery	Serotonin	NO, BK_{Ca}	Mughal et al.[34]

Ang II: Angiotensin II; **NO:** Nitric oxide; **ET-1:** Endothelin-1; **NE:** Norepinephrine; **BK_{Ca}:** Large-conductance calcium-activated potassium channels.

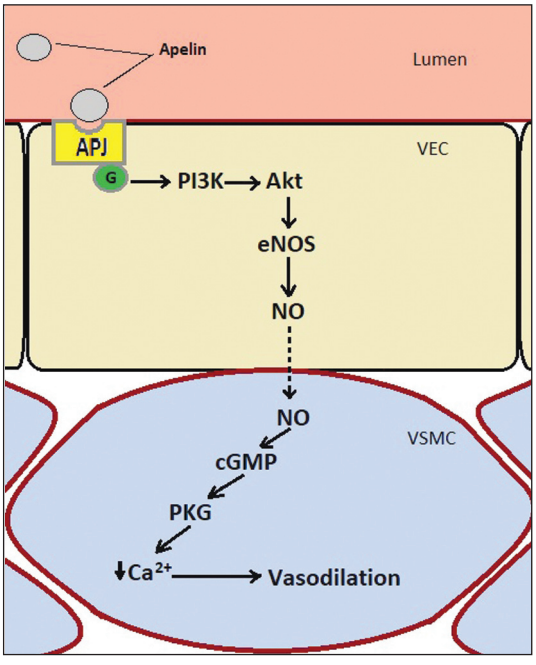

FIGURE 1: Proposed mechanism of apelin-induced vasodilation.
VEC: Vascular endothelial cell; VSMC: Vascular smooth muscle cell; APJ: Apelin receptor; G: G protein; PI3K: Phosphatidylinositol 3-kinase; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; cGMP: Cyclic guanosine monophosphate; PKG: Protein kinase G.

thermore, it has been shown that activation of BK_{Ca} channels in vascular smooth muscle cells in the rat coronary artery and stimulation of prostanoids in the human internal thoracic artery are important in the vasodilator effect of apelin.[21,34] As a result of endothelial removal, the vasodilator effect of apelin does not completely disappear.[33] Therefore, apelin may also have an endothelium-independent vasodilator effect.

Apelin has a vasoconstrictor effect in some vessels in some pathological conditions, or in cases where the endothelium is removed experimentally. It has been suggested that stimulation of APJ in vascular smooth muscle cells causes vasoconstriction.[39] Katugampola et al. showed that [Pyr1]apelin-13 caused a contraction in the endothelium-denuded human saphenous vein.[40] Similarly, vasoconstrictor effect has been observed in the endothelium-denuded human internal thoracic artery due to the administration of [Pyr1]apelin-13.[21] In the same study, it has been determined that [Pyr1]apelin-13, apelin-13, and apelin-36 cause a potent vasoconstrictor effect in the endothelium-denuded human saphenous vein.[21] Pitkin et al. demonstrated that administration of [Pyr1]apelin-13 caused vasoconstriction in the human coronary arteries obtained from atherosclerosis patients.[41] Wang et al. showed that apelin-13 exhibited vasoconstrictor effect in the rat caudal artery whose endothelium was damaged by asymmetric dimethylarginine (ADMA).[42] In a study that used endothelium-denuded mouse thoracic aorta, apelin-induced vasoconstrictor effect has been found to involve activation of pertussis toxin-sensitive G protein, PKC, Na^+/H^+ exchanger (NHE), and Na^+/Ca^{2+} exchanger (NCX).[43] Mughal et al. determined that apelin-13 inhibited the bradykinin-induced relaxation in the rat cerebral artery through the inhibition of the endothelium-dependent and NO-mediated activation of BK_{Ca} channels.[44] In contrast to the previous studies, Gurzu et al. reported that apelin-13 didn't cause vasoconstriction in the endothelium-denuded rat portal vein.[29] In that study, it has been shown that apelin-13 decreases the Ang II-induced vasoconstriction.[29]

In the absence of a functional endothelium, apelin causes PLC activation through binding to APJ in the vascular smooth muscle cells.[43] Activated PLC provides inositol trisphosphate (IP3) and diacylglycerol (DAG) generation. After activation of IP3 receptor channels and Ca^{2+} release from the sarcoplasmic reticulum, ryanodine receptor channels are also activated, and then cytoplasmic calcium increases.[37] On the other hand, DAG stimulates PKC. NCX and NHE which are activated by PKC contribute to the cytoplasmic calcium increase.[36-38,43] Moreover, the activation of voltage-dependent L-type calcium channels and the inhibition of calcium-activated potassium channels are also thought to play a role in the cytoplasmic calcium increase.[39] After the increase of intracellular calcium, vasoconstriction occurs through the stimulation of phosphorylation of myosin light chains (Figure 2). Furthermore, apelin inhibits myosin light-chain phosphatase activation and increases myosin light chain phosphorylation further.[43]

Apelin participates in the peripheral regulation of blood pressure. In the studies where apelin is administered peripherally, generally a decrease in arterial blood pressure has been observed. It has been

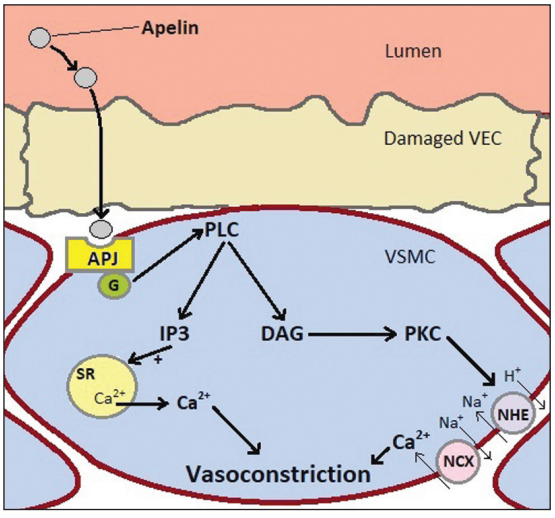

FIGURE 2: Proposed mechanism of apelin-induced vasoconstriction.
VEC: Vascular endothelial cell; VSMC: Vascular smooth muscle cell; APJ: Apelin receptor; G: G protein; PLC: Phospholipase C; IP3: Inositol trisphosphate; DAG: Diacylglycerol; PKC: Protein kinase C; SR: Sarcoplasmic reticulum; NHE: Na+-H+ exchanger; NCX: Na+-Ca2+ exchanger.

reported that intravenous (IV) administration of apelin isoforms such as apelin-12, apelin-13, apelin-36, and [Pyr1]apelin-13 causes a decrease in blood pressure in rats.[1,2,45,46] In healthy people or heart failure cases, a decrease in blood pressure has been observed due to IV administration of [Pyr1]apelin-13.[24,25] Najafipour et al. reported that IV administration of apelin-13 decreased systolic and diastolic blood pressure in chronic two-kidney-one-clip hypertensive rats.[47] Contrary to those studies, some studies have reported hypertensive effects due to IV administration of apelin. This finding is consistent with the vasoconstrictor effect of apelin. Charles et al. determined that IV administration of apelin-13 in sheep showed the biphasic effect in blood pressure in the form of a decrease firstly and then an increase.[48] Kagiyama et al. showed that IV administration of [Pyr1]apelin-13 increased mean arterial blood pressure (MABP) in conscious rats.[49] Han et al. demonstrated that IV administration of [Pyr1]apelin-13 increased systolic blood pressure in mice treated with eNOS inhibitor N(ω)-nitro-L-arginine methyl ester.[50] Nagano et al. reported that apelin-13 increased systolic blood pressure in rats who have endothelial damage induced by ADMA.[51]

It is suggested that apelin also participates in the central regulation of blood pressure. In spontaneous hypertensive rats, the increased apelin expression has been reported in the rostral ventrolateral medulla (RVLM) and paraventricular nucleus (PVN).[52,53] Zhang et al. determined that apelin gene transfer to RVLM caused hypertension in normotensive rats.[53] An increase in blood pressure has been observed after administration of [Pyr1]apelin-13 or apelin-13 to PVN, nucleus tractus solitarius or RVLM via intracerebroventricular (ICV) route in rats.[52-55] In a study where apelin-13 is administered via ICV to conscious rats, an increase in MABP has been observed, but this effect has been reduced by chronic stress or a high-fat diet.[56] In another study, Reaux et al. demonstrated that ICV administration of [Pyr1]apelin-13 caused no change in blood pressure in anesthetized rats.[1] In a study where apelin-13 is administered to subfornical organ, a decrease in blood pressure has been observed in anesthetized rats.[57] All those studies show that the administration route of apelin is especially important for the effect pattern of apelin on blood pressure. Furthermore, other experimental procedures such as anesthesia may cause variability in the effect of apelin on blood pressure.

Apelin has an improver effect on impaired vascular functions in some pathological conditions. Zhong et al. reported that apelin improved impaired Ang II and acetylcholine (Ach) responses in the aorta of diabetic mice.[58] In that study, it has been shown that Akt and eNOS phosphorylation play a role in the improver effect of apelin.[58] Zhong et al. determined that apelin corrected increased Ang II and decreased Ach responses in the renal arteries of diabetic mice through the stimulation of eNOS phosphorylation and NO production.[59] Andersen et al. demonstrated that apelin improved pulmonary hypertension by decreasing mean pulmonary artery pressure.[60]

The plasma half-life of apelin is very short and does not exceed 8 minutes. The shorter duration of action restricts the therapeutic potential of apelin. In recent years, it has been trying to develop longer-acting and more potent APJ agonists. MM07 developed by Brame et al. has a plasma half-life of about 17 minutes which is longer than the plasma half-life of [Pyr1]apelin-13 (Plasma half-life of [Pyr1]apelin-13: 2.3±0.51 minutes).[61] Brame et al. determined that

MM07 significantly increased forearm blood flow and cardiac output.[61] Iturrioz et al. demonstrated that APJ receptor agonist E339-3D6 caused relaxation in the pre-contracted rat thoracic aorta at lower doses than that of Ach.[62] Gerbier et al. showed that apelin-17 analogs P92 and LIT01-196 showed vasodilator effect in the rat thoracic aorta and glomerular arterioles, and they have a quite long half-life.[63]

ELABELA AND VASCULAR FUNCTION

Another endogenous APJ ligand elabela (apela, toddler, ela) was found in 2013 and 2014 by two separate research groups.[64,65] APELA gene encoding elabela is located on chromosome 4 in human. The elabela isoforms formed from the precursor peptide which consists of 54 amino acids are ela-32 (mature isoform of elabela), ela-21, and ela-11.[15,17,64,65] Elabela, which is necessary for normal heart development and angiogenesis, is extensively expressed in the cardiovascular endothelium.[15,17] Similar to apelin, elabela exhibits vasodilator and positive inotropic effects.[33,66] Perjés et al. demonstrated that ERK1/2 activation played a role in the positive inotropic effect of elabela.[66] It has been suggested that apelin and elabela together prevent pathological conditions such as cardiac hypertrophy and cardiac fibrosis through antagonizing the renin-angiotensin system which plays an important role in the control of arterial blood pressure.[67,68]

Studies investigating the vascular functional effects of elabela are very limited. Vascular functional effects of elabela are generally similar to apelin. Wang et al. determined that ela-32 caused endothelium-dependent and endothelium-independent vasodilation in mouse aortic rings pre-contracted with U46619.[33] In that study, the researchers indicated that ela-32 caused vasodilation at a maximum of 73.7% and apelin-13 at a maximum of 79%.[33] In that study, it has been also shown that NO does not play a role in the ela-32-mediated vasodilator effect.[33] Furthermore, in that study, it has been demonstrated that the vasodilator effect of ela-32 decreases approximately 20% as a result of endothelial removal.[33] In the same study, the ela-32-mediated vasodilator effect has been found less endothelium dependent than apelin-13-mediated vasodilator effect.[33] Perjés, et al. showed that ela-32 caused coronary vasodilation in rats.[66] It has been reported that the mechanism of action of elabela differs from apelin. Wang et al. showed that the NO-mediated mechanism didn't play a role in the vasodilator effect of elabela.[33]

Similar to apelin, elabela shows a hypotensive effect in the peripheral administration. Murza et al. reported that elabela and its analogs decreased arterial blood pressure in rats.[69] Ho et al. showed that exogenous elabela administration improved hypertension.[70] Li et al. determined that plasma elabela level decreased and negatively correlated with systolic and diastolic blood pressure in essential hypertension patients.[71] In that study, a positive correlation has been found between plasma elabela level and endothelial dysfunction.[71] Therefore, it is suggested that elabela may be a marker for endothelial dysfunction.[71]

CONCLUSION

Numerous in vivo and in vitro studies have shown that apelin generally has a vasodilator effect in the presence of a functional endothelium. If the endothelium is removed, damaged, or dysfunctional, apelin exhibits a vasoconstrictor effect. Different results are obtained in arterial blood pressure depending on the administration route of apelin and experimental procedures. Generally, a hypotensive effect is seen in the peripheral administration of apelin while a hypertensive effect is seen in the central administration of apelin. The vasodilator effect of apelin is mediated by PI3K/Akt/eNOS pathway. PLC activation, increased cytoplasmic calcium, stimulation of myosin light chain phosphorylation, and suppression of myosin phosphatase are held responsible for the apelin-mediated vasoconstrictor effect. Although less known about elabela, vascular functional effects of elabela are similar to apelin. The main difference is in the mechanism of action. It has been shown that NO plays no role in the vasodilator effect of elabela. The data suggest that new drugs may be developed for the treatment of hypertensive diseases such as essential hypertension via the apelinergic system due to their its vasodilator and antihypertensive effects. The half-lives of apelin and elabela are short. Although this is a serious problem, it is being tried to develop more effective and long-lasting apelinergic analogs and APJ agonists. Further studies are

needed on the central and peripheral vascular functional effects and mechanisms of action of the apelinergic system.

Learning Points

- The apelinergic system consists of APJ and endogenous APJ ligands. Two known endogenous APJ ligands are apelin and elabela.
- The apelinergic system exhibits vasodilator and hypotensive effects.
- The vasodilator effect of apelin is mediated by PI3K/Akt/eNOS pathway.
- Vascular functional effects of elabela are similar to apelin. The main difference is in the mechanism of action.
- It is suggested that NO doesn't play a role in the vasodilator effect of elabela.
- Because of vasodilator and hypotensive effects of the apelinergic system, apelinergic analogs and AP agonists may be a new treatment modality in common diseases such as essential hypertension and pulmonary hypertension.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Serdar Şahintürk, Naciye İşbil, Sadettin Demirel;* ***Design:*** *Serdar Şahintürk, Naciye İşbil, Sadettin Demirel;* ***Control/Supervision:*** *Serdar Şahintürk, Naciye İşbil;* ***Data Collection and/or Processing:*** *Serdar Şahintürk, Sadettin Demirel, Naciye İşbil;* ***Analysis and/or Interpretation:*** *Serdar Şahintürk, Naciye İşbil;* ***Literature Review:*** *Serdar Şahintürk, Sadettin Demirel;* ***Writing the Article:*** *Serdar Şahintürk, Naciye İşbil, Sadettin Demirel;* ***Critical Review:*** *Serdar Şahintürk, Naciye İşbil.*

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