A 'switch' in Alzheimer's and stroke patient brains that prevents the generation and survival of neurons

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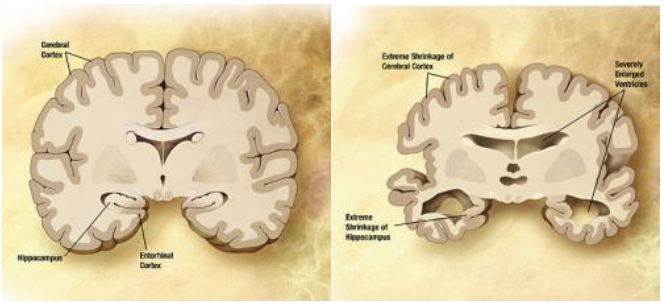

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

A new study by researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham) has identified a chemical "switch" that controls both the generation of new neurons from neural stem cells and the survival of existing nerve cells in the brain. The switch that shuts off the signals that promote neuron production and survival is in abundance in the brains of Alzheimer's patients and stroke victims. The study, published July 3 in *Cell Reports*, suggests that chemical switch, MEF2, may be a potential therapeutic target to protect against neuronal loss in a variety of neurodegenerative diseases, such as Alzheimer's, Parkinson's and autism.

"We have shown that when nitric oxide (NO)—a highly reactive free radical—reacts with MEF2, MEF2 can no longer bind to and activate the genes that drive neurogenesis and neuronal survival," said Stuart Lipton, M.D., Ph.D., director and professor in the Neuroscience and Aging Research Center at Sanford-Burnham, and a practicing clinical neurologist. "What's unique here is that a single alteration to MEF2 controls two distinct events—the generation of new neurons and the survival of existing neurons," added Lipton, who is senior author of the study.

In the brain, transcription factors are critical for linking external stimuli to protein production, enabling neurons to adapt to changing environments. Members of the MEF2 family of transcription factors have been shown to play an important role in neurogenesis and neuronal survival, as well as in the processes of learning and memory. And, mutations of the MEF2 gene have been associated with a range of neurodegenerative disorders, including Alzheimer's and autism.

The process of NO-protein modifications—known as S-nitrosylation—was first described by Lipton and collaborators some 20 years ago. S-nitrosylation has important regulatory functions under normal physiological conditions throughout the body. However, with aging, environmental toxins, or stress-related injuries, abnormal S-nitrosylation reactions can occur, contributing to disease pathogenesis.

"Our laboratory had previously shown that S-nitrosylation of MEF2 controlled neuronal survival in Parkinson's disease," said Lipton. "Now we have shown that this same reaction is more ubiquitous, occurring in other neurological conditions such as stroke and Alzheimer's disease. While the major gene targets of MEF2 may be different in various diseases and brain areas, the remarkable new finding here is that we may be able to treat each of these neurological disorders by preventing a common S-nitrosylation modification to MEF2.

"The findings suggest that the development of a small therapeutic molecule—one that can cross the blood-brain barrier and block S-nitrosylation of MEF2 or in some other way increase MEF2 transcriptional activity—could promote new brain cell

growth and protect existing cells in several neurodegenerative disorders," added Lipton.

"We have already found several such molecules in our high-throughput screening and drug discovery efforts, so the potential for developing new drugs to attack this pathway is very exciting," said Lipton.

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