# OHSU researchers identify master switch that regulates blood pressure

November 1 2007

A team of Oregon Health & Science University researchers studying a rare form of hypertension has identified the mechanism by which they believe a protein complex in the kidney operates as a master switch that regulates blood pressure, a finding that has broad implications for the treatment of more common forms of hypertension.

The team led by David H. Ellison, M.D. – whose findings are described in a paper being published today (NOV. 1) in the Journal of Clinical Investigation – likens the switch to a rheostat that modulates the balance of salt and potassium in the kidney, thereby raising or lowering blood pressure.

When the switch malfunctions, the group suggests, high blood pressure or hypertension occurs, as it does when certain mutations in the WNK kinase protein complex are present. Those genetic defects cause a disease called familial hyperkalemic hypertension (FHHt), also called pseudohypoaldosteronism type 2 or Gordon's syndrome. The OHSU group and others have focused on FHHt, which is rare, in a search for clues to how blood pressure is regulated in the more common form of high blood pressure, known as essential hypertension, often labeled the silent killer.

Hypertension affects at least 50 million Americans and untold millions around the world and is a major cause of heart attacks, strokes and kidney failure. The root cause is unknown in 95 percent of cases. If the study's conclusions are borne out in further research, they can lead to

better targeted and more effective drugs for the disease, said Ellison, a professor of medicine in the OHSU School of Medicine and head of its Division of Nnephrology and Hypertension.

“It is not widely understood by the general public that hypertension is most often a kidney disease,” said Ellison. “If we can figure out the ways the kidney adjusts salt excretion, we can devise methods to prevent hypertension, cure it or design better treatments for it. Our findings in this study get us a step closer, we think.”

Ellison and his colleagues, Chao-Ling Yang, M.D., and Xiaoman Zhu, M.D., M.S., focused in the study on the complex interactions between the WNK1, WNK3 and WNK4 kinases in regulating NCC, a protein that normally keeps salt in the body. They explain for the first time that WNK 3 plays a key role in this process and that none of the WNK kinases act alone but function as a unit.

“These WNKs form a protein signaling complex,” said Ellison. “All three WNKs talk to each other. Only when you understand how they work together and talk to each other can you understand the real biology of the disease. The complex acts as a rheostat-controlled amplifier that modulates the activity of NCC, the salt transporter gene, in response to physiological needs. The disease really is caused by a glitch in communications between the different WNKs regulating NCC.”

Protein kinases constitute one of the largest human gene families and are key regulators of cell function. There are 518 of them – referred to as the human kinome – and they coordinate a wide variety of complex biological functions. The WNK kinases, which were discovered in 2000, have been a subject of intense interest among medical researchers since 2001 when a group at the Yale University School of Medicine found a link between this class of kinases and FHHt. Ellison and his group subsequently found that mutations in WNK1 and WNK4 cause this

disease by modulating NCC activity.

The current OHSU study explains how aldosterone, a hormone produced in the adrenal gland, can have different effects on sodium and potassium balance at different times. The hormone sometimes increases salt absorption and at other times increases potassium excretion, but how it knows which role to play has been a mystery.

“We think the answer is the WNK kinases, which switch aldosterone from a sodium chloride (salt) -retaining hormone to a potassium-wasting hormone,” said Ellison. “When you inherit a mutation in one of the WNK kinases the switch gets turned in the wrong direction. The switching mechanism explains for the first time why eating a high potassium diet lowers blood pressure. High potassium not only stimulates aldosterone secretion but also modulates WNK kinase activity; together aldosterone and certain WNK kinases cause the kidney to rid itself of potassium rather than reabsorbing salt.”

The OHU study also breaks new ground in refining the explanation of how WNK mutations cause FHHt.

“We showed that the way the mutations cause the disease is with the participation of WNK3,” said Ellison. “Unlike WNK4, which inhibits NCC, the salt cotransporter, WNK3 has a stimulative effect. If there’s more WNK3, you’ll have more salt reabsorption, and if there’s more WNK4, you’ll have less. What also happens is that WNK4 normally inhibits WNK3, but mutant WNK4 blocks this effect, thereby generating more active WNK3, increasing salt transport and causing the disease.”

Source: Oregon Health & Science University