Inexpensive hypertension drug could be multiple sclerosis treatment

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Turning serendipity into science, researchers at the Stanford University School of Medicine have found a link, in mice and in human brain tissue, between high blood pressure and multiple sclerosis. Their findings suggest that a safe, inexpensive drug already in wide use for high blood pressure may have therapeutic value in multiple sclerosis, as well.

While neurology professor Lawrence Steinman, MD, senior author of the new study, cautioned that extensive clinical trial work is needed to determine if the drug, known as lisinopril, can do in humans what it does in mice, he is excited that "we were able to show that all the targets for lisinopril are there and ready for therapeutic manipulation in the multiple-sclerosis lesions of human patients. Without that, this would be just another intriguing paper about what's possible in the mouse."

The paper will be published online Aug. 17 by the Proceedings of the National Academy of Sciences.

The genesis for the paper can be traced to about seven years ago, when Steinman learned he had high blood pressure. His doctor put him on lisinopril, which is used by millions of people all over the world and has an excellent safety profile. Chagrined, Steinman went home and, researcher that he is, immediately did a Google search on the drug. (Steinman is a renowned multiple sclerosis investigator whose earlier work on the inflammatory features of the disease spurred development of a blockbuster class of anti-inflammatory multiple-sclerosis therapeutics. The drug natalizumab, marketed under the trade name

Tysabri, is one.)

Long ago, a glitch crept into Steinman's home computer: No matter what keywords he types into the search field, the computer automatically inserts the additional term, "multiple sclerosis." Thus, to his surprise, a list of medical literature popped up offering tantalizing, if vague, hints of a possible connection between multiple sclerosis and a fast-acting hormone, angiotensin, whose receptors abound on blood-vessel walls throughout the body.

In response to, say, a change in posture, angiotensin immediately causes blood vessels to constrict. "That raises your blood pressure so when you stand up to get out of a chair, you don't fall down and faint," said Steinman, who is also the George A. Zimmerman Professor in the medical school. But angiotensin overactivity causes chronic hypertension. Lisinopril controls blood pressure by blocking an enzyme that converts angiotensin's precursor into the active hormone. The drug also appears to have certain anti-inflammatory properties.

Multiple sclerosis is a chronic and occasionally lethal autoimmune disease in which the body's immune system mounts recurring assaults on the myelin sheathing of nerve cells in the brain. This causes nerves to malfunction and can lead to blindness and paralysis. Both multiple sclerosis and atherosclerosis involve inflammatory processes.

Eventually, Steinman and his colleagues decided to test the angiotensin/multiple-sclerosis relationship using modern scientific techniques. First, they examined the multiple-sclerosis lesions of brain samples from autopsied patients. In those lesions, well-established molecular-detection methods turned up significantly elevated levels of both the angiotensin receptor and the angiotensin-producing enzyme blocked by lisinopril.

Next, the investigators turned to an equally well-established animal model: a laboratory-bred strain of mouse that, after being immunized with a particular chemical, develops brain lesions very similar to those observed in multiple sclerosis. When, before immunization with the disease-triggering chemical, mice got lisinopril dosages equivalent to those prescribed for humans with high blood pressure, they didn't develop the paralysis characteristic of disease progression. Strikingly, if it was given after the mice developed full-blown symptoms, lisinopril reversed their paralysis.

The team also found that lisonopril administration reduced numerous molecular measures of inflammation that accompany multiple sclerosis in humans and its analog in the animal model. But, importantly, the drug didn't inhibit the mice's overall immune competence.

An additional observation was that lisinopril administration triggered proliferation of an important class of immune cells, called regulatory T cells, that prevent autoimmune diseases by dialing down the activity of other immune cells erroneously targeting cells and tissues that should be left alone. It's likely, Steinman said, that this proliferation was a key component in the protection provided by the drug, as an infusion of regulatory T cells from mice that had been given lisinopril was sufficient to prevent or reverse the disease process in mice that had been given none.

Steinman's results have major public-health implications, said Marc Feldmann, an Imperial College London immunologist who is familiar with the study but did not participate in it. He noted that the current therapies for multiple sclerosis (including Tysabri) are pricey monoclonal antibodies, costing tens of thousands of dollars annually for each patient treated. "If multiple-sclerosis patients can be treated with lisinopril at something like 1 percent of the price of treatment with Tysabri, then far more patients will receive adequate therapy, at a

substantially lower cost to those paying for it," Feldmann said.

Source: Stanford University Medical Center