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What is the role of Urotensin II in cardiovascular disease?

Urotensin II (UII) is a somatostatin-like endogenous peptide first described in the goby fish in 1969. In the goby fish it is involved in osmoregulation but little was known about its effects in humans until the last decade. UII is the most potent vasoconstrictor substance known and has some intriguing pharmacological properties, being both a potent (low efficacy) constrictor in some vessels and acting to produce vasodilatation in others. In anaesthetized non-human primates (cynomolgus monkeys) intravenous UII increased total peripheral resistance with associated regional wall motion abnormalities causing profound cardiovascular collapse.[1]

UII binds to a Gq protein-coupled Urotensin II receptor, UT (originally identified as the orphan receptor GPR14). Binding of UII to UT is irreversible and of low efficacy. UT is found in cardiac myocytes, vascular smooth muscle cells, endothelial cells, the kidneys, spinal cord and CNS.[2-4] There are species-specific differences but exogenous UII has positive inotropic effects *in vitro*. In general, activation of UT on human vascular smooth muscle causes direct vasoconstriction whereas activation of endothelial UT produces vasodilation via nitric oxide and other mediators. Conversely basal cardiovascular dynamics and response to vasopressors are unaffected in UII knockout mice. The administration of UII to healthy volunteers has few cardiovascular effects. In contrast, iontophoresed UII causes vasoconstriction (assessed by laser Doppler velocimetry) in patients with heart failure or hypertension. Together, these data suggest that the Urotensin system is largely inactive or desensitised in health. However there is increasing evidence that the Urotensin system is involved in a number of disease states, particularly in cardiovascular disease.

Plasma UII concentrations are increased in heart failure, hypertension, diabetes and renal failure, and recent evidence suggests upregulation of UT in heart failure, with direct UII production from the heart.[2-6] Because the interaction between peptide and receptor is not straightforward, and there are variations between assays, plasma concentrations do not directly reflect tissue concentrations or activity. However, the current consensus opinion is that elevated UII is a potentially useful serum biomarker of congestive heart failure. Unlike N-

BNP, UII appears to be elevated in systolic dysfunction irrespective of severity. In addition plasma UII is not affected by age or gender.

The UII system is also involved in vascular and cardiac fibrosis, coronary atherosclerosis and cardiac remodelling, diabetes and the metabolic syndrome. It upregulates cellular adhesion

molecules (ICAM-1, VCAM-1) and tissue factor to promote endothelial damage, thrombosis, vascular smooth muscle proliferation and coronary atherosclerosis.[7] [8] UT is found in atherosclerotic lesions of the carotid and abdominal aorta, mostly localised within the hyperplasic intima. UII also induces the formation of foam cells and increases vascular wall permeability, thereby increasing lipid accumulation and the development of atherosclerosis.[4]

Urotensin and heart failure

The relevance of anaesthesia-based research into urotensin may not be intuitive, but as anaesthetists we commonly administer drugs with potent cardiovascular effects; furthermore many of our patients are elderly with co-existing cardiovascular disease or acutely altered cardiovascular physiology. Research in themes outside the immediate vicinity of the anaesthetic room is also an integral part of the NIAA's strategy for academic anaesthesia.

Following early pharmacological studies in conjunction with colleagues at the University of Ferrara, Italy,[9] our research group first established that UII was present in CSF, and that concentrations were related to arterial pressure in hypertensive patients.[10] [11] We established that UII seemed unaffected by general anaesthesia, surgery or sepsis but that concentrations were increased in cigarette smokers.[12] [13] More recently we investigated UII and UT in human heart tissues and found an inverse relationship between right atrial tissue and ventricular ejection fraction.[14] The underlying aim of our work has been to try to establish the role of UII and UT in heart failure. The incidence of heart failure is increasing: it is the leading cause of hospital admission in western world, the most costly cardiovascular disorder and it affects over 10 million patients in the USA and Europe.

Other human tissue studies have shown that myocardial UT expression is upregulated in heart failure both on myocardial and non-myocardial cells. Exogenous UII seems to have opposite effects in failing and normal hearts. A recent study found UII caused dose-dependent increases in contractility in non-failing heart, but dose-dependent *decreases* in developed force, rates of force generation and relaxation in failing hearts.[6] In the same study, administration of a UT antagonist increased contractility in the failing hearts. These data suggest that ventricular UT is upregulated in heart failure and under these conditions, endogenous UII inhibits contractility. UT antagonists may therefore be a new therapeutic option for heart failure.

Urotensin anatagonists- a new therapeutic option?

Animal studies have shown that the UII antagonist SB-611812 decreased intimal fibrosis and cardiac remodelling in experimental heart failure, though no human data are available. Palurosan is a non-peptide UT antagonist which has undergone clinical trials in humans with hypertension and diabetic nephropathy.[5] Results in these conditions were equivocal: the published studies were small (n<20), the dose almost certainly inadequate and data may have been confounded by the co-administration of angiotensin receptor blockers and ACE

inhibitors. More recently, doubts have been expressed about the selectivity for and efficacy of palurosan at the UT receptor and further clinical studies of palurosan are thought to be unlikely. However, other UT antagonists are in development. Further research is needed to determine whether these new UT antagonists can reverse upregulation of UII-UT activity. Such drugs might then be used as novel antihypertensive agents or vasodilators in for patients with heart failure.

Summary

In the Macintosh lecture I will discuss the pharmacology of UII and UT with special consideration given to the available data relating to UT in normal physiology and disease. I will describe recent and potential work on UII and UT in heart failure and sepsis and speculate on possible future directions with respect to the therapeutic use of UT antagonists.

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