J Anesth (2007) 21:378–389
DOI 10.1007/s00540-007-0524-z

© JSA 2007

Role of urotensin II and its receptor in health and disease

John McDonald, Madura Batuwangala, and David G. Lambert

Department of Cardiovascular Sciences, Pharmacology and Therapeutics Group, Division of Anaesthesia, Critical Care and Pain Management, University of Leicester, LRI, Leicester, LE1 5WW, UK

Abstract
Urotensin II (U-II) is currently the most potent vasoconstrictor identified. This action is brought about via activation of a $G_{q/11}$-protein coupled receptor (UT receptor). U-II activation of the UT receptor increases inositol phosphate turnover and intracellular Ca^{2+}. In addition to producing vasoconstriction, dilation and ionotropic effects have also been described. There is considerable variation in the responsiveness of particular vascular beds from the same and different species, including humans. Receptors for U-II are located peripherally on vascular smooth muscle (contractile responses) and endothelial cells (dilatory responses via nitric oxide). In humans, plasma U-II is elevated in heart failure, renal failure, liver disease, and diabetes. Iontophoresis of U-II in healthy volunteers produces vasodilation (of the forearm) while in patients with heart failure or hypertension a constriction is observed. To date there is only one clinical study using a UT receptor antagonist (palosuran) in diabetic patients with macroalbuminuria. This antagonist reduced albumin excretion, probably by increasing renal blood flow. Studies in other disease conditions are eagerly awaited. In summary, the U-II / UT receptor system has clinical potential, and for the anesthesiologist, this novel peptide-receptor system may be of use in the intensive care unit.

Key words Urotensin II · Pharmacology · Heart disease · Diabetes · Renal failure

Introduction

Urotensin II (U-II) is a cyclic peptide first isolated from the caudal neurosecretory system of goby fish in 1969 [1]. Subsequent gene bank searches using the carp U-II sequence yielded a match to a human expressed sequence with 25% identity. Ames et al. [2] subsequently isolated a 688-base pair (bp) complementary DNA sequence encoding the human U-II peptide. U-II produces potent but variable constrictor effects in some but not all vascular beds. Indeed, U-II is currently described as "the most potent vasoconstrictor identified" [2]. U-II has also been shown to act as a potent vasodilator in some isolated vessels; for example, human small pulmonary and abdominal arteries [3]. In addition to these vascular actions, U-II is a positive inotrope in human right atrial trabeculae and also exhibits arrythmogenic activity [4]. Human urotensin II (hU-II) and its receptor (UT receptor) display greatest expression in the peripheral vasculature, heart, and kidney [5] although both are found in other tissues, notably the central nervous system [6]. In this short review we describe the basic pharmacology of this system and its role in several disease states that are of interest to anesthesiologists. We have been selective in what we have covered, but there are several other reviews on this subject, with varying emphasis on basic and clinical aspects [1,7–13].

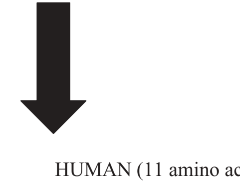
Receptor and peptide

At the time of isolation of the peptide U-II its target receptor was unknown. Ames et al. [2] used a reverse pharmacology technique to de-orphanize the orphan G-protein coupled receptor (GPCR), GPR14 (or SENR) and showed that U-II was the endogenous ligand for this receptor, now termed the "UT receptor" [14]. Activation of recombinant and native UT receptor causes a rise in intracellular calcium via coupling to the $G_{q/11}$ family of G-proteins [15–18] .

U-II is derived from a larger precursor prepropeptide, pre-pro-U-II, encoded by a single gene [13]. In humans, two prepropeptides have been identified; one is 124 amino acids in length, the other, 139, and proteolytic cleavage of either results in release of a single 11-

Address correspondence to: D.G. Lambert
Received: January 10, 2007 / Accepted: March 15, 2007

$_2$HN-Glu^1-Thr^2-Pro^3-Asp^4-[**Cys^5-Phe^6-Trp^7-Lys^8-Tyr^9-Cys^{10}**]-Val^{11}-OH



ETPD[**CFWKYC**]V HUMAN (11 amino acids)

QHGAAPE[**CFWKYC**]I MOUSE (14 amino acids)

QHGTAPE[**CFWKYC**]I RAT (14 amino acids)

AGTAD[**CFWKYC**]V GOBY (12 amino acids)

G, Glycine (Gly); *P*, proline (Pro); *A*, alanine (Ala); *V*, valine (Val); *I*, isoleucine (Ile); *C*, cysteine (Cys); *F*, phenylalanine (Phe); *Y*, tyrosine (Tyr); *W*, tryptophan (Trp); *H*, histidine (His); *K*, lysine (Lys); *Q*, glutamine (Gln); *E*, glutamic acid (Glu); *D*, aspartic acid (Asp); *T*, threonine (Thr)

Fig. 1. Amino acid structure of human urotensin II (U-II) and comparison with common rodent species and the goby. The peptide contains a conserved cyclised hexapeptide

amino-acid sequence U-II. U-II is characterized by a disulfide-linked C-terminal structure. The cyclic region of U-II, which confers biological activity, has been conserved in evolution from fish to mammals [19–22]. The N-terminus of the peptide is known to vary in length and sequence, giving species/isoform differences [22] (Fig. 1). Urotensin II-related peptide (URP) has also been described [23,24].

At both recombinant and natively expressed UT receptors, the dissociation of U-II is essentially irreversible, after 90 min only ~15% of [^{125}I]U-II was dissociated by the addition of an excess (1 μM) of cold U-II in human SJRH30 rhabdomyosarcoma cells [16]. In Chinese hamster ovary (CHO) cells expressing the human UT receptor, we have shown that the binding of [^{125}I]U-II was irreversible, such that addition of 1 μM unlabelled U-II did not displace [^{125}I]U-II binding over a 2-h period [17]. This irreversibility of binding is an important determinant of UT receptor functionality and may result from the cyclic nature of the peptide. In the presence of irreversible binding, circulating U-II would be expected to occupy and desensitise the system, implicating functional silence. If this supposition is correct then a lack of effect of gene knockout might be predicted (see below) and alterations in function may result from modulation of UT receptor expression.

Structure activity relationship (SAR) studies have shown that the disulfide bridged cyclic hexapeptide region of U-II is crucial for biological activity, with side chains of the residues Trp^7, Lys^8, and Tyr^9 being required for receptor recognition and activation [25]. The Lys^8 residue is believed to the most important residue for biological activity. SAR studies on hU-II have shown that the shortest biologically active sequence is an N-terminally truncated peptide, hU-II (4–11). Ligands of reduced efficacy, such as [Orn^8]hU-II, Urantide, and UFP-803 have been identified; see Table 1 [15,26–28]. Palosuran has been identified as a potent nonpeptide, orally active antagonist of the human UT receptor, binding studies showed the ligand to have 100-fold greater affinity for human UT receptor over rat UT receptor [29]. Other synthetic ligands, e.g., agonists: AC-7954,1 [30] and antagonists: SB-706375 [31] have been identified. For a review of UT receptor antagonists the reader is directed to [32]. See also Table 1.

Intracellular signalling pathways

U-II activation of UT receptor increases phosphoinositide (PI) turnover, with a subsequent increase in intracellular Ca^{2+} [2,17,18,33]. Interestingly, the potency for increased Ca^{2+} is similar to that causing vasoconstriction, indicating a possible close relationship between these events [15,34]. Inhibition of phospholipase C (PLC) with 2-nitro-4-carboxyphenyl-*N*, *N*-diphenylcarbamate (NCDC) inhibited both PI turnover and contractile responses induced by U-II [35].

At recombinant UT receptors expressed in CHO and human embryonic kidney (HEK) cells, U-II leads to an increase in PI turnover and intracellular calcium [2,28]. Influx of extracellular calcium, through the activation of L-type calcium channels, is also responsible for the U-II induced increase in intracellular calcium and hence vasoconstrictor actions [36]. We have also shown an influx component to U-II response in CHO cells where U-II produced a biphasic increase in Ca^{2+}, with the peak being independent of extracellular Ca^{2+} and the plateau phase being extracellular Ca^{2+}-dependent, implying influx (Fig. 2). This influx may simply be a refilling transient [17]. U-II increases Ca^{2+} at native UT receptor in rhabdomyosarcoma cells [16,37] and in cultured neurones [18]. In cultured neonatal cardiomyocytes, U-II causes hypertrophic growth and phenotypic changes to include enlargement of cells and sarcomere reorganization [38]. These cellular responses were attributed to U-II stimulating phosphorylation of mitogen-activating protein kinases (MAPK) extracellular signal-regulated kinase (ERK) 1/2 and p38. U-II activation of ERK 1/2 and p38 was dependent, to varying degrees, on epidermal growth factor receptor (EGFR) *trans*-activation, although EGFR-independent mechanisms are also involved in ERK 1/2 activation [38]. In the study of Onan et al. [38], PKC activation was not involved in ERK 1/2 activation and cardiac hypertrophy; however, there is evidence to show that the activation of specific isoforms of PKC is important in these processes [39,40].

Table 1. Binding affinity and potency of a selected number of urotensin (UT) receptor ligands at both the recombinant and native UT receptor

Ligand	Structure	Tissue preparation	pK_i	pEC_{50}	pA_2/pK_B	Comment	Reference no.
hU-II	Glu-Thr-Pro-Asp-c[Cys-Phe-Trp-Lys-Tyr-Cys]-Val	Rat thoracic aorta	9.1	8.3	—	Full agonist endogenous ligand	[79]
		CHO_{hUT}	—	8.6			
URP	Ala-c[Cys-Phe-Trp-Lys-Tyr-Cys]-Val	CHO_{hUT}	9.77 (170 pM)	8.32 (41.8 nM)			[24]
		CHO_{rUT}	10.04 (91 pM)	9.26 (0.55 nM)			
hU-II (4–11)	Asp-c[Cys-Phe-Trp-Lys-Tyr-Cys]-Val	Rat thoracic aorta	9.6	8.6	—	Shortest biologically active sequence	[79]
[Pen[5]]hU-II (4–11)	Asp-c[Pen-Phe-Trp-Lys-Tyr-Cys]-Val	Rat thoracic aorta	9.7	9.6	—		[79]
[Orn[8]]hU-II	Asp-c[Pen-Phe-Trp-Orn-Tyr-Cys]-Val	HEKhUT	—	7.93	6.56	High-efficacy partial agonist	[15]
		Rat thoracic aorta	—	—			
Urantide	Asp-c[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val	$CHO/K1_{hUT}$	8.3	—	8.3	Partial agonist, relative intrinsic activity tissue-dependent	[27]
		CHO_{hUT}	—	8.1	7.6		
UFP-803	Asp-c[Pen-Phe-DTrp-Dab-Tyr-Cys]-Val	Rat thoracic aorta	—	—	7.46	Low-efficacy partial agonist	[26]
		CHOhUT	—	8.09	—		
		HEK_{hUT}	—	—	8.59		
AC-7954, 1		NIH-3T3 cells transiently transfected with hUT		6.5		Selective nonpeptide agonist	[30]
GSK248451		Rat thoracic aorta	7.89 (12.8 nM)		8.23 (5.9 nM)	Low-efficacy peptide	[80]
		Human recombinant UT					
SB-706375		HEKhUT			8.0	Nonpeptide antagonist	[31]
		Rat thoracic aorta			7.47		
Palosuran		CHO_{hUT}	8.44 (3.6 nM)		7.7 (17 nM)*	Nonpeptide antagonist	[29]
		CHO_{rUT}	5.83 (1475 nM)		>10,000 nM*		

*Palosuran inhibition data are IC_{50} values for the inhibition of 30-nM U-II-induced calcium mobilization

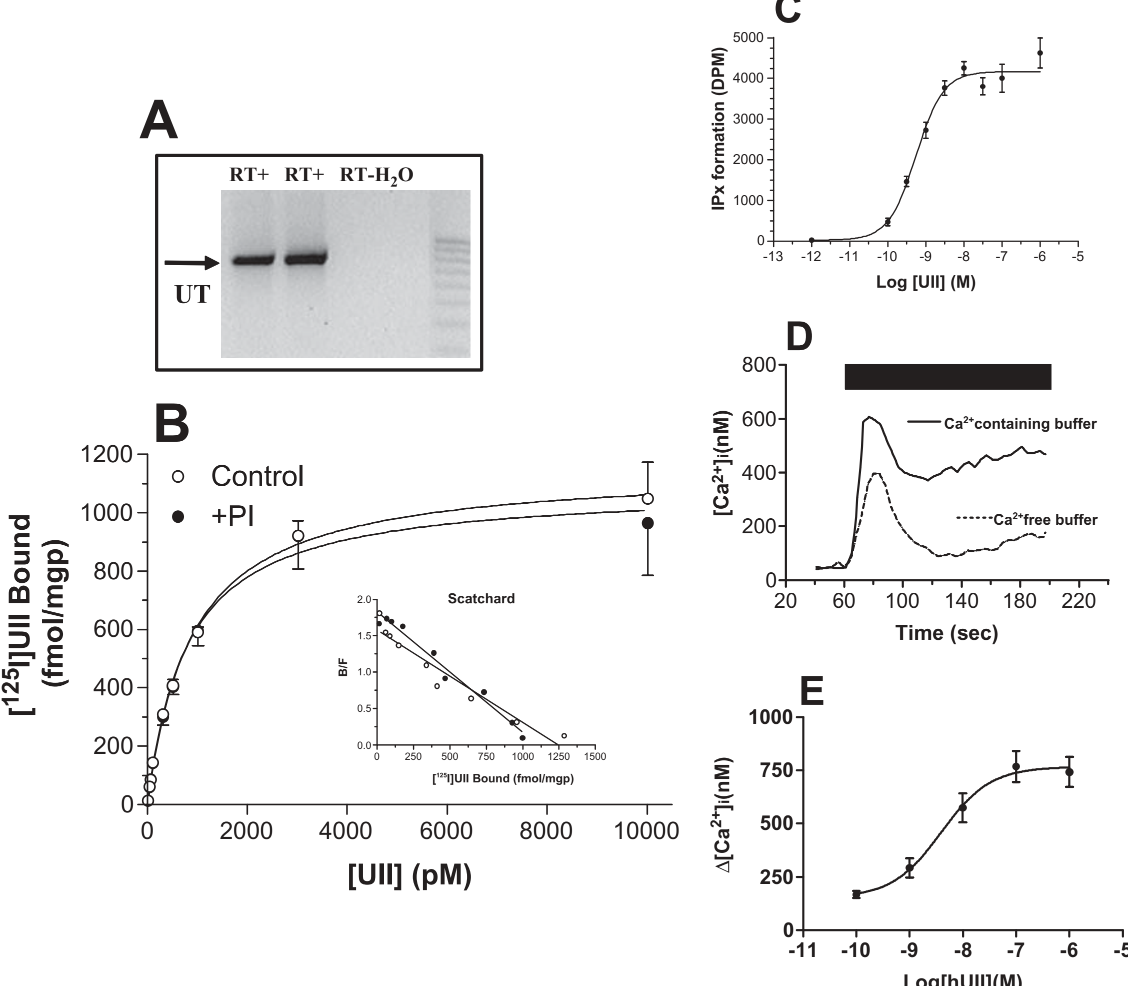


Fig. 2A–E. Typical receptor binding and signal transduction profile of recombinant human urotensin II receptor (hUT) expressed in Chinese hamster ovary (CHO) cells. In **A** and **B**, receptor expression is described using standard polymerase chain reaction (PCR) and radioligand binding protocols, respectively. In **B** a saturation isotherm is depicted along with Scatchard transformation (*inset*). The binding of [^{125}I]U-II was concentration-dependent (K_D, 742 pM), saturable (B_{max}, 1110 fmol·mg^{-1}), and unaffected by the inclusion of a peptidase inhibitor cocktail, i.e., the peptide is stable in vitro. In **C**, activation of UT receptor increases the turnover of inositol phosphates *IPx*; (measured using [^{3}H]inositol-labelled cells). Increased inostiol phosphate production releases Ca^{2+} from intracellular stores. In **D**, a time course of U-II (100 nM, *black bar*) addition in the absence and presence of extracellular Ca^{2+} is shown. In the absence of extracellular Ca^{2+}, the plateau phase is absent, indicating that the peak is due to a release from intracellular stores and the plateau is due to the entry of extracellular Ca^{2+}. In **E**, the concentration-response relationship for U-II peak Ca^{2+} response (stores) is depicted. The effective concentration (EC_{50}) for Ca^{2+} of 1.3 nM is close to that in **C** of 0.6 nM for IPx, implying close coupling (data are from reference [17] and unpublished data). *RT*, reverse transcription

ERK 1/2 activation has also been demonstrated in CHO_{hUT} cells; in these cells, a role for $G_{i/o}$-protein coupling and the involvement of phosphatidylinositol-3-kinase, phospholipase C, and calcium channel-mediated mechanisms was implicated in the MAPK activation [41]. If UT receptor is expressed on the vascular endothelium, then increased Ca^{2+} would activate nitric oxide synthase (NOS) to produce nitric oxide (NO) and induce vasodilation [42,43]. Some of the signalling pathways consequent upon UT receptor activation are shown in Fig. 3.

In vitro (tissue/vessel) studies

Contractile responses

There is great variation in U-II-induced contraction, not only differing between the same tissue/vascular beds derived from one species, but also from distinct regions of a specific vessel. U-II is best described as a high-potency low-efficacy peptide. For example, in rabbit, contractile responses were measured using thoracic aorta and coronary arteries, yet no response to

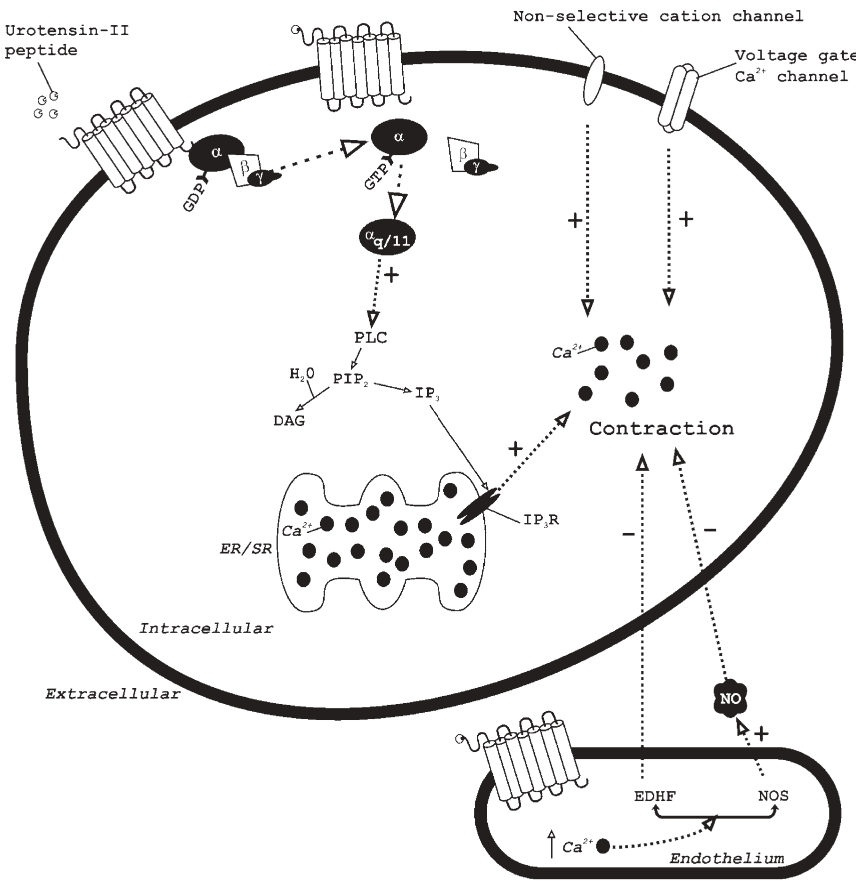


Fig. 3. Proposed basic signal transduction mechanisms in the U-II / UT receptor system (some membrane events are depicted in the cytosol for clarity). In vascular smooth muscle (larger structure), U-II peptide binds to its respective UT receptor, leading to the dissociation of the G-protein complex αβγ to yield active $G\alpha_{q/11}$, which, in turn causes the hydrolysis of phosphatidylinositol 4, 5 bisphosphate (*PIP_2*) to inositol 1, 4, 5-trisphosphate (*IP_3*) and diacylglycerol (*DAG*) by phospholipase C (*PLC*). IP_3 causes intracellular calcium to rise by binding to the IP_3 receptor (*IP_3R*), which releases Ca^{2+} from the endoplasmic/ sarcoplasmic reticulum (*ER/SR*), thereby leading to contraction. Cytoplasmic Ca^{2+} concentrations are also elevated as a consequence of the opening of channels on the plasma membrane. On the endothelium, UT receptor activation culminates in the synthesis and release of nitric oxide (*NO*) and endothelium-derived hyperpolarizing factor (*EDHF*), which causes vasodilation. *GTP*, guanosine triphosphate; *GDP*, guanosine diphosphate; *NOS*, nitric oxide synthase. Adapted from references 8, 9

U-II could be measured in pulmonary artery or ear artery/vein [44]. This tissue heterogeneity of response to U-II is highlighted in other species. In rat, reduced U-II reactivity is observed in the aorta the more distal to the aortic arch. In the thoracic aorta, U-II produces a greater response than in rat carotid artery, while there is little or no response in the abdominal aorta [45]. This reduced responsiveness correlates with reduced UT receptor expression. Indeed, it has been shown in rat isolated blood vessels that a loss of U-II contractile activity follows a loss of receptor expression, as measured with $[I^{125}]$-goby U-II [46].

A recent study examined the effect of aging on the vascular contractile effect of hU-II in rat thoracic aorta [47]. The maximal contractile response to U-II in aorta from young rats (2–3 months) was markedly greater than that in aorta from aged (25–27 months) rats, at 79% and 12% of KCl_{max}, respectively (KCl response did not change between young and old animals). The contractile response of rat aorta to U-II was decreased in the presence of an intact endothelium, from 79% (endothelium-denuded) to 33% (intact endothelium) of KCl_{max}. The role of NO in U-II responsiveness was further investigated. In aorta from young animals with an intact endothelium, the presence of the NOS inhibitor N^G-nitro-L-arginine (L-NNA) increased U-II maximal contractions from 33% to 50% of KCl_{max}. Potentiation of the U-II response by L-NNA was not apparent in aged animals, and this may explain why some studies have shown no effect of the endothelium or NO inhibitors on vasoconstriction of rat aorta [47,48]. Despite these variations, rat thoracic aorta represents a sensitive U-II / UT receptor assay system.

Contractile responses to U-II have also been studied in human-derived vascular tissue, and contractile responses can be measured in venous tissues. Unlike other species, human vessels responding to U-II are more ubiquitous, with vasoconstriction being reported in coronary, mammary, and radial arteries, as well as saphenous and umbilical veins (see [11] for review). However, in humans, like other species, there is great variation in the contractile response to U-II; for example, in small pulmonary arteries, only 30% of vessels tested responded to U-II and of those the efficacy varied from 14% to 220% (relative to the contraction caused by 50 mM KCl). Further, these pulmonary artery responses were only evident in the presence of N^G-nitro-L-arginine methylester (L-NAME), an inhibitor of NO synthesis [49].

Vasodilation

Vasodilatory responses to U-II appear to be dependent on the presence of an intact endothelium. In 5HT-precontracted rat coronary arteries, hU-II caused endothelium-dependent relaxation. This effect was abolished in the presence of the NOS inhibitor L-NAME [48]. U-II-mediated relaxation has also been demonstrated in isolated aorta from rabbits and rats, and is endothelium-dependent [47,48,50]. Vasodilation is caused by U-II-mediated increases in intracellular calcium in endothelial cells (Fig. 3), resulting in release of the endothelial-derived relaxing factors; NO and endothelium-derived hyperpolarizing factor (EDHF). U-II-mediated release of NO and its resultant dilatory action has been shown to attenuate U-II-mediated contraction in the rat aorta and NO inhibitors were shown to potentiate U-II contractility [47]. Endothelial factors might modulate the actions of U-II in humans, so contributing to contractile variability. In addition to endothelial factors, variations in both the vasodilatory and constrictor responses to U-II might reflect the expression of the UT receptor, which, in part, will depend on the size and location of the vessel [1].

In vivo studies

In conscious rats, U-II causes an overall depressor effect, causing dilatation of vascular beds, resulting in reduced mean arterial blood pressure and a tachycardia. This later effect is only apparent at a very high doses, of 3000 pmol·kg^{-1} [51]. In conscious rats, 6-h infusion of hU-II leads to a dose-related tachycardia and a slowly developing (90–120 min) increase in blood flow. Using Doppler to measure vascular conductance, rat hindquarters were the only region to show change, i.e., an increase in conductance—inferred to be a vasodilatation of this vascular bed. Left renal and superior mesenteric arteries showed no change in Doppler measurements. U-II-mediated effects were largely via cyclooxygenase (COX)-dependent pathways, given that indomethacin abolished these responses. The cardiovascular effects of infused U-II were also reduced by L-NAME, indicating the involvement of NO [52]. The observation that U-II causes vasodilatation in the presence of an intact endothelium suggests this depressor effect may be the more important in vivo action of U-II.

Coronary perfusion pressure (CPP) in isolated rat hearts was increased by U-II to a maximum at 100 nM; at higher concentrations, the responses decreased back to basal. L-NAME and indomethacin alone increased CPP by around 25 mmHg, suggesting basal control of coronary pressure by NO and COXs. In the presence of these agents, U-II caused a concentration-dependent increase in CPP, but these responses were greater and did not decline at high U-II doses. Endothelial-derived dilators such as NO and prostaglandin (PG)I2 appeared to act to limit the constrictor activity of U-II. Indeed, it could be argued that U-II is self-limiting, in that higher concentrations reduce constrictor activity, presumably through the U-II-mediated release of NO and PGs. Reduced CPP from high U-II concentrations is not apparent in the presence of NO and PG inhibitors, adding substance to this argument [53].

In vivo studies in cynomolgus monkeys have revealed that low i.v. doses of hU-II result in an increase in cardiac output and regional vasodilation, while high doses lead to a fatal combination of increased vascular resistance and only moderate reduction in blood pressure, coupled with a decrease in cardiac output (80%) [2].

Knockout studies

Deletion of the UT receptor in UT receptor knockout (KO) mice does not affect basal hemodynamics in comparison to wild-type (WT) mice. U-II caused a dose-dependent vasoconstriction of isolated aortae in wild-type mice that was absent in the KO model. Both WT and KO tissue responded to other vasoactive agents—KCl, phenylephrine, and carbachol—demonstrating that UT receptor deletion selectively abolished U-II-induced responses without affecting reactivity to the agents tested [54]. Studies of apolipoprotein E (ApoE) knockout (ApoE$^{-/-}$) mice demonstrated increased expression of the UT receptor in ApoE$^{-/-}$ species. In these studies, mice 18, 28, and 38 weeks of age were examined. Increased UT receptor mRNA and [^{125}I]U-II binding was noted in aortae from the ApoE$^{-/-}$ mice at all ages compared to WT (ApoE$^{+/+}$). Interestingly, the 28-week mice showed significantly higher expression compared to 18- and 38-week mice [55].

Central actions

In rats, *U-II* gene expression has been reported in sacral cord motor neurones [56] and U-II immunoreactivity is also detectable in spinal cord and brainstem [57]. UT receptors appear to be functionally active, in that U-II increases intracellular Ca^{2+} ($[Ca^{2+}]_i$) in dissociated spinal cord neurones [18]; see later. The observation that both U-II peptide and its receptor are situated within conserved regions of the central nervous system, such as the brainstem and medulla oblongata, suggest a central role in cardiovascular physiology. Indeed, in rats, microinjection of U-II into the A1 region of the medulla oblongata resulted in both hypotension and a bradycardiac response, while U-II administration to the A2 region of

the medulla produced no measurable effects on mean arterial blood pressure or heart rate. However, central administration has also been shown to produce a tachycardia [58]. In ewes, i.c.v. administration produced tachycardia, a positive ionotropic response, and an increase in cardiac output, increased sympathetic outflow, and neuroendorine activation [59].

Peptide/receptor expression

In common with other peptide and receptor systems, distribution has been probed by (i) using specific antibodies, (ii) by measuring peptide and receptor mRNA levels, and (iii) using radiolabelled peptides.

U-II peptide immunoreactivity has been located in the following tissues: (i) central; abducens nucleus, hypoglossal nucleus, thalamus, trigeminal nucleus, and spinal cord, (ii) peripheral; heart, kidney, and liver. Interestingly, U-II is also found in human coronary atherosclerotic plaque tissue [2]. UT receptor immunoreactivity has also been located in the following tissues: (i) central; hippocampus, hypothalamus, medulla, and thalamus, (ii) peripheral; heart, kidney, pancreas, and liver (see [12,13] for complete list of tissue expression).

mRNA for prepro-U-II has been identified in the following human tissues: (i) central; spinal cord, medulla oblongata, and (ii) peripheral; wide range of vascular tissues, kidney, spleen, and placenta. mRNA for the UT receptor has been identified in the following human tissues: (i) central; brain cortex, hypothalamus, medulla oblongata, (ii) peripheral; wide range of vascular tissues, kidney, and atrium and ventricle of the heart [12,13,60]. Clearly there is overlap of U-II and UT receptor expression.

Iodinated U-II has also been used to describe receptor expression from a variety of human tissues [60]. Autoradiographic analysis revealed the presence of the receptor in the renal cortex, skeletal muscle, dorsal root ganglion of the spinal cord, cerebral cortex, and cardiovascular tissue, including the epicardial coronary artery and myocytes in the left ventricle. Skeletal muscle displays the greatest density, and saturation analysis reported maximum receptor density (B_{max}) values in the region of $2\,fmol{\cdot}mg^{-1}$ [60].

Of particular relevance to UT receptor distribution, it has been hypothesized that the variability in tissue responsiveness to U-II is due to either: (i) the presence of irreversibly prebound U-II to its receptor or (ii) differential receptor expression and efficiency of second-messenger coupling varying between cell/tissue types [10].

Clinical studies

Circulating U-II levels

Several studies have detailed circulating levels of U-II peptide in healthy subjects relative to patients with a range of different diseases. These studies have revealed great disparity in circulating U-II concentrations in healthy volunteers, with values ranging from $6\,pg{\cdot}ml^{-1}$ [61] to $3.6\,ng{\cdot}ml^{-1}$ [62]. See Table 2 for a summary of studies measuring plasma U-II concentrations. While variation in U-II plasma levels is to be expected for different disease states, the large variability in control groups is unexpected and makes interstudy comparisons awkward. One possible explanation for this variability may lie in U-II assay methodology. Two commonly used assay formats are radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA). Both use antibodies directed against U-II. Some of these antibodies may recognize not only the mature U-II peptide but also its precursor protein and various truncated U-II fragments [63].

Heart failure/hypertension studies

There are many studies detailing plasma U-II levels in various heart failure models (see Table 2). The Consensus is that heart disease increases U-II concentrations (although there are some exceptions). In addition there appears to be upregulation of UT receptor in cardiomyocytes, endothelial cells, and smooth muscle cells from patients with heart failure [64]. Of particular interest is the study of Lim et al. [65], who compared the effects of iontophorezed U-II in the forearms of healthy volunteers and patients with heart failure. Microvascular tone was measured using Doppler laser velocimetry. In healthy volunteers, U-II caused a dose-dependent vasodilation, but in patients with heart failure, U-II caused vasoconstriction. Depending on how the studies are interpreted, U-II increases as a function of blood pressure in some studies but not others (see Table 2). We have compared plasma and cerebrospinal fluid (CSF) U-II concentrations in normotensive and hypertensive patients and have shown that CSF levels were ~15% lower than paired blood plasma. While U-II concentrations were not increased in hypertensive patients relative to the normotensive controls, there was a positive correlation in the hypertensive group between mean arterial pressure and the U-II concentration of the CSF [66]. In patients with markedly elevated pressures; e.g., those with pre-eclampsia/eclampsia, an increase and no change have been reported [67,68]. U-II has also been iontophorezed in the forearms of hypertensive patients with Doppler measurement of blood flow. U-II produced a dose-dependent increase in flow, i.e., dilation, but in hypertensives a decrease in flow, signifying vaso-

Table 2. Plasma U-II levels[a] in humans with different disease states, and in healthy controls

Disease	Healthy control	Diseased	Reference no.
Chronic heart failure	9.16 $pg \cdot ml^{-1}$ (6.6 $pmol \cdot l^{-1}$)	30.6 pg/ml (22 pmol/l)	[81]
Acute myocardial infarction	0.58 $pg \cdot ml^{-1}$ (0.42 $fmol \cdot ml^{-1}$)	1.94 pg/ml (1.40 fmol/ml)	[82]
Congestive heart failure	84–11 $pg \cdot ml^{-1}$	Unchanged—for both moderate and severe congestive heart failure	[83]
Congestive heart failure	4.35 $pg \cdot ml^{-1}$	1.41 pg/ml	[84]
Congestive heart failure	22.7 $pg \cdot ml^{-1}$—Dependent on site. Value from aortic root	230.9 pg/ml—Aortic root	[85]
Coronary heart disease	3.20 $pg \cdot ml^{-1}$	1.61 pg/ml	[86]
Chronic heart failure	3290 $pg \cdot ml^{-1}$—at rest	2990 pg/ml—At rest	[87]
Congestive heart failure	0.84 $pg \cdot ml^{-1}$	1.17 pg/ml—moderate 1.49 pg/ml—severe	[88]
Acute coronary syndrome	3300 $pg \cdot ml^{-1}$	3450 pg/ml—stable artery disease 2530 pg/ml—acute coronary syndrome	[89]
Coronary artery disease	1409 $pg \cdot ml^{-1}$	Increased—complex sub-grouping analysis	[90]
Ischemic cardiomyopathy	1137 $pg \cdot ml^{-1}$	NYHA I 1884 pg/ml NYHA II 2294 pg/ml NYHA III 4822 pg/ml NYHA IV 6631 pg/ml	[91]
Heart failure	2.6 $pg \cdot ml^{-1}$ (1.9 $pmol \cdot l^{-1}$)	5.4 pg/ml (3.9 pmol/l)	[92]
Congenital heart disease (children)	1.18 $pg \cdot ml^{-1}$ (0.85 $pmol \cdot l^{-1}$)	2.9 pg/ml (2.09 pmol/l)	[93]
Hypertension	12.2 $pg \cdot ml^{-1}$ (8.8 pM)	18.9 pg/ml (13.6 pM)	[94]
Cirrhosis and portal hypertension	3600 $pg \cdot ml^{-1}$ (3.6 $ng \cdot ml^{-1}$)	Central venous—1290 pg/ml (1.29 ng/ml) Portal venous blood—1100 pg/ml (1.1 pg/ml)	[62]
Hypertension	Plasma, 11.85 $pg \cdot ml^{-1}$ CSF, 8.24 $pg \cdot ml^{-1}$ Cord, 10.10 $pg \cdot ml^{-1}$	Plasma, 9.29 pg/ml CSF, 8.73 pg/ml Cord, 13.10 pg/ml	[66]
Renal dysfunction	6.11 pg/ml(4.4 fmol/ml)	No dialysis—elevated two-fold Dialysis—elevated three-fold	[70]
Diabetes mellitus	7.22 pg/ml (5.2 $fmol \cdot ml^{-1}$)	Creatinine clearance ≥ 70 ml/min, 15.13 pg/ml (10.9 fmol/ml) Creatinine clearance ≥ 30 ml/min and <70 ml/min, 15 pg/ml (10.8 fmol/ml) Creatinine clearance <30 $ml \cdot min^{-1}$, 22.1 pg/ml (15.9 fmol/ml)	[71]
Diabetes mellitus	6.11 $pg \cdot ml^{-1}$ (4.4 fmol U-II$\cdot ml^{-1}$)	Nonproteinuric—10.8 pg/ml (7.8 fmol U-II/ml) Proteinuric—10.1 pg/ml (7.3 fmol U-II/ml)	[61]
Nephrotic syndrome (children)	37.31 $pg \cdot ml^{-1}$ (Remission)	31.09 pg/ml (relapse)	[95]
Endstage renal disease	3100 $pg \cdot ml^{-1}$	6500 pg/ml endstage	[96]
Endstage renal disease	3300 $pg \cdot ml^{-1}$	5300 pg/ml With cardiovascular event 7100 pg/ml Without cardiovascular event	[97]
Pre-eclampsia	Plasma, 23.05 $pg \cdot ml^{-1}$ CSF, 19.27 $pg \cdot ml^{-1}$	Plasma, 21.88 pg/ml CSF, 17.87 pg/ml	[67]
Pre-eclampsia/eclampsia	3.93 $pg \cdot ml^{-1}$	10.11 pg/ml	[68]

[a] U-II levels are normalized to $pg \cdot /ml^{-1}$; original presentation of data is given in parentheses

constriction was observed [69]. It would appear from these iontophoresis studies in healthy volunteers at least, that U-II in the forearm produces vasodilation. However, intravenous infusion of U-II failed to produce any gross hemodynamic changes; see below.

Renal disease, diabetes, and diabetic nephropathy

There have been several studies from Totsune et al. [61,70,71], who have shown that plasma U-II is elevated in renal failure and that this increase was greater in patients with a creatinine clearance of less than 30 ml·min^{-1} (compared with ≥70 ml·min^{-1}) [71], and those on dialysis [70]. These increases in U-II may be attributed to decreased excretion of the peptide from the kidney, rather than increased expression. However, it has also been suggested that elevated U-II in diabetes may come from damaged vascular endothelial cells. In non-proteinuric and proteinuric diabetic patients, plasma hU-II levels were also elevated (relative to healthy controls), by 1.8- and 1.7-fold, respectively. A lack of correlation between U-II levels and fasting blood sugar levels demonstrated that hyperglycemia was not the cause of the U-II elevation [61]. See Table 2 for other plasma U-II data.

The gene encoding human preproU-II (*UTS2*) contains five exons and is located at 1p36. The gene is modified post-translationally at exon 2 to produce preproU-IIa and preproU-IIb, with 139 and 124 amino acids, respectively. The difference resides in the N-terminal sequence. In contrast, the gene encoding UT receptor (*UTS2R*), located at 17q25.3, is intronless and encodes a 389-amino-acid protein [8]. There are multiple single-nucleotide polymorphisms (SNPs) in *UTS2* (41 using National Center for Biotechnology Information [NCBI] and a further 19 using the Applied Biosystems [Foster city, CA, USA] database) and in *UTS2R* (8 using NCBI and a further 15 using the Applied Biosystems database). Several of these polymorphisms have been studied in non-caucasian subjects, and there is disease association. In Japanese, SNP 3836C>T (S89N) in UTS is associated with insulin resistance and type 2 diabetes mellitus [72,73]. In Hong Kong Chinese, Ong et al. [74] showed that the *UTS2* haplotype GGT (−605G, 143G, 3836T) and the *UTS2R* haplotype AC (−11640A, −8515C) were associated with elevated plasma glucose following an oral glucose tolerance test. These data further implicate the U-II/UT receptor system in the pathophysiology of diabetes mellitus.

Administration of U-II and U-II receptor antagonist in humans

U-II has been infused intraarterially in healthy human volunteers (0.001–300 pmol·min^{-1}) with subsequent measurement of forearm blood flow [75]. While plasma U-II concentrations were seen to rise, there was no change in blood flow. In a further investigation from the same group [76], U-II was infused intravenously in healthy volunteers (0 [saline], 3, 30, and 300 pmol·min^{-1}). In this placebo-controlled study, there was no change in systemic hemodynamics, despite rising U-II concentrations.

As described above (Table 2), patients with renal disease (diabetic) have increased plasma U-II concentrations, and this may reduce renal blood flow. The U-II antagonist palosuran increased renal blood flow and delayed the development of proteinuria and renal damage in rats [77]. In macroalbuminuric diabetic patients, palosuran (125 mg twice daily for 13.5 days) decreased (relative to baseline) the 24-h urinary albumin excretion rate by 26.2% in patients with normal to mildly impaired renal function and by 22.3% in patients with moderate to severely impaired renal function [78]. This is the first study using U-II receptor antagonists in humans and suggests that palosuran may benefit diabetic patients with renal failure. Further studies with this and the other UT receptor antagonists available are eagerly awaited.

Conclusions

That U-II is a potent (low-efficacy) vasoactive peptide is unequivocal. It also appears that it plays a relatively minor role in health, as shown by knockout studies in mice and infusion studies in humans. Its role in disease is less clear. This peptide's concentrations are elevated in heart failure, renal dysfunction, diabetes, and hepatic impairment. From a therapeutic viewpoint, U-II antagonists appear the most promising, and early studies in humans have already begun. For the anesthesiologist, this novel peptide-receptor system may be of use in the intensive care unit.

Acknowledgments. Our work on U-II has been funded by the *British Journal of Anaesthesia*/Royal College of Anaesthetists, and the British Heart Foundation. M.B. is a departmentally funded Ph.D. student. We thank Dr. Girolamo Calo (University of Ferrara, Italy) for critically reading this manuscript. A simple PubMed search for "Urotensin II" yields ~400 hits, so we apologize to those authors whose work we were unable to cite due to limitations of space.

References

1. Onan D, Hannan RD, Thomas WG (2004) Urotensin II: the old kid in town. Trends Endocrinol Metab 15:175–182
2. Ames RS, Sarau HM, Chambers JK, Willette RN, Aiyar NV, Romanic AM, Louden CS, Foley JJ, Sauermelch CF, Coatney RW, Ao Z, Disa J, Holmes SD, Stadel JM, Martin JD, Liu WS, Glover GI, Wilson S, McNulty DE, Ellis CE, Elshourbagy

NA, Shabon U, Trill JJ, Hay DW, Douglas SA (1999) Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature 401:282–286
3. Stirrat A, Gallagher M, Douglas SA, Ohlstein EH, Berry C, Kirk A, Richardson M, MacLean MR (2001) Potent vasodilator responses to human urotensin-II in human pulmonary and abdominal resistance arteries. Am J Physiol Heart Circ Physiol 280:H925–928
4. Russell FD, Molenaar P, O'Brien DM (2001) Cardiostimulant effects of urotensin-II in human heart in vitro. Br J Pharmacol 132:5–9
5. Matsushita M, Shichiri M, Imai T, Iwashina M, Tanaka H, Takasu N, Hirata Y (2001) Co-expression of urotensin II and its receptor (GPR14) in human cardiovascular and renal tissues. J Hypertens 19:2185–2190
6. Jegou S, Cartier D, Dubessy C, Gonzalez BJ, Chatenet D, Tostivint H, Scalbert E, LePrince J, Vaudry H, Lihrmann I (2006) Localization of the urotensin II receptor in the rat central nervous system. J Comp Neurol 495:21–36
7. Davenport AP, Maguire JJ (2000) Urotensin II: fish neuropeptide catches orphan receptor. Trends Pharmacol Sci 21:80–82
8. Ong KL, Lam KS, Cheung BM (2005) Urotensin II: its function in health and its role in disease. Cardiovasc Drugs Ther 19: 65–75
9. Zhu YC, Zhu YZ, Moore PK (2006) The role of urotensin II in cardiovascular and renal physiology and diseases. Br J Pharmacol 148:884–901
10. Douglas SA, Dhanak D, Johns DG (2004) From "gills to pills": urotensin-II as a regulator of mammalian cardiorenal function. Trends Pharmacol Sci 25:76–85
11. Douglas SA (2003) Human urotensin-II as a novel cardiovascular target: "heart" of the matter or simply a fishy "tail"? Curr Opin Pharmacol 3:159–167
12. Watson AM, May CN (2004) Urotensin II, a novel peptide in central and peripheral cardiovascular control. Peptides 25:1759–1766
13. Douglas SA, Ohlstein EH (2000) Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of cardiovascular disease. Trends Cardiovasc Med 10:229–237
14. Douglas SA, Ohlstein EH (2000) Urotensin receptors. In: Girdlestone D (ed), *The IUPHAR compendium of receptor characterisation and classification.* IUPHAR Media, London, pp 365–372
15. Camarda V, Guerrini R, Kostenis E, Rizzi A, Calo G, Hattenberger A, Zucchini M, Salvadori S, Regoli D (2002) A new ligand for the urotensin II receptor. Br J Pharmacol 137: 311–314
16. Douglas SA, Naselsky D, Ao Z, Disa J, Herold CL, Lynch F, Aiyar NV (2004) Identification and pharmacological characterization of native, functional human urotensin-II receptors in rhabdomyosarcoma cell lines. Br J Pharmacol 142:921–932
17. Song W, McDonald J, Camarda V, Calo G, Guerrini R, Marzola E, Thompson JP, Rowbotham DJ, Lambert DG (2006) Cell and tissue responses of a range of urotensin II analogs at cloned and native urotensin II receptors. Evidence for coupling promiscuity. Naunyn Schmiedebergs Arch Pharmacol 373:148–157
18. Filipeanu CM, Brailoiu E, Le Dun S, Dun NJ (2002) Urotensin-II regulates intracellular calcium in dissociated rat spinal cord neurons. J Neurochem 83:879–884
19. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M (1999) Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14). Biochem Biophys Res Commun 265:123–129
20. Coulouarn Y, Lihrmann I, Jegou S, Anouar Y, Tostivint H, Beauvillain JC, Conlon JM, Bern HA, Vaudry H (1998) Cloning of the cDNA encoding the urotensin II precursor in frog and human reveals intense expression of the urotensin II gene in motoneurons of the spinal cord. Proc Natl Acad Sci USA 95: 15803–15808
21. Bern HA, Pearson D, Larson BA, Nishioka RS (1985) Neurohormones from fish tails: the caudal neurosecretory system. I. "Urophysiology" and the caudal neurosecretory system of fishes. Recent Prog Horm Res 41:533–552
22. Kinney WA, Almond Jr HR, Qi J, Smith CE, Santulli RJ, de Garavilla L, Andrade-Gordon P, Cho DS, Everson AM, Feinstein MA, Leung PA, Maryanoff BE (2002) Structure-function analysis of urotensin II and its use in the construction of a ligand-receptor working model. Angew Chem Int Ed Engl 41:2940–2944
23. Mori M, Fujino M (2004) Urotensin II-related peptide, the endogenous ligand for the urotensin II receptor in the rat brain. Peptides 25:1815–1818
24. Sugo T, Murakami Y, Shimomura Y, Harada M, Abe M, Ishibashi Y, Kitada C, Miyajima N, Suzuki N, Mori M, Fujino M (2003) Identification of urotensin II-related peptide as the urotensin II-immunoreactive molecule in the rat brain. Biochem Biophys Res Commun 310:860–868
25. Flohr S, Kurz M, Kostenis E, Brkovich A, Fournier A, Klabunde T (2002) Identification of nonpeptidic urotensin II receptor antagonists by virtual screening based on a pharmacophore model derived from structure-activity relationships and nuclear magnetic resonance studies on urotensin II. J Med Chem 45: 1799–1805
26. Camarda V, Spagnol M, Song W, Vergura R, Roth AL, Thompson JP, Rowbotham DJ, Guerrini R, Marzola E, Salvadori S, Cavanni P, Regoli D, Douglas SA, Lambert DG, Calo G (2006) In vitro and in vivo pharmacological characterization of the novel UT receptor ligand [Pen(5),DTrp(7),Dab(8)]urotensin II(4-11) (UFP-803). Br J Pharmacol 147:92–100
27. Patacchini R, Santicioli P, Giuliani S, Grieco P, Novellino E, Rovero P, Maggi CA (2003) Urantide: an ultrapotent urotensin II antagonist peptide in the rat aorta. Br J Pharmacol 140: 1155–1158
28. Camarda V, Song W, Marzola E, Spagnol M, Guerrini R, Salvadori S, Regoli D, Thompson JP, Rowbotham DJ, Behm DJ, Douglas SA, Calo G, Lambert DG (2004) Urantide mimics urotensin-II induced calcium release in cells expressing recombinant UT receptors. Eur J Pharmacol 498:83–86
29. Clozel M, Binkert C, Birker-Robaczewska M, Boukhadra C, Ding SS, Fischli W, Hess P, Mathys B, Morrison K, Muller C, Muller C, Nayler O, Qiu C, Rey M, Scherz MW, Velker J, Weller T, Xi JF, Ziltener P (2004) Pharmacology of the urotensin-II receptor antagonist palosuran (ACT-058362; 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulfate salt): first demonstration of a pathophysiological role of the urotensin System. J Pharmacol Exp Ther 311:204–212
30. Croston GE, Olsson R, Currier EA, Burstein ES, Weiner D, Nash N, Severance D, Allenmark SG, Thunberg L, Ma JN, Mohell N, O'Dowd B, Brann MR, Hacksell U (2002) Discovery of the first nonpeptide agonist of the GPR14/urotensin-II receptor: 3-(4-chlorophenyl)-3-(2-(dimethylamino)ethyl)isochroman-1-one (AC-7954). J Med Chem 45:4950–4953
31. Douglas SA, Behm DJ, Aiyar NV, Naselsky D, Disa J, Brooks DP, Ohlstein EH, Gleason JG, Sarau HM, Foley JJ, Buckley PT, Schmidt DB, Wixted WE, Widdowson K, Riley G, Jin J, Gallagher TF, Schmidt SJ, Ridgers L, Christmann LT, Keenan RM, Knight SD, Dhanak D (2005) Nonpeptidic urotensin-II receptor antagonists I: in vitro pharmacological characterization of SB-706375. Br J Pharmacol 145:620–635
32. Carotenuto A, Grieco P, Rovero P, Novellino E (2006) Urotensin-II receptor antagonists. Curr Med Chem 13:267–275
33. Gibson A, Conyers S, Bern HA (1988) The influence of urotensin II on calcium flux in rat aorta. J Pharm Pharmacol 40:893–895
34. Camarda V, Rizzi A, Calo G, Gendron G, Perron SI, Kostenis E, Zamboni P, Mascoli F, Regoli D (2002) Effects of human urotensin II in isolated vessels of various species; comparison with other

vasoactive agents. Naunyn Schmiedebergs Arch Pharmacol 365: 141–149

35. Saetrum Opgaard O, Nothacker H, Ehlert FJ, Krause DN (2000) Human urotensin II mediates vasoconstriction via an increase in inositol phosphates. Eur J Pharmacol 406:265–271
36. Maguire JJ, Davenport AP (2002) Is urotensin-II the new endothelin? Br J Pharmacol 137:579–588
37. Batuwangala M, McDonald J, Calo G, Ng LL, Lambert DG (2006) Characterization of native urotensin II receptors expressed in SJCRH30 rhabdomyosarcoma cells. Br J Anaesth 97:440
38. Onan D, Pipolo L, Yang E, Hannan RD, Thomas WG (2004) Urotensin II promotes hypertrophy of cardiac myocytes via mitogen-activated protein kinases. Mol Endocrinol 18:2344–2354
39. Sugden PH, Clerk A (1998) Cellular mechanisms of cardiac hypertrophy. J Mol Med 76:725–746
40. Clerk A, Sugden PH (1999) Activation of protein kinase cascades in the heart by hypertrophic G protein-coupled receptor agonists. Am J Cardiol 83:64H–69H
41. Ziltener P, Mueller C, Haenig B, Scherz MW, Nayler O (2002) Urotensin II mediates ERK1/2 phosphorylation and proliferation in GPR14-transfected cell lines. J Recept Signal Transduct Res 22:155–168
42. Luscher TF (1991) Endothelium-derived nitric oxide: the endogenous nitrovasodilator in the human cardiovascular system. Eur Heart J 12(Suppl E):2–11
43. Moncada S, Higgs EA (2006) Nitric oxide and the vascular endothelium. Handb Exp Pharmacol 213–254
44. Camarda V, Rizzi A, Calo G, Gendron G, Perron SI, Kostenis E, Zamboni P, Mascoli F, Regoli D (2002) Effects of human urotensin II in isolated vessels of various species; comparison with other vasoactive agents. Naunyn Schmiedebergs Arch Pharmacol 365:141–149
45. Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN (2000) Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey. Br J Pharmacol 131:1262–1274
46. Itoh H, McMaster D, Lederis K (1988) Functional receptors for fish neuropeptide urotensin II in major rat arteries. Eur J Pharmacol 149:61–66
47. Ishihata A, Sakai M, Katano Y (2006) Vascular contractile effect of urotensin II in young and aged rats: influence of aging and contribution of endothelial nitric oxide. Peptides 27:80–86
48. Bottrill FE, Douglas SA, Hiley CR, White R (2000) Human urotensin-II is an endothelium-dependent vasodilator in rat small arteries. Br J Pharmacol 130:1865–1870
49. MacLean MR, Alexander D, Stirrat A, Gallagher M, Douglas SA, Ohlstein EH, Morecroft I, Polland K (2000) Contractile responses to human urotensin-II in rat and human pulmonary arteries: effect of endothelial factors and chronic hypoxia in the rat. Br J Pharmacol 130:201–204
50. Muramatsu I, Fujiwara M, Hidaka H, Akutagawa H (1979) Pharmacological analysis of urotensin-induced contraction and relaxation in isolated rabbit aortas. In: Yamamoto K (ed), *The caudal neurosecretory system of fishes (16th Gunma Symposium in Endocrinology)*. Gunma University, Maebashi, Japan, pp 39–47
51. Gardiner SM, March JE, Kemp PA, Davenport AP, Bennett T (2001) Depressor and regionally-selective vasodilator effects of human and rat urotensin II in conscious rats. Br J Pharmacol 132:1625–1629
52. Gardiner SM, March JE, Kemp PA, Maguire JJ, Kuc RE, Davenport AP, Bennett T (2006) Regional heterogeneity in the haemodynamic responses to urotensin II infusion in relation to UT receptor localisation. Br J Pharmacol 147:612–621
53. Gray GA, Jones MR, Sharif I (2001) Human urotensin II increases coronary perfusion pressure in the isolated rat heart: potentiation by nitric oxide synthase and cyclooxygenase inhibition. Life Sci 69:175–180
54. Behm DJ, Harrison SM, Ao Z, Maniscalco K, Pickering SJ, Grau EV, Woods TN, Coatney RW, Doe CP, Willette RN, Johns DG, Douglas SA (2003) Deletion of the UT receptor gene results in the selective loss of urotensin-II contractile activity in aortae isolated from UT receptor knockout mice. Br J Pharmacol 139:464–472
55. Wang ZJ, Shi LB, Xiong ZW, Zhang LF, Meng L, Bu DF, Tang CS, Ding WH (2006) Alteration of vascular urotensin II receptor in mice with apolipoprotein E gene knockout. Peptides 27:858–863
56. Coulouarn Y, Fernex C, Jegou S, Henderson CE, Vaudry H, Lihrmann I (2001) Specific expression of the urotensin II gene in sacral motoneurons of developing rat spinal cord. Mech Dev 101: 187–190
57. Dun SL, Brailoiu GC, Yang J, Chang JK, Dun NJ (2001) Urotensin II-immunoreactivity in the brainstem and spinal cord of the rat. Neurosci Lett 305:9–12
58. Lin Y, Tsuchihashi T, Matsumura K, Abe I, Iida M (2003) Central cardiovascular action of urotensin II in conscious rats. J Hypertens 21:159–165
59. Watson AM, Lambert GW, Smith KJ, May CN (2003) Urotensin II acts centrally to increase epinephrine and ACTH release and cause potent inotropic and chronotropic actions. Hypertension 42:373–379
60. Maguire JJ, Kuc RE, Davenport AP (2000) Orphan-receptor ligand human urotensin II: receptor localization in human tissues and comparison of vasoconstrictor responses with endothelin-1. Br J Pharmacol 131:441–446
61. Totsune K, Takahashi K, Arihara Z, Sone M, Ito S, Murakami O (2003) Increased plasma urotensin II levels in patients with diabetes mellitus. Clin Sci (Lond) 104:1–5
62. Heller J, Schepke M, Neef M, Woitas R, Rabe C, Sauerbruch T (2002) Increased urotensin II plasma levels in patients with cirrhosis and portal hypertension. J Hepatol 37:767–772
63. Aiyar N, Guida B, Ao Z, Disa J, Naselsky D, Behm DJ, Su JL, Kull FC, Jr, Douglas SA (2004) Differential levels of "urotensin-II-like" activity determined by radio-receptor and radioimmunoassays. Peptides 25:1339–1347
64. Douglas SA, Tayara L, Ohlstein EH, Halawa N, Giaid A (2002) Congestive heart failure and expression of myocardial urotensin II. Lancet 359:1990–1997
65. Lim M, Honisett S, Sparkes CD, Komesaroff P, Kompa A, Krum H (2004) Differential effect of urotensin II on vascular tone in normal subjects and patients with chronic heart failure. Circulation 109:1212–1214
66. Thompson JP, Watt P, Sanghavi S, Strupish JW, Lambert DG (2003) A comparison of cerebrospinal fluid and plasma urotensin II concentrations in normotensive and hypertensive patients undergoing urological surgery during spinal anesthesia: a pilot study. Anesth Analg 97:1501–1503
67. Cowley E, Thompson JP, Sharpe P, Waugh J, Ali N, Lambert DG (2005) Effects of pre-eclampsia on maternal plasma, cerebrospinal fluid, and umbilical cord urotensin II concentrations: a pilot study. Br J Anaesth 95:495–499
68. Balat O, Aksoy F, Kutlar I, Ugur MG, Iyikosker H, Balat A, Anarat R (2005) Increased plasma levels of urotensin-II in preeclampsia-eclampsia: a new mediator in pathogenesis? Eur J Obstet Gynecol Reprod Biol 120:33–38
69. Sondermeijer B, Kompa A, Komesaroff P, Krum H (2005) Effect of exogenous urotensin-II on vascular tone in skin microcirculation of patients with essential hypertension. Am J Hypertens 18:1195–1199
70. Totsune K, Takahashi K, Arihara Z, Sone M, Satoh F, Ito S, Kimura Y, Sasano H, Murakami O (2001) Role of urotensin II in patients on dialysis. Lancet 358:810–811
71. Totsune K, Takahashi K, Arihara Z, Sone M, Murakami O, Ito S, Kikuya M, Ohkubo T, Hashimoto J, Imai Y (2004) Elevated plasma levels of immunoreactive urotensin II and its increased urinary excretion in patients with Type 2 diabetes mellitus: asso-

ciation with progress of diabetic nephropathy. Peptides 25:1809–1814

72. Wenyi Z, Suzuki S, Hirai M, Hinokio Y, Tanizawa Y, Matsutani A, Satoh J, Oka Y (2003) Role of urotensin II gene in genetic susceptibility to Type 2 diabetes mellitus in Japanese subjects. Diabetologia 46:972–976
73. Suzuki S, Wenyi Z, Hirai M, Hinokio Y, Suzuki C, Yamada T, Yoshizumi S, Suzuki M, Tanizawa Y, Matsutani A, Oka Y (2004) Genetic variations at urotensin II and urotensin II receptor genes and risk of type 2 diabetes mellitus in Japanese. Peptides 25: 1803–1808
74. Ong KL, Wong LY, Man YB, Leung RY, Song YQ, Lam KS, Cheung BM (2006) Haplotypes in the urotensin II gene and urotensin II receptor gene are associated with insulin resistance and impaired glucose tolerance. Peptides 27:1659–1667
75. Wilkinson IB, Affolter JT, de Haas SL, Pellegrini MP, Boyd J, Winter MJ, Balment RJ, Webb DJ (2002) High plasma concentrations of human urotensin II do not alter local or systemic hemodynamics in man. Cardiovasc Res 53:341–347
76. Affolter JT, Newby DE, Wilkinson IB, Winter MJ, Balment RJ, Webb DJ (2002) No effect on central or peripheral blood pressure of systemic urotensin II infusion in humans. Br J Clin Pharmacol 54:617–621
77. Clozel M, Hess P, Qiu C, Ding SS, Rey M (2006) The urotensin-II receptor antagonist palosuran improves pancreatic and renal function in diabetic rats. J Pharmacol Exp Ther 316:1115–1121
78. Sidharta PN, Wagner FD, Bohnemeier H, Jungnik A, Halabi A, Krahenbuhl S, Chadha-Boreham H, Dingemanse J (2006) Pharmacodynamics and pharmacokinetics of the urotensin II receptor antagonist palosuran in macroalbuminuric, diabetic patients. Clin Pharmacol Ther 80:246–256
79. Grieco P, Carotenuto A, Campiglia P, Zampelli E, Patacchini R, Maggi CA, Novellino E, Rovero P (2002) A new, potent urotensin II receptor peptide agonist containing a Pen residue at the disulfide bridge. J Med Chem 45:4391–4394
80. Behm DJ, Stankus G, Doe CP, Willette RN, Sarau HM, Foley JJ, Schmidt DB, Nuthulaganti P, Fornwald JA, Ames RS, Lambert DG, Calo G, Camarda V, Aiyar NV, Douglas SA (2006) The peptidic urotensin-II receptor ligand GSK248451 possesses less intrinsic activity than the low-efficacy partial agonists SB-710411 and urantide in native mammalian tissues and recombinant cell systems. Br J Pharmacol 148:173–190
81. Ng LL, Loke I, O'Brien RJ, Squire IB, Davies JE (2002) Plasma urotensin in human systolic heart failure. Circulation 106: 2877–2880
82. Khan SQ, Bhandari SS, Quinn P, Davies JE, Ng LL (2007) Urotensin II is raised in acute myocardial infarction and low levels predict risk of adverse clinical outcome in humans. Int J Cardiol 117:323–328
83. Dschietzig T, Bartsch C, Pregla R, Zurbrugg HR, Armbruster FP, Richter C, Laule M, Romeyke E, Neubert C, Voelter W, Baumann G, Stangl K (2002) Plasma levels and cardiovascular gene expression of urotensin-II in human heart failure. Regul Pept 110: 33–38
84. Zhong P, Li ZL, Wu HC, Tang CS, Lu Q (2003) Clinical study of changes of urotensin II in patients with congestive heart failure (in Chinese). Di Yi Jun Yi Da Xue Xue Bao (Academic journal of the first medical college of PLA) 23:121–123
85. Russell FD, Meyers D, Galbraith AJ, Bett N, Toth I, Kearns P, Molenaar P (2003) Elevated plasma levels of human urotensin-II immunoreactivity in congestive heart failure. Am J Physiol Heart Circ Physiol 285, H1576–1581
86. Fang SH, Li ZL, Wu HC, Tang CS, Lu Q, Liu HC, Yan QN (2004) Clinical study of plasma urotensin II in patients with coronary heart disease (in Chinese). Di Yi Jun Yi Da Xue Xue Bao (Academic journal of the first medical college of PLA) 24:563–565
87. Kruger S, Graf J, Kunz D, Stickel T, Merx MW, Hanrath P, Janssens U (2005) Urotensin II in patients with chronic heart failure. Eur J Heart Fail 7:475–478
88. Gruson D, Rousseau MF, Ahn SA, van Linden F, Ketelslegers JM (2005) Circulating urotensin II levels in moderate to severe congestive heart failure: its relations with myocardial function and well established neurohormonal markers. Peptides 27: 1527–1531
89. Joyal D, Huynh T, Aiyar N, Guida B, Douglas S, Giaid A (2006) Urotensin-II levels in acute coronary syndromes. Int J Cardiol 108:31–35
90. Heringlake M, Kox T, Uzun O, Will B, Bahlmann L, Klaus S, Eleftheriadis S, Armbruster FP, Franz N, Kraatz E (2004) The relationship between urotensin II plasma immunoreactivity and left ventricular filling pressures in coronary artery disease. Regul Pept 121:129–136
91. Lapp H, Boerrigter G, Costello-Boerrigter LC, Jaekel K, Scheffold T, Krakau I, Schramm M, Guelker H, Stasch J-P (2004) Elevated plasma human urotensin-II-like immunoreactivity in ischemic cardiomyopathy. Int J Cardiol 94:93–97
92. Richards AM, Nicholls MG, Lainchbury JG, Fisher S, Yandle TG (2002) Plasma urotensin II in heart failure. Lancet 360:545–546
93. Simpson CM, Penny DJ, Stocker CF, Shekerdemian LS (2006) Urotensin II is raised in children with congenital heart disease. Heart 92:983–984
94. Cheung BM, Leung R, Man YB, Wong LY (2004) Plasma concentration of urotensin II is raised in hypertension. J Hypertens 22:1341–1344
95. Balat A, Pakir IH, Gok F, Anarat R, Sahinoz S (2005) Urotensin-II levels in children with minimal change nephrotic syndrome. Pediatr Nephrol 20:42–45
96. Mallamaci F, Cutrupi S, Pizzini P, Tripepi G, Zoccali C (2005) Urotensin II in end-stage renal disease: an inverse correlate of sympathetic function and cardiac natriuretic peptides. J Nephrol 18:727–732
97. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P, Malatino L (2006) Urotensin II is an inverse predictor of incident cardiovascular events in end-stage renal disease. Kidney Int 69: 1253–1258