Researchers' discovery may lead to hypertension treatment

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Frank Schroeder inserts a natural product sample into a nuclear magnetic resonance spectrometer in the Department of Chemistry and Chemical Biology. NMR spectroscopy has evolved into the most important tool for identifying new biologically active compounds. Credit: Jason Koski

For more than 40 years, researchers have suspected there must be a natural hormone that could safely flush sodium out of the body and could be harnessed to develop more effective and safer treatments for high blood pressure, or hypertension. Currently, drugs that lower sodium levels all have serious side effects because they also reduce potassium levels.

Researchers at Cornell and the Boyce Thompson Institute for Plant Research (BTI) have used a new technique and identified a hormone from human urine -- a xanthurenic-acid derivative -- that seems able to

do the job. The discovery opens the door to developing novel medications to control sodium levels and treat hypertension.

Frank Schroeder, an assistant scientist at BTI and co-author of the paper, which appeared in a recent issue of *Proceedings of the National Academy of Sciences*, developed a new technique for analyzing complex mixtures of small molecules, making it possible to finally identify the hormone.

Prior to the discovery, researchers knew that a human steroid called aldosterone activates the kidney to reabsorb sodium and excrete potassium, which led them to suspect that there must be another hormone that would trigger the kidney to do the opposite: excrete sodium and reabsorb potassium. Many had tried to find such a hormone in human urine, but urine contains a mix of hundreds of molecules, and the correct one could not be isolated, probably because the suspected hormone breaks down easily during traditional chemical analysis.

Most researchers had given up searching for this "holy grail" of kidney hormones, until, in 2003, a private company, Naturon Corp., contacted Schroeder, then a research associate at Cornell and Harvard Medical School.

To do the job, Schroeder developed an approach based on nuclear magnetic resonance (NMR) spectroscopy of partially purified urine. Traditionally, NMR spectroscopy, arguably the most powerful tool chemists use to determine the structures of unknown compounds, has only been used for the analysis of purified compounds. Schroeder's approach allows NMR to identify compounds without isolating them, for example in a complex mixture such as partially fractionated urine. The technique revealed three completely new compounds, each of which was subsequently synthesized and injected into rats. The rats' urine was then monitored.

Two of the identified compounds, both derivatives of a common metabolite xanthurenic-acid, raised sodium levels in the rat's urine but kept potassium levels constant. Schroeder said that while aldosterone (which does the opposite) is a steroid hormone, this newly discovered molecule is structurally more similar to such amino acid-derived neurotransmitters as dopamine and serotonin and, therefore, may also play other roles in the body.

"Now, we want to know what other functions these compounds have and whether they directly influence blood pressure," said Schroeder.

Source: Cornell University