Blood pressure drug protects against symptoms of multiple sclerosis in animal models

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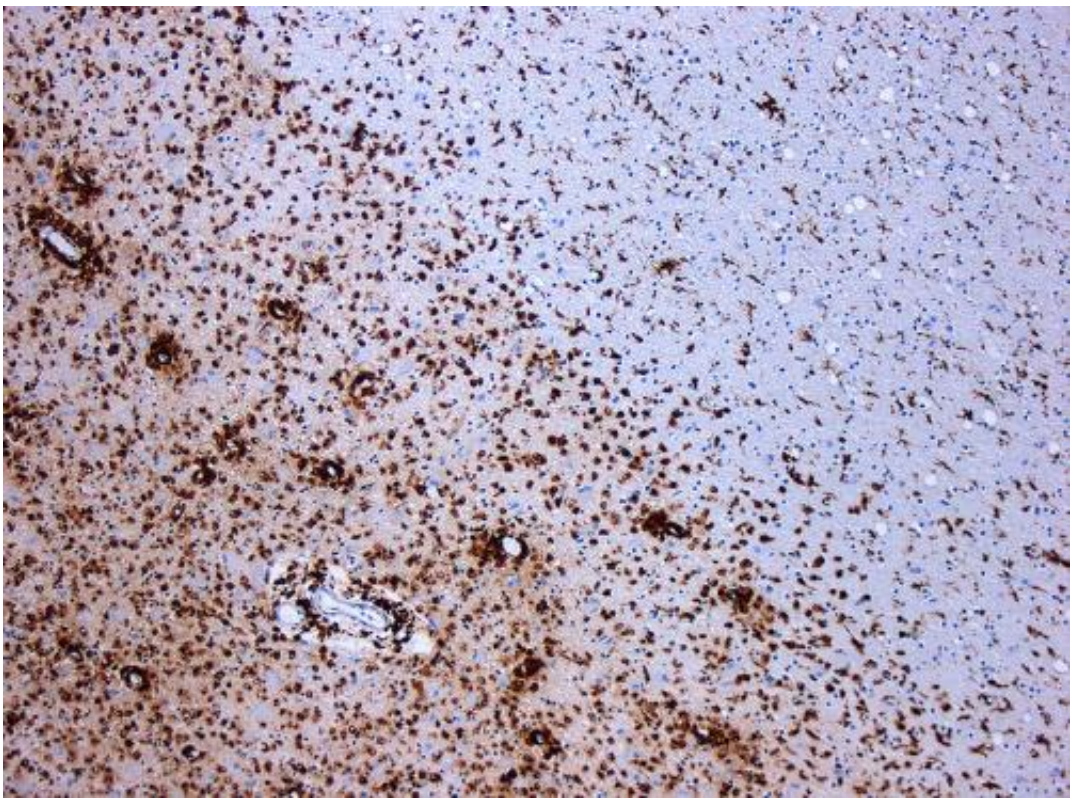

Demyelination by MS. The CD68 colored tissue shows several macrophages in the area of the lesion. Original scale 1:100. Credit: CC BY-SA 3.0 Marvin 101/Wikipedia

An FDA-approved drug for high blood pressure, guanabenz, prevents

myelin loss and alleviates clinical symptoms of multiple sclerosis (MS) in animal models, according to a new study. The drug appears to enhance an innate cellular mechanism that protects myelin-producing cells against inflammatory stress. These findings point to promising avenues for the development of new therapeutics against MS, report scientists from the University of Chicago in *Nature Communications* on March 13.

"Guanabenz appears to enhance the cell's own protective machinery to diminish the loss of myelin, which is the major hallmark of MS," said senior study author Brian Popko, PhD, Jack Miller Professor of Neurological Disorders at the University of Chicago "While there have been many efforts to stimulate re-myelination, this now represents a unique protective approach. You don't have to repair the myelin if you don't lose it in the first place."

Multiple sclerosis is characterized by an abnormal immune response that leads to inflammation in the brain and the destruction of myelin - a fatty sheath that protects and insulates nerve fibers. MS is thought to affect more than 2.3 million people worldwide and has no known cure.

Popko and his colleagues have previously shown that oligodendrocytes, the brain cells which produce myelin, possess an innate mechanism that responds to stressors such as inflammation. It temporarily shuts down almost all normal protein production in the cell and selectively increases the production of protective proteins. When this mechanism is malfunctioning or overloaded - by the chronic inflammation seen in MS, for example - oligodendrocyte death and demyelination is significantly increased.

A recent study found evidence that guanabenz, a drug approved for oral administration for hypertension, enhances this stress response pathway independent of its anti-hypertension actions. To test the suitability of guanabenz as a potential treatment for MS, Popko and his team exposed

cultured oligodendrocyte cells to interferon gamma - a molecule that increases inflammation - resulting in greatly increased myelin loss and cell death.

Treating these cells with guanabenz prevented myelin loss and restored cell survival to near normal levels. Oligodendrocytes that were not exposed to interferon gamma were unaffected by guanabenz, suggesting that it enhances only an active stress response pathway.

The team then tested the drug on multiple mouse models of MS. When treated with guanabenz, mice that are genetically engineered to express high amounts of interferon gamma in their brains were protected against oligodendrocyte and myelin loss. Treated mice retained several times more myelination and oligodendrocytes than untreated mice.

To study a chronic model of MS, the researchers immunized mice with a component of myelin, triggering an immune response against myelin similar to MS in humans. Clinical symptoms developed, but guanabenz administered a week after immunization significantly delayed the onset of these symptoms and reduced peak severity. Treatment also prevented around 20 percent of mice from developing symptoms at all.

To study the suitability of guanabenz as a therapeutic after MS symptoms have already appeared and peaked, the researchers used a mouse model in which symptoms relapse and remit - cycling from high severity to low severity to high again over time. They administered guanabenz immediately after symptoms peaked, and found a nearly 50 percent reduction in severity during the next relapse cycle.

"Human MS predominantly follows a relapsing-remitting pattern," said co-author Sharon Way, PhD, a National MS Society Postdoctoral Fellow at the University of Chicago. "Our hope is that this approach would provide protection against future relapses by making them milder and

less frequent."

The team confirmed that guanabenz acts by temporarily blocking the reactivation of a protein known as eukaryotic translation initiation factor 2 (eIF2α). When deactivated, eIF2α initiates the stress response pathway. Blocking its reactivation results in a prolonged stress response and provides protection against cell death. The researchers hypothesize that guanabenz stimulates a protective cascade - because fewer oligodendrocytes die, less immune cells are recruited to the brain, which results in a decreased inflammatory response and preservation of myelin levels.

The Myelin Repair Foundation, which funded this work as part of a multi-institutional effort to accelerate research and development of treatments for MS, has entered into a cooperative agreement with the National Institutes of Health to assess guanabenz as a therapeutic candidate in MS clinical studies.

"Guanabenz will probably not be a standalone drug, but we hope that it can be developed for use in combination with other medications," Popko said. "Some current treatments can have severe side effects - for example dangerous infections in the brain. It would be of tremendous benefit for patients to have effective, less-risky therapies.

More information: Pharmaceutical integrated stress response enhancement protects oligodendrocytes and provides a potential multiple sclerosis therapeutic, *Nature Communications*, 2015.

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