Sleep chemical central to effectiveness of deep brain stimulation

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A brain chemical that makes us sleepy also appears to play a central role in the success of deep brain stimulation to ease symptoms in patients with Parkinson's disease and other brain disorders. The surprising finding is outlined in a paper published online Dec. 23 in *Nature Medicine*.

The work shows that adenosine, a brain chemical most widely known as the cause of drowsiness, is central to the effect of deep brain stimulation, or DBS. The technique is used to treat people affected by Parkinson's disease and who have severe tremor, and it's also being tested in people who have severe depression or obsessive-compulsive disorder.

Patients typically are equipped with a "brain pacemaker," a small implanted device that delivers carefully choreographed electrical signals to a very precise point in the patient's brain. The procedure disrupts abnormal nerve signals and alleviates symptoms, but doctors have long debated exactly how the procedure works.

The new research, by a team of neuroscientists and neurosurgeons at the University of Rochester Medical Center, gives an unexpected nod to a role for adenosine and to cells called astrocytes that were long overlooked by neuroscientists.

"Certainly the electrical effect of the stimulation on neurons is central to the effect of deep brain stimulation," said Maiken Nedergaard, M.D., Ph.D., the neuroscientist and professor in the Department of

Neurosurgery who led the research team. “But we also found a very important role for adenosine, which is surprising.”

Adenosine in the brain is largely a byproduct of the chemical ATP, the source of energy for all our cells. Adenosine levels in the brain normally build as the day wears on, and ultimately it plays a huge role in making us sleepy – it’s the brain’s way of telling us that it’s been a long day, we’ve expended a lot of energy, and it’s time to go to bed.

The scientists say the role of adenosine in deep brain stimulation has not been realized before. Even though scientists have recognized its ability to inhibit brain cell signaling, they did not suspect any role as part of DBS’s effect of squelching abnormal brain signaling.

“There are at least a dozen theories of what is happening in the brain when deep brain stimulation is applied, but the fact is that no one has really understood the process completely,” said Robert Bakos, M.D., a neurosurgeon at the University of Rochester and a co-author of the paper, who has performed more than 100 DBS surgeries in the last decade. “We’ve all been focused on what is happening to the nerve cells in the brain, but it may be that we’ve been looking at the wrong cell type.”

Nedergaard’s team showed that the electrical pulses that are at the heart of DBS evoke those other cells – astrocytes – in the area immediately around the surgery to release ATP, which is then broken into adenosine. The extra adenosine reduces abnormal signaling among the brain’s neurons.

The team also showed that in mice, an infusion of adenosine itself, without any deep brain stimulation, reduced abnormal brain signaling. They also demonstrated that in mice whose adenosine receptors had been blocked, DBS did not work; and they showed that a drug like caffeine

that blocks adenosine receptors (the reason why caffeine helps keep us awake) also diminishes the effectiveness of DBS.

“It may be possible to enhance the effectiveness of deep brain stimulation by taking advantage of the role of agents that modulate the pathways initiated by adenosine,” said Nedergaard. “Or, it’s possible that one could develop another type of procedure, perhaps using local targeting of adenosine pathways in a way that does not involve a surgical procedure.”

The latest work continues Nedergaard’s line of research showing that brain cells other than neurons play a role in a host of human diseases. ATP in the brain is produced mainly by astrocytes, which are much more plentiful in the brain than neurons. Astrocytes were long thought of as simple support cells, but in recent years, Nedergaard and colleagues have shown that they play an important role in a host of diseases, including epilepsy, spinal cord disease, migraine headaches, and Alzheimer’s disease.

The research on DBS came about as a result of a presentation Nedergaard made to colleagues about her research on astrocytes. Bakos linked her detailed description of astrocyte activity to what he sees happening in the brain when deep brain stimulation is applied. Based on Bakos’ experience in the operating room and with funding from the National Institute of Neurological Disorders and Stroke, Nedergaard went back to the laboratory and analyzed the effects of deep brain stimulation in a way that no one had ever before considered.

“The correlation between what we see in the clinic and Dr. Nedergaard has found in the laboratory is really quite startling,” said Bakos. “All the credit goes to her and her team. This has been a nice interchange of information between the clinic and the laboratory, to speed a discovery that really could have an impact on patients.”

Source: University of Rochester