Advance in understanding of blood pressure gene could lead to new treatments

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Research by scientists at UCL (University College London) has clearly demonstrated for the first time the structure and function of a gene crucial to the regulation of blood pressure. The discovery could be important in the search for new treatments for illnesses such as heart disease, the UK's biggest killer.

In a paper published online today in Nature Medicine, the team, led by Professor Patrick Vallance and Dr James Leiper, UCL Department of Medicine, reveal the role of the human gene dimethylarginine dimethylaminohydrolase (DDAH), showing that loss of DDAH activity disrupts nitric oxide (NO) production. NO is critical in the regulation of blood pressure, nervous system functions and the immune system.

The role of DDAH is to break down modified amino acids (Asymmetric dimethylarginine (ADMA) and monomethyl arginine (L-NMMA)) that are produced by the body and have been shown to inhibit NO synthase. These molecules accumulate in various disease states including diabetes, renal failure and pulmonary and systemic hypertension, and their concentration in plasma (the fluid component of blood) is strongly predicative of cardiovascular disease and death.

In a healthy human body, the majority of ADMA is eliminated through active metabolism by DDAH. Scientists have hypothesised that if DDAH function is impaired, NO production is reduced, and that this could be an important feature of increased cardiovascular risk.

To examine this pathway in more detail, the researchers deleted the DDAH gene in mice. These mice went on to develop hypertension, or high blood pressure. They also designed specific inhibitors (small molecules) which bind to the active site of human DDAH. These small molecule inhibitors also induced hypertension in mice, confirming the importance of DDAH in the regulation of blood pressure.

Dr Leiper, UCL Medicine, said: “These genetic and chemical approaches to disrupt DDAH showed remarkably consistent results, and provide compelling evidence that loss of DDAH function increases the concentration of ADMA and thereby disrupts vascular NO signalling.

“There has been considerable scientific interest in this pathway and the role of ADMA as a novel risk factor, but so far there’s been little evidence to support the idea that it’s a cause of disease, rather than just a marker. Genes and their pathways are crucial to our understanding of cardiovascular disease and a better understanding of DDAH-1 could lead to important new treatments.

“It could help us to establish if genetic variation predisposes certain people to these diseases, or whether environmental factors exert some of their effects through modulation of DDAH activity.

“Our research also shows that this pathway could be harnessed therapeutically to limit production of NO in certain situations where too much nitric oxide is a bad thing; for example, hypotension and septic shock. These are some of the biggest problems in intensive care medicine and there is a huge unmet need for drug treatments.”

The study, which was carried out at UCL’s Rayne Institute, was funded by grants from the British Heart Foundation, the Wellcome Trust and the Medical Research Council.

Professor Jeremy Pearson, Associate Medical Director of the British Heart Foundation, said:

"The unexpected finding in the 1980s that a simple gas, nitric oxide (NO), is made by cells in the blood vessel wall and is a powerful control of blood vessel relaxation led to the award of the Nobel Prize in 1998 to its discoverers.

"More recently, there has been increasing evidence that impairment of NO production is likely to be an important factor in the development of heart and circulatory disease, but the mechanisms responsible are not fully understood.

"This study suggests for the first time that the loss of the activity of the enzyme DDAH-1 leads to reduced NO production and may cause heart and circulatory disease. These findings are likely to be important in the search for new ways to optimise the health of our blood vessels."

Source: University College London