New model suggests feared side effect of Alzheimer's drugs is unlikely

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The first trial of a new model for testing Alzheimer's treatments has reassured researchers that a promising class of drugs does not exacerbate the disease if treatment is interrupted.

Scientists at Washington University School of Medicine in St. Louis and Merck & Co. Inc studied the effects of a class of drugs known as gamma secretase inhibitors. Researchers had worried that these drugs might cause a build-up of proteins linked to Alzheimer's disease and that this build-up could be unleashed in a surge when patients went off the medications. But the new study suggests that they do not.

"This is important because it eases some concerns that have been raised about this potentially useful class of medications," says senior author Randall Bateman, MD, a Washington University neurologist who treats patients at Barnes-Jewish Hospital.

The findings appeared recently in *The* Journal of Neuroscience.

Gamma secretase inhibitors block proteins involved in the creation of amyloid beta, the main ingredient of Alzheimer's plaques. Patients cannot continuously take these drugs because nonstop inhibition of the gamma secretase enzyme has harmful side effects. One study had revealed that when physicians temporarily halted used of the inhibitors in humans, amyloid beta levels in the blood surged. An animal study suggested cessation of treatment also led to an amyloid beta increase in the brain. Researchers have been watching for similar effects in current human clinical trials of gamma secretase inhibitors.

The new study used a technique for measuring production and clearance of amyloid beta developed by Bateman and his colleagues at Washington University. It was the first time stable-isotope-labeling kinetics (SILK) was used in primates.

In a preliminary assessment of normal amyloid beta production and clearance rates, scientists found that the amyloid beta turnover in the subjects, a group of rhesus macaques, was 10 percent per hour.

"This is much closer to the human turnover rate of 8 percent per hour than other animal models," says co-first author Kristin Wildsmith, PhD, a postdoctoral research scholar. "That means we can be more confident that preclinical testing of Alzheimer's treatments in this model will produce results that accurately predict what the effects will be in humans."

When scientists gave the animals gamma secretase inhibitors, SILK testing showed that the drugs reduced production of amyloid beta. When researchers stopped inhibitors, blood levels of amyloid beta increased above normal levels. But SILK showed there was no increase in amyloid beta levels in the central nervous system.

"It appears that blood testing may not be the best way to monitor amyloid beta levels in the central nervous system," says Bateman, who says that the source of amyloid beta in the blood is unclear.

Brain amyloid beta is a fragment of a larger protein regularly disassembled as a part of normal metabolism. Wildsmith showed that treatment with gamma secretase inhibitors shifts this disassembly from an amyloid-beta-producing path to an alternative pathway that precludes the production of amyloid beta.

More information: Cook JJ, Wildsmith KR, Gilberto DB, Holahan MA, Kinney GG, Mathers PD, Michener MS, Price EA, Shearman MS, Simon AJ, Wang JX, Wu G, Yarasheski KE, Bateman RJ. Acute gamma-secretase inhibition of nonhuman primate CNS shifts amyloid precursor protein (APP) metabolism from amyloid-beta production to alternative APP fragments without amyloid-beta

rebound. Journal of Neuroscience 2010 30: 6743-6750.

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