The endothelins are a family of 21-amino acid vasoconstrictor peptides comprising three isoforms, endothelin-1, endothelin-2, and endothelin-3. Endothelins mediate their actions via two receptor types, classified as the ET-A and ET-B receptors. All three endothelins contain four cysteine residues, which form two intramolecular disulfide bonds and show structural similarity to the family of sarafotoxins originally isolated from snake venom. The endothelins are synthesized as prepro-endothelins. These are cleaved by furin-like convertases to produce big endothelins, which are further processed to the mature, active peptides by endothelin-converting enzymes. The endothelin system is involved in developmental processes of neural crest-derived structures and plays an important role in vascular homeostasis and in various pathological conditions such as pulmonary arterial hypertension, atherosclerosis and cancer.
In 1988 Yanagisawa and co-workers reported the isolation of a 21-residue vasoconstrictor peptide, endothelin, from the culture supernatant of porcine aortic endothelial cells. The peptide, now known as endothelin-1 (ET-1), is the most potent mammalian vasoconstrictor identified to date with EC_{50} values in the subnanomolar range. ET-1 caused a slowly developing and sustained vasoconstriction, which could be reversed by the β-adrenergic receptor agonist isoproterenol or the anti-anginal vasodilator nitroglycerin. Further studies indicated that ET-1 acts directly on smooth muscle cells, and that influx of extracellular Ca^{2+} is required for its activity.

In 1989 two additional endothelins were identified: ET-2 and ET-3, which differ from ET-1 in two and six amino acids, respectively (Fig. 1). The members of the endothelin family contain four cysteine residues, which form two intra-chain disulfide bridges linking cysteine residues 1 to 15 and 3 to 11. The two disulfide bonds are a rather unusual feature, compared to other bioactive peptides. The murine-derived peptide vasoactive intestinal contractor peptide (VIC) represents another potent vasoactive and smooth muscle contracting factor. It varies from ET-2 in one amino acid and may be considered as murine ET-2.

The tertiary structures of ET-1 and ET-2 were found by NMR studies to be essentially the same, and in mammalian preparations both peptides are equipotent.

The major source of ET-1 are endothelial cells, but it is also produced by epithelial cells, macrophages, fibroblasts, cardiac myocytes, and neurons. ET-1 is likely to be present and to have a role in controlling perfusion in every organ in the body.

In endothelial cells, ET-1 is synthesized in a dual pathway, which is unusual for vasoactive peptides. In a constitutive pathway, it is thought to be continuously released. This may serve to maintain the normal vascular tone. In a second pathway, it is believed to be stored in special Weibel-Palade storage granules. These are unique to endothelial cells and degranulate upon external stimulus, which can be of chemical or mechanical nature. This presumably serves to produce further vasoconstriction.

For ET-2, the available data suggests a more restricted organ distribution. ET-2 is expressed in intestinal epithelial cells and at lower levels also in the heart. ET-3 is expressed in brain neurons, kidney, and intestinal epithelial cells.

A number of 31-amino acid endothelins have been described. They are derived from the selective hydrolysis of big endothelins (Big-ETs) at the Tyr^{31}-Gly^{32} bond by human mast cell chymase. These peptides, which exhibit a trachea-constricting effect, may play a role in the hyper-responsive airway in allergic inflammation.

The endothelins show very close structural and functional relationship to the sarafotoxins, snake venom peptides originally isolated from the Israeli burrowing asp, Atractaspis engaddensis. The sarafotoxins comprise four isoforms, which are S6A, S6B, S6C and S6D, or, according to a diverging nomenclature, SRTX-A, -B, -C and -D.

S6A and S6B, which differ by a single substitution at position 13, have similar toxicity. S6C, the most abundant isoform in the venom, varies in 3 and 4 amino acids to S6A and S6B, respectively. S6C is about 30-fold less toxic, than S6A and S6B.

Recently, a diverging respiratory effect of the 21 amino acid S6B (SRTX-B), and the...
Endothelins

Endothelin-1 (human, bovine, dog, mouse, porcine, rat)

Endothelin-2 (human, canine)

Endothelin-3 (human, mouse, rabbit, rat)

Sarafotoxin A

Sarafotoxin B

Sarafotoxin C

Fig. 1. Structure of endothelins and sarafotoxins. Amino acids different to the primary sequence of ET-1 are shown in blue color.
three amino acid longer SRTX-M from the species *Atractaspis microlepidota microlepidota*, has been described. This presumably is caused by the C-terminal extension of SRTX-M, but more data is required to support this finding.

**Endothelin Converting Enzymes**

Mature endothelins are created by sequential proteolytic processing of the preproendothelins. Removal of the signal peptide by signal peptidases and further processing of the proendothelins at dibasic amino acid residues by furin-like convertases, results in the production of the physiological inactive endothelin precursors, the big endothelins (Fig. 2). These propeptides are further cleaved at Trp-Val residues (for ET-1 and ET-2) or Trp-Ile residues (for ET-3) by the phosphoramidon-sensitive endothelin converting enzymes (ECE) to form the active peptides.

ECE are type II membrane proteins of the peptidase family M13 (neprilysin family), with an N-terminal cytosolic tail and a catalytic ectodomain. They are expressed as covalent dimers. Each subunit has a zinc atom coordinated by three zinc ligands. The two known members, ECE-1 and ECE-2, exist in various isoforms (ECE-1 A-D and ECE-2 A-C, respectively), which are identical in their extracellular and transmembrane domains. The differences in their N-terminal cytoplasmic sequences might contribute to their subcellular distribution. The same accounts for their phosphorylation as demonstrated for ECE-1.

ECE-1 is expressed in endothelial cells and in a variety of other cells. It has an activity peak at neutral pH and processes Big ETs both, on the surface and within the cell. ECE-2 is found in neurons and diverse other cell types. Since it has an activity peak at a more acidic pH, it is likely to be an intracellular processing enzyme.

Although ECE-2 efficiently converts Big ET-1, it is able to process other biologically active peptides, which must be considered for the evaluation of ECE-2 selective antagonists.
The endothelin system is important in embryological development. Gene knockout experiments in mice have revealed that ET-1, ET-A receptor, and ECE-1 are necessary for the patterning and development of cephalic and cardiac neural crest-derived craniofacial and cardiac outflow structures. On the other hand, ET-3, ET-B, and ECE-1 are required for the correct development of neural crest-derived epidermal melanocytes and enteric neurons.

**Regulation of Endothelin Expression**
The majority of studies on the regulation of ET gene expression have focused on ET-1. Expression of ET-1 is mainly regulated at the transcriptional level, but post-transcriptional mechanisms have also been described. The synthesis and secretion of ET-1 is increased by various growth factors, cytokines and vasoactive factors such as angiotensin II, vasopressin, bradykinin, norepinephrine, and ET-1 itself (Fig. 3). Hypoxia and shear stress have also been shown to increase ET-1 release from endothelial cells. ET-1 expression is suppressed by several factors including atrial natriuretic peptide, nitric oxide, prostacyclin, and heparin.

ET-1 peptide is rapidly cleared from the plasma with a half-life of several minutes. Clearance of ET-1 has been suggested to occur through cleavage by extracellular neutral endopeptidase (NEP) and by ET-B receptor-mediated uptake followed by lysosomal degradation. The latter takes place predominantly in liver, kidney and lungs.

**Endothelin Receptors**
Two types of mammalian endothelin receptors, the ET-A and the ET-B receptors, have been identified in several species. Both types of receptors belong to the superfamily of the seven transmembrane G-protein coupled receptors (GPCRs) with an extracellular N-terminal and an intracellular C-terminal domain. They are encoded by distinct genes on separate chromosomes, while their genomic DNAs show a similar structural organization. The human ET-A receptor consists of 427 amino acids, whereas the human ET-B receptor has a length of 442 amino acids. The transmembrane domains and the cytoplasmic loops are highly conserved between the human endothelin receptors. Their extracellular loops, N-terminal domains, and their C-terminal domains vary both in length and in the amino acid composition. ET-A and ET-B receptors from other species differ in the amino acid sequence partly from the human orthologues.

Sequence analysis of the ET receptor genes revealed the presence of an N-terminal signal sequence and several post-translation modifications. This includes consensus sites for N-glycosylation, several potential sites for palmitoylation, and serine residues
that may be sites for regulatory phosphorylation by serine threonine kinases; the palmitoylation presumably serves to anchor the receptors to the membrane.

The ET-A receptor mRNA can be found in vascular smooth muscle cell layers of a variety of tissues including aorta, coronary arteries, brain blood vessels, and renal arterioles but also in bronchial smooth muscle, myocardium, and the pituitary gland. The ET-B receptor mRNA is most abundant in vascular endothelial cells. Ligand binding studies moreover identified particularly high fractions of ET-B, compared to ET-A, in brain, where the subtype ET-B constitutes about 90% of the expressed ET receptors. High ET-B densities were also found in lungs, kidney, liver and portal vein. The high abundancies of ET-B in kidney, liver and lungs can be explained from its function for clearing of ET-1.

ET-A and ET-B receptors have contrasting functions under physiological conditions. The stimulation of ET-A receptors in the smooth muscle leads to constriction, whereas activation of the ET-B receptors in the endothelial cells leads to the release of vasodilators such as nitric oxide, prostacyclin or endothelium-derived hyperpolarizing factor.

ET-1 and ET-2 have similar binding affinities for the ET-A receptor, but differ slightly in their affinities for the ET-B receptor (Fig. 4). ET-3 preferentially binds to the ET-B receptor with binding affinities similar to those of ET-1 and can therefore be considered as moderately selective ET-B agonist. ET-3 is the only endogenous ET peptide that distinguishes the two receptor subtypes.

The affinity of ET-1 to both, ET-A and ET-B resembles an autocrine feedback mechanism, since both receptors are counteracting. This mechanism presumably is important for the cardiovascular homeostasis. Obviously, low levels of ET-1 promote vasodilatation, whereas higher and pathophysiological concentrations increase blood pressure and total peripheral vascular resistance. Vasodilatation could also be observed for high levels of ET-3. The formation of homo- or hetero-dimers of ET-A and ET-B receptors could have pathological relevance, but further evidence from native tissues is still missing.

A number of antagonists of ET-A and ET-B receptors have been described, typically classified as ET-A-selective, ET-B-selective, or mixed (less selective or non-selective). Selective agonist compounds for ET-A to date have not yet been found.

**Current Medical Research**

The endothelin system has been implicated in a variety of physiological and pathophysiological processes. Due to the complexity of the system’s interplay with other factors and the diverse expression patterns of its components, the precise functions still remain to be defined.

It is generally agreed that the endothelin system plays an important role in vascular homeostasis and in various pathologi-
Endothelins

cal conditions including pulmonary arterial hypertension (PAH), atherosclerosis, myocardial infarction, and vasospasms after subarachnoid hemorrhage. Recently, the ET-1 system had also been linked to the increased risk of hypertension and atherosclerotic vascular disease in overweight and obese people.

These observations have raised substantial interest in endothelin receptor antagonists as drugs for the treatment of such medical conditions. Beneficial effects in the therapy of PAH were found for bosentan, an ET-A and ET-B receptor antagonist, which received FDA approval for the treatment of this life-threatening disease in year 2001. Approvals for the ET-A selective antagonist ambrisentan (2007) as well as for the mixed antagonist macitentan (2013) followed. Other drugs like sitaxsentan, which initially showed favorable results, had been withdrawn due to issues relating to hepatic toxicity. In general, the question whether selective ET-A receptor antagonists are clinically advantageous over dual ET-A/ET-B antagonists, is still under debate.

ET-1 could be an important component in the pathogenesis of atrial fibrillation (AF), a disease which basically resembles an abnormal heart rhythm. However, further research is required to establish the pathophysiological significance of ET-1 and its receptors, and its possible predictive and therapeutic value for the treatment of AF.

Apart from their role in the cardiovascular system, the endothelin peptides and their receptors are also involved in the control of kidney functions such as renal blood flow, water and sodium excretion, and acid-base balance. The endothelin system may contribute to renal failure. Diabetic nephropathy is associated with an enhanced renal synthesis of ET-1, and is the leading cause of end stage renal disease in industrialized countries. Avosentan (SPP301), an ET-A receptor antagonist, is under clinical trial for treatment of diabetic nephropathy. However, to date no FDA approval had been obtained for avosentan, referring to a current review by Davenport et al. (2016).

During the last decade it became evident that the endothelin system is involved in cancer-relevant processes including cell proliferation, extracellular matrix remodeling as well as tumor stroma development, apoptosis inhibition, angiogenesis and bone metastasis. ET-1 might play a role in the growth and progression of a variety of tumors such as prostatic, ovarian, colorectal and brain tumors as well as cervical carcinomas and melanomas.

Preliminary data on endothelin receptor antagonists suggest that this class of compounds might be applicable alone or in combination with cytotoxic drugs in anti-cancer therapies. Other studies point at a role of ET-1 expression as indicator of progression and poor prognosis in non-small cell lung carcinoma. The generation of monoclonal antibodies against GPCRs in general is challenging, but for example monoclonal antibodies against ET-B with toxic payloads are another interesting approach in the treatment of cancer.

It has been a major discovery that GPCRs can act in a biased way, since they have more than one active state. Biased in this respect means that they are stabilized by the ligand in a conformation, which only activates a subpopulation of the G-protein dependent or independent cascades. This bears potential for the treatment of several ET receptor mediated disease patterns.

For example, the selective activation of the ET-A mediated G-protein (Gαs) signaling pathway and subsequent activation of protein kinase A suppresses the expression of angiogenic and metastasis genes. The latter are switched on by an ET-A mediated, non-G-protein (β-arrestin) pathway. The selective activation of the Gαs-signaling by the use of biased ligands had recently been proposed as a new strategy to treat ovarian cancer.

ET-1 has been described as a pain mediator. Pain signaling is thought to occur by binding of ET-1 to ET-A receptors, localized on nociceptors. ET-A antagonists could serve as pain relieving agents in many acute diseases such as various types of cancer,


also for patients suffering chronic pain. The effect of the ET-B receptor on pain mediating pathways seems to be more complex and still is not well understood. Another current research topic is the application of cell-penetrating peptides (CPPs) for the activation or blocking of the ET receptor mediated downstream signaling. CPPs of interest are the protein-derived CPPs as well as pepducins, which remain tethered to the cell membrane. A number of pepducin agonists and antagonists acting on GPCRs already had been described, and a first CPP acting on ET-B receptors has been reported as well.

Several studies have demonstrated that ET-1 is linked to a proinflammatory effect. This involves the activation of transcription factors such as NF-κB and expression of cytokines including TNF-α, IL-1 and IL-6. Furthermore, ET-1 enhances the expression of adhesion molecules on vascular endothelial cells and stimulates the aggregation of polymorphonuclear neutrophils, contributing to inflammation and endothelial dysfunction.

The role of endothelins and their receptors in the development of sepsis is currently under investigation, and the nonselective endothelin receptor antagonists bosentan and tezosentan, and selective antagonists such as BQ123 and BQ788, are currently receiving attention in this respect.

For the treatment of preeclampsia, a disease for which effective therapeutic options are still not available, ET-A receptor blockers would be a promising approach. However, this requires that the drugs do not cross the maternal-fetal interface in order to avoid that the fetus is harmed by the medication. For this, experiments have been performed with small peptide inhibitors of the ET-A receptor, but their clinical potential so far is hindered as they are rapidly hydrolyzed in the systemic circulation and gastrointestinal tract. An orally active, non-peptide ET-A selective receptor antagonist has been developed, but studies on the efficacy or teratogenic effects are still missing.

In Hirschsprung’s disease, a multigenic developmental disorder in which ganglion cells are absent in a distal segment of the large intestine, the ET-3, ET-B, and ECE-1 genes have been identified as susceptibility genes.

ET receptor antagonists in clinical applications carry the risk of embryo-fetal toxicity, as indicated by studies in mice. Therefore, an allosteric modulation, which reduces but not blocks the action of ET-1, could be an interesting way to go. For example, an allosteric effect of the ET-A antagonist BQ123 recently had been described, which changes the affinity for orthosteric ligands. The potential of specific, agonist-selective ET-receptor allosteric antagonists is topic of current research.

Overall, endothelins and their receptors constitute a complex system with various expression patterns in tissues and organs, which is involved in numerous physiological and pathophysiological processes, and a number of new therapeutic strategies are under investigation. Thereby, endothelins, modified endothelins and other peptides acting on ET receptors are indispensable experimental tools to investigate the processes and mechanisms associated with these multifaceted GPCRs.

Please explore our broad offering of endothelin research peptides, and set up your next scientific experiment.
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Endothelins are peptides with exceptional vasoconstrictor potency. They play an important role in intercellular communications.
ENDOTHELINS

Big Endothelin-1 (human)  
H-9030  
CSCSSLMDKECVYFCHLDIIWNTPEHV-VPYGLGSPRS  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Big Endothelin-1 (1-31) (human, bovine)  
H-5818  
CSCSSLMDKECVYFCHLDIIWNTPEHV-VPY  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Big Endothelin-1 (porcine)  
H-9135  
CSCSSLMDKECVYFCHLDIIWNTPEHIV-PYGLGSPRS  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Big Endothelin-1 fragment (22-38) (human)  
H-7875  
VNTPEHVVPYGLGSPRS

Big Endothelin-2 (human)  
H-7566  
CSCSSWLDKECVYFCHLDIIWNTPEQTA-PYGLGNPPR

Big Endothelin-3 (1-41) amide (human)  
H-7572  
CTCFTYKDKECVYCHLDIIWNTPEQTV-PYGLSNYRGSFR-NH₂

Big Endothelin-3 (22-41) amide (human)  
H-7568  
INTPEQTVPYGLSNYRGSFR

Endothelin-1 (human, bovine, dog, mouse, porcine, rat) acetate salt  
H-6995  
CSCSSLMDKECVYFCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Endothelin-1 (human, bovine, dog, mouse, porcine, rat) trifluoroacetate salt  
H-7758  
CSCSSLMDKECVYFCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

([¹³C₆]Leu⁶)-Endothelin-1 (human, bovine, dog, mouse, porcine, rat)  
H-7254  
CSCSSLMDKECVYFCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Endothelin-2 (human, canine) acetate salt  
H-9020  
CSCSSWLDKECVYFCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Endothelin-2 (human, canine) trifluoroacetate salt  
H-7768  
CSCSSWLDKECVYFCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Endothelin-3 (human, mouse, rabbit, rat) acetate salt  
H-9025  
CTCFTYKDKECVYCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)

Endothelin-3 (human, mouse, rabbit, rat) trifluoroacetate salt  
H-7772  
CTCFTYKDKECVYCHLDIIW  
(Disulfide bonds between Cys¹ and Cys¹⁵/Cys³ and Cys¹¹)
SELECTIVE ET-A RECEPTOR ANTAGONISTS

Acetyl-(D-Trp¹⁹)-Endothelin-1 (16-21)
H-8850
Ac-wLDIIW

BQ-123
H-1252
c(wdPvL)

BQ-610
H-4914
Azepane-1-carbonyl-Lw(For)w

Cyclo-(D-Glu-Ala-D-allo-Ile-Leu-D-Trp) (BE-18275B)
H-8405
c(eA-D-allo-Ile-Lw)

SELECTIVE ET-B RECEPTOR ANTAGONISTS

BQ-788
H-2492
N-cis-2,6-Dimethylpiperidinocarbonyl-β-tBu-Ala-D-Trp(1-methoxycarbonyl)-D-Nle-OH

BQ-788 ammonium salt
H-8242
N-cis-2,6-Dimethylpiperidinocarbonyl-β-tBu-Ala-D-Trp(1-methoxycarbonyl)-D-Nle-OH

BQ-788 sodium salt
H-8152
N-cis-2,6-Dimethylpiperidinocarbonyl-β-tBu-Ala-D-Trp(1-methoxycarbonyl)-D-Nle-OH

Cyclo(-D-Ser-Pro-D-Val-Leu-D-Trp) (JKC-302)
H-3064
c(sPvLw)

JKC-301
H-3008
c(PiLw)

Cyclo(-Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp-Oh (RES-701-1)
H-2508
c(GNWHGTAPD)WFFNYYW

Cyclo(-Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Val-Tyr-Phe-Ala-His-Leu-Asp-Ile-Ile-Trp-Oh
H-4074
c(GNWHGTAPD)WVYFAHLIIW

Endothelin-1 (11-21) (IRL-1038)
H-1658
CVYFCHLDIIW
(Disulfide bond)
### Endothelins

#### Selective ET-B Receptor Agonists

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<th>Formula</th>
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<td>(Ala&lt;sup&gt;1,3,11,15&lt;/sup&gt;)-Endothelin-1</td>
<td>H-3066</td>
<td>ASASSLMDEAVFAHLDIIW</td>
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<td>Acetyl-(Ala&lt;sup&gt;11-15&lt;/sup&gt;)-Endothelin-1 (6-21)</td>
<td>H-8520</td>
<td>Ac-LMDKEAVFAHLDIIW</td>
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<td>Endothelin (16-21)</td>
<td>H-5772</td>
<td>HLDIIW</td>
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#### Sarafotoxins

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<tr>
<td>Sarafotoxin A</td>
<td>H-1046</td>
<td>CSCKDMTDECLNFCHQDVIIW (Disulfide bonds between Cys&lt;sup&gt;1&lt;/sup&gt; and Cys&lt;sup&gt;15&lt;/sup&gt;/Cys&lt;sup&gt;3&lt;/sup&gt; and Cys&lt;sup&gt;11&lt;/sup&gt;)</td>
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<td>Sarafotoxin B</td>
<td>H-7980</td>
<td>CSCKDMTDEGCLFCHQDVIIW (Disulfide bonds between Cys&lt;sup&gt;1&lt;/sup&gt; and Cys&lt;sup&gt;15&lt;/sup&gt;/Cys&lt;sup&gt;3&lt;/sup&gt; and Cys&lt;sup&gt;11&lt;/sup&gt;)</td>
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<td>Sarafotoxin C</td>
<td>H-7985</td>
<td>CTCNDMTECLNFCHQDVIIW (Disulfide bonds between Cys&lt;sup&gt;1&lt;/sup&gt; and Cys&lt;sup&gt;15&lt;/sup&gt;/Cys&lt;sup&gt;3&lt;/sup&gt; and Cys&lt;sup&gt;11&lt;/sup&gt;)</td>
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<tr>
<td>(Lys&lt;sup&gt;4&lt;/sup&gt;)-Sarafotoxin C</td>
<td>H-7985</td>
<td>CTCNDMTECLNFCHQDVIIW (Disulfide bonds between Cys&lt;sup&gt;1&lt;/sup&gt; and Cys&lt;sup&gt;15&lt;/sup&gt;/Cys&lt;sup&gt;3&lt;/sup&gt; and Cys&lt;sup&gt;11&lt;/sup&gt;)</td>
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#### ECE-1 Substrate

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<tr>
<td>Mca-(Ala&lt;sup&gt;9&lt;/sup&gt;,Lys(Dnp)&lt;sup&gt;9&lt;/sup&gt;)-Bradykinin</td>
<td>M-2405</td>
<td>Mca-RPPGFSAFK(Dnp)</td>
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#### Related Products

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<td>Glutaryl-Phe-Ala-Ala-Phe-AMC</td>
<td>I-1535</td>
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<td>H-6032</td>
<td>SFLLRNPNKYEFP-NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>H-p-Chloro-Phe-D-Cys-β-(3-pyridyl)-Ala-D-Trp-Lys-Val-Cys-p-chloro-Phe-NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H-5916</td>
<td>H-p-Chloro-Fc-β-(3-pyridyl)-AwKVC-p-chloro-F-NH&lt;sub&gt;2&lt;/sub&gt; (Disulfide bond)</td>
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Coloured scanning electron micrograph (SEM) of an ovarian artery that has been freeze-fractured to show internal details. An ovarian artery is a blood vessel that supplies oxygenated blood to the ovary. In cross-section the endothelium (tunica intima) can be seen in brown, comprising of specialised epithelial cells that line the circulatory system. Surrounding this layer is the tunica media (brick red), which is made up of smooth muscle cells and elastic tissue. The outermost layer (purple and white), which surrounds the tunica media, is called the tunica externa, and is mainly composed of collagen. This collagen anchors the blood vessels to nearby organs, providing stability. Magnification: x780 when original image printed 10 centimeters wide.

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