Urotensin II (U-II) is a cyclic peptide first isolated from the urophysis of the teleost fish *Gillichthys mirabilis* where it is involved in osmoregulation. The human isoform was identified in 1998, and 1 yr later its cognate Gq G-protein coupled receptor, UT (de-orphanized GPR14) was identified. Human U-II is composed of 11 amino acids and is cleaved from a larger precursor. An additional urotensin-related peptide has also been identified. Human UT is encoded on chromosome 17q25.3, is intronless, and is composed of 389 amino acids. There are several single nucleotide polymorphisms of both U-II and UT and their association with the range of cardiovascular disease phenotypes is largely undefined. The peptide and receptor show diverse distribution, including brain, respiratory system, heart, vasculature, and kidney. U-II is currently described as the most potent vasoconstrictor. However, the responses it produces are extremely variable and are of low efficacy.4–12

Interaction of U-II with UT leads to activation of phospholipase C and the liberation of inositol (1,4,5) trisphosphate [Ins(1,4,5)P₃]. This interacts with the Ins(1,4,5)P₃ receptor located on the endoplasmic/sarcoplasmic reticulum to release Ca²⁺ from intracellular stores leading to a tissue-dependent response. In the cardiovascular system, if the receptor is located on the cardiomyocyte, increased contractility would be anticipated. In the vasculature, constrictor and dilator responses have been recorded if the receptor is located on vascular smooth muscle cell or endothelium, respectively. Activation of the endothelial Ca²⁺ dependent enzyme nitric oxide synthase increases nitric oxide which diffuses into the vascular smooth muscle to produce a vasodilatation.4–12

Unlike the majority of transmitter molecules, the binding of U-II to its receptor is essentially irreversible; this has been reported for both recombinant and native UT. This irreversibility of binding is probably related to the presence of the highly conserved cyclic hexapeptide core. Irreversibility of binding has important consequences for regulation of receptor-driven signalling.6 8 Under ‘normal’ conditions, the receptor-peptide system is likely to be functionally silent. This rather bold statement is based on the following observations.

(i) There are no major physiological consequences in mice deficient in the U-II receptor (UT-knockouts). (ii) As U-II binding to UT is irreversible, circulating U-II may desensitize the receptor, essentially creating a knockout phenotype. U-II/UT responsiveness would then be predicted to result from increased receptor expression rather than U-II production. The situation in disease is intriguing where both peptide and receptor appear to be variably up-regulated in heart failure, hypertension, diabetes, and renal disease.

The effects of U-II are extremely variable between species, between vascular beds in the same species, and within the same vessel. For example, in rats, U-II constricts the thoracic aorta with high potency but low efficacy, yet this peptide is ineffective in abdominal portions of the same vessel. Responsiveness correlates with differences in receptor expression along the vessel. The basis of this is not yet known and is puzzling, especially if the system is silenced under normal physiological conditions. In some vascular beds, dilation is reported and, as expected from the comments above, this is endothelium-dependent. In humans, vasoconstrictor responses can also be recorded. In addition to the noted effects on the heart and vasculature, this peptide has actions on the kidney, brain, and airways (Fig. 1).

Targeting of peptide-receptor systems in clinical medicine is common, and most anaesthetists will see patients receiving angiotensin-II-converting enzyme inhibitors or angiotensin-II receptor antagonists and the majority of surgical patients will receive opioids in one form or another. The clinical potential of U-II is being explored from three angles:

(i) measurement of U-II in various biological fluids as a function of disease presentation;
(ii) measurement of UT expression as a function of disease presentation; and
(iii) administration of U-II and UT antagonists in man.

U-II is elevated in heart disease and hypertension, although some studies have not confirmed this, and there is some relationship with the degree of heart failure and level of hypertension. In addition, plasma U-II is elevated in renal disease, diabetes, and hepatic disease.\(^{11,12,17}\) We have previously reported, in pre-eclamptic patients that maternal plasma, umbilical cord plasma, and maternal cerebrospinal fluid U-II levels were not elevated when compared with those from normotensive control pregnancies.\(^{18}\) However, Balat and colleagues\(^{19}\) reported an increase in pre-eclamptic patients compared with controls. The variable data are a common observation in urotensin studies and encompass basic \(\text{ex vivo}\) animal/human tissue response studies through to these plasma measurements. UT is similarly increased in cardiomyocytes, endothelial cells, and smooth muscle cells from diseased hearts.\(^{20}\)

In two volunteer studies, U-II has been infused intra-arterially and i.v.\(^{21,22}\) After intra-arterial infusion, plasma concentrations rose, but there was no change in forearm blood flow. As part of a placebo-controlled study, i.v. infusion of U-II concentrations also failed to affect systemic haemodynamics. This might be consistent with the suggestion that, in healthy individuals, the system is functionally silent. This suggestion will, of course, require rigorous experimental validation. The situation in disease states is very different. In two simple but elegant studies,\(^{23,24}\) U-II has been administered to patients with heart failure or hypertension and to normal controls using an iontophoresis technique, with subsequent measurement of microvascular blood flow using Doppler flow probes. In both studies, the control groups displayed increased blood flow consistent with a dilatory response indicating that U-II was probably interacting with an endothelial target. These data are also at variance with the notion of U-II/UT functional silence. More interestingly, in the heart failure and hypertensive groups a decrease in blood flow was observed, indicating vasoconstriction. This information is a clear clinical lead for the use of U-II antagonists to reverse these constrictor effects.

The first clinical use of a UT antagonist in man was published late last year by researchers from Actelion.\(^{25}\) This paper detailed the pharmacokinetics and pharmacodynamics of palosuran (a U-II antagonist) in macroalbuminuric diabetic patients. The rationale for the study was that diabetes increases plasma U-II and this may constrict renal vessels and reduce blood flow. On the basis of two phase 1 safety/tolerability studies in healthy volunteers,\(^{26,27}\) an oral dose of 125 mg twice daily was chosen and the treatment continued for 13.5 days. Type 2 diabetic patients with hypertension and of both sexes (\(n=18\)) were subdivided into two groups based on renal function, normal/mild impairment, and moderate/severe impairment. In both groups, palosuran was rapidly absorbed, reaching a peak \(C_{\text{max}}\approx 110–140\,\text{ng}\,\text{ml}^{-1}\) at around 1 h. Urinary albumin excretion decreased significantly (26.2%) in the normal/mild impairment group. There was a 22.3% reduction in the moderate/severe impairment group but this failed to reach statistical significance. Overall, in both groups (18 patients) there was a significant 24.3% decrease in urinary albumin excretion and palosuran was well tolerated. The authors suggest further larger studies should be performed with palosuran as monotherapy or as combination therapy in patients with renal failure. These further studies are eagerly awaited.

With the availability of U-II receptor antagonists, such as palosuran (and no doubt several more in the clinical pipeline), the future for this peptide-receptor system is

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**Fig 1** U-II is an 11 amino acid cyclic peptide (conserved cyclic hexapeptide core is noted c(Cys\(^5\)-Phe\(^6\)-Trp\(^7\)-Lys\(^8\)-Tyr\(^9\)-Cys\(^10\)) cleaved from a larger precursor, of which there are two isoforms in man. The effects of this peptide on major physiological systems (obtained from laboratory animal and human data) are summarized in boxes (1) to (5). i.c.v., intracerebroventricular; REM, rapid eye movement. See text for further description and references.
encouraging. For the anaesthetist, such drugs may be of use in the care of patients in the intensive care and peri-operative settings, for example those with heart and renal failure. From an experimental point of view, the interaction of some of the commonly used anaesthetic agents with this system remains to be explored.

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