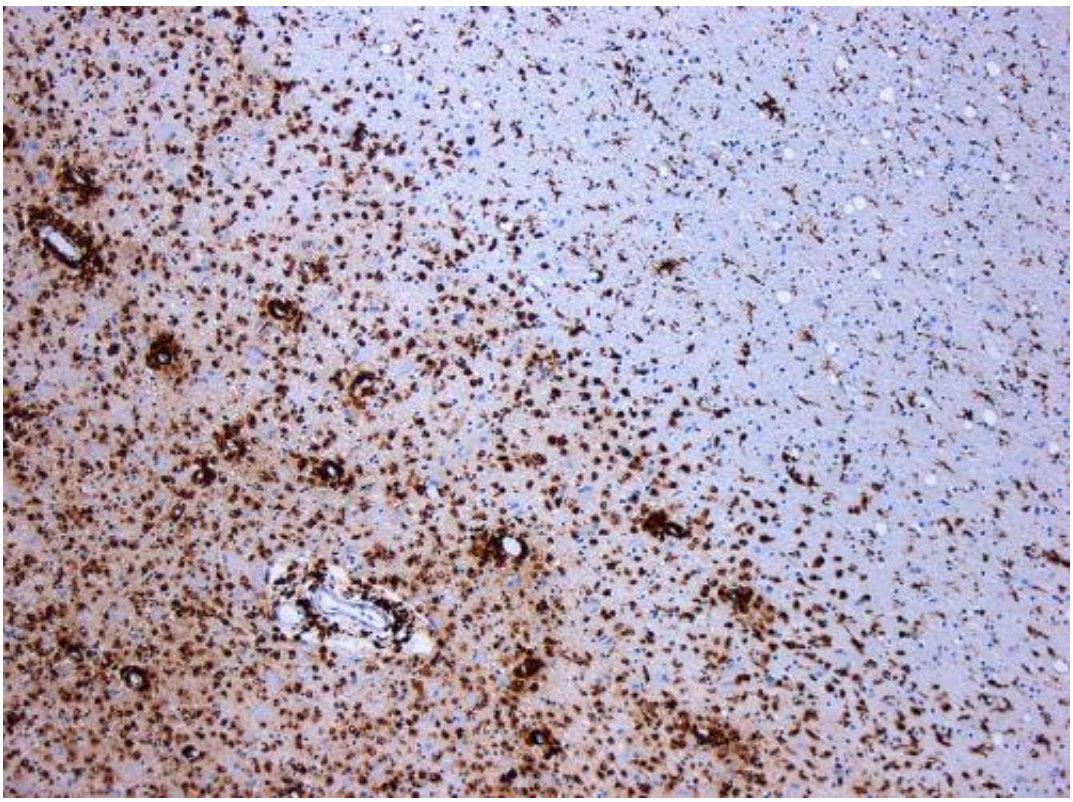
Basic research shows that drug used to treat multiple sclerosis may have beneficial effects on memory

May 28 2014, by Eric Peters



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

(Medical Xpress)—Virginia Commonwealth UniversitySchool of

Medicine researchers have uncovered a new mechanism of action of fingolimod, a drug widely used to treat multiple sclerosis: elimination of adverse or traumatic memories.

The findings shed light on how the drug works on the molecular level – something that has not been well understood until now.

Fingolimod, or FTY720, which is the first orally available drug for treatment of multiple sclerosis, works by suppressing the immune system. Fingolimod is a prodrug that is phosphorylated in the body to its active form, FTY720-phosphate.

In a study published by the *Nature Neuroscience* journal on May 25 as an Advanced Online Publication, researchers used a mouse model to show that fingolimod accumulates in the brain and inhibits histone deacetylases, which are enzymes important to regulate gene expression. The team observed an increased expression of a limited number of genes important for certain memory processes. Fingolimod acted similarly to the natural signaling lipid, sphingosine-1-phosphate, which it closely resembles.

"Our work suggests that some of the beneficial effects of FTY720/fingolimod that are not well understood might be mediated by this new activity that we have discovered," said first author Sarah Spiegel, Ph.D., an internationally renowned researcher and professor and chair of the Department of Biochemistry and Molecular Biology in the VCU School of Medicine.

"It will be important in the future to determine whether this prodrug can reduce loss of cognitive functions and can erase adverse memories," she said.

Spiegel added that other histone deacetylase inhibitors have long been

used for treatment of psychiatric and neurological disorders, yet the mechanism of their effectiveness is not fully understood.

"FTY720/fingolimod may be a useful adjuvant therapy to help stop aversive memories such as in post-traumatic stress disorder and other anxiety disorders," Spiegel said.

"The work has not been extended to show effectiveness in humans at this time. We are still working to fully understand the molecular underpinnings of the drug and its link to memory," she said.

The work is based on previous findings by Spiegel's group that were published in *Science* in 2009. They had reported that sphingosine-1-phosphate formed in the nucleus of cells is a natural inhibitor of histone deacetylases and a regulator of gene expression.

More information: "Active, phosphorylated fingolimod inhibits histone deacetylases and facilitates fear extinction memory." Nitai C Hait, et al. Nature Neuroscience (2014) DOI: 10.1038/nn.3728. Received 07 March 2014 Accepted 25 April 2014 Published online 25 May 2014

Provided by Virginia Commonwealth University