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International Union of Pharmacology. XXIX. Update on Endothelin Receptor Nomenclature

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Abstract*——In mammals, the endothelin (ET) family comprises three endogenous isoforms, ET-1, ET-2, and ET-3. ET-1 is the principal isoform in the human cardiovascular system and remains the most potent and long-lasting constrictor of human vessels discovered. In humans, endothelins mediate their actions via only two receptor types that have been cloned and classified as the ET_A and ET_B receptors in the first NC-IUPHAR (International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification) report on nomenclature in 1994. This report was compiled before the discovery of the majority of endothelin receptor antagonists (particularly nonpeptides) currently used in the characterization of receptors and now updated in the present review. Endothelin receptors continue to be classified according to their rank order of potency for the three endogenous isoforms of endothelin. A selective ET_A receptor agonist has not been discovered, but highly selective antagonists include peptides (BQ123, cyclo-[D-Asp-L-Pro-D-Val-L-Leu-D-Trp-]; FR139317, *N*- [(hexahydro-1-azepinyl)carbonyl]L-Leu(1-Me)D-Trp-3 (2-pyridyl)-D-Ala) and the generally more potent nonpeptides, such as PD156707, SB234551, L754142, A127722, and TBC11251. Sarafotoxin S6c, BQ3020 ([Ala^{11,15}]Ac-ET-1$_{(6-21)}$), and IRL1620 [Suc-(Glu^9, Ala^{11,15})-ET-1$_{(8-21)}$] are widely used synthetic ET_B receptor agonists. A limited number of peptide (BQ788) and nonpeptide (A192621) ET_B antagonists have also been developed. They are generally less potent than ET_A antagonists and display lower selectivity (usually only 1 to 2 orders of magnitude) for the ET_B receptor. Radioligands highly selective for either ET_A (^{125}I-PD151242, ^{125}I-PD164333, and ^{3}H-BQ123) or ET_B receptors (^{125}I-BQ3020 and ^{125}I-IRL1620) have further consolidated classification into only these two types, with no strong molecular or pharmacological evidence to support the existence of further receptors in mammals.

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I. Introduction

In mammals, the endothelin (ET[1]) family comprises three endogenous isoforms, ET-1, ET-2, and ET-3 (Yanagisawa et al., 1988; Inoue et al., 1989). These peptides mediate their actions via two receptor types, classified as the ET_A and ET_B receptors in the first NC-IUPHAR (International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification) receptors report on nomenclature by Masaki et al. (1994). This report was compiled before the discovery of the majority of ET receptor antagonists (particularly nonpeptides) currently used in the characterization of receptors and now updated in the present review. The single proposed ET_B receptor antagonist included by Masaki et al. (1994) was subsequently shown to lack efficacy and was withdrawn by the original discoverers (Urade et al., 1994). This review reflects both peptide and nonpeptide ET_B antagonists that are the compounds of choice. A second major change is the inclusion of radioligands that are highly selective for either ET_A (^{125}I-PD151242, ^{125}I-PD164333, and ^{3}H-BQ123 (cyclo-[D-Asp-L-Pro-D-Val-L-Leu-D-Trp-]) or ET_B receptors [^{125}I-BQ3020 ([Ala^{11,15}]Ac-ET-1$_{(6-21)}$) and ^{125}I-IRL1620 (Suc-(Glu^{9}, Ala^{11,15})-ET-1$_{(8-21)}$)] that have been crucial to consolidating the present classification. Masaki et al. (1994) referred to a gene encoding a third receptor (P32940) cloned from the amphibian *Xenopus laevis* dermal melanophores, which was reported to be ET-3 specific (ET-3 > ET-1), the so-called ET_C receptor. However, to date, molecular and ligand binding techniques have failed to identify a mammalian homolog. Since NC-IUPHAR is predominantly interested in human receptors, with an extension to mammalian receptors, this review follows the recommendation to exclude consideration of nonmammalian receptors in the classification.

ET-1 is the principal isoform in the human cardiovascular system and remains the most ubiquitous, potent, and unusually long-lasting constrictor of human vessels discovered. ET-1 is unusual among the mammalian bioactive peptides in being released from a dual secretory pathway (Russell et al., 1998). The peptide is continuously released from vascular endothelial cells by the constitutive pathway, producing intense constriction of the underlying smooth muscle and contributing to the maintenance of endogenous vascular tone (Haynes and Webb, 1994). The peptide is also released from endothelial cell-specific storage granules (Weibel-Palade bodies) in response to external physiological, or perhaps pathophysiological, stimuli producing further vasoconstriction (Russell et al., 1998). Thus, ET-1 functions as a locally released, rather than circulating, hormone, and concentrations are comparatively low in plasma and other tissues. ET-2 has been less extensively studied than other ET peptides, but it is present in human cardiovascular tissues and was as potent a vasoconstrictor as ET-1 in human arteries and veins (Maguire and Davenport, 1995). Endothelial cells do not synthesize ET-3, but the mature peptide is detectable in plasma (Matsumoto et al., 1994) and other tissues, including heart and brain. ET-3 is unique in that it is the only endogenous isoform that distinguishes between the two endothelin receptors. It has the same affinity at the ET_B receptor as ET-1 but, at physiological concentrations, has little or no affinity for the ET_A.

The only endogenous peptides with a high degree of sequence similarity to the ETs are the sarafotoxins (S6a, S6b, S6c, and S6d). This family of 21-amino acid (aa) peptides was originally discovered in the venom of a snake, *Atractaspis engadensis* (Takasaki et al., 1988).

II. Cloned Endothelin Receptors

Receptors can be identified by their amino acid structure and provide unambiguous evidence for expression of a gene encoding a particular type in specific cells or tissues. An increasing number of mammalian species have been studied, but only two ET receptors have been isolated and cloned (Table 1; Arai et al., 1990; Sakurai et al., 1990; Adachi et al., 1991; Lin et al., 1991; Nakamuta et al., 1991; Saito et al., 1991; Baynash et al., 1994). The deduced amino acid sequences for the two human receptors display only 59% similarity and are shown in Table 2. The amino acid sequences of ET_A receptors also differ between humans and other species, for example by 9% between human and rat ET_A receptors and by 12% for the ET_B. These may contribute to differences in efficacy and potency of selective agonists and antagonists.

The structures of the mature receptors have been deduced from the nucleotide sequences of the cDNAs.

TABLE 1
Cloned mammalian endothelin receptors

Potency:	Mammalian	
	ET_A	ET_B
	ET-1 = ET-2 > ET-3	ET-1 = ET-2 = ET-3
Human	427	442
Bovine	427	441
Rat	426	442
Mouse		442
Porcine	427	443
Equine		443

91% (Human–Rat); 94% (Human–Bovine); 59% (Human ET_A–Human ET_B); 89% (Human–Bovine ET_B); 88% (Human–Rat ET_B)

Values are the number of amino acids in the predicted receptor protein. Percentages indicate the degree of sequence similarity between receptor types. References: Arai et al., 1990; Sakuri et al., 1990; Hosoda et al., 1991; Kozuka et al., 1991; Lin et al., 1991; Nakamuta et al., 1991; Elshourbagy et al., 1992; Hosoda et al., 1994; Nishimura et al., 1995; Yang et al., 1998.

[1] Abbreviations: ET, endothelin; aa, amino acid(s); NC-IUPHAR, International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification; 7TM, seven-transmembrane; FR139317, *N*-[(hexahydro-1-azepinyl)carbonyl]L-Leu(1-Me)D-Trp-3(2-pyridyl)-D-Ala; BQ123, cyclo-[D-Asp-L-Pro-D-Val-L-Leu-D-Trp-]; IRL1620, Suc-(Glu^{9}, Ala^{11,15})-ET-1$_{(8-21)}$; BQ3020, [Ala^{11,15}]Ac-ET-1$_{(6-21)}$; PD142893, Ac-(β-Phynyl) D-Phe-L-Leu-L-Asp-L-lle-L-lle-L-Trp; SB209670, (1*RS*,2*SR*,3*RS*)-3-(2-carboxymethoxy-4-methoxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid.

TABLE 2
Amino acid sequences of the human ET_A and ET_B receptors

ET_A	M----------ETLCLRASF
ET_B	MQPPPSLCGRALVALVLACGLSRIWGEERGFPPDRA----TP- LLQTAEIMTPPTKTL
ET_A	WLALVGCVISDNPERYSTNLSNHVDDFTTFRGTELSFLVTTHQPTNLVLPSNGSMHNYC
ET_B	W----------PKGSNASLARSLAPAEVPKGDR----TAGSPPRTISPPP-------C
	I
ET_A	PQQTKITSAFKYINTVISCTIFIVGMVGNATLLRIIYQNKCMRNGPNALIASLALGDLI
ET_B	QGPIEIKETFKYINTVVSCLVFVLGIIGNSTLLRIIYKNKCMRNGPNILIASLALGDLL
	II III
ET_A	YVVIDLPINVFKLLAGRWPFDHNDFGVFLCKLFPFLQKSSVGITVLNLCALSVDRYRAV
ET_B	HIVIDIPINVYKLLAEDWPFGAE-----MCKLVPFIQKASVGITVLSLCALSIDRYRAV
	IV
ET_A	ASWSRVQGIGIPLVTAIEIVSIWILSFILAIPEAIGFVMVPFEYRGEQHKTCMLNATSK
ET_B	ASWSRIKGIGVPKWTAVEIVLIWVVSVVLAVPEAIGFDIITMDYKGSYLRICLLHPVQK
ET_A	--FMEFYQDVKDWWLFGFYFCMPLVCTAIFYTLMTCEMLNRRNGSLRIALSEHLKQRRE
ET_B	TAFMQFYKTAKDWWLFSFYFCLPLAITAFFYTLMTCEML-RKKSGMQIALNDHLKQRRE
	VI VII
ET_A	VAKTVFCLVVIFALCWFPLHLSRILKKTVYNEMDKNRCELLSFLLLMDYIGINLATMNS
ET_B	VAKTVFCLVLVFALCWLPLHLSRILKLTLYNQNDPNRCELLSFLLVLDYIGINMASLNS
ET_A	CINPIALYFVSKKFKNCFQSCLCCCCYQSKSLMTSVPMNGTSIQWKNHDQNNHNTDRSS
ET_B	CINPIALYLVSKRFKNCFKSCLCCWCQSFEEKQSLEEKQSCLKFKANDHGYDNFRSSNK
ET_A	HKDSMN
ET_B	YSSS

Membrane-spanning domains (I–VII) are shown underlined.

The encoded proteins contain seven stretches of 20 to 27 hydrophobic aa residues in both receptors, consistent with both subtypes belonging to the seven-transmembrane (7TM) domain , G protein-coupled rhodopsin-type receptor superfamily. Both receptors have an N-terminal signal sequence, which is rare among heptahelical receptors, with a relatively long extracellular N-terminal portion preceding the first transmembrane domain. There are two separate ligand interaction subdomains on each endothelin receptor. The extracellular loops, particularly between TM 4 to 6, determine selectivity.

At present, there is no justification for further types beyond the current classification into ET_A and ET_B in mammalian tissue. Functional studies have suggested that PD142893 [Ac-(beta-phynyl) D-Phe-L-Leu-L-Asp-L-lle-L-lle-L-Trp], a hexapeptide antagonist, can block the vasodilator actions of ET-1 at endothelial ET_B receptors but not constrictor responses mediated by ET_B smooth muscle receptors (Warner et al., 1993; Douglas et al., 1995). However, in the ET_B receptor gene knockout mouse, both the PD142893-sensitive vasodilator response and the PD142893-resistant contractile response to the ET_B agonist sarafotoxin S6c were completely absent. These results indicate that the pharmacologically heterogeneous responses to S6c are mediated by ET_B receptors derived from the same gene (Mizuguchi et al., 1997). In agreement, a very detailed binding study (including PD142893) was unable to distinguish between ET_B receptors expressed by human isolated endothelial cells compared with smooth muscle cells in culture (Flynn et al., 1998). Furthermore, in human tissue, both ET_A- and ET_B-selective radiolabeled ligands bound with a single affinity and Hill slopes close to unity (Molenaar et al., 1992; Davenport et al., 1994, 1998; Davenport, 1997). Similarly, competition studies using unlabeled ligands provided no evidence for further subtypes (Peter and Davenport, 1996; Russell and Davenport, 1996).

III. Mammalian Splice Variants of Endothelin$_A$ and Endothelin$_B$ Receptors

Alternative splice variants of ET receptors have been reported but to date these variants either show little or no change in binding characteristics and their physiological or pathophysiological significance is unclear. The following is intended to be a guide only because the field has not developed sufficiently with unequivocal quantitative evidence for significant expression and function in native tissues rather than artificial cell lines, to make any firm recommendation for classification.

The existence of alternative splice variants of the ET_B receptor in human and porcine tissue has been reported. A variant human ET_B receptor that results in a 10-aa increase in the length of the second cytoplasmic domain has been described (Shyamala et al., 1994). Messenger RNA measured by reverse transcription-polymerase chain reaction in a limited number of human tissues was found only in low abundance in human brain (which expresses one of the highest densities of ET_B receptors) as well as the heart, lung, and placenta but was not detected in other species tested (bovine, porcine, and rat). The increase in amino acids did not result in any change in either ligand affinities or signal transduction (cAMP and inositol phosphate turnover), and the physiological importance of this variant receptor is unclear.

Elshourbagy et al. (1996) discovered a second splice variant from a human placental library. Analysis indicated that the deduced polypeptide was identical to the

native ET_B sequence except that the 42 aa of the intracellular carboxy terminus of the former was replaced with an alternative 36-aa sequence, bearing no significant homology with other known proteins. Northern blot analysis indicated an mRNA species of 2.7 kilobases, which was expressed in all of a limited number of human tissues tested (lung, placenta, kidney, and skeletal muscle) in addition to mRNA encoding the native ET_B receptor. However, mRNA encoding the variant was not particularly abundant. The relative ratio of each individual variant mRNA was less than 10% of the total ET_B mRNA, with the intriguing exception of skeletal muscle where it represented more than 40%. Two cell types were also examined, endothelial and smooth muscle cells, but only mRNA encoding the native receptor was detected. The cloned variant receptors expressed in COS cells displayed similar binding properties for ET peptides compared with expressed native receptors in the same cells, indicating unsurprisingly that the splice variant had little or no effect on ligand binding. However, functional studies showed that ET-stimulated inositol phosphate accumulation in expressed native receptors was abolished in cells transfected with the splice variant. These data suggest the difference in the amino acid sequences between the two receptors may alter functional coupling in the variant receptor.

Nambi et al. (2000) detected a novel cDNA from another species, porcine cerebellum, that was predicted to encode an ET_B receptor also with alternate splicing of the carboxy terminus, resulting in a deduced polypeptide of 429 aa, 14 residues shorter than the wild-type receptor. The relative abundance of mRNA encoding the splice variant compared with the wild-type receptor was not reported, but mRNA was detected in ET_B-rich tissues including porcine lung, kidney, and cerebellum. However, the splice variant did not alter the binding of radiolabeled ET-1 or functional coupling when expressed in COS cells. The lack of effect on inositol phosphate accumulation is in marked contrast to the human variant (see above) previously described by this group. Combined with the lack of sequence similarity between the human (38 aa) and porcine (29 aa) carboxy terminal splice variants, it is not clear whether the porcine variant is a homolog of the human or whether these are distinct splice variants.

Cheng et al. (1993) identified cDNA from rat brain, which they described as producing a receptor protein with four amino acid substitutions that displayed equal affinity for the three ET isoforms. However, Cheng et al. (1993) probably described the correct rat ET_B sequence, correcting a sequencing error in the previously deduced sequence of Sakurai et al. (1990), for the following reasons. The Cheng et al. (1993) sequence has 3 extra bases in a 9-base span, which corrects a pair of adjacent frameshifts in the Sakurai et al. sequence, making the DNA sequence identical to the mouse sequence (Hosoda et al., 1994) in the same region and matching 3 of 4 amino acids in the human sequence as opposed to 0 of 4 with the Sakurai et al. sequence. Cheng et al. (1993) also report a different sequence in the 5′-untranslated region, which could be an alternative first exon, reflecting transcription initiating from an alternative promoter. It is also possible, although less likely, that one of the 5′-untranslated region sequences is an artifact, such as a chimeric cDNA or sequencing assembly error.

The human ET_A receptor gene has been proposed to give rise to at least three alternatively spliced ET_A receptor transcripts corresponding to deletion of exon 3 (producing a protein with two membrane-spanning domains), exon 4 (producing a protein with three membrane-spanning domains), and exon 3 plus exon 4 (producing a protein lacking the third and fourth domain) (Miyamoto et al., 1996; Bourgeois et al., 1997). Although alternative transcripts were identified in human tissues including lung, aorta, and atrium, the truncated receptors when expressed in COS cell lines did not bind ET-1 (Miyamoto et al., 1996), and a physiological role remains unclear. Intriguingly, mRNA encoding the putative truncated receptor with the deletion of exon 3 plus 4 was more abundant than the wild type in human melanoma cell lines and melanoma tissue (Zhang et al., 1998).

IV. Physiological Role of Receptors

Endothelin receptors are widely expressed in all tissues, which is consistent with the physiological role of endothelins as ubiquitous endothelium-derived vasoactive peptides, contributing to the maintenance of vascular tone. In humans, ET_A receptors predominate on the smooth muscle of blood vessels, and the low density of ET_B receptors ($<15\%$) also present on the smooth muscle contributes little to vasoconstriction in either normal or diseased tissue (Maguire and Davenport, 1995). ET_B receptors are the principal type in the kidney, localizing to nonvascular tissues. Evidence is emerging that the ET_B receptor functions as a "clearing receptor" to remove ET from the circulation. ET_B receptors localized to the single layer of endothelial cells that line all blood vessels, may play a role in the release of endothelium-derived relaxing factors, such as nitric oxide and prostanoids (Warner et al., 1989), where all three isoforms have a similar potency (de Nucci et al., 1988). Although ET_A receptors present on smooth muscle cells are mainly responsible for contraction throughout the human vasculature, the situation in animals is more complex since the relative contribution from activating constrictor ET_B receptors can vary, depending on the species and vascular bed. In some blood vessels, such as the rabbit saphenous vein, rabbit jugular vein, rat renal vascular bed, and porcine pulmonary vein, ET_B receptors mediate vasoconstriction. In other vessels, ET-1 is thought to mediate vasoconstriction by activating both receptors.

Receptors are also localized to nonvascular structures, such as epithelial cells, as well as occurring in the central nervous system on glia and neurones. Endothelin stimulates proliferation in a number of different cell types, including smooth muscle cells (mainly via the ET_A subtype) or astrocytes (ET_B). In most of these cells, ET is thought to be comitogenic, potentiating the actions of other growth factors such as platelet-derived growth factor.

V. Endogenous and Synthetic Agonists

ET receptors continue to be classified (Table 3; Davenport, 2000) according to their rank order of potency for the endogenous ET isoforms. A selective ET_A receptor agonist has not been discovered.

Sarafotoxin S6c is one of the most widely used ET_B-selective agonists, displaying over 200,000-fold selectivity in the rat (William et al., 1991), although the peptide is much less selective in human tissues, perhaps reflecting species differences in the receptors (Russell and Davenport, 1996). [$Ala^{1,3,11,15}$]ET-1 (Saeki et al., 1991), the linear analog of ET-1 in which the disulfide bridges have been removed by substitution of Ala for Cys residues, is ET_B-selective. The truncated linear synthetic analogs BQ3020 and IRL1620 are the most widely used selective synthetic agonists to characterize ET_B receptors. The compounds cause endothelium-dependent vasodilatation in preparations such as porcine pulmonary artery, which is consistent with ET_B receptor-mediated release of relaxing factors from the endothelium.

VI. Radiolabeled Agonists

Most studies characterizing and localizing ET receptors use ^{125}I-ET-1, directly labeled via the Tyr^{13} (Table 3). This ligand binds with the same affinity to both ET_A and ET_B receptors and is stable under nonphysiological binding conditions with little or no degradation of labeled ET-1 being detected. ^{125}I-ET-2, ^{125}I-vasoactive intestinal contractor (the murine isoform of ET-2), and ^{125}I-sarafotoxin 6b have been labeled and used in saturation assays where they also bind to both receptors (Davenport and Morton, 1991; Maguire et al., 1996).

ET-3 can be labeled at Tyr^6, Tyr^{13}, and Tyr^{14}. Tyr^6 is generally used, as it is more difficult to separate ^{125}I-ET-3 labeled at the latter two Tyr residues, although all three ET-3 ligands have similar affinities. The selectivity of ET-3 for ET_B versus ET_A receptors is often only about two orders and it is difficult to precisely delineate the two receptors using this labeled peptide in saturation assays. ET_B receptors are usually characterized using ^{125}I-BQ3020 (Ihara et al., 1992b; Molenaar et al., 1992), which binds with subnanomolar affinity to the ET_B receptor, with at least 1500-fold selectivity for this receptor over the ET_A. Alternatively, the truncated analog ^{125}I-IRL1620 can also be used, particularly in animal tissues (Watakabe et al., 1992).

VII. Antagonists

Antagonists are currently classified as either ET_A-selective, ET_B-selective, or mixed antagonists that display similar affinity for both receptors. The most highly selective peptide antagonists (4 to 5 orders of selectivity) for the ET_A receptors are the cyclic pentapeptide BQ123 (Ihara et al., 1992a) and the modified linear peptide FR139317 (*N*-[(hexahydro-1-azepinyl)carbonyl]L-Leu(1-Me)D-Trp-3(2-pyridyl)-D-Ala; Aramori et al., 1993). Unlike peptide antagonists, many nonpeptide ET_A receptor-selective antagonists have oral bioavailability and some may cross the blood-brain barrier. The majority are more potent, with pA_2 values of up to 10 compared with 7 or 8 for BQ123 or FR139317, but are less selective, and plasma binding may also be significant in vivo.

VIII. Radiolabeled $Endothelin_A$ Selective Antagonists

^{125}I-PD151242 is widely used to characterize and localize ET_A receptors. This linear tetrapeptide analog of FR139317, binds with subnanomolar affinity to the ET_A receptor and has about 10,000-fold selectivity for this receptor in human and animal tissues. A nonpeptide ET_A-selective ligand has also been developed, ^{125}I-PD164333 (Davenport et al., 1998) with comparable affinity as well as a tritiated ligand, ^{3}H-BQ123 (Ihara et al., 1995). The above ligands are available commercially either as catalog items or custom syntheses.

IX. $Endothelin_B$ Selective Antagonists

A more limited number of peptide (e.g., BQ788) and nonpeptide (e.g., A192621) ET_B antagonists have been developed, reflecting the lack of clinical need for this type of compound. They are less potent than ET_A antagonists and display lower selectivity (usually only 1 to 2 orders of magnitude) for the ET_B receptor (Table 3).

X. $Endothelin_A$/$Endothelin_B$ Antagonists

The distinction between antagonists that are ET_A-selective and those that block both ET_A and ET_B receptors is not precise but generally the former display greater than 100-fold selectivity for the ET_A subtype, and the latter less than 100-fold. These compounds are seldom reported as having equal affinity for both receptors, and this should be taken into consideration in experimental designs. Nonpeptide compounds included bosentan (RO470203, Tracleer; Actelion, San Francisco, CA) (Clozel et al., 1994), SB209670 (Elliott et al., 1994), SB217242 (enrasentan; Ohlstein et al., 1996), and RO610612 (tezosentan; Clozel et al., 1999). Plasma binding may also be significant in vivo.

TABLE 3
Classification of endothelin receptors

Receptor	ET_A
Receptor Code	2.1:ET:1:ETA:
Previous names	None
Structural information	7TM h 427 aa, P25101, chr, 4; (Adachi et al., 1991) r 426 aa, P26684; (Lin et al., 1991)
Functional assays	Vasoconstriction in rat aorta
Agonists	Selective: none
Agonist potencies	ET-1 = ET-2 > S6b ≫ ET-3 (human coronary artery)
Antagonist potencies	BQ123 (pA_2 6.9–7.4; Ihara et al., 1992a) PD155080 (8–8.5; Maguire et al., 1995) FR139317 (7.3–7.9; Aramori et al., 1993) PD156707 (8–8.7; = CI1020; Doherty et al., 1995) SB234551 (9; Ohlstein et al., 1998) L754142 (7.7–8.7; Williams et al., 1995) BMS182874 (6.2; Stein et al., 1994) A127722 (9–10.5; ABT627; Opgenorth et al., 1996) TBC11251 (8.0; Wu et al., 1997) LU127043 (7.3; Raschack et al., 1995) LU135252; (Münter et al., 1996)
Radioligand assays	human, rat and porcine heart; A10 smooth muscle cells
Radioligands	^{125}I-ET-1 (K_d = 0.01–5 nM) Davenport, 1997 ^{125}I-PD151242 (0.5 nM) Davenport et al., 1994 ^{125}I-PD164333 (0.2 nM) Davenport et al., 1998 ^{3}H-BQ123 (3.2 nM) Ihara et al., 1995
Transduction mechanisms	G protein-coupled: increase in phosphatidyl inositol turnover with elevation of $[Ca^{2+}]_i$; activation of Ca^{2+} influx
Receptor distribution	Mainly vascular smooth muscle and therefore in all tissues receiving a blood supply, including heart, lung, and brain
Tissue functions	Vasoconstriction; positive inotrope, cell proliferation (e.g., smooth muscle, mesangial cells)
Phenotypes	Craniofacial and cardiovascular malformations in ET_A knockout mice (Clouthier et al., 1998)
Receptor	ET_B
Receptor Code	2.1:ET:2:ETB:
Previous names	None
Structural information	7TM h 442 aa, P24530, chr. 13; (Nakamuta et al., 1991) r 441 aa, P21451; (Sakurai et al., 1990) m 442 aa, P48302; (Baynash et al., 1994)
Functional assays	Initial depressor response in vivo, NO release, PI generation; vasoconstriction in some vascular beds depending on species (e.g., rabbit pulmonary artery)
Agonists	selective: [$Ala^{1,3,11,15}$]ET-1; (Saeki et al., 1991) BQ3020; (Ihara et al., 1992b) IRL 1620; (Takai et al., 1992) S6c; (William et al., 1991)
Agonist potencies	ET-1 = ET-2 = ET-3 = S6b (rat glomeruli)
Antagonist potencies	IRL2500 (pA_2 7.8; Balwierczak et al., 1995) RES7011 (6.0; Tanaka et al., 1994) BQ788 (6.9; Ishikawa et al., 1994) Ro468443 (pA_2 8.1; Clozel and Breu, 1996) A192621 (8.1; von Geldern et al., 1999)
Radioligand assays	Brain, lung, placenta, and kidney
Radioligands	^{125}I-ET-1 (K_d = 0.01–5 nM) Davenport, 1997 ^{125}I-BQ3020 (0.1 nM) Ihara et al., 1992b ^{125}I-[$Ala^{1,3,11,15}$]ET-1 (0.2 nM) Molenaar et al., 1992 ^{125}I-IRL 1620 (0.02 nM) Watakabe et al., 1992
Transduction mechanisms	G protein-coupled: increase in phosphotidyl inositol turnover with elevation of $[Ca^{2+}]_i$; activation of Ca^{2+} influx
Receptor distribution	Vascular, endothelial cells; high densities present in the brain, lung, heart, and intestine
Tissue functions	Vasodilatation, bronchoconstriction, vasoconstriction, cell proliferation (e.g., astrocytes)
Phenotypes	Polymorphism (N104I; Tanaka et al., 1998) and mutations (S390R and C109R, Tanaka et al., 1998; W276C, Puffenburger et al., 1994) in human ET_B receptor gene in Hirschsprung's disease. ET_B knockout mice have aganglionosic megacolon (Hosoda et al., 1994; resembling Hirschsprung's disease), associated with coat color spotting, and are deficient in sensing inflammatory pain (Griswold et al., 1999)

chr., chromosome; NO, nitric oxide; h, human; m, mouse; r, rat.

XI. Conclusions

In humans, ET peptides mediate their actions via only two receptor types, classified as ET_A and ET_B. There is no strong evidence to support the existence of further receptors in mammals. Further research is required to establish whether any of the potential splice variants in the ET_B receptor have a physiological or pathophysiological role.

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