Endothelins: A Family of Regulatory Peptides

State-of-the-Art Lecture

Michael S. Simonson and Michael J. Dunn

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eptide hormones are nearly ubiquitous in the body and play a major role in regulating homeostasis. Serving in an endocrine, paracrine, or neuroendocrine role, peptide hormones regulate such diverse physiological processes as cardiovascular hemodynamics; neurotransmission or neuromodulation; contractility of skeletal, cardiac, or smooth muscle; and control of cell proliferation. Peptide hormones also have been postulated to play a major pathophysiological role in such processes as atherosclerosis, hypertension, and perhaps even oncogenesis. Thus, it comes as no surprise that the recent discovery of a new peptide hormone, endothelin (ET), has attracted much attention. This review is intended to serve two functions: first, to provide an overview and bibliographic guide to ET biochemistry and physiology, and second, to outline what is known about the pathways of transmembrane signaling by which ET peptides elicit diverse biological actions. Limitations of space preclude exhaustive references; thus, the reader is directed to several recent reviews on specialized topics.

The Endothelin Family of Regulatory Peptides

Structure of Endothelin Isopeptides

The term "endothelin" refers to a family of acidic, 21-amino acid peptides found in at least four distinct isoforms: ET-1, ET-2, ET-3, and endothelin \( \beta \) (or vasoactive intestinal contractor). ET isoforms share sequence homology and a common design (Figure 1). ET peptide chains are held in a hairpin loop configuration by two disulfide bonds between Cys-1 and Cys-15 and Cys-3 and Cys-11. Other notable features are the presence of polar, charged amino acid side chains within the hairpin loops (residues 6–10) and a hydrophobic C-terminus containing the aromatic indole side chain at Trp-21. Numerous structure and activity studies reveal that the hydrophobic C-terminus is requisite for bioactivity but that the hairpin loop configuration is also important. As with other peptides of similar size and configuration, elements of ET secondary and tertiary structure are likely to stabilize the interaction between ET and receptors at the plasma membrane interface.

Both in structure and bioactivity, ET peptides are closely related to sarafotoxins, peptide toxins isolated from venom of an Egyptian asp, Atractaspis engaddensis. It seems likely that the two peptide families share a common evolutionary origin, and the high degree of sequence homology between ET and sarafotoxins suggests that ET genes have evolved under strong pressure to conserve the structure and function of mature ET peptides.

Synthesis of Endothelin

Relatively little is known about the synthetic pathway of ET peptides. Similar to other hormones and neurotransmitters, ET peptides arise through proteolytic processing of isopeptide-specific prohormones. PreproETs are large polypeptides (approximately 200 amino acids) with species- and isopeptide-specific differences in amino acid sequence. In addition, preproETs also contain a cysteine-rich, "ET-like" region (15 amino acids), but the activity and biological significance of this region remains unclear. Unlike other peptide hormones, processing of the preprohormone to the prohormone does not simply involve cleavage of the NH\(_2\)-terminal signal sequence but also involves the loss of considerable sequences toward the COOH-terminus. Co-translational and posttranslational modifications of the preproET species are unclear.

In cultured cells, preproET-1 is proteolytically cleaved to form a 38 (human) or 39 (porcine) amino acid proET-1. Then a putative "endothelin-converting enzyme" cleaves at Trp-21-Val-22 of proET-1 to form the mature ET-1 peptide. To date, the endothelin-converting enzyme has been difficult to study, but characterization of this endopeptidase will have important implications for our understanding of how ET synthesis is regulated and for possible pharmacological blockade of ET synthesis.

It currently is unclear whether ET is stored in secretory granules or whether de novo synthesis is required for secretion. Immunostaining in the posterior pituitary suggests that ET is present in granules and that these granules are depleted on water deprivation.

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These results suggest classical secretion of an endocrine peptide. In contrast, ET synthesis and release in other cell types appears to be dependent on differential regulation of ET gene expression. The reason for this apparent paradox is unclear but may reflect different signaling modes (i.e., endocrine, neuroendocrine, paracrine) for ET peptides in different tissues. A variety of stimuli have been shown to increase ET synthesis, including Ca²⁺ ionophores, phorbol esters, thrombin, transforming growth factor β, endotoxin, fluid-mechanical shear stress, and anoxia (see References 3, 4, and 12 for review). ET appears to have a short t½ in plasma, and the majority of circulating ET is cleared after one pass through the lungs, although it remains unclear whether ET is metabolically inactivated or removed by receptor-dependent endocytosis. These findings and others have been cited as evidence that ET functions as a local hormone synthesized by specific endothelial or epithelial cells and acts in either a paracrine or autocrine mode on adjacent target cells. It remains possible, however, that under some conditions, ET released into the peripheral circulation might act as a classical endocrine hormone. Accumulating evidence suggests that ET synthesis is not limited to endothelial and epithelial cells; for example, glial cells and glomerular mesangial cells also synthesize endothelin.

**Endothelin Is a Multigene Family**

Abundant evidence suggests that each ET isopeptide is encoded by a different gene. Genomic DNA blot analysis reveals single genes for preproET in the human, rat, and porcine genomes. In humans, loci for preproET-1 and preproET-3 have been mapped to chromosomes 3 and 20, respectively. The gene for human preproET-1 (approximately 6.8 kb) contains five exons and four introns; sequences encoding mature ET-1 are located in the second exon, and those for the 15-amino acid ET-like peptide are located within the third exon. In both the preproET-1 and ET-3 genes, it seems likely that the second and third exon derive from a common progenitor exon, leading Bloch and coworkers to hypothesize that the ET-1, ET-2, and ET-3 genes evolved by gene duplication events. The promoter region of the preproET-1 gene contains a typical eukaryotic TATA box and CAAT sequence. Moreover, 5' upstreamputative cis-acting sequences exist for activating protein 1, nuclear factor 1, and acute phase response trans-acting factors, although transcriptional regulation via these sequences has yet to be demonstrated experimentally. Functional analysis of the preproET-1 gene promoter by Lee and coworkers reveals two promoter regions, located at sequence -148 to -117 and -117 to -98, that appear to be necessary for transcriptional activation. In heterologous promoter constructs using a DNA fragment containing these two regions, this sequence acted in a positive and endothelial cell-specific fashion. Further analysis of this promoter should reveal how ET peptides are differentially expressed only in specific tissues. It also is important to note that analysis of the 3' noncoding region of preproET-1 mRNA reveals AU-rich sequences thought to decrease mRNA stability in the cytoplasm. Indeed, the t½ of preproET-1 mRNA is short (approximately 15 minutes), and the mRNA transcripts are superinduced by cycloheximide. Thus, preproET-1 gene expression appears to be regulated at several levels, including transcriptional control and mRNA stability.

**Biological Effects of Endothelin**

**Cardiovascular Effects: Hemodynamic and Cardiac**

ET has a surprisingly wide range of biological actions in diverse tissues and species (Table 1). Intravenous injection of ET into conscious or anes-
TABLE 1. Biological Actions of Endothelin Peptides

<table>
<thead>
<tr>
<th>Hemodynamic effects</th>
<th>Cardiac effects</th>
<th>Neuroendocrine effects</th>
<th>Renal effects</th>
<th>Smooth muscle effects</th>
<th>Promotogenic effects</th>
<th>Gene expression</th>
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<tr>
<td>- Initial depressor action followed by sustained pressor effect</td>
<td>- Positive inotropic and chronotropic effects on myocardium</td>
<td>- Increases plasma levels of atrial natriuretic factor, renin, aldosterone, and catecholamines</td>
<td>- Increases renal vascular resistance</td>
<td>- Contracts vascular smooth muscle; veins probably more sensitive than arteries</td>
<td>- Stimulates mitogenesis in vascular smooth muscle cells, 3T3 fibroblasts, and glomerular mesangial cells</td>
<td>- Upregulates steady-state mRNA for VL-30, c-fos, and c-myc proto-oncogenes.</td>
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ET first evoke a transient depressor phase, which has been attributed to endothelial release of prostacyclin and endothelin-derived relaxing factor, followed by a marked and extended pressor phase. The duration of the pressor phase is longer than with any constrictor peptide yet tested, and 1–3 hours typically are required for mean arterial pressure to return to baseline levels. As expected, ET is a potent contractile agent for numerous vascular smooth muscle strips in vitro. Much attention has focused on the ability of ET to regulate cardiac function. ET exerts a strong, dose-dependent positive inotropic effect on the myocardium. Blockers of β-adrenergic, α-adrenergic, serotonergic, and histaminergic receptors and pretreatment with indomethacin failed to inhibit the inotropic action of ET, suggesting a direct effect on the myocardium. ET appears to augment inotropic activity by elevating cytosolic free \([Ca^{2+}]\), either by increasing the opening probability of L-type, voltage-activated \([Ca^{2+}]\) channels or by increasing activity of the phosphoinositide cascade with subsequent release of intracellular \([Ca^{2+}]\) from the inositol 1,4,5-trisphosphate \((Ins[1,4,5]P_3)\)-sensitive intracellular stores. In the guinea pig right atria, ET also elicits a positive chronotropic effect, but the mechanism involved is not understood. The coronary arteries also are an important site of action for ET peptides. Coronary arteries have a high density of binding sites for ET-1 and ET-2, and infusion of these peptides causes intense vasoconstriction leading in some cases to lethal myocardial ischemia. ET has been postulated to play a role in cardiovascular disease. Plasma levels of ET are increased in myocardial infarction, cardiogenic shock, congestive heart failure, and hypertension. Moreover, ET has been suggested to contribute to the development of postischemic myocardial injury and hypertension.

Endocrine Effects of Endothelin

In addition to having primary effects as a potent peptide hormone, ET also exerts indirect actions through interactions with diverse endocrine systems. Infusion of ET into humans and dogs causes a rapid increase in the plasma levels of atrial natriuretic factor, renin, aldosterone, and circulating catecholamines. In most studies, ET increases epinephrine more than norepinephrine, which suggests that sympathetic stimulation of the adrenal medulla accounts for the increased circulating catecholamine levels. It remains uncertain whether the ability of ET to increase the level of circulating hormones is a direct effect or is secondary to the hemodynamic effects of ET. However, the finding that renin and aldosterone, which would preserve extracellular fluid volume and increase blood pressure, increase after infusion of a vasoconstrictor peptide suggests mechanisms other than secondary effects due to the increase in arterial pressure. In addition, cultured bovine adrenal cortical cells, ET enhances adrenocorticotropic-stimulated aldosterone.

Endothelin as a Neuropeptide

ET also appears to regulate synaptic transmission in both the central and peripheral nervous systems by acting as a neuromodulator and perhaps even as a neurotransmitter. For example, ET modulates the release of catecholamines from sympathetic terminal and from chromaffin cells in the adrenal medulla. There also is indirect evidence that ET functions as a neurotransmitter in the central nervous system.

Several observations suggest that ET functions as a neuropeptide regulating the hypothalamic–pituitary axis. ET-1 stimulates the release of luteinizing hormone and follicle-stimulating hormone from cells of the anterior pituitary; in fact, ET is as potent as gonadotropin-releasing hormone itself in stimulating gonadotroph release. Similar to gonadotropin-releasing hormone, ET increases cytosolic free \([Ca^{2+}]\), which in turn stimulates secretion of the gonadotrophs from the anterior pituitary. Although gonadotropin-releasing hormone and ET bind to separate receptors on pituitary cells, these ligands appear to use the same signal transduction pathways to evoke hormone secretion. ET gene expression also has been demonstrated in the hypothalamus and in the axons and postsynaptic terminals of paraventricular and supraoptic neurons. ET–like immunoreactive material also has been demonstrated in postsynaptic paraventricular neurons, and these products are re-
leashed by water deprivation, suggesting secretion of ET by physiological stimuli. Thus, like the classical hormones of the posterior pituitary, arginine vasopressin and oxytocin, ET appears to be synthesized in the hypothalamus, transported to the posterior pituitary, and secreted upon appropriate neuroendocrine stimuli. The neural inputs controlling ET release and the target hormones remain to be characterized.

**Endothelin Is a Potent Renal Peptide**

The intrarenal effects of ET include dramatic reductions in renal blood flow, with efferent glomerular arteriolar constriction being greater than that of afferent glomerular arterioles. Contraction of the arcuate and interlobular arteries contributes to the decline in renal blood flow. Glomerular filtration rate also decreases in response to the reductions in flow and as a result of decreases in the glomerular ultrafiltration coefficient. ET also causes marked reductions in urine volume and either modest increases or marked reductions in Na⁺ excretion, depending on the dose of ET administered. ET actions on sodium handling are complex and include reductions in the filtered load of sodium to tubular reabsorptive sites and attenuation of Na⁺,K⁺-ATPase activity in the medullary collecting duct via a prostaglandin E₂-dependent mechanism. It perhaps is surprising that ET increases urine flow rate and free water clearance despite the dramatic decline in glomerular filtration rate and renal blood flow. One possible explanation is that ET increases water excretion by inhibiting the effect of arginine vasopressin to stimulate water permeability in collecting ducts, but this hypothesis remains to be tested. There also is evidence that ET contributes to the pathogenesis of cyclosporine nephrotoxicity, glomerular inflammation, and postischemic renal injury (see Reference 38 for review). For example, cyclosporine increases ET synthesis from the damaged endothelium, and infusion of neutralizing antibodies against ET prevents the renal vasoconstriction and glomerular dysfunction associated with cyclosporine-induced renal disease. Because hypoxia is a potent stimulus of ET release, Firth et al suggested that ET mediates hemodynamically induced acute renal failure. Support for this view comes from the work of Kon and coworkers, who showed in a model of posts ischemic renal injury that ET-neutralizing antibodies reverse the reduction in single nephron glomerular filtration rate and renal blood flow. Thus, ET released by damaged endothelium or mesangial cells might contribute to the hypoperfusion and hypofiltration seen in postischemic renal injury.

**Other Biological Actions**

Other biological actions of ET remain poorly understood. ET contracts numerous nonvascular smooth muscle preparations from the gastrointestinal tract, trachea, lung, and bladder. ET also is a potent mitogen in vitro for vascular smooth muscle cells, 3T3 fibroblasts, and glomerular mesangial cells. The consequences of ET-induced mitogenesis in vivo are unknown, but similar to other regulatory peptides, it seems possible that the promitogenic effect of ET could contribute to vascular or glomerular remodeling in inflammation or other adaptive responses to vascular injury, including hypertension. Another potentially important biological action of ET is regulation of gene expression. ET increases the steady-state mRNA level of the VL-30 gene in 3T3 fibroblasts and of the c-fos and c-myc proto-oncogenes in vascular smooth muscle, 3T3 fibroblasts, and mesangial cells. The mechanisms by which ET regulates gene expression remain unknown; however, the finding that ET evokes the phosphoinositide cascade (see below) raises the possibility that ET upregulates inducible enhancers with phorbol ester- or Ca²⁺-responsive elements.

**Regulation of Transmembrane Signaling**

From the preceding discussion, it is clear that ET peptides are involved in a large array of biological functions. How can ET peptides perform these diverse actions? Abundant evidence suggests that ET initially activates a transduction process involving a cell-surface receptor, a coupling G protein, and phospholipase C. The consequences of activating this ubiquitous signal transduction process is outlined below.

**Receptors for Endothelin**

ET binds to specific plasma membrane receptors that are widely distributed in the lung, kidney, heart, intestine, adrenal gland, eye, and nervous system. [¹²⁵I]ET binding is not displaced by Ca²⁺ channel blockers, peptide neurotoxins, adrenergic agonists, or other regulatory peptides, suggesting that ET binds to a specific cognate receptor and not directly to an ion channel or other nonspecific receptor. Scatchard analysis in vitro demonstrates a range of apparent dissociation constants of approximately 0.1–10 nM and a high density of binding sites. Both saturation and competitive displacement analysis suggest that multiple subtypes of ET receptors exist with different affinities for ET isopeptides and tissue-specific distributions. Recent cross-linking studies of ET receptors support the existence of multiple receptor subtypes and further support the previous binding and pharmacological data. Although these experiments support the view that ET binds to plasma membrane receptor subtypes coupled to G proteins, a full understanding awaits purification, cloning, and sequencing of ET receptors. (See “Note Added in Proof.”)

**Endothelin Peptides Evoke the Phosphoinositide Cascade**

Cultured glomerular mesangial cells have been a useful model to study the pathways of transmembrane signaling after activation of ET receptors. With the exceptions discussed below, the data from mesangial cells closely parallel those in other cells, such as vascular smooth muscle cells, fibroblasts, and neurons. Activation of phospholipase C is the initial transmembrane event after activation of ET receptors in mesan-
gial cells. For example, ET-1 causes a dose-dependent increase in phosphatidylinositol turnover measured at 15 minutes in the presence of LiCl. Activation of phospholipase C by ET produces at least two second messengers: 1) the neutral diacylglycerol, which remains within the plane of the plasma membrane and activates protein kinase C (PKC); and 2) the water-soluble Ins(1,4,5)P₃, which diffuses and binds to a receptor-gated Ca²⁺ channel to release Ca²⁺ from specialized stores within the endoplasmic reticulum, or calciosome. ET-1 also elevates the cytosolic concentration of another inositol phosphate isomer, Ins(1,3,4,5)P₄, which appears to contribute to the complex patterns of Ca²⁺ signaling by ET. Activation of the phosphoinositide cascade by ET peptides is thought to mediate many of the biological actions of ET, including contraction by pharmacomechanical coupling, secretion, and perhaps mitogenesis. Although we focus here primarily on Ca²⁺ signaling, activation of PKC by diacylglycerol is thought to mediate many of the biological actions after ET receptor activation (see References 3 and 5).

Ca²⁺ Signaling by Endothelin Peptides

Using mesangial cells loaded with the fluorescent Ca²⁺ indicator fura-2, we have investigated Ca²⁺ signaling by ET peptides. ET isopeptides cause a biphasic increase in cytosolic free [Ca²⁺] (i) consisting of a rapid (2–5 seconds) spike increase followed by a lesser but sustained phase (Figure 2). The sustained phase of [Ca²⁺] is especially pronounced, and in some coverslips Ca²⁺ returned to basal levels only after 20 minutes. ET-1–induced Ca²⁺ signaling requires conversion of proET-1 to ET-1, suggesting that in proET-1, the mature ET-1 peptide is constrained in an inactive conformation. Although similar results have been observed for all ET isopeptides, the increment in [Ca²⁺] is dose-dependent, with ET-2=ET-1>sarafotoxin S6b>ET-3. Thus, ET isopeptides and S6b evoke similar elevations of [Ca²⁺] in mesangial cells but with dissimilar potencies and kinetics.

Two distinct but interdependent mechanisms contribute to ET-induced increments in [Ca²⁺]. ET releases Ca²⁺ from intracellular stores, presumably through the action of Ins(1,4,5)P₃, to gate an intracellular Ca²⁺ channel, but ET also increases influx of extracellular Ca²⁺ into the cytosol. These two mechanisms (intracellular release and extracellular influx) work in concert to produce an integrated Ca²⁺ signal. In mesangial cells, for example, the spike increase in [Ca²⁺], results from both intracellular release of Ca²⁺ and extracellular influx of Ca²⁺, whereas the sustained phase of [Ca²⁺], depends on extracellular influx (Figure 2). Influx of extracellular Ca²⁺ occurs through voltage-gated channels or through receptor-gated, voltage-independent channels. Our experiments in cultured rat and human mesangial cells demonstrate that ET promotes Ca²⁺ entry by receptor-gated Ca²⁺ channels and that voltage-gated, dihydropyridine-sensitive channels play little or no role. Although the molecular mechanisms and functions of receptor-gated Ca²⁺ entry are incompletely understood, it seems likely that receptor-mediated Ca²⁺ entry by ET contributes to rapid or localized Ca²⁺ signaling as well as to maintenance of the sustained elevation of [Ca²⁺]. In other cell types, such as vascular smooth muscle, ET not only activates receptor-mediated Ca²⁺ entry but also indirectly modulates the activity of L-type voltage-operated Ca²⁺ channels. Thus, ET evokes multiple, cell-specific pathways of Ca²⁺ influx to produce diverse Ca²⁺ signals.
Ca²⁺ signaling by ET peptides in human mesangial cells, especially ET-1 and ET-2, results in periodic oscillations of [Ca²⁺], after the spike increase. These oscillations can be initiated but not sustained in the absence of extracellular Ca²⁺. These oscillations of [Ca²⁺], represent synchronized Ca²⁺ signaling in a population of cells, as opposed to the commonly observed oscillations in single cells. It seems likely that in human mesangial cells, the ET-stimulated increment in [Ca²⁺], passes through gap junctions to trigger a wave of Ca²⁺ in neighboring cells. Because mesangial cells in vivo are connected by an extensive network of gap junctions, we hypothesize that ET peptides might recruit local populations of mesangial cells to function as a syncytium.

Turning Off the Signal

Like most signal transduction systems, ET-mediated Ca²⁺ signaling is tightly regulated. We have touched on several mechanisms by which ET stimulates Ca²⁺ signaling, and we now will address at least three mechanisms that function as negative-feedback signals to regulate Ca²⁺ signaling by ET peptides. First, activation of PKC attenuates Ca²⁺ signaling by ET peptides. PKC is a Ca²⁺- and phospholipid-dependent protein kinase that modulates Ca²⁺ channel activity and Ca²⁺ signaling. Preincubation with phorbol esters or diacylglycerol analogues, which activate PKC, markedly attenuates both the spike and sustained phases of Ca²⁺ signaling by ET peptides (Figure 3). Further evidence for the notion that PKC downregulates Ca²⁺ signaling by ET comes from studies of PKC downmodulation to test the requirement for PKC. In mesangial cells depleted of PKC, ET stimulates greater increases of [Ca²⁺] than in concurrent controls (Figure 3). Because Ca²⁺ influx was unaffected in PKC-depleted cells, we conclude that activation of PKC by ET acts as a negative-feedback signal to attenuate release of Ca²⁺ from intracellular stores. PKC might downregulate Ca²⁺ signaling by decreasing phosphoinositide turnover or by inhibiting refilling of intracellular Ca²⁺ stores.

A second mechanism for turning off Ca²⁺ signaling by ET relates to PKC-independent desensitization by ET ligands. ET isopeptides and S6b desensitize the increase in [Ca²⁺], caused by subsequent additions of the same ET agonist. Preincubation with any ET isopeptide or S6b reduces or abolishes the [Ca²⁺], increase stimulated by the subsequent, equimolar addition of any other isopeptide. ET-mediated desensitization persists in cells depleted of PKC, suggesting that this adaptive response is independent of PKC. It is important to note that many investigators report complex, partially reversible binding of ET to its receptor; thus, continued receptor occupancy might account for some of the desensitization observed in our studies. However, it is also likely that other mechanisms such as phosphorylation of the ET receptor by homologous or heterologous pathways might contribute to desensitization induced by ET ligands.

In preliminary experiments, we have characterized a third negative-feedback mechanism to regulate Ca²⁺ signaling by ET. Using an inhibitor of the endoplasmic reticular Ca²⁺-ATPase, 2,5-Di-(tert-butyl)-1,4-benzohydroquinone (tBuBHQ), we have identified a Ca²⁺ efflux pathway stimulated by ET. tBuBHQ causes a sustained increase in [Ca²⁺], by preventing reuptake into intracellular stores. When added during the tBuBHQ-stimulated increase in [Ca²⁺], ET caused a steady decrease in [Ca²⁺], to
basal levels, but Ca\textsuperscript{2+} influx was not diminished. Taken together, these data demonstrate that ET-stimulated Ca\textsuperscript{2+} signaling is attenuated by a ligand-mediated Ca\textsuperscript{2+} efflux pathway independent of Ca\textsuperscript{2+} reuptake into the microsomal pool. This pathway might constitute a mechanism by which ET helps terminate its own signal. Similar results have been observed by Cass et al\textsuperscript{27} for other Ca\textsuperscript{2+}-mobilizing hormones.

In summary, ET is an important family of regulatory peptides synthesized by endothelial and epithelial cells, neurons, and perhaps specific connective tissue cells in vivo. ET synthesis and release is increased by a variety of stimuli, including Ca\textsuperscript{2+} ionophores, phorbol esters, thrombin, transforming growth factor \(\beta\), endotoxin, fluid-mechanical shear stress, and anoxia. ET appears to function mostly as a paracrine or autocrine hormone; however, ET also might function as a classical endocrine hormone as well. ET has numerous biological activities relating to vasoconstriction and smooth muscle contraction; cardiac, pulmonary, and renal function; neurotransmission; and mitogenesis and tissue remodeling. Although numerous signal transduction pathways are activated by ET, it is well-documented that induction of the phosphoinositide cascade mediates many of the actions of ET. ET also invokes complex mechanisms to stimulate a tightly regulated Ca\textsuperscript{2+} signaling system.


References


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