Scientists make link between brain acid and cognition

August 2 2010, By Meredith Cohn

Almost anyone who has faced a test or a deadline probably wished there was a smart pill to pop. New research suggests that this may eventually be possible.

University of Maryland scientists have linked a brain compound called kynurenic acid to cognition, potentially opening the door to development of a drug that could aid learning in healthy people -- and in those with disorders such as Alzheimer's disease.

"Workers might want to take a pill so they can work harder, and college students would be interested because they already are taking amphetamine-type pills so they will be sharper," said Robert Schwarcz, professor of psychiatry, pediatrics and pharmacology and experimental therapeutics at the University of Maryland School of Medicine. His research has focused on healthy people, but he says, "What happens with diseases would be a major add-on."

There are many other research projects around the country into brain function. They are examining a wide variety of factors -- vitamin supplements, estrogen, herbs, red wine -- as well as ways to bolster blood circulation and chemicals that initiate actions in the brain. Several drugs are already being used to improve cognition in Alzheimer's patients, but they aren't effective for every patient.

The odds are long for any new drug treatment gaining government approval for use in humans, but Schwarcz believes that the kynurenic

acid discovery could be the breakthrough needed by pharmaceutical companies to produce a commercial product. No human tests have been performed based on the findings, but he believes that at least four major companies have picked up on his research and have begun active drug development programs.

Other scientists think the research shows promise in a sorely needed area.

"There may be no more important target than how to address impaired cognition in humans," said Dr. William T. Carpenter, director of the Maryland Psychiatric Research Center. "That part is a biggie."

Schwarcz and other scientists have been studying the link for more than a decade and can now show that mice genetically engineered to produce 70 percent less kynurenic acid had markedly improved cognition. They were better able to explore and recognize objects, remember unpleasant experiences and navigate a maze.

In humans, the acid is produced after consuming food containing tryptophan, such as turkey. Tryptophan is an amino acid essential to the human diet because it helps the body produce serotonin, which promotes healthy sleep and stable mood.

Conversely, abnormally high levels of kynurenic acid are found in people with brain disorders such as schizophrenia, Alzheimer's and Huntington's, which may contribute to cognitive problems. Further, more acid is produced with age, possibly leading to dementia in some or creating those "senior moments" when people can't recall a memory or fact.

The acid inhibits brain receptors that stimulate learning and memory. So scientists needed to determine how they could reduce the acid and

interrupt the process without inhibiting the serotonin and another neurotransmitter, dopamine, which is associated with feelings of pleasure.

They examined how the acid and serotonin were produced, said Schwarcz, who published findings in the journal *Neuropsychopharmacology* earlier this year. They showed that serotonin is made in nerve cells in the brain, and kynurenic acid is made in glial cells. Scientists have long known of the existence of kynurenic acid and glial cells, but until this discovery, scientists thought the primary role of such cells was to provide support and protection for the nerve cells.

To interrupt the acid development, a chemical is needed to block production in the glial cells -- and the process of discovering the proper chemical is continuing. A chemical Schwarz has begun using in rats in his latest experiments may or may not translate to humans.

"We know where we want to go," Schwarcz said. "We'll see who gets the chemical right with no side effects."

Currently, healthy people who want better focus are turning to amphetamines -- or more often over-the-counter look-alike drugs such as NoDoz that contain caffeine and other stimulants. Such drugs work by stimulating the central nervous system with chemicals, but Schwarcz noted that they can be highly addictive and can cause cardiac trouble. Also, experts say that if they are used during study, they must be used when the information needs to be recalled, such as during a test or presentation.

Amphetamines are not used on schizophrenia patients because they are either blocked by antipsychotic medications or make symptoms worse, says Carpenter of the Maryland Psychiatric Research Center, where schizophrenia patients are treated.

Other problems and side effects could be triggered by a new drug to reduce kynurenic acid, once a chemical treatment is produced and tested in humans. He points out that the majority of drugs that show promise in experiments do not end up becoming safe, government-approved treatments.

Still, Carpenter is hopeful about Schwarcz's research because there are no approved drug treatments to bolster cognition specifically in schizophrenia, a disorder that affects more than 1 percent of American adults. And Schwarcz's mechanism for testing chemicals in animals shows promise for humans.

Carpenter said a drug addressing cognition may be particularly helpful to schizophrenia patients because they do not continue to deteriorate, as Alzheimer's patients do.

Such a drug could buy time for those with Alzheimer's if treatment were given early on. A schizophrenia patient, on the other hand, could benefit at any point, and the earlier the better -- a patient who gets help with learning early on could, for example, finish high school or college and get a job. That would improve the rest of his life, Carpenter said.

Another potential issue with a new smart pill would be its ethical implications, he said. Who would use it and when? He said there could be comparisons to doping in sports.

"In healthy people, there is a challenge to society on how to wisely control (drugs') use," he said. "From a disease perspective, we badly need drugs that can address cognition."

Cass Naugle, executive director of the Alzheimer's Association's Greater Maryland chapter, agreed. She said there are three drugs now used to improve cognition in Alzheimer's patients, but they aren't effective in all

people with the disease -- about 8 percent of people over 65 and almost half of people over 85.

She said signs of new research are encouraging, but added that there is a real problem in getting Alzheimer's patients into research studies. The association has set up a website to connect patients and healthy volunteers with government trials.

Discovering a drug that could delay the worst effects of the disease by even six months would not only benefit families who care for an Alzheimer's patient but would significantly lessen the enormous burden on Medicare and Medicaid, Naugle said. A new drug coupled with early diagnosis, before symptoms appear, would have an even greater effect.

"There is an urgency to find new treatments given the demographics of the baby boomers reaching the age of risk," she said. "We've learned so much about the disease and the brain in the last 30 years, there is a lot of hope."

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Citation: Scientists make link between brain acid and cognition (2010, August 2) retrieved 25 April 2024 from
https://medicalxpress.com/news/2010-08-scientists-link-brain-acid-cognition.html

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