

Pressemitteilung

Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch

Barbara Bachtler

05.04.2013

<http://idw-online.de/de/news526906>

Forschungsergebnisse
Biologie, Chemie, Medizin
überregional

MDC MAX-DELBRÜCK-CENTRUM
FÜR MOLEKULARE MEDIZIN
BERLIN-BUCH
IN DER HELMHOLTZ-GEMEINSCHAFT e.V.

MDC and FMP Researchers Identify Edema Inhibitor

Researchers of the Max Delbrück Center (MDC) and the Leibniz Institute of Molecular Pharmacology (FMP) in Berlin-Buch, Germany, have now detected a substance that can prevent the accumulation of fluid in body tissue and thus edema formation. The results of Dr. Jana Bogum (MDC/FMP) from the MDC research group led by Professor Walter Rosenthal and PD Dr. Enno Klußmann could be important in the future for the treatment of excessive fluid retention in patients with chronic heart failure. Using a novel approach, the researchers have also discovered a new molecular mechanism controlling water homeostasis in the kidneys (Journal of the American Society of Nephrology, doi:10.1681/ASN.2012030295)*.

Every day around 1 500 liters of blood flow through the kidneys. Of this total volume, the kidneys initially filter 180 liters of primary urine, which they concentrate to two liters and then excrete as the final urine. A key regulatory step of the concentration mechanism is the release of the hormone AVP (arginine-vasopressin) from the brain. This hormone triggers a multi-step signaling cascade in the kidneys which affects water channels (aquaporins) and in particular aquaporin-2. "The water channels, specifically aquaporin-2, and their redistribution play a key role in the regulation of the water balance," said Dr. Klußmann.

AVP, which is released from the brain upon thirst, induces aquaporin-2 located in the renal collecting duct principal cells to redistribute from the cell interior to the plasma membrane. The renal cells can then filter out the water from the primary urine flowing past the membrane via aquaporin-2. Dr. Klußmann explained: "To keep the renal cell from bursting and the body from dehydrating, the water is directed back via another group of water channels, aquaporin 3 and 4, into the bloodstream and body tissue. In contrast to aquaporin-2, these water channels are located in another domain of the plasma membrane in the renal principal cells and stay there permanently." Once the thirst is quenched, the levels of the hormone AVP are reduced and aquaporin-2 is shuttled back into the interior of the renal cell until it is needed again.

However, if the AVP level is too high, as is the case in patients with chronic heart failure, aquaporin-2 remains permanently in the plasma membrane of the renal principal cell and directs the water continuously from the primary urine into the renal collecting duct principal cells. These cells funnel the excess water into the body tissue. "This process contributes to edema," Dr. Klußmann said.

Discovery of how translocation of water channels can be inhibited
How can aquaporin-2 be prevented from settling permanently in the plasma membrane and thus triggering diseases or making them worse? Using a new research approach, the scientists were able to identify an inhibitor which prevents the translocation of the water channel aquaporin-2 into the cell membrane. At the same time they discovered a new regulatory mechanism of water homeostasis at the molecular level.

The researchers used "small molecules", low molecular weight organic compounds, which penetrate well into cells. They tested 17 700 such substances in renal cells and ultimately filtered out a substance that blocks the redistribution of

aquaporin-2 to the plasma membrane. The substance (4-acetyldiphyllin) prevents phosphorylation, an important biological and regulatory activation step. In particular, the compound prevents a phosphorylation reaction that is catalyzed by a protein termed protein kinase A. This protein is activated in the signaling cascade that is triggered by AVP in the renal principal cells. In the presence of 4-acetyldiphyllin protein kinase A cannot add a phosphate group to aquaporin-2, with the result that the water channels can no longer redistribute to the plasma membrane.

The new research findings may not only be of interest for the treatment of edema but also for the treatment of depression. Here, by contrast, medical researchers are seeking a way to shuttle aquaporin-2 to the plasma membrane of the renal principal cell, because lithium, which is often used to treat depression, prevents aquaporin-2 from redistributing to the plasma membrane, thus causing diabetes insipidus. If AVP is not released from the brain, or if the receptor for AVP in the renal cell is defective, this likewise results in diabetes insipidus, as Professor Rosenthal discovered several years ago. The affected individuals excrete 20 liters of urine every day. A similar effect, but not quite as drastic, is caused by alcohol. Drinking lots of beer causes the body to excrete large amounts of urine. The reason – alcohol prevents the brain from releasing the hormone AVP and thus prevents the redistribution of aquaporin-2 to the plasma membrane.

*Small molecule screening to reveal mechanisms underlying aquaporin-2 trafficking

Jana Bogum^{1,2,3}, Dorte Faust¹, Kerstin Zuhlke^{1,2}, Jenny Eichhorst², Marie C. Moutty^{1,2}, Jens Furkert², Adeeb Eldahshan¹, Martin Neuenschwander², Jens Peter von Kries², Burkhard Wiesner², Christiane Trimpert⁴, Peter M.T. Deen⁴, Giovanna Valentis⁵, Walter Rosenthal^{1,6} and Enno Klussmann¹

¹Max Delbrück Center for Molecular Medicine (MDC), Berlin, Germany

²Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin, Germany

³Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Germany

⁴Department of Physiology, RUNMC Nijmegen, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

⁵Department of General and Environmental Physiology, University of Bari, Italy

⁶Charité University Medicine Berlin, Germany

Contact:

Barbara Bachtler

Press Department

Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch

in the Helmholtz Association

Robert-Rössle-Straße 10

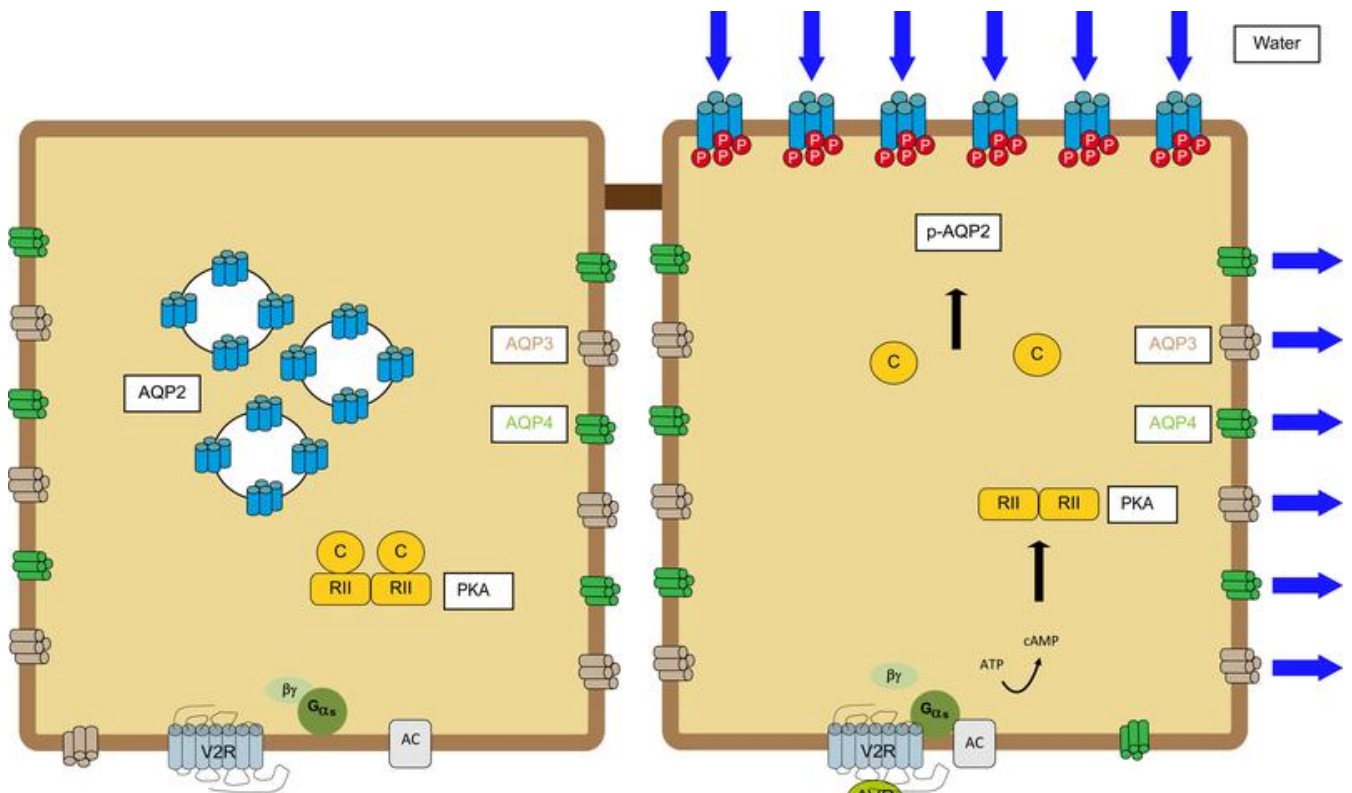
13125 Berlin, Germany

Phone: +49 (0) 30 94 06 - 38 96

Fax: +49 (0) 30 94 06 - 38 33

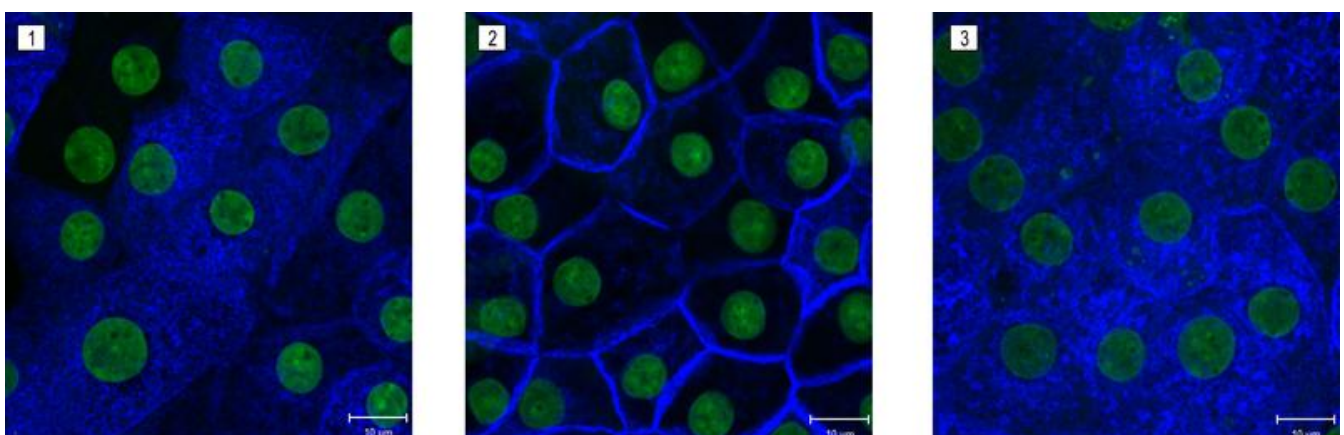
e-mail: presse@mdc-berlin.de

<http://www.mdc-berlin.de/>



Graphic of a renal cell with water channels (aquaporin-2, AQP2) in the cell (left image) and with aquaporin-2 in the plasma membrane (right image, above). For example, when a person is thirsty, the hormone AVP triggers a signaling cascade and thereby elicits the redistribution of the water channels from the cell interior to the plasma membrane. The cell then directs water from primary urine via other water channels (AQP3 and 4, Fig. on the right, the right side of the cell) into the bloodstream and tissues.

(Graphic: Enno Klußmann/ Copyright: MDC)



Renal principal cells with aquaporin-2 (blue) in the cell interior (image 1) and in the plasma membranes (image 2). The substance discovered by the MDC research group (4-acetyldiphyllin; image 3), prevents the redistribution of aquaporin-2 to the cell membrane. Nuclei are shown in green.

(Immunofluorescence microscopy: Jana Bogum, Kerstin Zühlke, Burkhard Wiesner, Jenny Eichhorst/ Copyright: MDC/FMP)

D