Statins have unexpected effect on pool of powerful brain cells

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Cholesterol-lowering drugs known as statins have a profound effect on an elite group of cells important to brain health as we age, scientists at the University of Rochester Medical Center have found. The new findings shed light on a long-debated potential role for statins in the area of dementia.

Neuroscientists found that statins, one of the most widely prescribed classes of medication ever used, have an unexpected effect on brain cells. Researchers looked at the effects of statins on glial progenitor cells, which help the brain stay healthy by serving as a crucial reservoir of cells that the brain can customize depending on its needs. The team found that the compounds spur the cells, which are very similar to stem cells, to shed their flexibility and become one particular type of cell.

The new findings come at a time of increasing awareness among neurologists and cardiologists of the possible effects of statins on the brain. Several studies have set out to show that statins provide some protection against dementia, but the evidence has been inconclusive at best. Meanwhile, there is some debate among physicians about whether statins might actually boost the risk of dementia. The new research published in the July issue of the journal *Glia* by Steven Goldman, M.D., Ph.D., and first author Fraser Sim, Ph.D., provides direct evidence for an effect of statins on brain cells.

"There has been a great deal of discussion about a link between statins and dementia, but evidence either way has been scant," said Goldman, a

neurologist who led the team. "This new data provides a basis for further exploration.

"These findings were made through experiments done in cell culture using human brain cells and exposing them to doses of statins used widely in patients. But this research was not done in people. There are a great number of questions that need to be explored further before anyone considers changing the way statins are used," Goldman added.

Goldman's team is recognized as a leader identifying and directing the molecular signals that direct the development of stem cells and their daughter cells, known as progenitor cells. In this study, Sim ran a genomic screen to see which genes are more active in these cells compared to other brain cells. Sim and Goldman found several related to cholesterol, including the enzyme HMG-CoA reductase, which is central to making cholesterol and is the main target of statins.

"It was quite surprising that the cholesterol-signaling pathways are so active in these cells," Goldman said. "Since such signaling is blocked with compounds used literally by millions of patients every day, we decided to take a closer look."

The team measured the effects of two widely used statins, simvastatin and pravastatin, on glial progenitor cells, which can become either astrocytes or oligodendrocytes. The team looked at progenitor cells from 16 patients who had brain tissue removed during surgery to treat epilepsy, tumors, or vascular problems.

Scientists found that both compounds, when used at doses that mimic those that patients take, spur glial progenitor cells to develop into oligodendrocytes. For example, in one experiment, they found about five times as many oligodendrocytes in cultures of human progenitor cells exposed to pravastatin compared to cultures not exposed to the

substance. Similarly, they found that the number of progenitor cells was just about one-sixth the level in cultures exposed to simvastatin compared to cultures not exposed to the compound.

To understand the process, think of a baseball team raising a group of great young prospects. They run fast, they throw hard, they hit well. Most teams will tailor their players to the positions the team needs – a few pitchers, for instance, and several batters. Any team that suddenly found itself with all pitchers or all hitters would be ill prepared to compete.

The Rochester team discovered that statins essentially push most of the raw talent in one direction.

Scientists don't really know the long-term effects of such a shift. Physicians are looking at statins as a possible treatment for multiple sclerosis, where the myelin coating that covers nerve cells in the central nervous system is damaged. Myelin is produced by oligodendrocytes – so spurring the development of oligodendrocytes might provide one way to reduce or repair the damage seen in M.S.

But the body maintains a pool of uncommitted glial progenitor cells for a reason. The body normally turns to that reservoir of cells when it needs to repair damage from a variety of causes, such as an infection, hemorrhage, a serious blow to the head, or inflammation within the brain, such as in patients with multiple sclerosis. No one knows the consequences if such cells weren't available when needed, though increased cognitive impairment might be one possibility.

"These are the cells ready to respond if you have a region of the brain that is damaged due to trauma, or lack of blood flow like a mini-stroke," said Sim, assistant professor of Neurology. "Researchers need to look very carefully at what happens if these cells have been depleted

prematurely."

Glial progenitor cells are distributed throughout the brain and, according to Sim, make up about 3 percent of our brain cells. While true stem cells that can become any type of cell are very rare in the brain, their progeny, progenitor cells, are much more plentiful. They are slightly more specialized than stem cells but can still develop into different cell types.

The work may be relevant to drugs commonly used by diabetics as well. That's because the team discovered that a signaling molecule called PPAR gamma is central to the effect of statins on glial progenitor cells. When PPAR gamma was blocked, the statins no longer had the effect. Since PPAR gamma is the main target of diabetes medications such as Avandia and Actos, which trigger the molecule, Goldman said it's likely that those medications have the same effect on progenitor cells. He also noted that many patients are on both diabetes drugs and statins, which could increase the effect.

"Our results suggest the need for awareness of the possible toxicities accruing to long-term statin use, and identify one such potential toxicity, the premature differentiation and attendant long-term depletion of oligodendrocyte progenitor cells of the adult brain," conclude the authors in their *Glia* paper.

Source: University of Rochester Medical Center