Researchers identify mediator of blood pressure regulation in the liver

January 26 2011

For 60 years, scientists have puzzled over the possibility of a hepatic osmoreceptor that influences blood pressure regulation. Now, researchers of the Max Delbruck Center for Molecular Medicine (MDC) Berlin-Buch, the Experimental and Clinical Research Center (ECRC) of the MDC and Charite and the Hannover Medical School (MHH) appear to have made a breakthrough discovery.

Dr. Stefan Lechner and Professor Gary R. Lewin (both of MDC), Professor Friedrich C. Luft (ECRC) and Professor Jens Jordan (ECRC; now MHH) have discovered a new group of sensory neurons in the mouse liver which mediates the regulation of blood pressure and metabolism. This peripheral control center outside of the brain is triggered simply by drinking water and leads to an elevation of blood pressure in sick and elderly people.

More than ten years ago Professor Jens Jordan, MD, then a research fellow at Vanderbilt University in Nashville, Tennessee, observed a phenomenon together with his colleagues, more or less by accident. Later, at the former Franz Volhard Clinic of the Charité in Berlin-Buch, Jens Jordan again observed that in patients with a damaged nervous system, blood pressure readings rose by as much as 50 mm Hg if the patients drank a half liter of water all at once. "In young people whose sympathetic nervous system was stimulated by drugs, water intake also caused blood pressure levels to rise," said Professor Friedrich C. Luft of the ECRC. "Even in healthy older people, water drinking triggers a regulator for blood pressure." The two clinicians invited neuroscientists

at MDC to collaborate with them and started a joint research project.

For 60 years researchers have suspected that there must also be a control center for the body's self-regulation located outside of the brain. Motivated by findings of recent studies, the researchers in Berlin-Buch therefore looked for sensory neurons specifically in organs peripheral to the central nervous system that would detect body changes caused by water intake and would thus be able to activate a regulator which in old and sick people causes blood pressure to rise and which stimulates metabolism in healthy young people.

"In this entire process, osmolality plays a key role," explained Dr. Stefan Lechner, a member of Professor Lewin's research group. "It is the measure of the body's water balance. And it indicates how many molecules are dissolved in a liter of fluid. Each species has a characteristic set point for osmolality, which depends to a great extent on the immediate living conditions. We wanted to know how deviations of osmolality are able to activate a regulator."

The researchers observed in the mouse model that specific neurons in the liver react actively to water intake. The water the mice drink is absorbed in the small intestine and reaches the blood system via the liver. Due to the sudden water intake, the osmolality in the blood vessels of the liver falls under its set-point value. This deviation is registered by sensory neurons in the liver, the so-called osmoreceptors, as the researchers could now demonstrate. They found that the osmoreceptors transform the information into an electrical signal, which in turn triggers a reflex and stimulates the hepatic blood vessels to raise blood pressure.

Ion Currents Help to Elucidate the Mechanisms

To study the activation of the osmoreceptors under realistic physiological conditions, the researchers stained this newly discovered

group of osmoreceptors in the liver with a dye. In their experiments they could thus show that after drinking water, even the slightest shifts of osmolality in the blood flowing through the liver activate nerve fibers in the liver and cause ion currents to flow. The ion currents were similar to those that can be measured in an ion channel located both in the central nervous system and in the internal organs (heart, liver, kidney, testicles, pancreas). This ion channel, abbreviated TRPV4, reacts very sensitively to changes and functions quasi as an osmoreceptor.

"The TRPV4 ion channel opens in just a few hundred milliseconds like the lens of a camera, letting the electrical signal through and thus activating a regulator," explained Dr. Stefan Lechner. "We were now interested in whether the TRPV4 ion channel is acting alone or whether it needs subunits to aid it, and we wanted to know how the whole thing works mechanically."

In further experiments, to elucidate the role and function of TRPV4 in this regulation process, the researchers studied mice in which the gene for the TRPV4 ion channel had been inactivated. After giving these knockout mice water to drink, they did not observe any activation of the osmoreceptors in the liver. No ion currents flowed and as a consequence, no reflex was triggered. The researchers concluded that the elevation of the blood pressure due to water intake must be associated with the presence of the TRPV4 ion channel.

Consequences for therapy

"We are now able to describe the characteristics of a completely new group of hepatic osmoreceptors on the molecular level, which in humans are possibly an extension of a very important regulating reflex," said Professor Lewin. "The research findings not only improve our understanding of the physiological role of osmoreceptors in mediating blood pressure, metabolism and osmolalic self-regulation, over the long

term they could also lead to new strategies in the treatment of diseases caused by the absence of the gene encoding the TRPV4 channel protein."

"The effect of drinking water on blood pressure regulation is already leading to therapeutic consequences in the daily routine of the hospital," Professor Jordan added. "We tell patients to drink water who, due to blood pressure regulation disorders, suffer from fainting attacks when standing. This alleviates the symptoms and at the same time we are able to reduce the amount of medication. Healthy people can also suffer fainting attacks when they stand for a long time or are otherwise under strain, e.g. when they donate blood. In many cases these can be avoided by drinking water. Our decade-long persistence in investigating osmolalic self-regulation has really paid off!"

More information: The molecular and cellular identity of peripheral osmoreceptors, *Neuron*, No. 69 (2) pp. 332-344.

Provided by Helmholtz Association of German Research Centres