



## Efficacy of Urotensin II in Cardiovascular System

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### ABSTRACT

Cardiovascular diseases (CVDs), including coronary arter disease, cerebrovascular events, rheumatic heart disease and arter diseases, remain the most common cause of death in the world. Changes in the regulation of vasoactive peptides in abnormal conditions, cardiovascular diseases; Endothelial dysfunction, which is the critical processes underlying vascular damage, results in vascular repair and inflammation. Studies with specific receptor antagonists; It will be very important to understand the physiological role of urotensin II and its receptor and to reveal its therapeutic potential. The aim of this study is to know the pathophysiological role of U-II following the development of UT receptor antagonists and to give an insight into the design of new drugs and to give a current perspective. The development of urotensin receptor antagonists may provide a useful diagnosis tool as well as a new treatment for cardiovascular diseases.

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### Introduction

Cardiovascular diseases are the leading reason of death both with high medical costs and high disability rates. Therefore, the use of cardiovascular biomarkers is needed to ensure the early diagnosis of coronary artery disease (CAD). In the expectation that they may allow the detection of atherosclerotic CAD, several recently identified bioactive peptide candidates have been studied. Particularly, new anti-atherogenic peptides and negative risk factors for CAD have been emphasized [1]. In myocardial and coronary vasculature; The endocrine and pleiotropic functions of these peptides represent an important aspect of health and disease effects. These agents are involved in the reorganization and structure of myocardium as well as the regulation of vascular tone. By deregulation of these vasoactive peptides; a series of processes which are the basis of vascular damage in cardiovascular diseases; events such as vascular remodeling, inflammation and endothelial dysfunction occur [2,3].

Urotensin II (U-II) is a vasoactive peptide which now shows attachment by binding to orphan G-protein-bound receptor 14 (GPR14). U-II, a somatostatin-like cyclic peptide, was originally derived from the urophysis of fish and is now known as one of the most potent vasoconstrictor agents [4]. However, the mechanism of molecular action of U-II has not yet been elucidated [5]. The effect of U-II differs from endothelin-1 that constructs approximately all of the vascular beds. The vasoactive effects of U-II have been reported to vary with both the species and the regional vascular bed examined [6]. Maguire et al. reported that urotensin (UT) receptors are located in the human vascular smooth muscle of blood vessels and mediate vasoconstriction in vitro in endothelial preparations of human arteries and veins [7]. Plasma U-II level is risen in diabetes mellitus, kidney failure, systemic hypertension, congestive heart failure and liver cirrhosis caused by portal hypertension. The effect of U-II on the vascular system varies depending on the species, the vessel bed and the diameter of the vessel. On vascular tone; it is effective by establishing a balance between endothelium-independent vasoconstriction and endothelium-dependent

vasodilatation [8]. Otherwise, in contrast to the role of U-II in the regulation of vascular tone, the represented role of this peptide in regulating vascular morphology is excessively unknown [6]. U-II expression is detected in atherosclerotic lesions. In there is a prominent rise in the expression of U-II and its receptor in atherosclerotic lesions of human aorta. In coronary arteries with atherosclerotic lesion, immunore activity of U-II is see in areas of macrophage infiltration [9,10].

### Discussion

Potential biomarkers have been broadly appraised in the field of cardiovascular medicine. However, only a restricted number of markers have indicated important diagnosis and/or therapeutic effect. Deeper sensation into the pathophysiology of atherosclerosis have lead to the exploration of additional new biomarkers [11]. Novel vasoactive agents, oxidative products and inflammatory cytokines that have charmed attentions have been included as potential biomarkers [12]. Atherosclerosis is an inflammatory response in vascular endothelial cells; It is a pathological injury process characterized by processes such as endothelial inflammation, reduction of nitric oxide production and monocyte adhesion and infiltration to neointima lesion. In the development of atherosclerotic lesions, proliferation of fibroblast and Vascular smooth muscle cell (VSMC) is also important [13]. Thus, a potential bioactive factor that modulates such pathogenic process may possibly be a clinical atherosclerotic biomarker. [14]. In addition, the peptidic U-II receptor (UT receptor) ligand blocked the contraction effect of U-II on isolated rat aorta, but was inactive against the hypotensive effect of U-II in vivo; This state draws attention to the existence of more than one receptor type for U-II [15]. Nevertheless, until now, such questions remain largely a puzzle. However, based on the trophic and mitogenic effects independent of blood pressure, U-II has been reported to function in pathological processes such as myocardial hypertrophy and fibrosis [16]. vascular smooth muscle cell (VSMC) proliferation [17], atherosclerosis [9]. After metabolic diseases and oncology drugs, Vasoactive peptide drugs in

cardiovascular diseases have become an third area of interest in the pharmaceutical industry. The use of vasoactive peptides in this field is widely evaluated in the scientific community in the treatment of CVDs, but more effort is needed to increase their therapeutic potential. On the structures, deepening efforts and binding to the respective receptors; it will be necessary for the development of mimetic peptides and low molecular weight compounds which will be considered as novel pharmacological and pharmaceutical means [18].

In many studies, the use of Sb-710411 as one of the effective U-II antagonists is known [19]. Ahmed et al. state that the effect of U-II in endothelial insufficiency, they reported that U-II's vasoconstriction effect was inevitable and that endothelial failure maintained the vasoactive capacity of the peptide. They noted that there were direct effects of mercury on receptor protein fragments. [20,21] which were probably distorted and partially lost their physiological properties. It is also noteworthy that the effect of mercury on the vascular response to Human U-II is reduced, as well as the inhibition of the ACE pathway. This is important results showing that the angiotensin II pathway plays a key role in both vascular impairment and in UI vasoconstriction [22]. Emphasized as a new finding, urotensin-II strongly demonstrates its effect in endothelial dysfunction. Accordingly, endothelin-1 and angiotensin-II pathways; It can be used extensively to modulate the effects of endothelial dysfunction and the vascular effects of vasoactive peptides [23].

Urotensin II and its receptor (UTR) cause an increase in the production of reactive oxygen species (ROS), leading to an increase and progression of CVDs. Silymarin (SMN) is a natural agent that can be used for anti-diabetic purposes. It is intriguing to investigate the antioxidant properties of SMN in the oxidative stress situation on the expression of the U-II / UTR system in the type 2 diabetic rat heart. SMN has been found to be effective for unwanted diabetic properties by modulation of oxidative stress in heart tissue in the heart tissue of type 2 diabetic rats, down-regulation in U-II and UTR gene expressions. It has been observed that effective interventions in UII and UTR gene expression may be effective in diabetic conditions [24]. U-II is also an effective peptide on myocytes. For studies on hypertrophy, the cardiomyocyte hypertrophy model induced by Urotensin II is widely known. However, the molecular mechanisms responsible for U-II-induced cardiomyocyte hypertrophy have not yet been fully elucidated [25]. It has been reported that the cause of U-II-induced cardiomyocyte hypertrophy is due to mechanisms associated with changes in the intracellular Ca<sup>2+</sup> concentration. U-II induces cardiomyocyte hypertrophy by upregulation of phospholamban (PLN) phosphorylation via protein kinase A (PKA) in Ser16. This may provide a new experimental basis for the prevention and / or treatment of cardiac hypertrophy [26]. In terms of the pathophysiological role of the U-II/UT receptor; The potential interest of the system and UT, the importance of receptor ligands as drug candidates, has led to the development of low molecular weight compounds as non-peptide UT receptor agonists and antagonists. Grieco and his research group have long focused on the development of UTR peptide ligands. In an optimization, the importance of identifying the peptide as a lead construct, improving its pharmacokinetic properties and identifying pharmacophore elements has been emphasized and thus it has been reported that these steps are important in determining the key amino acid residues involved in biological activity [27].

Lescot et al. [28]. have studied on three-dimensional model of the human urotensin-II receptor and have described; complete non-peptide antagonists and key binding domain residues that interact with hU-II. Although there are similarities with recent studies describing the automatic insertion of a potential peptide agonist (P5U) into a hUT-II model [29] they have reported differences in their study results. They reported that these results could be used to optimize lead compounds, design of structure-based drugs, and the design of novel non-peptide hU-II antagonists [28].

In addition, with more reliable positive results obtained with UT, receptor antagonists strengthen the idea that UII targeting is present. Thus, there are ongoing drug investigations that may be effective in the treatment of many diseases. The new synthetic UII antagonists continue to emerge, so that study results are approached to the introduction of safe and potent UT receptor blockers in the clinical field. In the studies for all urotensin II and cardiovascular systems, perfecting this intervention will continue to be the main target for today and the future [30,31].

### Conclusion

Despite many advances in the treatment of CVDs, more effective treatments are needed to address significant challenges. Numerous vasoactive agents have important physiological roles in regulating vascular tone, structure and reactivity. Urotensin II can be an important physiological mediator of vascular tone and blood pressure in humans, and vasoconstrictor effects are modulated by endothelial dependent vasodilators, which may be important in cases of endothelial dysfunction. Urotensin-II is commonly found in renal, endocrine and cardiovascular systems. The high expression levels of this peptide in humans are distributed in the myocardium, atrium and ventricles. Moreover, although the role of U-II in the regulation of vascular tone has been studied very much, there is much unknown about the predicted role in the regulation of vascular morphology. The development of urotensin receptor antagonists may provide a useful research tool as well as a novel treatment for cardiovascular diseases. For cardiovascular diseases, the development of urotensin receptor antagonists may be a useful marker of diagnosis development, furthermore may be very useful in the development of new therapeutic.

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