Urotensin II: a new player in vascular and myocardial disease?

There has been considerable excitement and a flurry of contemporary research into the physiological actions of the 11-amino-acid peptide, urotensin II; however, urotensin II itself is not a new discovery. It was first described approximately 35 years ago in the urophysis of the teleost fish [1]. It was, in fact, the discovery by Ames et al. [2], of an endogenous ligand for urotensin II (GPR 14) that has stimulated this recent research activity.

In many ways urotensin II mimics the actions of other key neurohormonal factors in driving a variety of cardiovascular and vascular disease processes [3]. These include vasodilatation (in some, but not all, vascular beds), as well as mitogenic, trophic and pro-fibrotic effects. However, key differences can be observed between urotensin II and other well-characterized systems, such as the renin–angiotensin–aldosterone system (RAAS) and the endothelin system. In particular, the vasoconstrictor effect of urotensin II is either weak or absent in a variety of human vascular beds [4,5]. Moreover, it may actually act as a vasodilator in certain beds, such as in the pulmonary vasculature [6] (via activation of nitric oxide, vasodilator prostaglandins and perhaps endothelium-derived hyperpolarizing factor). Furthermore, clear-cut data regarding the effect of exogenous arterial infusion of urotensin II on vascular tone in the human forearm vascular bed are lacking [7,8]. Thus, the precise role of urotensin II in modulating vascular tone in the resting state in man remains somewhat uncertain.

Even less clear is the role of urotensin II in cardiovascular disease states. Within the myocardium, there is evidence of activation of both urotensin II and its receptor in the post-myocardial infarction [9] and established chronic heart failure setting [10]. This activation may be of considerable pathophysiological significance, given the aforementioned hypertrophic and pro-fibrogenic effects [9] of activation of this system.

In addition, little is known about the role of urotensin II in the peripheral vasculature in disease states. The observations in this issue of Clinical Science by Totsune and colleagues [11] regarding the presence of urotensin II precursor mRNA, as well as that of the urotensin II receptor within endothelial cells, may be of importance in this regard. In particular, they suggest that urotensin II activity may be altered by and perhaps contribute to vascular disease associated with endothelial dysfunction.

Plasma levels of circulating peptides are generally extremely insensitive measures of their systemic activation, and may also poorly reflect local activity. Nevertheless, they can provide insight into pathophysiological associations of bioactive peptides with various disease states. For example, endothelin-1 is released primarily by peripheral vascular endothelial cells, with most of that release being in an abluminal direction, i.e. directed towards the vascular smooth muscle cell [12]. Approx. 20% of released endothelin-1 is directed towards the vessel lumen. Thus, elevated plasma levels denote a substantially activated endothelin system.

In contrast, the source of urotensin II in man is largely unknown, both in normal subjects and in disease states. Indeed, plasma levels may reflect release from a number of potential sources, including the kidney, central nervous system and adrenal gland [6], as well as from peripheral vascular endothelial cells.

Peptide plasma levels are the net result of both endogenous production and clearance. Clearance pathways for urotensin II are unknown. Some insight into urotensin II clearance via the kidney has been gleaned from the observation that urotensin II levels are roughly 2-fold higher in patients with renal dysfunction [13]. However, the authors of that study were unable to ascertain whether this was entirely due to reduced renal clearance or whether there was a contribution via the activation of urotensin II production. Similarly, patients with chronic heart failure have been shown to have elevated levels in some, but not all, studies [14–16]. Again, the relative contribution of impaired renal clearance to elevation of urotensin II peptide in this setting cannot be clearly determined based on available data.

Because diabetes mellitus is associated with accelerated vascular disease, as well as direct effects on the myocardium, the relationship of vasoconstrictor systems to this disease are of great interest. This interest is enhanced with respect to urotensin II because of the observation that there is increased expression of urotensin II in atherosclerotic lesions, specifically within infiltrating macrophages [17]. Vascular complications are in fact the major cause of morbidity and early mortality in diabetic patients. In addition to glucose-dependent pathways, such as hyperglycaemia and the formation of advanced glycation end-products, glucose-independent mechanisms are also major contributors to diabetic vasculopathy. The latter not only include the effects of hypertension and dyslipidaemia, but also the dysregulation of vasoactive hormone systems.

The RAAS has been the most extensively studied system in diabetes, where, despite suppression of systemic RAAS activity, therapeutic blockade with both angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers provide vascular protection. This apparent paradox has been explained by independent
regulation of systemic and local tissue-based systems, with the systemic endocrine RAAS suppressed by volume overload, whereas the local tissue-based system is activated by injury.

Endothelin, another potent vasoconstrictor peptide, has also been reported to be elevated in patients with diabetes, particularly in the presence of associated micro- and macrovascular complications [18]. There are also significant interactions noted between the endothelin system and the RAAS. For example, angiotensin II-induced vascular hypertrophy can be attenuated by endothelin-receptor blockade [19]. Whether similar interactions may also occur between urotensin II and other vasoactive hormone systems is at present unknown.

The observations made in this issue of Clinical Science by Totsune and colleagues [11] provide important a priori evidence for activation of the urotensin II system in diabetes mellitus. Plasma levels were increased roughly 2-fold in this setting, with presence of proteinuria seemingly not a major determinant of plasma levels.

Thus, to date, increased plasma urotensin II has been described in three states of volume overload: kidney failure [13], heart failure [14] and now diabetes [11]. Therefore, the increased urotensin II in diabetic subjects noted by Totsune et al. [11] may potentially reflect both a systemic response to volume overload and/or the tissue response to hyperglycaemic injury.

These observations are exciting, and will undoubtedly stimulate further research activity teasing out mechanisms that may modulate this activation. Nevertheless, there are some cautions that should be exercised when interpreting the results of Totsune et al. [11].

Firstly, very small numbers of patients were involved in this study. Even though the data appear clear-cut and statistically highly significant, one or two outliers in each of the diabetic groups could have had a major influence on the overall result.

Secondly, there are major differences in baseline characteristics of the diabetic and non-diabetic patients that may impact on this result, independent of diabetes status. These include greater elevation of systolic and diastolic blood pressure in the diabetic patients, and somewhat greater elevation in serum creatinine levels. These differences may be important in contributing to the overall increase in plasma urotensin II levels in this patient population. Furthermore, key data, such as body mass index and creatinine clearance, are not available in the controls for comparative purposes. We are also not told which drugs diabetic subjects are receiving (other than insulin), and this too may potentially influence plasma levels.

Finally, and most importantly, these data provide little insight into whether urotensin II elevations in plasma reflect a pathophysiological role for the peptide in diabetic vascular disease or are merely an epiphenomenon. Of course, this problem is not unique to the urotensin II system; it is also the subject of ongoing evaluation within other systems, such as with endothelin-1, in relation to its role in a variety of different disease states.

Despite the above caveats, the results presented by Totsune et al. [11] are intriguing and should serve to generate a number of hypotheses for a potentially important role for urotensin II in diabetes mellitus. The best way to tease out these questions is of course with highly specific and selective antagonists of the relevant system under scrutiny, in this case, that of the urotensin II system. Such agents have been developed [20]; their use in a variety of experimental and clinical settings should provide important insight into the pathophysiological relevance of this system in diabetes and other diseases involving the vasculature and myocardium.

HENRY KRUM* and RICHARD E. GILBERT†
*Clinical Pharmacology Unit, Departments of Epidemiology & Preventive Medicine, and Medicine, Monash University/Alfred Hospital, Prahran, Victoria, Australia, and †University of Melbourne Department of Medicine, St. Vincent’s Hospital, Fitzroy, Victoria, Australia

(ON BEHALF OF THE EDITORIAL BOARD)

REFERENCES