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Strategy developed to improve delivery of medicines to the brain

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New research offers a possible strategy for treating central nervous system diseases, such as brain and spinal cord injury, brain cancer, epilepsy, and neurological complications of HIV. The experimental treatment method allows small therapeutic agents to safely cross the blood-brain barrier in laboratory rats by turning off P-glycoprotein, one of the main gatekeepers preventing medicinal drugs from reaching their intended targets in the brain.

The findings appeared online Sept. 4 in the Proceedings of the National Academy of Sciences, and is the result of a study from scientists at the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health.

"Many promising drugs fail because they cannot cross the blood-brain barrier sufficiently to provide a therapeutic dose to the brain," said David Miller, Ph.D., head of the Laboratory of Toxicology and Pharmacology at NIEHS, and leader of the team that performed the study. "We hope our new strategy will have a positive impact on people with brain disorders in the future."

In a two-pronged approach, the research team first determined that treating rat brain capillaries with the multiple sclerosis drug marketed as Gilenya (fingolimod) stimulated a specific biochemical signaling pathway in the blood-brain barrier that rapidly and reversibly turned off P-glycoprotein. Team members then pretreated rats with fingolimod, and administered three other drugs that P-glycoprotein usually transports

away from the brain. They observed a dramatic decline in P-glycoprotein transport activity, which led to a threefold to fivefold increase in brain uptake for each of the three drugs.

Ronald Cannon, Ph.D., is a staff scientist in the Miller lab and first author on the paper. He said one of the burning questions the team wants to tackle next is to understand how the signaling system turns off P-glycoprotein. He equates the mechanism to what happens when a person flips a light switch.

"If you physically turn off a light using the button on the wall, the light will go out because the electrical current to the light bulb has been interrupted," Cannon explained. "But what happens when the signaling pathway shuts down P-glycoprotein? Does it bring in another protein to bind to the pump, take away its energy source, modify the structure of the pump, or something else?"

Cannon said the paper's findings open a new way of thinking regarding targets for drug design, a thought that is emotionally gratifying for him and many other researchers whose scientific discoveries generally don't directly translate into helping people with illnesses.

"Although much more research needs to be done, delivering therapeutics to the central nervous system is one of the final frontiers of pharmacotherapy, Cannon added."

More information: Cannon RE, Peart JC, Hawkins BT, Campos CR, Miller DS. 2012. Targeting blood-brain barrier sphingolipid signaling reduces basal P-glycoprotein activity and improves drug delivery to the brain. *Proc Natl Acad Sci* U S A; doi:10.1073/pnas.1203534109 [Online 4 September 2012].