Review Article

Urotensin II and the Circulatory System

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Urotensin II (UII), first isolated from the spinal cord of teleost fish, is the most potent vasoconstrictor known. It is more potent than endothelin-1 and acts through UT-II, a seven-transmembrane-domain, G-protein-coupled receptor. Human UII is an 11-amino-acid cyclic peptide that is expressed in various tissues, including the central nervous system, heart, kidney, and blood vessels. It circulates in human plasma, and its plasma level is elevated in renal failure, congestive heart failure, diabetes, and portal hypertension. In the kidney, UII has vasodilatory and natriuretic effects, mediated through nitric oxide. The development of UII-receptor antagonists may provide a useful research tool, and a novel treatment for cardiorenal diseases. [*Hong Kong J Nephrol* 2005;7(1):9–13]

Key words: hypertension, renal failure, urotensin, vasoactive peptides, vasoconstriction

Urotensin II (UII) 最初從硬骨魚類中分離出來，是目前已知最強的血管收縮物質，比 endothelin-1 更強效。UT-II 是 UII 的細胞膜受體，屬於 G 蛋白偶合受體，具有 7 個跨膜區段 (transmembrane domains)。人體 UII 是一個由11個胺基酸組成的環狀肽，其表現可見於多種組織，包括中樞神經、心臟、腎臟、及血管。在腎衰竭、鬱血性心衰竭、糖尿病、門脈高壓等狀況中，UII 的血漿濃度會出現上升。腎臟內的 UII 透過一氧化氮的作用，具備血管擴張及促尿鈉排泄效應。UII-受體拮抗劑的發展，除了有利於研究之外，亦可望為心、腎臟疾病提供一種嶄新的療法。

Introduction

Urotensin II (UII) was first isolated from the spinal cord of teleost fish and has been recognized as a hormone in the neurosecretory system of such fish for over 30 years [1,2]. It is the most potent vasoconstrictor known, being more potent than endothelin-1 (ET-1) [2]. This brief review summarizes what is known about UII and its receptor (UT-II), their function and relation to cardiovascular and renal diseases.

UII and its Receptor UT-II

UII is a cyclic peptide with an amino acid sequence similar to that of somatostatin (Figure 1). UII isoforms from human, monkey, pig, rat, mouse and goby contain a conserved C-terminal cyclic-hexapeptide sequence (Cys-Phe-Trp-Lys-Tyr-Cys) that confers most of the biologic activity, and an N-terminal that differs in length and sequence depending on the animal species [3].

Human UII is an 11-amino-acid cyclic peptide derived from a large precursor molecule (prepro-UII). The gene encoding the peptide, *UTS2*, is located at 1p36–p32 and contains five exons. Prepro-UII mRNA has been found in heart, aorta, vascular endothelial and smooth muscle cells, brain, spinal cord, kidney, lung, liver, skeletal muscle, adrenal gland, pituitary, spleen, the small intestines and colon [3]. UII-like immunoactivity is present abundantly in the epithelial cells of the distal convoluted and collecting tubules, and in the endothelial cells of the renal capillaries [4]. Thus, the kidney is an important site of UII synthesis.

In man, the UII receptor, UT-II, is a 389-amino-acid, G-protein-coupled receptor with seven transmembrane domains (Figure 2). The gene coding for

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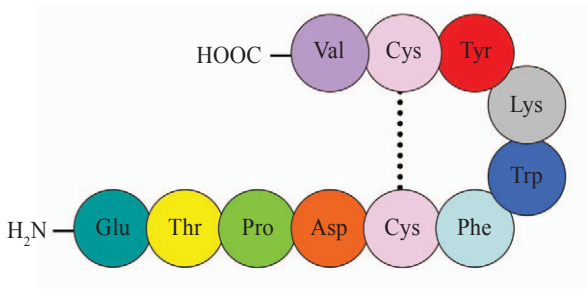

Figure 1. Structure of human urotensin II.

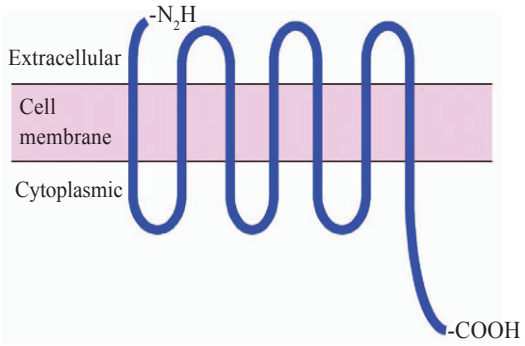

Figure 2. Simplified, diagrammatic representation of the urotensin II receptor.

human UT-II does not have an intron and is located at 17q25.3 in the long arm of chromosome 17 [5]. UT-II is found in human brain, spinal cord, ventricular myocardium, vascular endothelial and smooth muscle tissues, kidney cortex, and thyroid, with the highest density in skeletal muscle and the cerebral cortex [6]. The distribution of UII and UT-II suggests that UII may act as a local or circulating vasoactive hormone in cardiovascular regulation. Interestingly, UT-II has not been found in veins, and UII does not constrict isolated preparations of veins, except the saphenous and umbilical veins [6].

UT-II is coupled to the $G_{q/11}$ signal-transduction pathway, the activation of which leads to increased levels of inositol phosphate and mobilization of intracellular calcium ions [2,7]. Human UII induces arterial smooth muscle contraction, actin stress fiber formation and proliferation through activation of the small RhoA guanosine triphosphatase and its downstream effector, Rho-kinase [8]. UII also induces vascular smooth muscle proliferation via activation of integrin-mediated signaling pathways and phosphorylation of extracellular signal-regulated kinase (ERK) [9].

Physiologic Roles of UII

The vascular actions of UII vary with species and site. UII also influences sodium transport, and lipid and glucose metabolism, at least in fish [1]. The concentration of UII in the urine is more than three orders of magnitude greater than that in the plasma, suggesting that urinary UII is produced within the kidney [10]. Infusion of synthetic UII into the renal artery of anesthetized rats increases renal blood flow and glomerular filtration rate (GFR) in a dose-dependent manner; these effects can be completely abolished by adding a nitric oxide synthase inhibitor [11]. UII may play a role in regulating GFR via tubuloglomerular feedback and the reflex control of GFR [4]. UII also increases urinary water and sodium excretion by stimulating nitric oxide production, which, in turn, inhibits tubular ion transport activity [11]. Hence, in the kidney, UII exerts vasodilatory and natriuretic effects.

In the rat, UII produces both endothelium-independent vasoconstriction and endothelium-dependent vasodilatation [2,11,12]. In human arteries, UII is about 50 times more potent than ET-1, but the maximum response is significantly lower than that achieved by ET-1, and 30% of vessels do not respond to UII [6]. Conversely, UII relaxes the vasoconstriction induced by ET-1 in small pulmonary arteries and systemic resistance arteries [13]; this might be due to the release of nitric oxide and endothelium-derived hyperpolarizing factor from an intact endothelium. In the rat renal artery, UII induces nitric oxide synthesis in the endothelium and subsequent vasodilatation [11].

Intravenous administration of low-dose UII in monkeys increases cardiac output and reduces peripheral vascular resistance [2]. Higher doses cause cardiovascular collapse that may be lethal. Recently, the cat was found to be a useful model to study, since isolated feline arteries are highly responsive to UII [14]. Infusion of UII in the cat doubled systemic vascular resistance and blood pressure without markedly altering heart rate or cardiac output [14]. While Bohm and Pernow showed that UII caused potent vasoconstriction in man, with a dose-dependent decrease in forearm blood flow [15], Wilkinson et al found no increase in blood pressure or peripheral vascular resistance after infusion of UII in healthy men [16]. Moreover, intravenous infusion of UII did not affect systemic hemodynamics or arterial

stiffness, even with a 100-fold increase in plasma UII levels [17]. The absence of systemic vasoconstriction after UII infusion may be due to the modulating effect of other vasoactive substances such as nitric oxide. Further studies with a UT-II antagonist would clarify the physiologic role of UII in regulating vessel tone.

UII also possesses cardiostimulant effects in the human heart *in vitro* [18]. Human UII causes a concentration-dependent increase in contractile force with no change in duration of contraction in right atrial trabeculae from non-failing hearts, and a small increase in contractile force in right ventricular trabeculae from explanted hearts [18].

Potential Roles of UII in Human Disease

UII circulates in human plasma, and plasma levels of UII are elevated in renal failure [19,20], congestive heart failure [21,22], diabetes mellitus [23], and portal hypertension caused by liver cirrhosis [24]. Plasma levels of UII in patients with renal dysfunction who are not on hemodialysis, or who are on hemodialysis, are respectively 2-fold or 3-fold greater than in healthy individuals; this may be due to increased production or decreased excretion of UII [20]. Although there is no correlation between blood pressure and urinary UII level, an increased urinary UII level is observed in patients with essential hypertension, patients with both glomerular disease and hypertension, and patients with renal tubular disorders, but not in normotensive patients with glomerular disease [10]. UII may also have a mitogenic role in the human renal system; this is suggested by the abundant expression of UII in renal clear-cell carcinoma [4].

Plasma levels of UII are elevated in patients with diabetes, independent of blood glucose levels. UII inhibits insulin secretion in the rat pancreas in response to both glucose and arginine [25]. Interestingly, a single nucleotide polymorphism in the *UTS2* gene, T21M, is correlated with genetic susceptibility to type 2 diabetes in Han people, while the S89N polymorphism in *UTS2* has been associated with type 2 diabetes in Japanese individuals [26,27].

As UII is a vasoconstrictor, its role in hypertension is worthy of investigation. Normotensive and hypertensive patients have similar cerebrospinal fluid (CSF) levels of UII, but in hypertensive patients, CSF levels of UII correlate with mean arterial blood pressure [28]. However, a recent study of the role of UII in hypertension showed that it may have a causative role in hypertension and its complications since plasma levels of UII were raised in hypertensive patients relative to normotensive controls and were directly related to systolic blood pressure [29].

UII and UT-II are found in the heart and blood vessels, including atherosclerotic plaques, thus suggesting a role in cardiovascular diseases [19]. UII acts synergistically with mildly oxidized low-density lipoprotein to induce vascular smooth muscle cell proliferation [30]. In addition, serotonin (5-hydroxytryptamine) contained in platelets interacts synergistically with UII to induce such cellular proliferation, which may contribute to the rapid development of atherosclerosis in hypertensive vascular disease [31]. Moreover, atherosclerosis is associated with the diminished production of endothelial nitric oxide. When endothelial dysfunction exists, the vasoconstricting effect of UII is unopposed and unmasked.

Zuo et al demonstrated that hypertrophy of neonatal rat cardiomyocytes cultured *in vitro* can be induced by UII [32]. The hypertrophy of cardiac myocytes was mediated by the mitogen-activated protein kinases ERK1/2 and p38 [33].

Expression of UII and UT-II is upregulated in patients with end-stage heart failure [34]. UII is one of several neurohormonal systems activated in congestive heart failure [21,35,36]. An inverse correlation exists between UII expression or plasma UII concentration and ejection fraction [34,36]. UII may increase cardiac contractility [18] and peripheral vascular tone [37]. Although increased contractility may be beneficial in the short term, prolonged activation might lead to myocardial remodelling. Indeed, UII induces cardiac fibroblast proliferation and collagen type I mRNA expression [38]. Interestingly, UII causes vasodilatation in the skin vessels of healthy individuals, but causes vasoconstriction in patients with heart failure [37].

UII may play a role in myocardial ischemia and acute myocardial infarction. In the myocardium of rats with chronic hypoxia, UT-II expression is increased [39], and around infarct zones and in inflammatory cells, there is increased expression of UII and UT-II [40].

Conclusion

UII is the most potent vasoconstrictor known, and it also stimulates nitric oxide production. Thus, it may play an important role in regulating vascular tone and blood flow. There is increasing evidence that UII is associated with atherosclerosis, congestive heart failure, diabetes, hypertension, and renal dysfunction. More research is needed to elucidate the pathophysiology of UII and its receptor, UT-II, as well as the urotensin-converting enzyme(s) that produces UII from prepro-UII. The development of UT-II antagonists may provide both a useful research tool and a novel treatment for cardiorenal diseases.

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