

Raising hopes for high blood pressure

High blood pressure is one of the most prevalent health problems in the developed world. Existing treatments focus on lifestyle changes and relaxing or widening the blood vessels themselves. Now, a team led by **Prof Robert M Carey**, of the University of Virginia Health System, is exploring a new approach to treating high blood pressure, making use of molecular systems in the kidney which control the body's balance of water and salt.

is controlled through a molecular network known as the 'renin-angiotensin system' (RAS).

The key player in the RAS system is a molecule known as angiotensin II. This molecule can interact with two different receptor molecules, each controlling a different pathway of the RAS. If an angiotensin II molecule "meets" a 'type 1' receptor (known as AT₁R), a detrimental set of reactions is triggered which causes inflammation, blood vessel constriction, sodium accumulation, and increased blood pressure.

If, however, angiotensin II meets a 'type 2' receptor (AT₂R), an alternative, protective pathway is activated, stimulating the kidneys to excrete sodium, lowering blood pressure and reducing inflammation. Prof Carey's lab is currently working on a project, funded by the US National Institutes of Health, to understand and ultimately harness the AT₂R pathway, to develop new treatments for primary hypertension.

ACTIVATING AT₂R

Although the role of angiotensin II and AT₁R in increasing blood pressure has been relatively well studied, the second role of angiotensin II, via AT₂R, has – until now – slipped under the radar. Prof Carey's lab has recently begun to characterise this pathway and have already made multiple discoveries. Firstly, they found that AT₂R activation is most effective when angiotensin II is converted, by an enzyme called aminopeptidase, to a related molecule, angiotensin III. Animal models using rats have shown that the protective RAS pathway is impaired – i.e., sodium is not excreted and blood pressure is raised – in individuals in which angiotensin III is destroyed before it is able to interact with AT₂R.

Secondly, recent studies have suggested that medicines known as angiotensin receptor blockers, used to treat high blood

High blood pressure (hypertension) affects an astonishing one in four adults in the western world, and contributes to some of the leading causes of death and disability, including heart attacks, strokes, kidney disease and dementia.

Ninety percent of high blood pressure cases are classed as 'primary' hypertension (also known as 'essential' hypertension) which means there is no known underlying biological or medical cause. In these cases, the high blood pressure is usually put down to a mixture of genetic and environmental factors, and treated with a combination of lifestyle changes (reducing salt intake, alcohol consumption, and caffeine use; losing weight; increasing exercise; and improving sleep) and, if these measures fail, antihypertensive medication. Existing medications for high blood pressure tend to act on the blood vessels, either relaxing their walls or widening the vessels themselves, to reduce the pressure within.

SODIUM TAKES THE BLAME

However, the immediate cause of high blood

pressure is retention of sodium (one of the elements contained in salt, sodium chloride), by the kidneys. Sodium retention causes the body to retain fluids. The increased circulating volume increases pressure on blood vessels, causing hypertension. In fact, Prof Carey points out, all forms of hypertension, both in humans and laboratory animals, involve disruption of the body's natural systems for eliminating excess sodium.

Thus, any treatment that encourages the body to excrete sodium should help to lower fluid volume and, thereby, blood pressure. With this in mind, Prof Carey's lab is focusing on understanding the body's natural molecular pathway for sodium excretion by the kidneys, in the hope of finding targets for new drug treatments.

HARNESSING A NATURAL SYSTEM

Prof Carey is an international authority on hormonal control of blood pressure. Many of our body's physiological processes are controlled by hormones – and the maintenance of a healthy salt and water balance by the kidneys is no exception. Prof Carey's current research focuses on how this

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pressure by blocking the interaction between angiotensin II and AT₁R, may in fact have a dual-action effect, also activating AT₂R and its protective pathway, causing the kidneys to excrete sodium and thereby lower blood pressure.

Finally, Prof Carey's lab has also shown that AT₂R activation stimulates the production of molecules including nitric oxide. Nitric oxide can then stimulate the body to produce more molecules of AT₂R, forming a positive feedback loop that could reinforce the body's ability to excrete sodium and reduce hypertension. Thus, Carey's team is furthering our understanding of multiple steps in the protective pathway against high blood pressure, both before and after the AT₂R itself.

In their current study, the lab now aims to further test the hypothesis that high blood pressure can be caused by a failure to excrete sodium when the AT₂R-mediated pathway is impaired, and that this is due to a lack of angiotensin III. They then aim to test whether artificially activating AT₂R can improve sodium excretion and reduce hypertension, and whether AT₂R could ultimately be a useful target for therapies to prevent and reduce high blood pressure.

CO-OPTING COMPOUND 21

Research into the role of angiotensin and the AT₂R receptor in treating hypertension

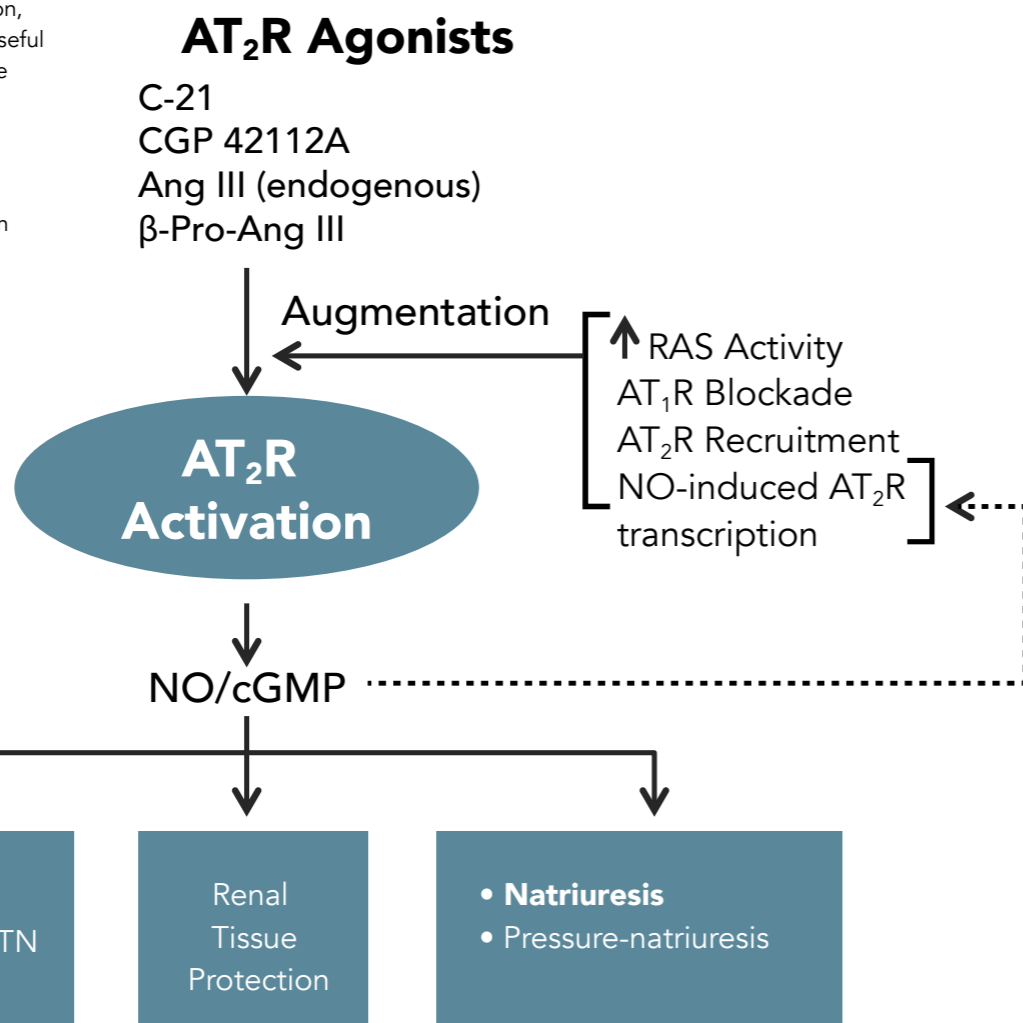
Schematic representation of the agents and conditions for and resulting actions of AT₂ receptor (AT₂R) activation in the kidney

Basic research to understand the underlying mechanisms of sodium retention by the kidneys is crucial for developing treatment for diseases such as hypertension

has recently been given a huge boost by the development of the mysterious 'Compound 21' – an artificial activator of AT₂R. Prof Carey's lab can make use of Compound 21 in two ways: firstly, they can use it experimentally to manipulate and characterise the function of AT₂R in the kidneys and its role in sodium excretion and reducing blood pressure. Secondly, Compound 21 may prove to be the first in a new class of therapeutic agents that could provide new treatments for hypertension and related conditions, either alone or in

combination with existing therapies such as angiotensin receptor blockers. In fact, in rats, the lab has shown that Compound 21 is as effective at preventing high blood pressure as it is at treating it.

The work of Prof Carey's lab shows that basic research to understand the molecular pathways underlying the workings of the human body can be crucial to developing potential treatments for, and even averting, disease.



Q&A

What are the problems and/or limitations of existing treatments for high blood pressure?

Three pharmacologic classes of antihypertensive agents are currently recommended as first-line for the treatment of hypertension: thiazide diuretics, calcium channel blockers and inhibitors of the renin-angiotensin system (RAS) (ACE inhibitors and ARBs). Approximately 13% of hypertensive patients do not achieve their blood pressure targets with all three classes taken together and are classified as having treatment resistant hypertension. The number of second line agents that are available to be added to bring blood pressure under control is limited, and we clearly need additional pharmacological classes to lower blood pressure in patients with refractory hypertension. Many of the current secondary agents are less effective and have more adverse side effects than the first line agents. Clearly, then, there is a need for additional pharmacological classes that provide complimentary actions to the first line agents. AT₂ receptor agonists likely provide complimentary actions for the inhibitors of the RAS and also an additional site of diuretic action within the kidney tubule.

What is the significance of angiotensin II's dual role within the RAS?

The dual role of angiotensin II is an important natural safety check on the RAS. Angiotensin II acting via AT₁ receptors increases sodium and fluid reabsorption in the kidney resulting in volume expansion and hypertension. Angiotensin II and especially its heptapeptide derivative angiotensin III acting via AT₂ receptors increases sodium and fluid excretion, lowering blood pressure. The beneficial action of angiotensin II at AT₂ receptors thus serves a protective function to limit abnormal increases in sodium, volume and

blood pressure induced by AT₁ receptor activation.

There seem to be many potential ways to use AT₂R to promote sodium excretion (through angiotensin receptor blockers, through nitric oxide, through new treatments such as compound 21, and I'm sure others). Which do you think is currently the most promising?

While inhibition of AT₁ receptors can increase AT₂ receptor activation, the best way of activating AT₂ receptors is direct activation with AT₂ receptor agonists. Indeed, direct AT₂ receptor activation improves sodium excretion and lowers blood pressure especially in animals that have already had their AT₁ receptors blocked.

Compound 21 is a potent, selective AT₂ receptor agonist that can be given orally and is ready for testing in humans based on experimental animal studies. In limited preliminary phase I trials, Compound 21 is safe to administer to humans. AT₂ receptors stimulate nitric oxide production, but since nitric oxide is a gas it cannot be administered to animals or humans; even if it could, targeting the correct and appropriate cellular and tissue distribution would be difficult to impossible in humans.

What do you find most exciting? Finding out how our bodies work? Or finding ways to treat them when they go wrong?

Both learning underlying mechanisms of disease and developing new treatments are important and exciting. However, one must know the underlying normal pathways and how they are deranged in disease in order to design new therapeutic approaches. Therefore, knowledge of the underlying mechanisms is prerequisite to introduction of new treatment.

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Detail

RESEARCH OBJECTIVES

Dr Carey's research focuses on determining new molecular targets for the treatment and prevention of hypertension. His lab's work has largely looked at the mechanisms of the renin-angiotensin system, particularly focusing on angiotensin II peptides.

FUNDING

• National Heart, Lung, and Blood Institute (NHLBI)

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BIO

Dr Carey received his medical degree from Vanderbilt University in 1965. He completed his medical residency at the New York Hospital-Cornell Medical Center and fellowships in endocrinology at Vanderbilt University and in hypertension at St. Mary's Hospital, London, England, before beginning his career in academic medicine at the University of Virginia in 1973. Between 1986 and 2002, he served as Dean of the University of Virginia School of Medicine.

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