Multiple sclerosis -- antihypertensive drug ameliorate inflammation in the brain

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Researchers in Heidelberg and Stanford have discovered a new signalling pathway of brain cells that explains how widely used antihypertensive drugs could keep inflammation in multiple sclerosis (MS) in check. The peptide angiotensin not only raises blood pressure but also activates the immunological messenger substance TGF beta on a previously unknown communication pathway in the brain.

The study was conducted by Professor Lawrence Steinman at Stanford University in California together with the group of Professor Platten and published in the "Journal of Clinical Investigation". The Heidelberg team of researchers consisted of Dr. Tobias Lanz, lead author of the study and Professor Dr. Michael Platten, lead author of the previous study on that topic. Professor Platten is the senior consultant at the Department of Neurooncology at Heidelberg University Hospital and the head of the Helmholtz University Young Investigators Group "Experimental Neuroimmunology" at the German Cancer Research Center (DKFZ) in Heidelberg.

Angiotensin II is known as a molecule that regulates blood pressure. Drugs that block the angiotensin receptors, (AT1R blockers), are prescribed to millions of people to lower high blood pressure. These receptors have now also been found on numerous organs and cells that have nothing to do with regulating blood pressure, for example on the T cells of the immune system. These are immune cells that are involved in autoimmune reactions and chronic-inflammatory diseases such as MS. MS is characterized by multifocal areas of inflammation in the brain and

spinal cord that lead to paralysis and other neurological symptoms.

Paralysis resolved in an animal model

The scientists working with Professor Platten showed in a mouse model that angiotensin II promotes inflammation in the brain and spinal cord. When the angiotensin receptors, i.e. the sites where angiotensin docks onto cells and can develop its effect, were blocked by the orally administered blood pressure drug Candesartan, the inflammation decreased and the paralysis resolved.

"Since AT1R blockers are frequently prescribed for lowering blood pressure and have a proven safety profile, it is an obvious step to test them soon in MS patients," says Platten. "Of course, in research it is important to search for specific drugs with new molecular targets. But in our study, we show that approved medications can also be successfully studied for benefits in other diseases. The potential use of these generic drugs with a proven safety profile would also have a great impact on reducing healthcare costs."

Protective mechanism works only in the central nervous system

The researchers know that angiotensin transfers its information to the cell via an increase in the messenger substance Transforming Growth Factor beta (TGF beta). Such a "network pathway" between angiotensin and TGF beta was previously unknown in the brain. TGF beta can have completely opposite effects - on the one hand it regulates and alleviates inflammatory reactions, but in other situations it causes inflammation and promotes it. Which function the factor has depends on the surrounding tissue and the interaction with other messenger substances.

With respect to the whole body, TGF beta appears to protect the organism from inflammation and autoimmune diseases. Paradoxically however, blockage of TGF beta production in the brain leads to a reduction of inflammation and thus to an improvement in symptoms. "AT1R blockers prevent only the peak concentrations of TGF beta in the brain triggered by angiotensin, which are responsible for the inflammatory reaction. The baseline levels of TGF beta are not affected, so that the protective function for the rest of the body is apparently sustained," explained Platten.

More information: References: Angiotensin II sustains brain inflammation in mice via TGF-ß. TV Lanz, Z Ding, PP Ho, J Luo, AN Agrawal, H Srinagesh, R Axtell, H Zhang, M Platten, T Wyss-Coray, L Steinman. Journal of Clinical Investigation, 2010, online published July 12. Doi:10.1172/JCI41709

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