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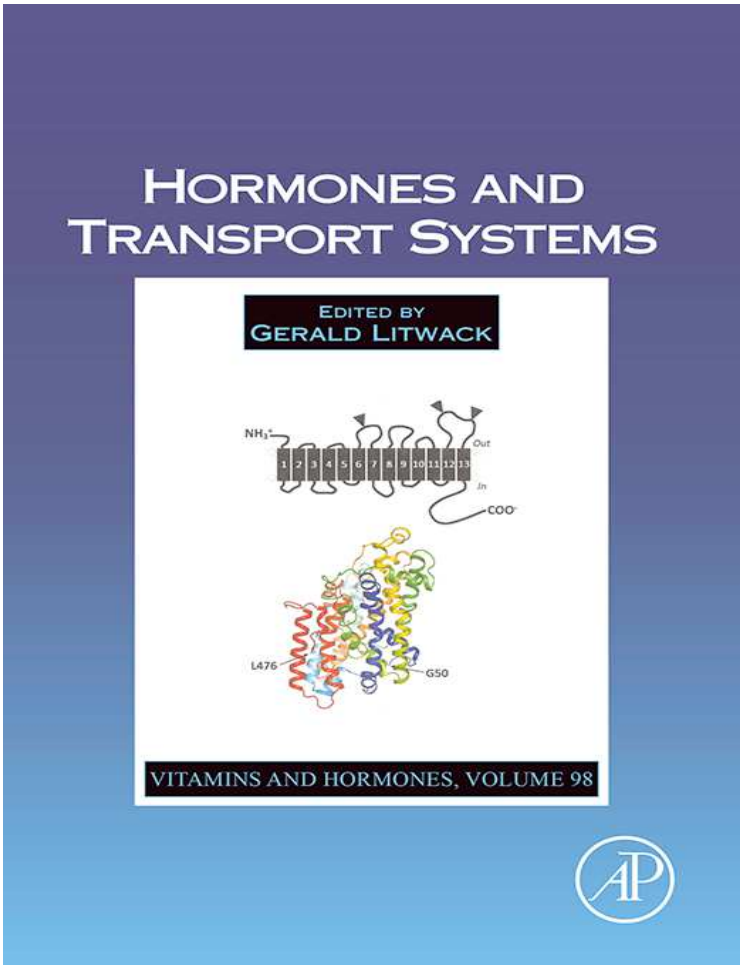

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CHAPTER TWELVE

Regulation of the Norepinephrine Transporter by Endothelins: A Potential Therapeutic Target

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Contents

Abstract

Neuronal norepinephrine (NE) uptake is a crucial step in noradrenergic neurotransmission that regulates NE concentration in the synaptic cleft. It is a key mechanism mediated by the NE transporter (NET) which takes the neurotransmitter into the presynaptic neuron terminal or the adrenal medulla chromaffin cell. The activity of NET is short and long terms modulated by phosphorylation mediated by protein kinases A, C, and G and calcium–calmodulin-dependent protein kinase, whereas the transporter availability at the cell surface is regulated by glycosylation. Several neuropeptides like angiotensins II, III, and 1–7, bradykinin, natriuretic peptides, as well as endothelins (ETs) regulate a

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wide variety of biological effects, including noradrenergic transmission and in particular neuronal NE uptake. Diverse reports, including studies from our laboratory, show that ETs differentially modulate the activity and expression of NET not only in normal conditions but also in diverse cardiovascular diseases such as congestive heart failure and hypertension. Current literature supports a key role for the interaction between ETs and NE in maintaining neurotransmission homeostasis and further suggests that this interaction may represent a potential therapeutic target for various diseases, particularly hypertension.

1. INTRODUCTION

The present review focuses on the participation of the endothelinergic system in the regulation of neuronal norepinephrine (NE) uptake which is the crucial step that ends NE activity at the synaptic cleft. The modulation of the NE transporter (NET) activity and expression by endothelin (ETs) is reviewed in normal animals and in different cardiovascular diseases focusing on the differential regulation exerted by ETs in diverse areas of the central nervous system (CNS) and peripheral nervous system. In addition, the contribution of other neuropeptides to the regulation of NET is briefly described. This review is divided into three sections: the first section describes the main features of NET regulation; the second section involves the description of ETs biosynthesis, receptors, and coupled intracellular signaling pathways and main biological actions; and the third section focuses on the regulation of NET by ETs and other neuropeptides.

2. NEURONAL NE UPTAKE

2.1 General aspects

Catecholamines (CAs) are classic neurotransmitters of low-molecular-weight that share a catechol group in their structure. The biosynthetic pathway begins with the stereospecific uptake of the CA precursor L-tyrosine into the cytoplasm where it is transformed to L-DOPA by tyrosine hydroxylase (TH). This is the limiting step in CA biosynthetic pathway. Then, by the action of L-aromatic amino acid decarboxylase, L-DOPA is converted to dopamine that enters into the synaptic vesicle through a monoamine vesicular transporter, where it is transformed to NE by dopamine-β-hydroxylase. In response to diverse stimuli, NE is released from vesicles

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through a complex exocytotic calcium-dependent mechanism to the synaptic cleft where it binds to specific adrenergic receptors localized at the pre- and/or postsynaptic levels to exert diverse biological effects. The amine is then removed mainly by uptake mechanisms which will be discussed in more detail in the following section (Fig. 1; Flatmark, 2000; Kvetnansky, Sabban, & Palkovits, 2009).

2.2 NE inactivation

NE exerts its actions on target cells by binding to and activating adrenergic receptors. The target cell expression of different receptor types determines the ultimate cellular effect, and thus NE has different actions on different cell types. The signal is terminated by the removal of NE through distinct uptake mechanisms that may eventually be followed by enzymatic degradation. Although part of the neurotransmitter may be lost through its diffusion across the synaptic cleft to the blood, it is a route of minor importance for NE inactivation (Brandao, 1976; Kvetnansky et al., 2009). The extracellular uptake of NE into the cytosol, either by presynaptically (uptake 1) or by nonneuronal cells in the vicinity (uptake 2), represents the major mechanisms for NE inactivation (Hahn & Blakely, 2007; Kvetnansky et al., 2009). Part of the NE is transported by the monoamine vesicular transporter into synaptic vesicles to be further released upon stimuli, but uptake may be followed by rapid degradation to various metabolites through monoamine oxidase (MAO) or catechol-*O*-methyl transferase (COMT) enzymes (Eisenhofer, Kopin, & Goldstein, 2004; Kopin, 1994; Youdim & Riederer, 1988). In neurons, MAO converts NE to the corresponding aldehyde which is then nonenzymatically further oxidized (Eisenhofer et al., 2004; Kopin, 1994). Similarly, but in nonneuronal cells, COMT methylates the m-hydroxyl group of the phenyl ring of NE, rendering it less active (Eisenhofer et al., 2004; Youdim & Riederer, 1988).

2.2.1 Nonneuronal uptake or uptake 2

Nonneuronal uptake occurs in nonneuronal cells like myocytes, hepatocytes, chromaffin cells, as well as glial, renal, and smooth muscle cells (Hughes, 1972; Iversen & Salt, 1970; Kvetnansky et al., 2009; Trendelenburg, 1988; Vatta et al., 1997). It is mediated by the classic corticosterone-sensitive extraneuronal MAO transporter and two organic cation transporters (OCT1 and OCT2) localized on extraneuronal structures (Eisenhofer, 2001; Friedgen, Wolfel, Russ, Schomig, & Graefe, 1996; Haag et al., 2004). It is a nonstereo-specific, low-affinity, and

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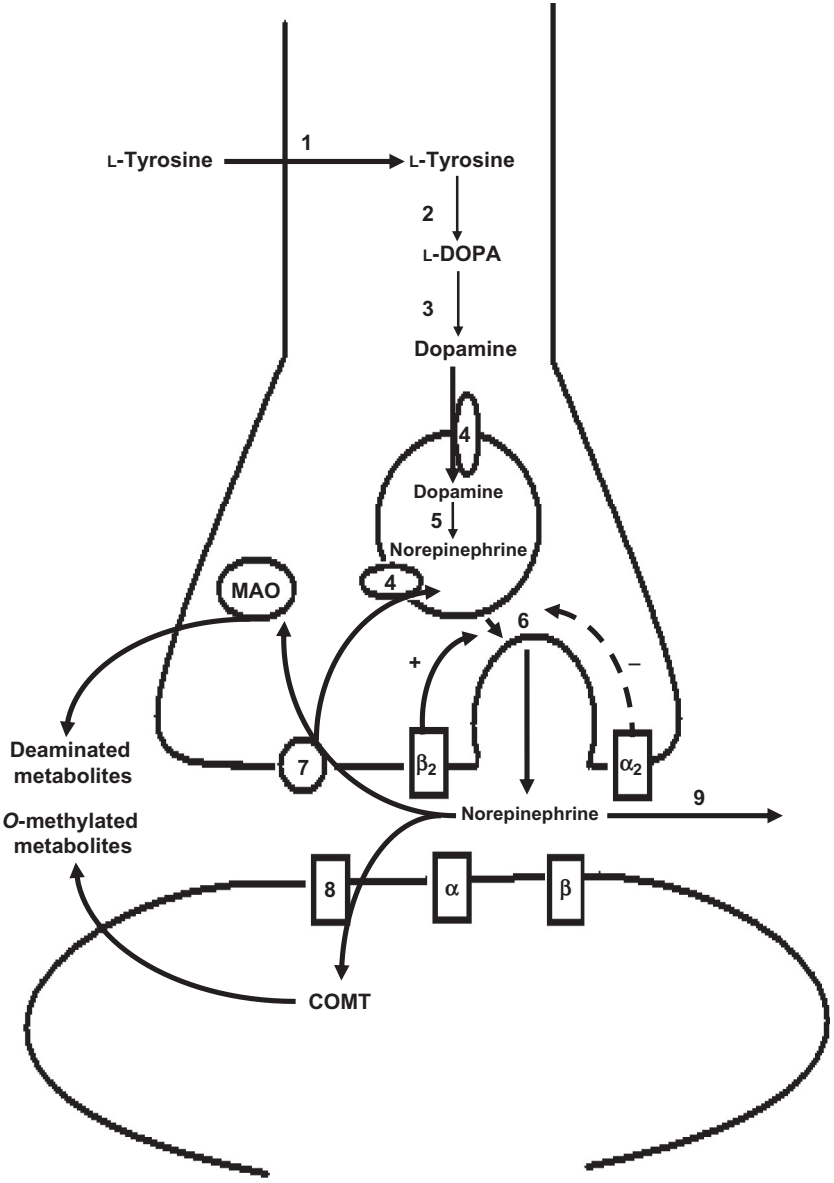

Figure 1 Schematic representation of the events occuring at the noradrenergic terminal and an effector cell. A Na^+-dependent cotransport of aromatic amino acid uptakes L-tyrosine (1) to be converted to L-DOPA by the tyrosine hydroxylase enzyme (2). Subsequently, the L-aromatic amino acid decarboxylase enzyme converts L-DOPA to dopamine (3) which by a vesicular transport of amines (4) is taken back into vesicles, where it is finally converted to norepinephrine (NE) by the dopamine-β-hydroxylase enzyme (5). Upon appropriate stimuli, NE is released by a calcium-dependent mechanism into the

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high-capacity mechanism that it is independent of Na^+ and Cl^- (Eisenhofer, 2001). Nonneuronal uptake is not inhibited by usual inhibitors of neuronal uptake but by metanephrine and corticosteroids like hydrocortisone (Olivier, Soudijn, & van Wijngaarden, 2000). This mechanism primarily clears circulating CA, rather than neuronal NE, although it may contribute to the clearance of synaptic NE under conditions of diminished NET function. Nonneuronal uptake is followed by enzymatic degradation of CA.

2.2.2 Neuronal uptake or uptake 1

Neuronal uptake of CA is a high-affinity and Na^+- and Cl^--dependent system mediated by the NET, dopamine transporter (DAT), and serotonin transporter (SERT) proteins (Iversen, 2006). Uptake of NE into the presynaptic neuron by NET represents the primary mechanism for NE inactivation (Bönish & Brüss, 2006; Wersinger, Jeannotte, & Sidhu, 2006; Zahniser & Doolen, 2001). Approximately, 80–90% of the released NE to the synaptic cleft is transported into neurons by NET (Esler et al., 1990). In the late 1950s and early 1960s, Julius Axelrod revealed the existence of neuronal uptake as a key mechanism for CA inactivation (Axelrod, 1957, 1962). Before this finding, it was accepted that inactivation of CA was mediated by rapid enzymatic degradation at the synaptic cleft like it occurs with acetylcholine which is hydrolyzed by acetylcholinesterase. At present, it is well established that CA inactivation is primarily mediated by transporter proteins belonging to the solute carrier 6 (SLC6) transport family (Kristensen et al., 2011; Pramod, Foster, Carvelli, & Henry, 2013).

2.3 NE transporter

The NET has a pivotal role in the regulation of synaptic NE in the brain and in peripheral tissues. This transporter is highly relevant given that it is a molecular target for diverse antidepressants, like the tricyclics, and abused

synaptic cleft (6), where NE binds to adrenoceptors localized at the pre- and postsynaptic membrane. The α2 and β2 receptors placed at the presynaptic membrane down- or upregulate neuronal NE release, respectively. The biological inactivation of NE occurs not only by neuronal uptake or uptake 1 mediated by the norepinephrine uptake transporter (NET) (7), but also by extraneuronal uptake or uptake 2 (8) or diffusion into the extracellular space (9). The neurotransmitter transported by NET is either internalized into vesicles by the amine vesicular transporter (4) or degraded by the monoamine oxidase (MAO) enzyme to deaminated metabolites. NE undergoing nonneuronal uptake is metabolized to *O*-methylated derivatives by catechol-*O*-methyltransferase (COMT).

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substances as cocaine and amphetamines (Iversen, 2000; Kristensen et al., 2011; Schlessingera et al., 2011).

The NET is localized on the membrane of noradrenergic neurons, and it not only regulates NE availability at the synaptic cleft but also plays an important role in the neurotransmitter homeostasis between presynaptic and postsynaptic nerve endings (Liang, 2007; Matthies et al., 2009; Xu et al., 2000). The NET can also transport dopamine and epinephrine, and although it has higher affinity for dopamine than NE, it is not expressed in dopaminergic nerve terminals (Apparsundaram, Moore, Malone, Hartzell, & Blakely, 1997; Buck & Amara, 1994; Giros et al., 1994). Nevertheless, it is believed that it may contribute to clear dopamine in certain brain areas (Carboni, Tanda, Frau, & Di Chiara, 1990; Moron, Brockington, Wise, Rocha, & Hope, 2002). The affinity rank order for NET is dopamine > NE > epinephrine.

NE uptake by NET is a secondary active transport dependent on Na^+ and Cl^- ions. Uptake is driven by an inwardly directed Na^+ gradient maintained by the action of the Na^+–K^+-ATPase (Bönish & Brüss, 2006; Kristensen et al., 2011; Kvetnansky et al., 2009). The NET belongs to the SLC6 transport family, which consists of four groups based on the substrate they transport: the neurotransmitter transporters which besides NET (SLC6A2) include DAT, γ-aminobutyric acid (GABA) transporter, SERT, and glycine transporter; the amino acid transporters; the osmolyte transporters; and creatine transporters (Kristensen et al., 2011; Pramod et al., 2013).

2.3.1 NET: Structure and function

The human and rat NET contains 617 amino acids, and its distribution is consistent with the distribution of noradrenergic pathways. The human gene encoding NET is localized to chromosome 16q12.2 (Brüss, Kunz, Lingen, & Bönisch, 1993; Gelernter et al., 1993). Alternative mRNA splicing variants of the transporter which results in the expression of NET that differ in carboxyl-terminal regions have been reported (Pörzgen, Bönisch, Hammermann, & Brüss, 1998; Sogawa et al., 2007). These variants from alternative splicing may influence maturation as well as trafficking of the transporter to the cell surface. In addition, several polymorphisms in the coding and noncoding regions of human NET gene have also been shown (Hahn & Blakely, 2002; Iwasa, Kurabayashi, Nagai, Nakamura, & Tanaka, 2001; Shannon et al., 2000; Stöber et al., 1996; Tellioglu & Robertson, 2001).

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The NET is mostly expressed in the *locus coeruleus* that sends projections to cerebellum, cortex, and thalamus and in the A1 and A2 cell groups that project to the hypothalamus, preoptic area, and forebrain (Kvetnansky et al., 2009; Matthies et al., 2009; Schroeter et al., 2000). In addition, NET is present in the sympathetic neurons of the autonomic nervous system and the chromaffin cells of the adrenal medulla (Kippenberger et al., 1999; Schroeter et al., 2000; Wehrwein et al., 2008).

Sequence analysis combined with biochemical approaches revealed that these transporters have 12 hydrophobic transmembrane spanning domains with intracellular amino and carboxy termini and a large extracellular loop between transmembrane helices TM3 and TM4 that contains three N-glycosylation sites (Kristensen et al., 2011; Pramod et al., 2013; Ramamoorthy, Shippenberg, & Jayanthi, 2011; Yamashita, Singh, Kaeate, Jin, & Gouaux, 2005). Another structural feature is a pair of Cys residues in extracellular loop 2 that form an intraloop disulfide bridge. The N-glycosylation sites modulate the activity and the structural stability of the transporter. The structure has an inverted symmetry given by the TM1–TM5 and TM6–TM10 domains (Kristensen et al., 2011; Pramod et al., 2013; Yamashita et al., 2005). Within the amino and carboxy termini and within its internal domain, the NET contains consensus sites for serine/threonine phosphorylation (Ramamoorthy et al., 2011). The NET shares high homology with the other monoamine transporters (DAT and SERT), particularly at TM1, TM2, and TM4–8 domains (Pramod et al., 2013).

The ligand-binding site is in close vicinity with Na^+ which allows a coupled movement between NE and the ion (Hahn & Blakely, 2007; Torres & Anara, 2007; Yamashita et al., 2005). Kinetic studies show that the entry of Na^+ and Cl^- is a requisite for NE binding (Apparsundaram, 2011; Bönish & Brüss, 2006; Gouaux, 2009). Removal of Na^+ or Cl^- abolishes NET-mediated NE uptake. NET is believed to translocate one substrate molecule with two Na^+ and one Cl^- (Kristensen et al., 2011). The transporter is inhibited by cocaine, desipramine, and nisoxetine among other drugs (Apparsundaram, 2011; Hahn & Blakely, 2007; Robinson, 2003).

The activity and expression of NET is regulated by short- and long-term mechanisms. Short-term regulation involves phosphorylation, trafficking, and protein–protein interaction, whereas long-term modulation involves transcriptional modifications.

The abundance of NET on the plasma membrane depends on NE release rate thus avoiding asynchrony between the release and uptake of the neurotransmitter (Oaks & Sidhu, 2011; Quick, 2006; Ramamoorthy et al.,

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2011). NET can be internalized into endosomal compartments or recycled to the membrane upon demand (Oaks & Sidhu, 2011). The rate of recycling/internalization can be as high as 3–5% transporters/min.

SNARE proteins (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) present in the vesicles (v-SNARES) and in the plasma membrane (t-SNARE) regulate neuronal release and inactivation of NE (Oaks & Sidhu, 2011; Quick, 2006; Ramamoorthy et al., 2011). Synaptobrevin or vesicle associated membrane proteins (VAMP) (v-SNARE) as well as syntaxin and SNAP-25 (t-SNARES) are involved in NE release as well as the NET recycling/internalization process.

A stable ternary complex (1:1:1) is formed by SNARE proteins which interact with N- and P/Q-type calcium channels to allow the fusion of vesicles with the plasma membrane and the eventual release of NE (Chen & Scheller, 2001; Jena, 2011; Rizo & Südhof, 2002; Sheng, Rettig, Cook, & Catterall, 1996). Syntaxin A1 interacts with NET to regulate the availability of the transporter in the membrane and to inhibit NE release (Sung & Blakely, 2007). If the syntaxin/NET complex is dissociated, NE inactivation is retarded (Sung et al., 2003).

High calcium concentrations favor not only NET insertion in the membrane but also NET/syntaxin complex formation, whereas the absence of calcium reduces NET recycling (Sung & Blakely, 2007). Protein kinase C (PKC) activation leads to decreased transport (reduced V_{max}) as a result of redistribution of the transporter from the surface to intracellular compartments (Apparsundaram, Galli, DeFelice, Hartzell, & Blakely, 1998; Jayanthi, Samuvel, & Ramamoorthy, 2004). Mutation of Thr258 and Ser259 to Ala significantly reduces transporter phosphorylation and prevents phorbol 12-myristate 13-acetate-induced decrease in NE uptake and NET internalization, an effect that was not observed upon substitution of the other potential phosphorylation sites in the transporter (Jayanthi, Annamalai, Samuvel, Gether, & Ramamoorthy, 2006). Stimulation of calcium–calmodulin-dependent protein kinase (CaMKII) activity in PC12 cells, which endogenously express NET, correlates with enhanced NET transport activity (Ramamoorthy et al., 2011; Sung & Blakely, 2007; Uchida, Kiuchi, Ohno, Yura, & Oguchi, 1998). Protein phosphatases like protein phosphatases 1 and 2 play a relevant role in maintaining NET in a relatively dephosphorylated state (Bauman et al., 2000). The phosphorylation sites appear to be potential sites for the presynaptic modulation of NET activity. Nevertheless, despite numerous studies, the molecular basis of the processes by which phosphorylation controls the transporter function still remains to be fully elucidated.

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2.3.2 Involvement of the NET in disease

Impairment of NET has been associated with diverse neurological diseases like Alzheimer and Parkinson; psychiatric disorders like depression and attention-deficit hyperactivity disorder; as well as cardiovascular diseases like congestive heart failure, blood pressure elevation, and postural tachycardia syndrome (Bönish & Brüss, 2006; Esler et al., 2006; Kristensen et al., 2011; Liang, 2007; Schroeder & Jordan, 2012; Shannon et al., 2000; Tellioglu & Robertson, 2001; Whiskey & Taylor, 2013). Whether NET impairment is involved in the genesis and/or maintenance of these pathophysiological conditions remains to be further elucidated.

3. ENDOTHELINS

3.1 General aspects

ETs are a family of vasoactive isopeptides comprised by ET-1, ET-2, and ET-3 that were first evidenced by Hickey, Rubanyi, Paul, and Highsmith (1985). They provided the first evidence for a potent vasoconstrictor substance derived from bovine aortic cells (Hickey et al., 1985). In 1988, these substances were then isolated, purified, and further characterized from porcine and rat aortic endothelial cells (Itoh et al., 1988; Yanagisawa, Kurihara, et al., 1988). ETs are 21 amino acid peptides with a hydrophobic C-terminus and two cysteine bridges at the N-terminus, which are essential for the biological activity (Kimura et al., 1988; Yanagisawa, Inoue, et al., 1988). ET-1, the first characterized member of the family, induces a strong long-lasting pressor response when intravenously injected (Yanagisawa & Masaki, 1989). ET-1, ET-2, and ET-3 are encoded in rodents, porcine, and humans by different independent genes localized to the 6, 1, and 20 chromosomes, respectively (Arinami et al., 1991; Inoue et al., 1989; Yanagisawa, Inoue, et al., 1988). Phylogenetic studies show that ETs are highly conserved in different species like humans, fishes, insects, mollusks, and annelids (Kasuya, Kobayashi, & Uemura, 1991; Kuwaki et al., 1997). ET-1 gene expression is enhanced by stress, and it plays a relevant role in diverse systemic disorders associated with endothelium injury like hypertension, uremic hemolytic syndrome, thrombocytopenic purpura, and heart failure (Hynynen & Khalil, 2006; Itoh et al., 1988). Immunoreactive ET-1 and mRNA ET-1 were reported in the blood vessels, heart, liver, kidney, peripheral nervous system, and CNS (Giaid et al., 1989; Kuddus, Nalesnik, Subbotin, Rao, & Gandhi, 2000; Naicker & Bhoola, 2001; Naidoo, Mahabeer, & Raidoo, 2001; Naidoo, Naidoo, Mahabeer, &

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Raidoo, 2004; Rubanyi & Botelho, 1991; Zhan & Rockey, 2011). ET-1 is the peptide with most potent vasoconstrictor property known (Yanagisawa, Inoue, et al., 1988; Yanagisawa, Kurihara, et al., 1988).

ET-2 is principally expressed in vascular endothelium, and minor in kidney, heart, placenta, uterus, CNS, and in the gastrointestinal tract (Takizawa et al., 2005; Uchide, Adur, Fukamachi, & Saida, 2000), whereas ET-3 is primarily localized in the CNS, and also in pituitary, intestine, pancreas, and liver (Matsumoto, Suzuki, Onda, & Fujino, 1989; Sluck, Lin, Katolik, Jeng, & Lehmann, 1999). ET-2 and ET-3 differ from ET-1 in the amino acid sequence but share similar biological properties (Fig. 2).

The venom of the burrowing asp *Atractaspis engaddensis* contains several 21 amino acid residue peptides known as sarafotoxins. The sarafotoxins are homologous to the mammalian ET family, and they have similar biological activities (Kloog et al., 1988; Kochva, Bdolah, & Wollberg, 1993).

The precursors of ETs are processed by peptidases to create mature active forms. The 203-residue pre–pro-ETs (212 in human) are cleaved by furin-like endopeptidases to form inactive intermediates of 39 amino acids termed big-ETs or pro-ETs (Fig. 3; Sluck et al., 1999). Processing is mediated by zinc metalloproteases from the neprilysin superfamily, termed endothelin-converting enzymes (ECEs) that cleave big-ETs into the biological active

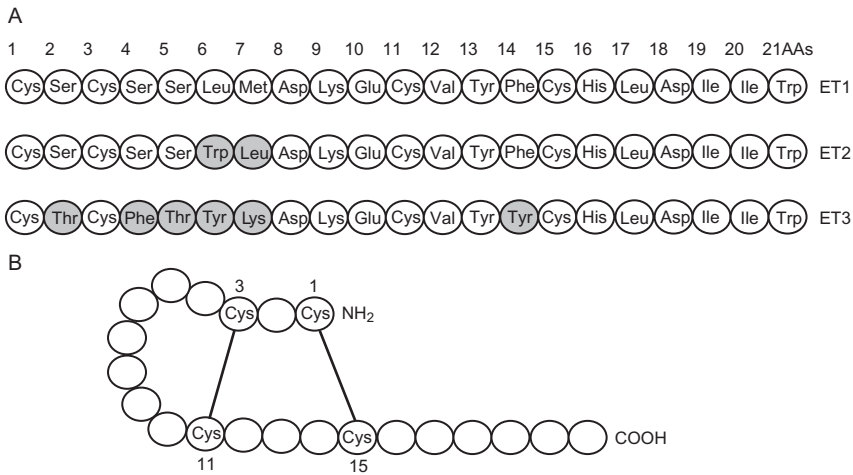

Figure 2 Endothelins structure. (A) The amino acid sequence of the endothelin family isoforms. Filled circles represent the amino acid residues different from ET-1 sequence. (B) Cyclic endothelin structure that includes two disulfide bridges joining the cysteine residues in positions 1–15 and 3–11. AAs: amino acids and ET-1, ET-2, and ET-3: endothelins 1, 2, and 3.

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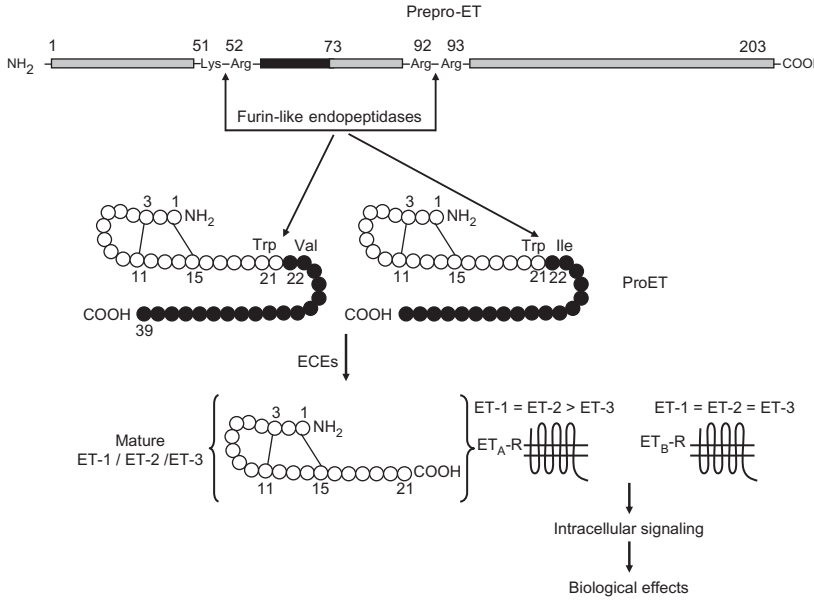

Figure 3 Endothelin biosynthetic pathway and affinity for endothelin receptors. ET-1, ET-2, and ET-3: endothelins 1, 2, and 3; ECEs: endothelin-converting enzymes; and ET_A-R and ET_B-R: endothelin receptor type A and endothelin receptor type B.

peptides (Opgenorth, Wu-Wong, & Shiosaki, 1992; Sluck et al., 1999). Although several isoforms of ECEs have been described, isoforms ECE-1, ECE-2, and ECE-3 are the most important in ETs' cleavage (Hasegawa et al., 1998; Kawanabe & Nauli, 2011; Opgenorth et al., 1992). ECE-1 is a membrane-bound metalloprotease that acts at neutral pH, whereas ECE-2 acts at acidic intracellular pH (Emoto & Yanagisawa, 1995). While ECE-1 and ECE-2 cleave pro-ET-1, these enzymes display low affinity for big-ET-2 and big-ET-3. ECE-3, originally purified from iris microsomes, would be specific for the cleavage of big-ET-3 to ET-3 (Hasegawa et al., 1998).

Once synthetized, ETs are secreted through two distinct secretory pathways. One is the classical exocytotic pathway activated in response to stimuli like hypothermia, stretch, and diverse agonists (Khimji & Rockey, 2010; Macarthur, Warner, Wood, Corder, & Vane, 1994; Russell & Davenport, 1999; Yoshitomi, Kojima, Ogi, & Kuramochi, 1998). The other secretory via is constitutive secretion that results in elevated ETs release as a consequence of increased biosynthesis without peptide package into vesicles (Khimji & Rockey, 2010; Ohkita, Tawa, Kitada, & Matsumura, 2012; Russell & Davenport, 1999).

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3.2 Receptors and intracellular signaling pathways

ETs mediate their biological actions through two well-characterized G protein-coupled receptors (GPCRs) termed ET_A and ET_B (Fig. 3; Sokolovsky, 1995a, 1995b). The ET_A receptor displays higher affinity for ET-1 and ET-2 than for ET-3, whereas ET_B binds the three isopeptides with similar affinity (Fig. 3; D'Orleans-Juste et al., 2002; Meyers & Sethna, 2013).

In rodents, ET_A is highly expressed in the heart, blood vessels, and lungs whereas to a lesser extent in the liver, kidney, CNS, and the reproductive system (King, Gude, Di Iulio, & Brennecke, 1995; Kohan, Rossi, Inscho, & Pollock, 2011; Koyama, 2013; Kurokawa, Yamada, & Ochi, 1997; Kuwaki et al., 1997; Opgenorth, 1995). Conversely, ET_B is expressed mainly in the CNS, although it is also found in lungs, pancreas, heart, kidneys, and the endocrine and reproductive systems (D'Orleans-Juste et al., 2002; King et al., 1995; Koyama, 2013; Kuwaki et al., 1997; Yamamoto & Uemura, 1998).

Both ET receptors can be pharmacologically identified by selective antagonists and agonists (Fig. 4). However, several studies support the existence of receptors other than ET_A and ET_B given that diverse biological effects mediated by ETs fail to be mimicked by ET agonists or inhibited by ET antagonists. These receptors were termed *atypical receptors* or ET_{AX} and ET_{BX} (di Nunzio, Legaz, Rodano, Bianciotti, & Vatta, 2004; Nabhen et al., 2009, 2011; Nambi et al., 1997; Pate et al., 1999; Perfume et al., 2007, 2008; Sokolovsky, 1995a, 1995b). Whether they represent ET_A and ET_B receptor subtypes or additional ET receptors remains to be investigated.

A third receptor subtype termed ET_C with higher affinity for ET-3 was cloned in *Xenopus laevis* (Karne, Jayawickreme, & Lerner, 1993; Kumar et al., 1994). Although it has not been cloned in mammals so far, it is believed that this receptor coupled to the phosphoinositide pathway would mediate various ET-3 biological effects like the neuronal release of NE in the posterior hypothalamus (di Nunzio et al., 2004). Diverse studies show that ET receptors may associate between themselves and with other receptors. It was shown that ET receptors interact to form homodimers and heterodimers (Evans & Walker, 2008; Gregan, Jürgensen, et al., 2004; Gregan, Schaefer, Rosenthal, & Oksche, 2004; Watts, 2010). Associations of ET receptors and other non-ET receptor were also reported, like dimerization between ET receptors and dopamine D3 receptor (D_3) or angiontensin type 1 receptors (AT1) (Watts, 2010; Yu et al., 2009; Zeng et al., 2005).

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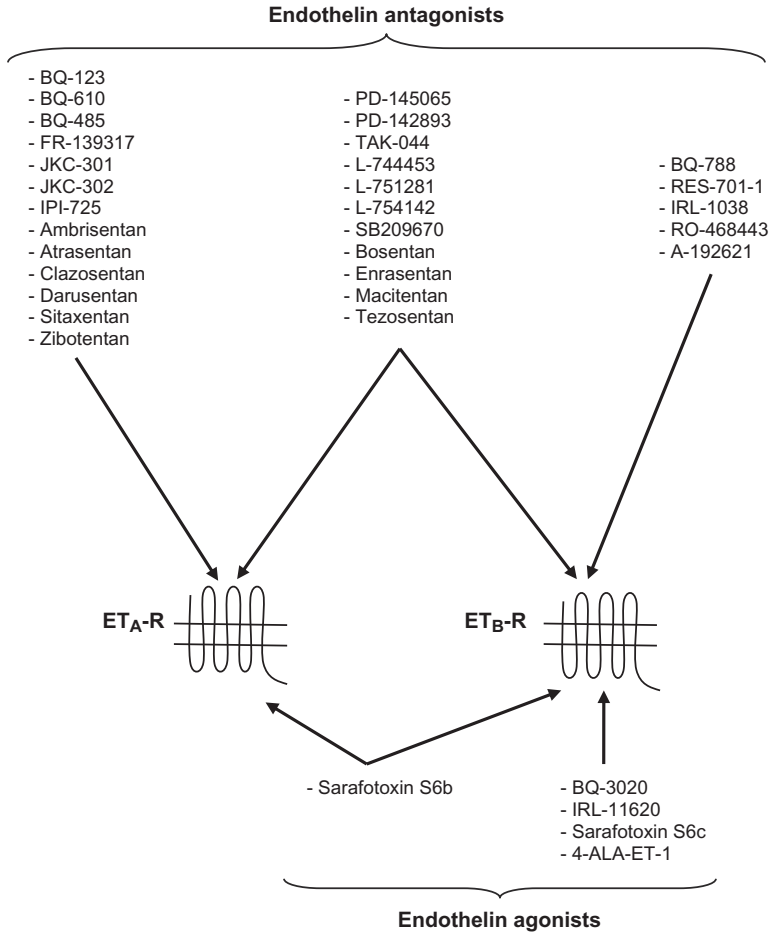

Figure 4 Endothelin receptor antagonists and agonists. ET_A-R and ET_B-R: endothelin receptor type A and endothelin receptor type B.

ET_A and ET_B can activate different G proteins (Gq, Gs, Go, or Gi) and thus trigger multiple signaling pathways depending on the ligand concentration and cell type involved (Hersch, Huang, Grider, & Murthy, 2004; Kitamura et al., 1999; Kuwaki et al., 1999; Shraga-Levine & Sokolovsky, 2000; Sokolovsky, 1995a, 1995b).

ETs activate phospholipase C (PLC) resulting in the cleavage of the phospholipid phosphatidylinositol 4,5-biphosphate into diacylglycerol which stimulates PKC and inositol 1,4,5-triphosphate (IP_3) which binds to IP_3 receptors in the smooth endoplasmic reticulum causing cytosolic

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calcium concentration to increase (Deacon & Knox, 2010; Jain, Olovsson, Burton, & Yung, 2012; Kato et al., 2013; Kuwaki et al., 1997; Sokolovsky, 1995a, 1995b).

ETs can also stimulate phospholipase A_2, which releases arachidonic acid, a precursor of eicosanoids including prostaglandins and leukotrienes and phospholipase D that catalyzes the hydrolysis of phosphatidylcholine to generate phosphatidic acid and choline (Deacon & Knox, 2010; Kuwaki et al., 1997; Robin, Chouayekh, Bole-Feysot, Leiber, & Tanfin, 2005; Sokolovsky, 1995a, 1995b).

The activation of ET receptors also increases cytosolic calcium through the Na^+/H^+ cotransporter and the calcium voltage and/or ligand channels that induce a sustained calcium influx. The increase in cytosolic calcium activates CaMK and also nitric oxide synthases (NOSs) which through cGMP activate protein kinase G (PKG). ETs can also inhibit or stimulated adenylyl cyclase by activating either Gi or Gs (Kuwaki et al., 1997, 1999; Pollock, Keith, & Highsmith, 1995).

3.3 Biological actions of ETs

ETs and ET receptors are widely distributed in different tissues and cell types supporting a broad spectrum of biological effects. The main effects of ETs with focus on the cardiovascular system and the CNS are discussed in the following sections.

3.3.1 Effects of ETs on the cardiovascular function

Intravenous or intraarterial infusion of ETs causes a sustained vasoconstriction preceded by a transient vasodilation (Cocks, Broughton, Dib, Sudnir, & Angus, 1989; Haynes, Ferro, & Webb, 1995; Haynes, Strachan, & Webb, 1995). It is now known that ET_A receptor activation is responsible for the ETs vasoconstrictor property (Clozel, Gray, Breu, Löfler, & Osterwalder, 1992; Harrison, Randiantsoa, & Schoffter, 1992; Moreland, McMullen, Delaney, Lee, & Hunt, 1992). ET_B agonists can also elicit vasoconstriction, but it depends on the vessel type and size as well as the specie involved (King et al., 1995).

ETs infusion to anesthetized rats or chemically denervated rats, either normotensive or spontaneously hypertensive, results in a rapid and transient decrease in blood pressure followed by a sustained increase (Winquist, Bunting, Garsky, Lumma, & Schofield, 1989). The initial vasodepressor response is mediated by ET_B receptor activation and endothelium-derived vasodilator substances like nitric oxide (NO) and prostaglandins, whereas the

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sustained pressor response would be direct or indirect through sympathetic activation but mediated by ET_A receptors (Knuepfer, O'Brien, Hoang, Gan, & Song, 1994).

ETs are involved in maintaining the vascular tone not only in physiological but also in pathophysiological conditions like vascular spasm, diabetes mellitus, insulin resistance, and hypertension (Hall et al., 2012; Haynes & Webb, 1998; Ivey, Osman, & Little, 2008; Meyers & Sethna, 2013; Nasser & El-Mas, 2014; Schiffrin, 1998; Schneider, Boesen, & Pollock, 2007).

ETs also induce hemodynamic changes in different vascular beds when applied to the brain. Recent reports in agreement with studies from our laboratory suggest that the central cardiovascular effects elicited by ETs are mediated by the activation of noradrenergic activity in the brain (Chen et al., 2012; di Nunzio, Jaureguiberry, Rodano, Bianciotti, & Vatta, 2002; di Nunzio et al., 2004; Hope, Schmipp, Rossi, Bianciotti, & Vatta, 2008; Kuwaki et al., 1999; Morgazo et al., 2005; Nabhen et al., 2009, 2011; Perfume et al., 2007, 2008).

3.3.2 Effects of ETs on the CNS

ET receptors are expressed in different brain regions and nuclei supporting that ETs mediate numerous biological actions (Kohan et al., 2011; Kurokawa et al., 1997; Kuwaki et al., 1997, 1999; Stojilkovic & Catt, 1996).

ETs in the CNS regulate cardiovascular and renal functions as well as the synthesis and release of diverse hormones and neurohormones like vasopressin, renin, aldosterone, follicle-stimulating hormone, growth hormone, and prolactin (Chan, Tang, & O, 2008; Kanyicska, Sellix, & Freeman, 2003; Kuhlmann, Amann, Schlotzer-Schrehardt, Kruse, & Cyrsiefen, 2005; Kuwaki et al., 1997; ThanThan et al., 2010; Yamamoto et al., 1991).

The intracerebroventricular injection of ET-1 elicits a sustained rise in blood pressure (Gulati, Rebello, Roy, & Saxena, 1995; Lu et al., 2007; Nishimura et al., 1990, 1991; Ouchi et al., 1989; Sirén & Feuerstein, 1989). Similar effects elicit ET-1 microinjections in the area postrema of anesthetized rats (Yamamoto et al., 1991). Adrenergic receptor antagonists inhibit ET-1 pressor response, supporting that the peptide applied to the brain activates the catecholaminergic system in diverse areas of the CNS (Ferguson & Smith, 1990). Furthermore, ET-1 applied to the area postrema increases plasma CA levels (Matsumura et al., 1994), showing a close relationship between the endothelinergic and catecholaminergic systems. The administration of ET-1 low doses to areas like the rostral ventrolateral medulla increases blood pressure, and renal sympathetic activity, but in some

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animals induces cardiorespiratory collapse and death (Kumada, Cao, & Kuwaki, 2003; Mosqueda-García, Inagami, Appalsamy, Sugiura, & Robertson, 1993). The pressor response following ET-1 administration is associated with sympathetic activation (Chen et al., 2012). Low doses of ET-3 applied to the solitarii tract nucleus also increase blood pressure and heart rate (Mosqueda-García et al., 1993).

Several studies suggest that ETs act as putative neurotransmitters or regulatory neuropeptides in the CNS (di Nunzio et al., 2002, 2004; Hope et al., 2008; Jaureguiberry, di Nunzio, Dattilo, Bianciotti, & Vatta, 2004; Kurokawa, Yamada, Liu, & Kudo, 2000; Kurokawa et al., 1997; Morgazo et al., 2005; Nabhen et al., 2009, 2011; Perfume et al., 2007, 2008; Yamada & Kurokawa, 1998). ETs enhance the release of monoamines from nerve endings that activate the renin–angiotensin system (Oparil et al., 1995; Yamada & Kurokawa, 1998). Webber, Pennefather, Head, and van den Buuse (1998) reported that ET-1 through ET_B receptors induces dopamine release in the striatum. It was also reported that ETs also stimulate substance P secretion from the hypothalamus and adenohypophysis (Calvo et al., 1990). In addition, both ET-1 and ET-3 increase NOS activity in the hypothalamus (di Nunzio et al., 2002; Jaureguiberry et al., 2004).

The hypothalamic areas and nuclei present high density of mRNA ET as well as ET receptors (Kurokawa et al., 1997; Kuwaki et al., 1997; Stojilkovic & Catt, 1996). Studies carried out in our laboratory show that ETs differentially regulate NE release in the anterior and the posterior hypothalamic regions of normotensive rats. The anterior and posterior hypothalamic areas are considered sympathoinhibitory and sympathoexcitatory, respectively. In the anterior hypothalamus, ET-1 and ET-3 diminish neuronal NE release through the activation of ET_B receptors coupled to the NO/soluble guanylyl cyclase/cGMP/PKG/$GABA_A$ pathway (di Nunzio et al., 2002; Jaureguiberry et al., 2004). However, in the posterior hypothalamus, ET-1 and ET-3 increase neuronal NE release through different intracellular pathways. ET-1 activates nonconventional (*atypical*) ET receptors and triggers different intracellular signaling involving a cross talk among PLC, PKC, and the adenylyl cyclase pathway, whereas ET-3 activates ET_C receptors and stimulates phosphoinositide signaling (di Nunzio et al., 2004). We also reported that ET-1 and ET-3 are involved in the short- and long-term modulations of activity and expression of TH in the anterior and posterior hypothalamic regions. The regulation of TH by ETs is very complex and involves different ET receptor subtypes, including nonconventional or *atypical* receptors and multiple signaling pathways (Karne et al., 1993; Perfume et al., 2007, 2008). In the rat anterior hypothalamic region, ET-1 and

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ET-3 decrease TH activity through ET_B receptors coupled to the activation of the phosphoinositide, CaMKII, and NO/GMPc/PKG pathways (Morgazo et al., 2005; Perfume et al., 2008). ETs do not modify TH expression levels in the short term, but at long term, both peptides decrease it. In the posterior hypothalamus, ET-1 and ET-3 at short term decrease TH activity through a nonconventional receptor coupled to the phosphoinositide, CaMKII, and O/cGMP/PKG pathways, whereas TH protein level remains unaltered (Perfume et al., 2007). On the other hand, in the posterior hypothalamus, ET-1 and ET-3 increase TH activity and expression at long term through an *atypical* receptor coupled to protein kinase A (PKA), phosphoinositide, and CaMKII activation (Perfume et al., 2008). Studies from our laboratory also show that ET receptors are expressed in the rat olfactory bulb, and they regulate the activity and expression of TH. Short-term modulation of TH by ET-1 and ET-3 in the olfactory bulb results in a significant increase in the enzyme activity without changes in the enzyme expression (Nabhen et al., 2009). Both ETs also participate in the long-term modulation of TH by increasing its activity through different ET receptors and intracellular signaling pathways, its mRNA, and the phosphorylation of the enzyme at serine 19, 31, and 40 sites (Nabhen et al., 2011). Short-term modulation of TH results in the enzyme activation, whereas long-term regulation results in increased synthesis (Nabhen et al., 2009, 2011). Enhanced TH activity results from its phosphorylation at diverse serine sites. Ser-40 is the most promiscuous site given that it can be phosphorylated by PKA, PKC, CaMKII, and PKG. We also showed that ET-1 and ET-3 regulate neuronal NE release in the anterior and posterior hypothalamus and the olfactory bulbs of normotensive rats (di Nunzio et al., 2002, 2004; Nabhen et al., 2009, 2011).

ET-1 and ET-3 also regulate noradrenergic neurotransmission in pathophysiological conditions like hypertension. Recent studies from our laboratory show that both ETs differentially regulate NE neurotransmission in brain regions (anterior and posterior hypothalamus, and olfactory bulb) of desoxycortosterone acetate (DOCA)-salt hypertensive rats (Abramoff, T. et al., unpublished data).

Both ETs are also involved in the modulation of NET as will be further discussed in the present review.

3.3.3 Other biological effects

ETs behave as paracrine and/or autocrine factors. Autocrine effects include endothelium proliferation and NO synthesis and release (Goto et al., 2013; Hirata et al., 1993; King et al., 1995; Tsukahara, Ende, Magazine, Bahou, & Goligorsky, 1994). DNA synthesis as well as the proliferation, migration,

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and invasion of endothelial cells are mediated by ET_B receptor activation (Herman & Simonson, 1995; MacCumber, Ross, & Snyder, 1990; Morbidelli, Orlando, Maggi, Ledda, & Ziche, 1995).

Paracrine actions include the contraction and proliferation of smooth muscle cells (Eddahibi et al., 2006; Horinouchi, Terada, Higashi, & Miwa; 2013; Hynynen & Khalil, 2006; King et al., 1995; Opgenorth, 1995). ET-1 increases the expression of several proto-oncogenes (c-myc, c-fos, and c-jun) in the vascular smooth muscle (Chen, Qiong, & Gardner, 2006; Herman & Simonson, 1995; Hynynen & Khalil, 2006). Radioautographic studies show the presence of binding sites for ETs in endocrine and neuroendocrine organs like the hypothalamus, pituitary, and the adrenal gland supporting ETs modulation of the endocrine function (Filosa et al., 2012; Hatae et al., 2007; Hynynen & Khalil, 2006; Kurokawa et al., 2000; Kuwaki et al., 1997; Sluck et al., 1999; Yamamoto & Uemura, 1998).

Other studies from our laboratory show that centrally applied ET-1 and ET-3 induce either cholestasis or choleresis depending on the dose (Rodríguez et al., 2005, 2006). However, when ETs are peripherally infused in doses that not induce changes in portal venous pressure and blood flow, they induce choleresis mediated by ET_B receptors coupled to NOS activation and vago-vagal reflexes (Rodríguez et al., 2013).

4. ET AND NE NEURONAL UPTAKE INTERACTION

4.1 General aspects

Neuropeptides are defined as small protein-like molecules produced and released by neurons through the regulated secretory route and acting on neural substrates (Belzung, Yalcin, Griebel, Surget, & Leman, 2006; Burbach, 2011). They are the most diverse class of signaling molecules in the brain and the peripheral nervous system engaged in many physiological functions. The neuropeptide families involved in the regulation of cardiovascular function include angiotensins (Ang) II and III, kallikreins, natriuretic peptides, and ETs (AbdAlla, Abdel-Baset, Lother, el Massiery, & Quitterer, 2005; Duchene & Ahluwalia, 2009; Ganten, Paul, & Lang, 1991; Kohan et al., 2011; Kuwaki et al., 1997; Szczepańska-Sadowska, 2006; Vatta, Bianciotti, Perfume, Nabhen, & Hope, 2009).

Neuropeptides, also called high-molecular-weight neurotransmitters, colocalize with classic neurotransmitters in neurons and synapsis regulating the efficiency of neuronal communication (de Lartigue, 2014; Merighi, 2002; Tasker, Oliet, Bains, Brown, & Stern, 2012).

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Classic neurotransmitters are synthetized in the axon terminal, whereas neuropeptides are produced in the neuronal soma and packed in vesicles which travel by fast axonal transport down the axon (Hökfelt et al., 2000; Shakiryanova, Tully, Hewes, Deitcher, & Levitan, 2005). Neuropeptide synthesis is a dynamic process that easily adjusts to the activity of the neurons where they operate (Hökfelt, Bartfai, & Bloom, 2003; Hökfelt et al., 2000). However, it may undergo sustained adaptive changes in response to sustained environmental modifications (Barakat et al., 2006; Nostramo, Tillinger, Serova, Kvetnansky, & Sabban, 2013).

No membrane uptake system for neuropeptides was identified in neurons, so it is believed that they are inactivated by active peptidases. Neuropeptides remain in the synaptic cleft longer than classic neurotransmitters because their enzymatic degradation is slower thus allowing a more prolonged interaction with their receptors (Szczepańska-Sadowska, 2006).

Neuropeptides regulate not only neurons but also glial cells where their receptors are also expressed in those cell types (Filosa et al., 2012; Garrido-Gil, Rodríguez-Pallares, Dominguez-Meijide, Guerra, & Labandeira-Garcia, 2013; Hökfelt et al., 2003, 2000; Stern & Filosa, 2013). They regulate neuronal circuits involved in relevant biological functions like learning, memory, cognition and emotion, body temperature, thirst, appetite, metabolism, hypothalamic hormone release, as well as respiratory and cardiovascular activities (Bourque, Ciura, Trudel, Stachniak, & Sharif-Naeini, 2007; de Wied, Diamant, & Fodor, 1993; Dimicco & Zaretsky, 2007; Garcia-Segura, Lorenz, & DonCarlos, 2008; Guyenet, 2006; Pfaff, Kieffer, & Swanson, 2008; Plant, 2008; Wyss & Carlson, 2001).

Intense and sustained regulation by neuropeptides occur in diverse pathophysiological situations like addiction, cardiovascular diseases, energy disturbances, and sodium and water imbalances (Boutrel, 2008; Cottrell et al., 2009; de Lecea et al., 2006; Penna et al., 2006; Stepniakowski, Budzikowski, Loń, & Szczepańska-Sadowska, 1994; Szczepańska-Sadowska, Paczwa, Loń, & Ganten, 1998). These findings reveal the importance of studies aiming to understand the molecular mechanisms underlying neuropeptide regulation and the interaction with classical neurotransmitters.

4.2 Interaction with the endothelinergic system

Neuropeptides regulate diverse aspects of neurotransmission like the inactivation of neurotransmitters in the synaptic cleft. In the case of NE, its neuronal uptake is a complex mechanism highly regulated by neuropeptides.

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The interaction between ETs and NE was first described by Backs, Bresch, Lutz, Kristen, and Haass (2005). These authors, with the aim to determine the underlying causes of sympathetic cardiac activation in congestive heart failure, showed that ET-1 through the activation of ET_A receptors inhibits in a concentration- and time-dependent fashion [^{3}H]-NE uptake in isolated perfused hearts. In the same study they showed that the ET_A antagonist, darusetan, reduces [^{3}H]-NE uptake and the number of NET-binding sites in rats with transverse aortic constriction (an animal model of congestive heart failure; Backs et al., 2005).

In 2008, the first reports showing an interaction between NE uptake and ETs in the brain were published. It was shown that ET-1 and ET-3 reduce NE uptake without affecting nonneuronal uptake in the posterior hypothalamus of normotensive rats (Hope et al., 2008). The internalization of NET is the underlying mechanism responsible for ETs' response. Conversely, in the anterior hypothalamus, ET-3 stimulates neuronal NE uptake by enhancing NET recycling to the plasma membrane without increasing the *de novo* synthesis of the transporter (Hope et al., 2008). In contrast, ET-1 elicits the same response as that observed in the posterior hypothalamus (Hope et al., 2008). Further studies in the anterior hypothalamus show that ET-1 reduces NE uptake through the activation of ET_B receptors coupled to the cAMP/PKA pathway, whereas ET-3 increases the uptake of the amine through an *atypical* ET GPCR coupled to the PLC/PKC/IP_3 and cAMP/PKA pathways without involving NO generation (Abramoff, T. et al., unpublished data).

On the other hand, in the posterior hypothalamus both ETs diminish neuronal NE uptake through different signaling pathways. ET-1 activates ET_B receptors, whereas ET-3 an *atypical* ET GPCR, although both receptors are coupled to neuronal NOS activation. In addition, the *atypical* ET GPCR is coupled to the phosphoinositide pathway (Hope, Nabhen, Soria, Bianciotti, & Vatta, 2010).

We recently reported that ETs also modulate NE uptake in the olfactory bulbs. Both ET-1 and ET-3 dose dependently diminish the amine uptake through the activation of *atypical* ET GPCRs coupled to PKC, PKG, and CaMKII activation (Abramoff, T. et al., unpublished data).

Increasing reports in the literature support the involvement of NET in different pathophysiological conditions. In the last years, our laboratory focused the studies on the underlying mechanisms of ETs–NE interaction in experimental hypertension. In the DOCA-salt animal model of hypertension, we observed that ET-1 and ET-3 diminish neuronal NE uptake in the anterior hypothalamus. These findings reveal a distinct ET-3 response in normotensive and hypertensive animals in this hypothalamic area. Another

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interesting finding was that ETs decrease both glycosylated (expressed in plasma membrane) and nonglycosylated NET (internalized transporter). Taken together, these findings support that ETs induce NET down-regulation in the anterior hypothalamus of DOCA-salt hypertensive rats (Abramoff, T. et al., unpublished data).

On the other hand, ET-1 and ET-3 increase neuronal NE uptake in the posterior hypothalamus and olfactory bulbs of hypertensive animals due to an increase in the glycosylated form of NET (Abramoff, T. et al., unpublished data).

The evidence presented support that ETs play a relevant role in the regulation of NET activity, kinetic, and internalization.

4.3 Interaction with other neuropeptides

The renin–angiotensin system, and particularly Ang II, has been extensively studied regarding NE uptake. Palaic and Khairallah (1967a, 1967b, 1968) were the first to show that Ang II modulates NE uptake in the brain and the heart. These studies were later confirmed and extended by other authors. Ang II stimulates NE uptake in the hypothalamus and brain stem neuronal cultures (Sumners & Raizada, 1986; Sumners, Shalit, Kalberg, & Raizada, 1987). Conversely, studies from our laboratory show that Ang II and Ang III inhibit neuronal NE uptake in diverse brain areas and in the adrenal medulla (Fernández et al., 1990; Papouchado, Vatta, Escalada, Bianciotti, & Fernández, 1995; Vatta, Bianciotti, Locatelli, Papouchado, & Fernández, 1992; Vatta, Bianciotti, Papouchado, Locatelli, & Fernández, 1991). In addition, it was recently reported that Ang 1–7 increases the uptake of NE in the brain (Lopez-Verrilli et al., 2012).

Bradykinin also regulates NE uptake, although few reports exist in the literature. It was shown that bradykinin increases NE release without inhibiting NE uptake (Seyedi, Win, Lander, & Levi, 1997). However, studies from our laboratory report that bradykinin enhances the uptake of the amine in the hypothalamus and medulla oblongata and in the adrenal medulla of normotensive rats (Fernández, Vatta, & Bianciotti, 1993; Vatta, Bianciotti, & Fernández, 1993a).

Other neuropeptides involved in the regulation of NE uptake are natriuretic peptides. This family is comprised by atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Different studies show that ANP, BNP, and CNP increase NE uptake in the adrenal medulla and different areas and regions of the brain (Fermepín, Vatta, Bianciotti, Wolovich, & Fernández, 2000;

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Fernández et al., 1990; Vatta, Bianciotti, & Fernández, 1993b; Vatta et al., 1991, 1997; Vatta, Presas, Bianciotti, Zarrabeitia, & Fernández, 1996; Vatta et al., 1995, 1994).

5. CONCLUSION

Since the discovery of ETs in the late 1980s, most studies centered on their involvements in the regulation of cardiovascular and renal activities. From all the studies on ETs, only 10% focused on the role of these peptides in the brain, and approximately 1% focused on the interaction between ETs and noradrenergic neurotransmission. Future studies will surely unveil further aspects on the molecular mechanisms underlying the interaction between the endothelinergic system and noradrenergic transmission, and in particular NE uptake by NET in the brain. The role of this interaction is relevant not only in physiological but also in pathophysiological conditions like cardiovascular and neurodegenerative diseases, and mood disorders as being evidenced by emergic reports in the literature. Current evidence suggests that the interaction between ETs and NE uptake may represent a potential therapeutic target for various diseases, particularly hypertension.

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REFERENCES

AbdAlla, S., Abdel-Baset, A., Lother, H., el Massiery, A., & Quitterer, U. (2005). Mesangial AT1/B2 receptor heterodimers contribute to angiotensin II hyperresponsiveness in experimental hypertension. *Journal of Molecular Neuroscience*, *26*, 185–192.

Apparsundaram, S. (2011). Function and regulation of monoamine transporters: Focus on the norepinephrine transporter. *CNS Spectrums*, *6*(671–4), 677–678.

Apparsundaram, S., Galli, A., DeFelice, L. J., Hartzell, H. C., & Blakely, R. D. (1998). Acute regulation of norepinephrine transport: I. Protein kinase C-linked muscarinic receptors influence transport capacity and transporter density in SK-N-SH cells. *The Journal of Pharmacology and Experimental Therapeutics*, *287*, 733–743.

Apparsundaram, S., Moore, K. R., Malone, M. D., Hartzell, H. C., & Blakely, R. D. (1997). Molecular cloning and characterization of an L-epinephrine transporter from sympathetic ganglia of the bullfrog, Rana catesbiana. *The Journal of Neuroscience*, *17*, 2691–2702.

Arinami, T., Ishikawa, M., Inoue, A., Yanagisawa, M., Masaki, T., Yoshida, M. C., et al. (1991). Chromosomal assignments of the human endothelin family genes: The

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endothelin-1 gene (EDN1) to 6p23-p24, the endothelin-2 gene (EDN2) to 1p34, and the endothelin-3 gene (EDN3) to 20q13.2-q13.3. *American Journal of Human Genetics*, *48*, 990–996.

Axelrod, J. (1957). *O*-methylation of (epinephrine and other catecholamines) catecholamines in vitro and in vivo. *Science*, *126*, 400–401.

Axelrod, J. (1962). Purification and properties of phenylethanolamine-*N*-methyl transferase. *The Journal of Biological Chemistry*, *237*, 1657–1660.

Backs, J., Bresch, E., Lutz, M., Kristen, A. V., & Haass, M. (2005). Endothelin-1 inhibits the neuronal norepinephrine transporter in hearts of male rats. *Cardiovascular Research*, *67*, 283–290.

Barakat, Y., Pape, J. R., Boutahricht, M., El Ouezzani, S., Alaoui, A., Chaigniau, M., et al. (2006). Vasopressin-containing neurons of the hypothalamic parvocellular paraventricular nucleus of the jerboa: Plasticity related to immobilization stress. *Neuroendocrinology*, *84*, 396–404.

Bauman, A. L., Apparsundaram, S., Ramamoorthy, S., Wadzinski, B. E., Vaughan, R. A., & Blakely, R. D. (2000). Cocaine and antidepressant-sensitive biogenic amine transporters exist in regulated complexes with protein phosphatase. *The Journal of Neuroscience*, *20*, 7571–7578.

Belzung, C., Yalcin, I., Griebel, G., Surget, A., & Leman, S. (2006). Neuropeptides in psychiatric diseases: An overview with a particular focus on depression and anxiety disorders. *CNS & Neurological Disorders: Drug Targets*, *5*, 135–145.

Bönish, H., & Brüss, M. (2006). The norepinephrine transporter in physiology and disease. *Handbook of Experimental Pharmacology*, *175*, 485–524.

Bourque, C. W., Ciura, S., Trudel, E., Stachniak, T. J., & Sharif-Naeini, R. (2007). Neurophysiological characterization of mammalian osmosensitive neurones. *Experimental Physiology*, *92*, 499–505.

Boutrel, B. (2008). A neuropeptide-centric view of psychostimulant addiction. *British Journal of Pharmacology*, *154*, 343–357.

Brandao, F. (1976). A comparative study of the role played by some inactivation pathways in the disposition of the transmitter in the rabbit aorta and the saphenous vein of the dog. *Blood Vessels*, *13*, 309–318.

Brüss, M., Kunz, J., Lingen, B., & Bönisch, H. (1993). Chromosomal mapping of the human gene for the tricyclic antidepressant-sensitive noradrenaline transporter. *Human Genetics*, *91*, 278–280.

Buck, K. J., & Amara, S. G. (1994). Chimeric dopamine–norepinephrine transporters delineate structural domains influencing selectivity for catecholamines and 1-methyl-4-phenyl-pyridinium. *Proceedings of the National Academy of Sciences of the United States of America*, *91*, 12584–12588.

Burbach, J. P. (2011). What are neuropeptides? *Methods in Molecular Biology*, *789*, 1–36.

Calvo, J. J., González, R., De Carvalho, L. F., Takahashi, K., Kanse, S. M., Hart, G. R., et al. (1990). Release of substance P from rat hypothalamus and pituitary by endothelin. *Endocrinology*, *126*, 2288–2295.

Carboni, E., Tanda, G. L., Frau, R., & Di Chiara, G. (1990). Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: Evidence that dopamine is taken up in vivo by noradrenergic terminals. *Journal of Neurochemistry*, *55*, 1067–1070.

Chan, Y. F., Tang, F., & O, W. S. (2008). Adrenomedullin in the rat testis. II: Its production, actions on inhibin secretion, regulation by follicle-stimulating hormone, and its interaction with endothelin 1 in the Sertoli cell. *Biology of Reproduction*, *78*, 780–785.

Chen, S., Qiong, Y., & Gardner, D. G. (2006). A role for p38 mitogen-activated protein kinase and c-myc in endothelin-dependent rat aortic smooth muscle cell proliferation. *Hypertension*, *47*, 252–258.

Author's personal copy

Chen, Y. A., & Scheller, R. H. (2001). SNARE-mediated membrane fusion. *Nature Reviews. Molecular Cell Biology*, *2*, 98–106.

Chen, A. D., Xiong, X. Q., Gan, X. B., Zhang, F., Zhou, Y. B., Gao, X. Y., et al. (2012). Endothelin-1 in paraventricular nucleus modulates cardiac sympathetic afferent reflex and sympathetic activity in rats. *PLoS One*, *7*, e40748.

Clozel, M., Gray, G. A., Breu, V., Löfler, B. M., & Osterwalder, R. (1992). The endothelin ETB receptor mediates both vasodilation and vasoconstriction in vivo. *Biochemical and Biophysical Research Communications*, *186*, 867–873.

Cocks, T. M., Broughton, A., Dib, M., Sudnir, K., & Angus, J. A. (1989). Endothelin is blood vessel selective: Studies on a variety of human and dog vessels in vitro and on regional blood flow in the conscious rabbit. *Clinical and Experimental Pharmacology & Physiology*, *16*, 243–246.

Cottrell, E. C., Cripps, R. L., Duncan, J. S., Barrett, P., Mercer, J. G., Herwig, A., et al. (2009). Developmental changes in hypothalamic leptin receptor: Relationship with the postnatal leptin surge and energy balance neuropeptides in the postnatal rat. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *296*, R631–R639.

D'Orleans-Juste, P., Labonté, J., Bkaily, G., Choufani, S., Plante, M., & Honoré, J. C. (2002). Function of the endothelin (B) receptor in cardiovascular physiology and pathophysiology. *Pharmacology & Therapeutics*, *95*, 221–238.

de Lartigue, G. (2014). Putative roles of neuropeptides in vagal afferent signaling. *Physiology & Behavior*, *136C*, 155–169, pii: S0031-9384(14)00145-0.

de Lecea, L., Jones, B. E., Boutrel, B., Borgland, S. L., Nishino, S., Bubser, M., et al. (2006). Addiction and arousal: Alternative roles of hypothalamic peptides. *The Journal of Neuroscience*, *26*, 10372–10375.

de Wied, D., Diamant, M., & Fodor, M. (1993). Central nervous system effects of the neurohypophyseal hormones and related peptides. *Frontiers in Neuroendocrinology*, *14*, 251–302.

Deacon, K., & Knox, A. J. (2010). Endothelin-1 (ET-1) increases the expression of remodeling genes in vascular smooth muscle through linked calcium and cAMP pathways: Role of a phospholipase A(2)(cPLA(2)/cyclooxygenase-2 (COX-2)/prostacyclin receptor-dependent autocrine loop. *The Journal of Biological Chemistry*, *285*, 25913–25927.

di Nunzio, A. S., Jaureguiberry, M. S., Rodano, V., Bianciotti, L. G., & Vatta, M. S. (2002). Endothelin-1 and -3 diminish neuronal NE release through an NO mechanism in rat anterior hypothalamus. *American Journal of Physiology, Regulatory, Integrative and Comparative Physiology*, *283*, R615–R622.

di Nunzio, A. S., Legaz, G., Rodano, V., Bianciotti, L. G., & Vatta, M. S. (2004). Modulatory effect of endothelin-1 and -3 on neuronal norepinephrine release in the rat posterior hypothalamus. *Regulatory Peptides*, *118*, 51–59.

Dimicco, J. A., & Zaretsky, D. V. (2007). The dorsomedial hypothalamus: A new player in thermoregulation. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *292*, R47–R63.

Duchene, J., & Ahluwalia, A. (2009). The kinin B(1) receptor and inflammation: New therapeutic target for cardiovascular disease. *Current Opinion in Pharmacology*, *9*, 125–131.

Eddahibi, S., Guignabert, C., Barlier-Mur, A. M., Dewachter, L., Fadel, E., Dartevelle, P., et al. (2006). Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: Critical role for serotonin-induced smooth muscle hyperplasia. *Circulation*, *113*, 1857–1864.

Eisenhofer, G. (2001). The role of neuronal and extraneuronal plasma membrane transporters in the inactivation of peripheral catecholamines. *Pharmacology & Therapeutics*, *91*, 35–62.

Eisenhofer, G., Kopin, I. J., & Goldstein, D. S. (2004). Catecholamine metabolism: A contemporary view with implications for physiology and medicine. *Pharmacological Reviews*, *56*, 331–349.

Author's personal copy

Emoto, N., & Yanagisawa, M. (1995). Endothelin-converting enzyme-2 is a membrane-bound, phosphoramidon-sensitive metalloprotease with acidic pH optimum. *The Journal of Biological Chemistry*, *270*, 15262–16268.

Esler, M., Alvarenga, M., Pier, C., Richards, J., El-Osta, A., Barton, D., et al. (2006). The neuronal noradrenaline transporter, anxiety and cardiovascular disease. *Journal of Psychopharmacology*, *20*(4 Suppl.), 60–66.

Esler, M., Jennings, G., Lambert, G., Meredith, I., Horne, M., & Eisenhofer, G. (1990). Overflow of catecholamine neurotransmitters to the circulation: Source, fate, and functions. *Physiological Reviews*, *70*, 963–985.

Evans, N. J., & Walker, J. W. (2008). Endothelin receptor dimers evaluated by FRET, ligand binding, and calcium mobilization. *Biophysical Journal*, *95*, 483–492.

Ferguson, A. V., & Smith, P. (1990). Cardiovascular responses induced by endothelin microinjection into area postrema. *Regulatory Peptides*, *27*, 75–85.

Fermepín, M. R., Vatta, M. S., Bianciotti, L. G., Wolovich, T. J., & Fernández, B. E. (2000). B-type and C-type natriuretic peptides modify norepinephrine uptake in discrete encephalic nuclei of the rat. *Cellular and Molecular Neurobiology*, *20*, 763–771.

Fernández, B. E., Dominguez, A. E., Vatta, M. S., Mendez, M. A., Bianciotti, L. G., & Martinez-Seeber, A. (1990). Atrial natriuretic peptide and angiotensin II interaction on noradrenaline uptake in the central nervous system. *Archives Internationales de Pharmacodynamie et de Thérapie*, *307*, 11–17.

Fernández, B. E., Vatta, M. S., & Bianciotti, L. G. (1993). Comparative effects of bradykinin and atrial natriuretic factor on neuronal and non-neuronal noradrenaline uptake in the central nervous system of the rat. *Archives Internationales de Physiologie et de Biochimie*, *101*, 337–340.

Filosa, J. A., Naskar, K., Perfume, G., Iddings, J. A., Biancardi, V. C., Vatta, M. S., et al. (2012). Endothelin-mediated calcium responses in supraoptic nucleus astrocytes influence magnocellular neurosecretory firing activity. *Journal of Neuroendocrinology*, *24*, 378–392.

Flatmark, T. (2000). Catecholamine biosynthesis and physiological regulation in neuroendocrine cells. *Acta Physiologica Scandinavica*, *168*, 1–17.

Friedgen, B., Wolfel, R., Russ, H., Schomig, E., & Graefe, K. H. (1996). The role of extraneuronal amine transport systems for the removal of extracellular catecholamines in the rabbit. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *354*, 275–286.

Ganten, D., Paul, M., & Lang, R. E. (1991). The role of neuropeptides in cardiovascular regulation. *Cardiovascular Drugs and Therapy*, *5*, 119–130.

Garcia-Segura, L. M., Lorenz, B., & DonCarlos, L. L. (2008). The role of glia in the hypothalamus: Implications for gonadal steroid feedback and reproductive neuroendocrine output. *Reproduction*, *135*, 419–429.

Garrido-Gil, P., Rodríguez-Pallares, J., Dominguez-Meijide, A., Guerra, M. J., & Labandeira-Garcia, J. L. (2013). Brain angiotensin regulates iron homeostasis in dopaminergic neurons and microglial cells. *Experimental Neurology*, *250*, 384–396.

Gelernter, J., Kruger, S., Pakstis, A. J., Pacholczyk, T., Sparkes, R. S., Kidd, K. K., et al. (1993). Assignment of the norepinephrine transporter protein (NET1) locus to chromosome 16. *Genomics*, *18*, 690–692.

Giaid, A., Gibson, S. J., Ibraim, B. N., Legon, S., Bloom, S. R., Yanagisawa, M., et al. (1989). Endothelin 1, an endothelium-derived peptide, is expressed in neurons of the human spinal cord and dorsal root ganglia. *Proceedings of the National Academy of Sciences of the United States of America*, *86*, 7634–7638.

Giros, B., Wang, Y. M., Suter, S., McLeskey, S. B., Pifl, C., & Caron, M. G. (1994). Delineation of discrete domains for substrate, cocaine, and tricyclic antidepressant interactions using chimeric dopamine–norepinephrine transporters. *The Journal of Biological Chemistry*, *269*, 15985–15988.

Author's personal copy

Goto, A., Sumiyama, K., Kamioka, Y., Nakasyo, E., Ito, K., Iwasaki, M., et al. (2013). GDNF and endothelin 3 regulate migration of enteric neural crest-derived cells via protein kinase A and Rac1. *The Journal of Neuroscience*, *33*, 4901–4912.

Gouaux, E. (2009). The molecular logic of sodium-coupled neurotransmitter transporters. *Philosophical Transaction of the Royal Society of London Series B: Biological Sciences*, *364*, 149–154.

Gregan, B., Jürgensen, J., Papsdorf, G., Furkert, J., Schaefer, M., Beyermann, M., et al. (2004). Ligand-dependent differences in the internalization of endothelin A and endothelin B receptor heterodimers. *The Journal of Biological Chemistry*, *279*, 27679–27687.

Gregan, B., Schaefer, M., Rosenthal, W., & Oksche, A. (2004). Fluorescence resonance energy transfer analysis reveals the existence of endothelin-A and endothelin-B receptor homodimers. *Journal of Cardiovascular Pharmacology*, *44*, S30–S33.

Gulati, A., Rebello, S., Roy, S., & Saxena, P. R. (1995). *Journal of Cardiovascular Pharmacology*, *26*, S244–S246.

Guyenet, P. G. (2006). The sympathetic control of blood pressure. *Nature Reviews. Neuroscience*, *7*, 335–346.

Haag, C., Berkels, R., Gründemann, D., Lazar, A., Taubert, D., & Schömig, E. (2004). The localisation of the extraneuronal monoamine transporter (EMT) in rat brain. *Journal of Neurochemistry*, *88*, 291–297.

Hahn, M. K., & Blakely, R. D. (2002). Monoamine transporter gene structure and polymorphisms in relation to psychiatric disorders and other complex disorders. *Pharmacogenomics Journal*, *2*, 217–235.

Hahn, M. K., & Blakely, R. D. (2007). The functional impact of SLC6 transporter genetic variation. *Annual Review of Pharmacology and Toxicology*, *47*, 401–441.

Hall, J. E., Granger, J. P., do Carmo, J. M., da Silva, A. A., Dubinion, J., George, E., et al. (2012). Hypertension: Physiology and pathophysiology. *Comprehensive Physiology*, *2*, 2393–2442.

Harrison, V. J., Randiantsoa, A., & Schoffter, P. (1992). Heterogeneity of endothelin–sarafotoxin receptors mediating contraction of pig coronary artery. *British Journal of Pharmacology*, *105*, 511–513.

Hasegawa, H., Hiki, K., Sawamura, T., Aoyama, T., Okamoto, Y., Miwa, S., et al. (1998). Purification of a novel endothelin-converting enzyme specific for big endothelin-3. *FEBS Letters*, *428*, 304–308.

Hatae, N., Aksentijevich, N., Zemkova, H. W., Kretschmannova, K., Tomic, M., & Stojilkovic, S. S. (2007). Cloning and functional identification of novel endothelin receptor type A isoforms in pituitary. *Molecular Endocrinology*, *21*, 1192–1204.

Haynes, W. G., Ferro, C. E., & Webb, D. J. (1995). Physiologic role of endothelin in maintenance of vascular tone in humans. *Journal of Cardiovascular Pharmacology*, *3*, S183–S185.

Haynes, W. G., Strachan, F. E., & Webb, D. J. (1995). Endothelin ETA and ETB receptor cause vasoconstriction of human resistance and capacitance vessels in vivo. *Circulation*, *92*, 357–363.

Haynes, W. G., & Webb, D. J. (1998). Endothelin as a regulator of cardiovascular function in health and disease. *Journal of Hypertension*, *16*, 1081–1098.

Herman, W. H., & Simonson, M. S. (1995). Nuclear signaling by endothelin—1. A Ras pathway for activation of the c-fos serum response element. *The Journal of Biological Chemistry*, *270*, 11654–11661.

Hersch, E., Huang, J., Grider, J. R., & Murthy, K. S. (2004). Gq/G13 signaling by ET-1 in smooth muscle: MYPT1 phosphorylation via ETA and CPI-17 dephosphorylation via ETB. *American Journal of Physiology. Cell Physiology*, *287*, C1209–C1218.

Hickey, K. A., Rubanyi, G., Paul, R. J., & Highsmith, R. F. (1985). Characterization of a coronary vasoconstrictor produced by culture endothelial cells. *American Journal of Physiology. Cell Physiology*, *248*, C550–C556.

Author's personal copy

Hirata, Y., Emori, T., Eguchi, S., Kanno, K., Imai, T., Ohta, K., et al. (1993). Endothelin receptor subtype B mediates synthesis of nitric oxide by cultured bovine endothelial cells. *The Journal of Clinical Investigation*, *91*, 1367–1373.

Hökfelt, T., Bartfai, T., & Bloom, F. (2003). Neuropeptides: Opportunities for drug discovery. *The Lancet Neurology*, *2*, 463–472.

Hökfelt, T., Broberger, C., Xu, Z. Q., Sergeyev, V., Ubink, R., & Diez, M. (2000). Neuropeptides—An overview. *Neuropharmacology*, *39*, 1337–1356.

Hope, S. I., Nabhen, S. L., Soria, C., Bianciotti, L. G., & Vatta, M. S. (2010). Endothelin-1 and -3 modulate the neuronal norepinephrine transporter through multiple signalling pathways in the rat posterior hypothalamus. *Neurochemistry International*, *57*, 306–313.

Hope, S. I., Schmipp, J., Rossi, A. H., Bianciotti, L. G., & Vatta, M. S. (2008). Regulation of the neuronal norepinephrine transporter by endothelin-1 and -3 in the rat anterior and posterior hypothalamus. *Neurochemistry International*, *53*, 207–213.

Horinouchi, T., Terada, K., Higashi, T., & Miwa, S. (2013). Endothelin receptor signalling: New insight into its regulatory mechanisms. *Journal of Pharmacological Sciences*, *123*, 85–101.

Hughes, J. (1972). Evaluation of mechanisms controlling the release and inactivation of the adrenergic transmitter in the rabbit portal vein and vas deferens. *British Journal of Pharmacology*, *44*, 472–491.

Hynynen, M. M., & Khalil, R. A. (2006). The vascular endothelin system in hypertension—Recent patents and discoveries. *Recent Patents on Cardiovascular Drug Discovery*, *1*, 95–108.

Inoue, A., Yanagisawa, M., Kimura, S., Kasuya, Y., Miyauchi, T., Goto, K., et al. (1989). The human endothelin family: Three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proceedings of the National Academy of Sciences of the United States of America*, *86*, 2863–2867.

Itoh, Y., Yanagisawa, M., Ohkubo, S., Kimura, C., Kosaka, T., Inoue, A., et al. (1988). Cloning and sequence analysis of cDNA encoding the precursor of a human endothelium-derived vasoconstrictor peptide, endothelin: Identity of human and porcine endothelin. *FEBS Letters*, *231*, 440–444.

Iversen, L. (2000). Neurotransmitter transporters: Fruitful targets for CNS drug discovery. *Molecular Psychiatry*, *5*, 357–362.

Iversen, L. (2006). Neurotransmitter transporters and their impact on the development of psychopharmacology. *British Journal of Pharmacology*, *147*, S82–S88.

Iversen, L. L., & Salt, P. J. (1970). Inhibition of catecholamine Uptake2 by steroids in the isolated rat heart. *British Journal of Pharmacology*, *40*, 528–530.

Ivey, M. E., Osman, N., & Little, P. J. (2008). Endothelin-1 signalling in vascular smooth muscle: Pathways controlling cellular functions associated with atherosclerosis. *Atherosclerosis*, *199*, 237–247.

Iwasa, H., Kurabayashi, M., Nagai, R., Nakamura, Y., & Tanaka, T. (2001). Genetic variations in five genes involved in the excitement of cardiomyocytes. *Journal of Human Genetics*, *46*, 549–552.

Jain, A., Olovsson, M., Burton, G. J., & Yung, H. W. (2012). Endothelin-1 induces endoplasmic reticulum stress by activating the PLC-IP(3) pathway: Implications for placental pathophysiology in preeclampsia. *American Journal of Pathology*, *180*, 2309–2320.

Jaureguiberry, M. S., di Nunzio, A. S., Dattilo, M. A., Bianciotti, L. G., & Vatta, M. S. (2004). Endothelin 1 and 3 enhance neuronal nitric oxide synthetase activity through ETB receptors involving multiple signaling pathways in the rat anterior hypothalamus. *Peptides*, *25*, 1133–1138.

Jayanthi, L. D., Annamalai, B., Samuvel, D. J., Gether, U., & Ramamoorthy, S. (2006). Phosphorylation of the norepinephrine transporter at threonine 258 and serine 259 is linked to protein kinase C-mediated transporter internalization. *The Journal of Biological Chemistry*, *281*, 23326–23340.

Author's personal copy

Jayanthi, L. D., Samuvel, D. L., & Ramamoorthy, S. (2004). Regulated internalization and phosphorylation of the native norepinephrine transporter in response to phorbol esters. Evidence for localization in lipids rafts and lipid raft-mediated internalization. *The Journal of Biological Chemistry*, *279*, 19315–19326.

Jena, B. P. (2011). Role of SNAREs in membrane fusion. *Advances in Experimental Medicine and Biology*, *713*, 13–32.

Kanyicska, B., Sellix, M. T., & Freeman, M. E. (2003). Autocrine regulation of prolactin secretion by endothelins throughout the estrous cycle. *Endocrine*, *20*, 53–58.

Karne, S., Jayawickreme, C. K., & Lerner, M. R. (1993). Cloning and characterization of an endothelin-3 specific receptor (ETC receptor) from *Xenopus laevis* dermal melanophores. *The Journal of Biological Chemistry*, *268*, 19126–19133.

Kasuya, Y., Kobayashi, H., & Uemura, H. (1991). Endothelin-like immunoreactivity in the nervous system of invertebrates and fish. *Journal of Cardiovascular Pharmacology*, *7*, S463–S466.

Kato, K., Okamura, K., Hatta, M., Morita, H., Kajioka, S., Naito, S., et al. (2013). Involvement of IP3-receptor activation in endothelin-1-induced Ca(2+) influx in rat pulmonary small artery. *European Journal of Pharmacology*, *720*, 255–263.

Kawanabe, Y., & Nauli, S. M. (2011). Endothelin. *Cellular and Molecular Life Sciences*, *68*, 195–203.

Khimji, A., & Rockey, D. C. (2010). Endothelin—Biology and disease. *Cellular Signalling*, *22*, 1615–1625.

Kimura, S., Kasuya, Y., Sawamura, T., Shinmi, O., Sugita, Y., Yanagisawa, M., et al. (1988). Structure–activity relationships of endothelin: Importance of the C-terminal moiety. *Biochemical and Biophysical Research Communications*, *156*, 1182–1186.

King, R. G., Gude, N. M., Di Iulio, J. L., & Brennecke, S. P. (1995). Regulation of human placental fetal vessel tone: Role of nitric oxide. *Reproduction, Fertility, and Development*, *7*, 1407–1411.

Kippenberger, A. G., Palmer, D. J., Comer, A. M., Lipski, J., Burton, L. D., & Christie, D. L. (1999). Localization of then noradrenaline transporter in rat adrenal medulla and PC12 cells: Evidence for its association with secretory granules in PC12 cells. *Journal of Neurochemistry*, *73*, 1024–1032.

Kitamura, K., Shirashi, N., Singer, W. D., Handlogten, M. E., Tomita, K., & Miller, R. T. (1999). Endothelin B receptors activate Galpha13. *American Journal of Physiology. Cell Physiology*, *276*, C930–C937.

Kloog, Y., Ambar, I., Sokolovsky, M., Kochva, E., Wollberg, Z., & Bdolah, A. (1988). Sarafotoxin, a novel vasoconstrictor peptide: Phosphoinositide hydrolysis in rat heart and brain. *Science*, *242*, 268–270.

Knuepfer, M. M., O'Brien, D., Hoang, D., Gan, Q., & Song, C. (1994). Central sympathetic control of spinal endothelin release in the rat. *European Journal of Pharmacology*, *259*, 305–308.

Kochva, E., Bdolah, A., & Wollberg, Z. (1993). Sarafotoxins and endothelins: Evolution, structure and function. *Toxicon*, *31*, 541–568.

Kohan, D. E., Rossi, N. F., Inscho, E. W., & Pollock, D. M. (2011). Regulation of blood pressure and salt homeostasis by endothelin. *Physiological Reviews*, *91*, 1–77.

Kopin, I. J. (1994). Monoamine oxidase and catecholamine metabolism. *Journal of Neural Transmission*, *41*, 57–67.

Koyama, Y. (2013). Endothelin systems in the brain: Involvement in pathophysiological responses of damaged nerve tissues. *Biomolecular Concepts*, *4*, 335–347.

Kristensen, A. S., Andersen, J., Jørgensen, T. N., Sørensen, L., Eriksen, J., Loland, C. J., et al. (2011). SLC6 neurotransmitter transporters: Structure, function, and regulation. *Pharmacological Reviews*, *63*, 585–640.

Kuddus, R. H., Nalesnik, M. A., Subbotin, V. M., Rao, A. S., & Gandhi, C. R. (2000). Enhanced synthesis and reduced metabolism of endothelin-1 (ET-1) by

Author's personal copy

hepatocytes—An important mechanism of increased endogenous levels of ET-1 in liver cirrhosis. *Journal of Hepatology*, *33*, 725–732.
Kuhlmann, A., Amann, K., Schlotzer-Schrehardt, U., Kruse, F. E., & Cyrsiefen, C. (2005). Endothelin-1 and ETA/ETB receptor protein and mRNA: Expression in normal and vascularized human corneas. *Cornea*, *24*, 837–844.
Kumada, M., Cao, W., & Kuwaki, T. (2003). Effect of endothelin on vasomotor and respiratory neurons in the rostral ventrolateral medulla in rats. *Cellular and Molecular Neurobiology*, *23*, 691–707.
Kumar, C., Mwangi, V., Nuthulaganti, P., Wu, H. L., Pullen, M., Brun, K., et al. (1994). Cloning and characterization of a novel endothelin receptor from Xenopus heart. *The Journal of Biological Chemistry*, *269*, 13414–13420.
Kurokawa, K., Yamada, H., Liu, Y., & Kudo, M. (2000). Immunohistochemical distribution of the endothelin converting enzyme-1 in the rat hypothalamo–pituitary axis. *Neuroscience Letters*, *284*, 81–84.
Kurokawa, K., Yamada, H., & Ochi, J. (1997). Topographical distribution of neurons containing endothelin type A receptor in the rat brain. *The Journal of Comparative Neurology*, *389*, 348–360.
Kuwaki, T., Kurihara, H., Cao, W. H., Kurihara, Y., Unekawa, M., Yazaki, Y., et al. (1997). Physiological role of brain endothelin in the central autonomic control: From neuron to knockout mouse. *Progress in Neurobiology*, *51*, 545–579.
Kuwaki, T., Ling, G. Y., Onodera, M., Ishii, T., Nakamura, A., Ju, K. H., et al. (1999). *Clinical and Experimental Pharmacology & Physiology*, *26*, 989–994.
Kvetnansky, R., Sabban, E. L., & Palkovits, M. (2009). Catecholaminergic system in stress: Structural and molecular genetic approaches. *Physiological Reviews*, *89*, 535–606.
Liang, C. S. (2007). Cardiac sympathetic nerve terminal function in congestive heart failure. *Acta Pharmacologica Sinica*, *28*, 921–927.
Lopez-Verrilli, M. A., Rodríguez-Fermepín, M., Longo Carbajosa, N., Landa, S., Cerrato, B. D., García, S., et al. (2012). Angiotensin-(1–7) through Mas receptor up-regulates neuronal norepinephrine transporter via Akt and Erk1/2-dependent pathways. *Journal of Neurochemistry*, *120*, 46–55.
Lu, Y., Wang, L. G., Liao, Z., Tang, C. S., Wang, W. Z., & Yuan, W. J. (2007). Cardiovascular effects of centrally applied endothelin-1 1–31 and its relationship to endothelin-1 1–21 in rats. *Autonomic Neuroscience*, *133*, 146–152.
Macarthur, H., Warner, T. D., Wood, E. G., Corder, R., & Vane, J. R. (1994). Endothelin-1 release from endothelial cells in culture is elevated both acutely and chronically by short periods of mechanical stretch. *Biochemical and Biophysical Research Communications*, *200*(1), 395–400.
MacCumber, M. W., Ross, C. A., & Snyder, S. H. (1990). Endothelin in the brain: Receptors, mitogenesis, and biosynthesis in glial cells. *Proceedings of the National Academy of Sciences of the United States of America*, *87*, 2359–2363.
Matsumoto, H., Suzuki, N., Onda, H., & Fujino, M. (1989). Abundance of endothelin-3 in rat intestine, pituitary gland, and brain. *Biochemical and Biophysical Research Communications*, *164*, 74–80.
Matsumura, K., Abe, I., Fukuhara, M., Tominaga, M., Tsuchihashi, T., Kobayashi, K., et al. (1994). Naloxone augments sympathetic outflow induced by centrally administered endothelin in conscious rabbits. *American Journal of Physiology. Renal Physiology*, *266*, R1403–R1410.
Matthies, H. J. G., Han, Q., Shields, A., Wright, J., Moore, J. L., Danny, G., et al. (2009). Subcellular localization of the antidepressant sensitive norepinephrine transporter. *BMC Neuroscience*, *10*, 65.
Merighi, A. (2002). Costorage and coexistence of neuropeptides in the mammalian CNS. *Progress in Neurobiology*, *66*, 161–190.

Author's personal copy

Meyers, K. E., & Sethna, C. (2013). Endothelin antagonists in hypertension and kidney disease. *Pediatric Nephrology*, *28*, 711–720.

Morbidelli, L., Orlando, C., Maggi, C. A., Ledda, F., & Ziche, M. (1995). Proliferation and migration of endothelial cells is promoted by endothelins via activation of ETB receptors. *American Journal of Physiology Heart and Circulatory Physiology*, *269*, H686–H695.

Moreland, S., McMullen, D. M., Delaney, C. L., Lee, V. G., & Hunt, J. T. (1992). Venous smooth muscle contains vasoconstrictor ETB-like receptors. *Biochemical and Biophysical Research Communications*, *184*, 100–106.

Morgazo, C., Perfume, G., Legaz, G., di Nunzio, A. S., Hope, S. I., Bianciotti, L. G., et al. (2005). Involvement of nitric oxide pathways in short term modulation of tyrosine hydroxylase activity by endothelins 1 and 3 in the rat anterior hypothalamus. *Biochemical and Biophysical Research Communications*, *334*, 796–802.

Moron, J. A., Brockington, A., Wise, R. A., Rocha, B.-A., & Hope, B. T. (2002). Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: Evidence from knock-out mouse lines. *The Journal of Neuroscience*, *22*, 389–395.

Mosqueda-García, R., Inagami, T., Appalsamy, M., Sugiura, M., & Robertson, R. M. (1993). Endothelin as a neuropeptide. Cardiovascular effects in the brainstem of normotensive rats. *Circulation Research*, *72*, 20–35.

Nabhen, S. L., Morales, V. P., Guil, M. J., Hocht, C., Bianciotti, L. G., & Vatta, M. S. (2011). Mechanisms involved in the long-term modulation of tyrosine hydroxylase by endothelins in the olfactory bulb of normotensive rats. *Neurochemistry International*, *58*, 196–205.

Nabhen, S. L., Perfume, G., Battistone, M. A., Rossi, A., Abramoff, T., Bianciotti, L. G., et al. (2009). Short-term effects of endothelins on tyrosine hydroxylase activity and expression in the olfactory bulb of normotensive rats. *Neurochemical Research*, *34*, 953–963.

Naicker, S., & Bhoola, K. D. (2001). Endothelins: Vasoactive modulators of renal function in health and disease. *Pharmacology & Therapeutics*, *90*, 61–88.

Naidoo, V., Mahabeer, R., & Raidoo, D. M. (2001). Cellular distribution of endothelin-1 mRNA in human brain by in situ RT-PCR. *Metabolic Brain Disease*, *16*, 207–218.

Naidoo, V., Naidoo, S., Mahabeer, R., & Raidoo, D. M. (2004). Cellular distribution of the endothelin system in the human brain. *Journal of Chemical Neuroanatomy*, *27*, 87–98.

Nambi, P., Pullen, M., Kincad, J., Nuthulaganti, P., Aiyar, N., Brooks, D. P., et al. (1997). Identification and characterization of a novel endothelin receptor that binds both ETA- and ETB-selective ligands. *Molecular Pharmacology*, *52*, 582–589.

Nasser, S. A., & El-Mas, M. M. (2014). Endothelin ETA receptor antagonism in cardiovascular disease. *European Journal of Pharmacology*, *737*, 210–213.

Nishimura, M., Takahashi, H., Matsusawa, M., Ikegaki, I., Nakanishi, T., Hirabayashi, M., et al. (1990). Intracerebroventricular injections of endothelins increase arterial pressure in conscious rats. *Japanese Circulation Journal*, *54*, 662–670.

Nishimura, M., Takahashi, H., Matsusawa, M., Ikegaki, I., Sakamoto, M., Nakanishi, T., et al. (1991). Chronic intracerebroventricular infusions of endothelin elevate arterial pressure in rats. *Journal of Hypertension*, *9*, 71–76.

Nostramo, R., Tillinger, A., Serova, L., Kvetnansky, R., & Sabban, E. L. (2013). Bradykinin B2 receptor in the adrenal medulla of male rats and mice: Glucocorticoid-dependent increase with immobilization stress. *Endocrinology*, *154*, 3729–3738.

Oaks, A. W., & Sidhu, A. (2011). Sinuclein modulation of monoamine transporters. *FEBS Letters*, *585*, 1001–1006.

Ohkita, M., Tawa, M., Kitada, K., & Matsumura, Y. (2012). Pathophysiological roles of endothelin receptors in cardiovascular diseases. *Journal of Pharmacological Sciences*, *119*, 302–313.

Author's personal copy

Olivier, B., Soudijn, W., & van Wijngaarden, I. (2000). Serotonin, dopamine and norepinephrine transporters in the central nervous system and their inhibitors. *Progress in Drug Research*, *54*, 59–119.

Oparil, S., Chen, S. J., Meng, Q. C., Elton, T. S., Yano, M., & Chen, Y. F. (1995). Endothelin A receptor antagonist prevents acute hypoxia-induced pulmonary hypertension in the rat. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *268*, L95–L100.

Opgenorth, T. J. (1995). Endothelin receptor antagonism. *Advances in Pharmacology*, *33*, 1–65.

Opgenorth, T. J., Wu-Wong, J. R., & Shiosaki, K. (1992). Endothelin-converting enzymes. *FASEB Journal*, *6*, 2653–2659.

Ouchi, Y., Kim, S., Souza, A. C., Iijima, S., Hattori, A., Orimo, H., et al. (1989). Central effect of endothelin on blood pressure in conscious rats. *American Journal of Physiology. Heart and Circulatory Physiology*, *256*, H1747–H1751.

Palaic, D., & Khairallah, P. A. (1967a). Inhibition on noradrenaline uptake by angiotensin. *The Journal of Pharmacy and Pharmacology*, *19*, 396–397.

Palaic, D., & Khairallah, P. A. (1967b). Effect of angiotensin on uptake and release of norepinephrine by brain. *Biochemical Pharmacology*, *16*, 2291–2298.

Palaic, D., & Khairallah, P. A. (1968). Inhibition of norepinephrine re-uptake by angiotensin in brain. *Journal of Neurochemistry*, *15*, 1195–1202.

Papouchado, M. L., Vatta, M. S., Escalada, A., Bianciotti, L. G., & Fernández, B. E. (1995). Angiotensin III modulates noradrenaline uptake and release in the rat hypothalamus. *Journal of Autonomic Pharmacology*, *15*, 1–8.

Pate, M. A., Chester, A. H., Crabbe, D. S., Amrani, M., Brown, T. J., Roach, A. G., et al. (1999). Characterization of constrictor endothelin receptors in the human internal thoracic artery and saphenous vein. *Journal of Cardiovascular Pharmacology*, *33*, 567–572.

Penna, C., Rastaldo, R., Mancardi, D., Cappello, S., Pagliaro, P., Westerhof, N., et al. (2006). Effect of endothelins on the cardiovascular system. *Journal of Cardiovascular Medicine*, *7*, 645–652.

Perfume, G., Morgazo, C., Nabhen, S., Battistone, A., Hope, S. I., Bianciotti, L. G., et al. (2007). Short-term regulation of tyrosine hydroxylase activity and expression by endothelin-1 and endothelin-3 in the rat posterior hypothalamus. *Regulatory Peptides*, *142*, 69–77.

Perfume, G., Nabhen, S. L., Barrera, K. R., Otero, M. G., Bianciotti, L. G., & Vatta, M. S. (2008). Long-term modulation of tyrosine hydroxylase activity and expression by endothelin-1 and -3 in the rat anterior and posterior hypothalamus. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *294*, R905–R914.

Pfaff, D. W., Kieffer, B. L., & Swanson, L. W. (2008). Mechanisms for the regulation of state changes in the central nervous system: An introduction. *Annals of the New York Academy of Sciences*, *1129*, 1–7.

Plant, T. M. (2008). Hypothalamic control of the pituitary–gonadal axis in higher primates: Key advances over the last two decades. *Journal of Neuroendocrinology*, *20*, 719–726.

Pollock, D. M., Keith, T. L., & Highsmith, R. F. (1995). Endothelin receptors and calcium signaling. *FASEB Journal*, *9*, 1196–1204.

Pörzgen, P., Bönisch, H., Hammermann, R., & Brüss, M. (1998). The human noradrenaline transporter gene contains multiple polyadenylation sites and two alternatively spliced C-terminal exons. *Biochimica et Biophysica Acta*, *1398*, 365–370.

Pramod, A. B., Foster, J., Carvelli, L., & Henry, L. K. (2013). SLC6 transporters: Structure, function, regulation, disease association and therapeutics. *Molecular Aspects of Medicine*, *34*, 197–219.

Quick, M. W. (2006). The role of SNARE proteins in trafficking and function of neurotransmitter transporters. *Handbook of Experimental Pharmacology*, *175*, 181–196.

Ramamoorthy, S., Shippenberg, T. S., & Jayanthi, L. D. (2011). Regulation of monoamine transporter: Role of transporter phosphorylation. *Pharmacology & Therapeutics*, *129*, 220–238.

Author's personal copy

Rizo, J., & Südhof, T. C. (2002). SNAREs and Munc18 in synaptic vesicle fusion. *Nature Reviews. Neuroscience*, *3*, 641–653.

Robin, P., Chouayekh, S., Bole-Feysot, C., Leiber, D., & Tanfin, Z. (2005). Contribution of phospholipase D in endothelin-1-mediated extracellular signal-regulated kinase activation and proliferation in rat uterine leiomyoma cells. *Biology of Reproduction*, *72*, 69–77.

Robinson, M. B. (2003). Signaling pathways take aim at neurotransmitter transporter. *Science's STKE*, *2003*(207), pe50.

Rodríguez, M. R., Sabbatini, M. E., Santella, G., Dabas, P., Villagra, A., Vatta, M. S., et al. (2005). Endothelin-3 applied to the brain evokes opposite effects on bile secretion mediated by a central nitric oxide pathway. *Peptides*, *26*, 1219–1227.

Rodríguez, M. R., Sabbatini, M. E., Santella, G., Vescina, C., Vatta, M. S., & Bianciotti, L. G. (2006). Vagally mediated cholestatic and choleretic effects of centrally applied Endothelin-1 through ETA receptors. *Regulatory Peptides*, *135*, 54–62.

Rodríguez, M. R., Soria, L. R., Ventimiglia, M. S., Najenson, A. C., Di María, A., Dabas, P., et al. (2013). Endothelin-1 and -3 induce choleresis in the rat through ETB receptors coupled to nitric oxide and vago-vagal reflexes. *Clinical Science*, *125*, 521–532.

Rubanyi, G. M., & Botelho, L. H. (1991). Endothelins. *FASEB Journal*, *5*, 2713–2720.

Russell, F. D., & Davenport, A. P. (1999). Secretory pathways in endothelin synthesis. *British Journal of Pharmacology*, *126*, 391–398.

Schiffrin, E. L. (1998). Endothelin and endothelin antagonists in hypertension. *Journal of Hypertension*, *16*, 1891–1895.

Schlessingera, A., Geiera, E., Fana, H., Irwinb, J. J., Shoichet, B. K., Giacominia, K. M., et al. (2011). Structure-based discovery of prescription drugs that interact with the norepinephrine transporter, NET. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 15810–15815.

Schneider, M. P., Boesen, E. I., & Pollock, D. M. (2007). Contrasting actions of endothelin ET(A) and ET(B) receptors in cardiovascular disease. *Annual Review of Pharmacology and Toxicology*, *47*, 731–759.

Schroeder, C., & Jordan, J. (2012). Norepinephrine function and human cardiovascular disease. *American Journal of Physiology. Heart and Circulatory Physiology*, *303*, H1273–H1282.

Schroeter, S., Apparsundaram, S., Wiley, R. G., Miner, L. H., Sesack, S. R., & Blakely, R. D. (2000). Immunolocalization of the cocaine- and antidepressant-sensitive l-norepinephrine transporter. *The Journal of Comparative Neurology*, *420*, 211–232.

Seyedi, N., Win, T., Lander, H. M., & Levi, R. (1997). Bradykinin B2-receptor activation augments norepinephrine exocytosis from cardiac sympathetic nerve endings. Mediation by autocrine/paracrine mechanisms. *Circulation Research*, *81*, 774–784.

Shakiryanova, D., Tully, A., Hewes, R. S., Deitcher, D. L., & Levitan, E. S. (2005). Activity-dependent liberation of synaptic neuropeptide vesicles. *Nature in Neuroscience*, *8*, 173–178.

Shannon, J. R., Flattem, N. L., Jordan, J., Jacob, G., Black, B. K., Biaggioni, I., et al. (2000). Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *The New England Journal of Medicine*, *342*, 541–549.

Sheng, Z. H., Rettig, J., Cook, T., & Catterall, W. A. (1996). Calcium-dependent interaction of N-type calcium channels with the synaptic core complex. *Nature*, *376*, 451–454.

Shraga-Levine, Z., & Sokolovsky, M. (2000). Functional coupling of G proteins to endothelin receptors is ligand and receptor subtype specific. *Cellular and Molecular Neurobiology*, *20*, 305–317.

Sirén, A. L., & Feuerstein, G. (1989). Hemodynamic effects of endothelin after systemic and central nervous system administration in the conscious rat. *Neuropeptides*, *14*, 231–236.

Author's personal copy

Sluck, J. M., Lin, R. C., Katolik, L. I., Jeng, A. Y., & Lehmann, J. C. (1999). Endothelin converting enzyme-1-, endothelin-1-, and endothelin-3-like immunoreactivity in the rat brain. *Neuroscience*, *91*, 1483–1497.

Sogawa, C., Kumagai, K., Sogawa, N., Morita, K., Dohi, T., & Kitayama, S. (2007). C-terminal region regulates the functional expression of human noradrenaline transporter splice variants. *The Biochemical Journal*, *401*, 185–195.

Sokolovsky, M. (1995a). Endothelin receptor subtypes and their role in transmembrane signaling mechanisms. *Pharmacology & Therapeutics*, *68*, 435–471.

Sokolovsky, M. (1995b). Endothelin receptor heterogeneity, G-proteins, and signalling via cAMP and cGMP cascades. *Cellular and Molecular Neurobiology*, *15*, 561–571.

Stepniakowski, K., Budzikowski, A., Loń, S., & Szczepańska-Sadowska, E. (1994). Central cardiovascular effects of AVP and ANP in normotensive and spontaneously hypertensive rats. *Journal of the Autonomic Nervous System*, *47*, 33–43.

Stern, J. E., & Filosa, J. A. (2013). Bidirectional neuro-glial signaling modalities in the hypothalamus: Role in neurohumoral regulation. *Autonomic Neuroscience*, *175*, 51–60.

Stöber, G., Nöthen, M. M., Pörzgen, P., Brüsss, M., Knapp, M., Beckmann, H., et al. (1996). Systematic search for variation in the human norepinephrine transporter gene: Identification of five naturally occurring missense mutations and study of association with major psychiatric disorders. *American Journal of Medical Genetics*, *67*(6), 523–532.

Stojilkovic, S. S., & Catt, K. J. (1996). Expression and signal transduction pathways of endothelin receptors in neuroendocrine cells. *Frontiers in Neuroendocrinology*, *17*, 327–369.

Sumners, C., & Raizada, M. K. (1986). Angiotensin II stimulates norepinephrine uptake in hypothalamus–brain stem neuronal cultures. *American Journal of Physiology. Cell Physiology*, *250*, C236–C244.

Sumners, C., Shalit, S. L., Kalberg, C. J., & Raizada, M. K. (1987). Norepinephrine metabolism in neuronal cultures is increased by angiotensin II. *American Journal of Physiology. Cell Physiology*, *252*, C650–C656.

Sung, U., Apparsundaram, S., Galli, A., Kahling, K. M., Savchenko, V., Quick, M. W., et al. (2003). A regulated interaction syntaxin 1A with antidepressant-sensitive norepinephrine transporter establishes catecholamine clearance capacity. *The Journal of Neuroscience*, *23*, 1697–1709.

Sung, U., & Blakely, R. D. (2007). Calcium-dependent interactions of the human norepinephrine transporter with syntaxin 1A. *Molecular and Cellular Neurosciences*, *34*, 251–260.

Szczepańska-Sadowska, E. (2006). Neuropeptides in neurogenic disorders of the cardiovascular control. *Journal of Physiology and Pharmacology*, *57*(Suppl. 11), 31–53.

Szczepańska-Sadowska, E., Paczwa, P., Loń, S., & Ganten, D. (1998). Increased pressor function of central vasopressinergic system in hypertensive renin transgenic rats. *Journal of Hypertension*, *16*, 1505–1514.

Takizawa, S., Uchide, T., Adur, J., Kozakai, T., Kotake-Nara, E., Quan, J., et al. (2005). Differential expression of endothelin-2 along the mouse intestinal tract. *Journal of Molecular Endocrinology*, *35*, 201–209.

Tasker, J. G., Oliet, S. H., Bains, J. S., Brown, C. H., & Stern, J. E. (2012). Glial regulation of neuronal function: From synapse to systems physiology. *Journal of Neuroendocrinology*, *24*, 566–576.

Tellioglu, T., & Robertson, D. (2001). Genetic or acquired deficits in the norepinephrine transporter: Current understanding of clinical implications. *Expert Reviews in Molecular Medicine*, *2001*, 1–10.

ThanThan, S., Mekaru, C., Seki, N., Hidaka, K., Ueno, A., ThidarMyint, H., et al. (2010). Endogenous ghrelin released in response to endothelin stimulates growth hormone secretion in cattle. *Domestic Animal Endocrinology*, *38*, 1–12.

Author's personal copy

Torres, G., & Anara, S. G. (2007). Glutamate and monoamine transporters: New visions of form and function. *Current Opinion in Neurobiology*, *17*, 304–312.

Trendelenburg, U. (1988). The extraneuronal uptake and metabolism of catecholamines. In U. Trendelenburg (Ed.), *Handbook of experimental pharmacology* (pp. 279–319). Berlin: Springer-Verlag.

Tsukahara, H., Ende, H., Magazine, H. I., Bahou, W. F., & Goligorsky, M. S. (1994). Molecular and functional characterization of the non-isopeptide-selective ETB receptor in endothelial cells. Receptor coupling to nitric oxide synthase. *The Journal of Biological Chemistry*, *269*, 21778–21785.

Uchide, T., Adur, J., Fukamachi, T., & Saida, K. (2000). Quantitative analysis of endothelin-1 and vasoactive intestinal contractor/endothelin-2 gene expression in rats by real-time reverse transcriptase polymerase chain reaction. *Journal of Cardiovascular Pharmacology*, *36*, S5–S8.

Uchida, J., Kiuchi, Y., Ohno, M., Yura, A., & Oguchi, K. (1998). Ca(2+)-dependent enhancement of [3H]noradrenaline uptake in PC12 cells through calmodulin-dependent kinases. *Brain Research*, *809*, 155–164.

Vatta, M. S., Bianciotti, L. G., & Fernández, B. E. (1993a). Atrial natriuretic peptide and bradykinin interaction on norepinephrine uptake in rat adrenal medulla. *Archives Internationales de Physiologie et de Biochimie*, *101*, 129–132.

Vatta, M. S., Bianciotti, L. G., & Fernández, B. E. (1993b). Influence of atrial natriuretic factor on uptake, intracellular distribution, and release of norepinephrine in rat adrenal medulla. *Canadian Journal of Physiology and Pharmacology*, *71*, 195–200.

Vatta, M. S., Bianciotti, L. G., Locatelli, A. S., Papouchado, M. L., & Fernández, B. E. (1992). Monophasic and biphasic effects of angiotensin II and III on norepinephrine uptake and release in rat adrenal medulla. *Canadian Journal of Physiology and Pharmacology*, *70*, 821–825.

Vatta, M. S., Bianciotti, L. G., Papouchado, M. L., Locatelli, A. S., & Fernández, B. E. (1991). Effects of atrial natriuretic peptide and angiotensin III on the uptake and intracellular distribution of norepinephrine in medulla oblongata of the rat. *Comparative Biochemistry and Physiology Part C: Comparative Pharmacology and Toxicology*, *99*, 293–297.

Vatta, M. S., Bianciotti, L. G., Perfume, G., Nabhen, S. L., & Hope, S. I. (2009). Endothelins: A family of peptides with multiple biological functions. In G. Rodriguez de Lores Arnaiz (Ed.), *Function of Neuropepties at Central Nervus System* (pp. 149–169). Kerala: Research Signpost.

Vatta, M. S., Presas, M. F., Bianciotti, L. G., Rodríguez-Fermepín, M., Ambros, R., & Fernandez, B. E. (1997). B and C types natriuretic peptides modify norepinephrine uptake and release in the rat adrenal medulla. *Peptides*, *18*, 1483–1489.

Vatta, M. S., Presas, M., Bianciotti, L. G., Zarrabeitia, V., & Fernández, B. E. (1996). B and C natriuretic peptides modulate norepinephrine uptake and release in the rat hypothalamus. *Regulatory Peptides*, *65*, 175–184.

Vatta, M., Rodríguez-Fermepín, M., Bianciotti, L., Perazzo, J., Monserrat, A., & Fernández, B. (1995). Atrial natriuretic factor enhances norepinephrine uptake in circumventricular organs, locus coeruleus and nucleus tractus solitarii of the rat. *Neuroscience Letters*, *197*, 29–32.

Vatta, M., Travaglianti, M., Bianciotti, L., Coll, C., Perazzo, J., & Fernández, B. (1994). Atrial natriuretic factor effects on norepinephrine uptake in discrete telencephalic and diencephalic nuclei of the rat. *Brain Research*, *646*, 324–326.

Watts, S. W. (2010). Endothelin receptors: What's new and what do we need to know? *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *298*, R254–R260.

Webber, K. M., Pennefather, J. M., Head, G. A., & van den Buuse, M. (1998). Endothelin induces dopamine release from rat striatum via endothelin-B receptors. *Neuroscience*, *86*, 1173–1180.

Wehrwein, E. A., Parker, L. M., Wright, A. A., Spitsbergen, J. M., Novotny, M., Babankova, D., et al. (2008). Cardiac norepinephrine transporter protein expression is

Author's personal copy

inversely correlated to chamber norepinephrine content. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *295*, R857–R863.
Wersinger, C., Jeannotte, A., & Sidhu, A. (2006). Attenuation of the norepinephrine transporter activity and trafficking via interactions with alpha-synuclein. *The European Journal of Neuroscience*, *24*, 3141–3152.
Whiskey, E., & Taylor, D. (2013). A review of the adverse effects and safety of noradrenergic antidepressants. *Journal of Psychopharmacology*, *27*, 732–739.
Winquist, R. J., Bunting, P. B., Garsky, V. M., Lumma, P. K., & Schofield, T. L. (1989). Prominent depressor response to endothelin in spontaneously hypertensive rats. *European Journal of Pharmacology*, *163*, 199–203.
Wyss, J. M., & Carlson, S. H. (2001). The role of the nervous system in hypertension. *Current Hypertension Reports*, *3*, 255–262.
Xu, F., Gainetdinov, R. R., Wetsel, W. C., Jones, S. R., Bohn, L. M., Miller, G. W., et al. (2000). Mice lacking the norepinephrine transporter are supersensitive to psychostimulants. *Nature in Neuroscience*, *3*, 465–471.
Yamada, H., & Kurokawa, K. (1998). Histochemical studies on endothelin and the endothelin-A receptor in the hypothalamus. *Journal of Cardiovascular Pharmacology*, *31*, S215–S218.
Yamamoto, T., Kimura, T., Ota, K., Shoji, M., Inoue, M., Sato, K., et al. (1991). Central effects of endothelin-1 on vasopressin and atrial natriuretic peptide release and cardiovascular and renal function in conscious rats. *Journal of Cardiovascular Pharmacology*, *7*, S316–S318.
Yamamoto, T., & Uemura, H. (1998). Distribution of endothelin-B receptor like immunoreactivity in rat brain, kidney, and pancreas. *Journal of Cardiovascular Pharmacology*, *31*, S207–S2011.
Yamashita, A., Singh, S. K., Kaeate, T., Jin, Y., & Gouaux, E. (2005). Crystal structure of a bacterial homologue of Na^+/Cl^--dependent neurotransmitter transporters. *Nature*, *437*, 215–223.
Yanagisawa, M., Inoue, A., Ishikawa, T., Kasuya, Y., Kimura, S., Kumaagaye, S., et al. (1988). Primary structure, synthesis, and biological activity of rat endothelin, an endothelium-derived vasoconstrictor peptide. *Proceedings of the National Academy of Sciences of the United States of America*, *85*, 6964–6967.
Yanagisawa, M., Kurihara, H., Kimura, S., Tomobe, Y., Kobayashi, M., Mitsui, Y., et al. (1988). A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*, *332*, 411–415.
Yanagisawa, M., & Masaki, T. (1989). Endothelin, a novel endothelium-derived peptide. Pharmacological activities, regulation and possible role in cardiovascular control. *Biochemical Pharmacology*, *38*, 1877–1883.
Yoshitomi, Y., Kojima, S., Ogi, M., & Kuramochi, M. (1998). Acute renal failure in accidental hypothermia of cold water immersion. *American Journal of Kidney Diseases*, *31*, 856–859.
Youdim, M. B., & Riederer, P. (1988). Monoamine oxidase B; A misunderstood and misjudged enzyme. *Pharmacological Research Communications*, *20*(Suppl. 4), 9–14.
Yu, C., Yang, Z., Ren, H., Zhang, Y., Han, Y., He, D., et al. (2009). D3 dopamine receptor regulation of ETB receptors in renal proximal tubule cells from WKY and SHRs. *American Journal of Hypertension*, *22*, 877–883.
Zahniser, N. R., & Doolen, S. (2001). Chronic and acute regulation of Na^+/Cl^--dependent neurotransmitter transporters: Drugs, substrates, presynaptic receptors, and signaling systems. *Pharmacology & Therapeutics*, *92*, 21–55.
Zeng, C., Hopfer, U., Asico, L. D., Eisner, G. M., Felder, R. A., & Jose, P. A. (2005). Altered AT1 receptor regulation of ETB receptors in renal proximal tubule cells of spontaneously hypertensive rats. *Hypertension*, *46*, 926–931.
Zhan, S., & Rockey, D. C. (2011). Tumor necrosis factor α stimulates endothelin-1 synthesis in rat hepatic stellate cells in hepatic wound healing through a novel IKK/JNK pathway. *Experimental Cell Research*, *317*, 1040–1048.