Commonplace sugar compound silences seizures

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Though in clinical use for decades, a small, sweet-tasting compound is revealing a startling new face as a potential cure for epilepsy.

The compound 2-deoxy-glucose, or 2DG, has long been used in radio labeling, medical scanning and cancer imaging studies in humans. But now, researchers at the University of Wisconsin-Madison have found the substance also blocks the onset of epileptic seizures in laboratory rats.

Reported in the journal *Nature Neuroscience*, the findings have potentially huge implications for up to half of all epileptic patients who currently have no access to treatment, says senior author Avtar Roopra, a UW-Madison assistant professor of neurology.

"We pumped the rats full [of 2DG] and still saw no side effects," says Roopra, who estimates that the compound may be available for human use within five years. "I see 2DG as an epilepsy management treatment much like insulin is used to treat diabetes."

"All the available epilepsy treatments have focused on suppressing seizures," says co-author and renowned epilepsy expert Tom Sutula, a UW-Madison professor of neurology. "There has been hope that [new drugs] will not only suppress seizures, but modify their consequences. [2DG] appears to be a novel treatment that offers great promise to achieve that vision."

About 1 percent of the world's population suffers from epilepsy, a

neurological condition that makes people susceptible to seizures. Scientists believe that seizures, of which there are many kinds, occur due to sudden changes in how brain cells send electrical signals to each other. In about 30 to 50 percent of epilepsy patients, available treatments - including the removal of parts of the brain's temporal lobe - are largely ineffective.

2DG is essentially a more palatable version of the "ketogenic," or sugar-free, diets that some researchers have long recommended to epilepsy patients. Indeed, the notion of a sugar-free diet actually stretches back thousands of years to Biblical times, when healers sometimes prescribed starvation as a potent way to fend off seizures.

UW-Madison researchers first began to investigate the role of sugar in controlling seizures after early experiments showed that children on sugar-free diets can rapidly experience seizures when they consume even a small dose of carbohydrates, such as a cookie or a little piece of bread.

But ketogenic regimens can be a miserable experience. "The kids can't eat any sugar at all. Imagine no bread or Christmas cake," says Roopra. But 2DG would work as an effective substitute because it enters cells and clogs up certain cellular enzymes. As a result, the body can't use its own glucose.

Though ketogenic diets seem to work in many epilepsy patients in whom existing treatments have been unsuccessful, scientists have struggled to understand the exact cellular connection between no sugar and no seizures. The UW-Madison work for the first time clears up some of that mystery.

Roopra has long explored how certain proteins known as "transcription factors" turn neuronal genes on or off. He has been particularly intrigued by one transcription factor known as NRSF, which is thought to control

up to 1,800 genes in the brain, including many that are implicated in epilepsy. Like an electrical motherboard, NRSF ensures that neuronal genes switch "on" in the body's neurons, while remaining switched "off" in other regions where they normally play no role.

Roopra found that NRSF binds to another protein called CTBP. The finding "immediately raised alarm bells," Roopra says, because CTBP also binds to a free-floating molecule - NADH - that emerges when sugars break down in cells. To his surprise, Roopra found that CTBP binds to either NRSF or NADH. In other words, a cell with a lot of glucose generates a lot of NADH, so CTBP is more likely to bind with the sugar byproduct than NRSF. But without CTBP, NRSF most likely derails the normal function of certain neuronal genes - including those connected to epilepsy.

Scientists believe that NSRF also controls genes that potentially play a role in cancer. Roopra is planning future studies to test whether 2DG holds promise for combating breast cancer, or fast-spreading glioblastomas.

The UW-Madison team has patented 2DG for its use against epilepsy in collaboration with the Wisconsin Alumni Research Foundation, UW-Madison's technology transfer arm.

Source: University of Wisconsin-Madison, by Paroma Basu