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Study sheds new light on brain's source of power

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New research published today in the journal *Nature Communications* represents a potentially fundamental shift in our understanding of how nerve cells in the brain generate the energy needed to function. The study shows neurons are more independent than previously believed and this research has implications for a range of neurological disorders.

"These findings suggest that we need to rethink the way we look at brain metabolism," said Maiken Nedergaard, M.D., D.M.Sc., co-director of the University of Rochester Center for Translational Neuromedicine and lead author of the study. "Neurons, and not the brain's support cells, are the primary consumers of glucose and this consumption appears to correlate with brain activity."

The brain requires a tremendous amount of energy to do its job. While it only represents 2 percent of the body mass of the average adult human, the brain consumes an estimated 20 percent of body's energy supply. Consequently, unravelling precisely how the brain's cells - specifically, neurons - generate energy has significant implications for not only the understanding of basic biology, but also for neurological diseases which may be linked to too little, or too much, metabolism in the brain.

Our digestive system converts carbohydrates found in food into glucose, a sugar molecule that is the body's main source of energy, which is then transported throughout the body via the blood system. Once inside cells, the mitochondria, which serve as tiny cellular power plants, combine these sugars with oxygen to generate energy.

Unlike the rest of the body, the brain maintains its own unique ecosystem. Scientists have long believed that a support cell found in the brain, called the astrocyte, played an intermediary role in the supplying neurons with energy. This theory is called the lactate shuttle hypothesis.

Scientists have speculated that the astrocytes are the brain's primary consumer of glucose and, like a mother bird that helps its chicks digest food, these cells convert the molecules to another derivative (lactate) before it is passed along to the neurons. Lactate is a form of sugar molecule that is used by mitochondria for fuel.

"The problem with the lactate shuttle hypothesis is that by outsourcing lactate production to astrocytes, it places the neuron in a dangerous position," said Nedergaard. "Why would neurons, the cell type that is most critical for our survival, be dependent upon another cell for its energy supply?"

The new research, which was conducted in both mice and human brain cells, was possible due to new imaging technologies called 2-photon

microscopy that enable scientists to observe activity in the brain in real time.

Using a glucose analogue, the researchers found that it was the neurons, and not the astrocytes, that directly take up more glucose in the brain. They also found that when stimulated and more active, the neurons increase consumption of glucose, and when the mice where anesthetized, there was less neuronal uptake of glucose. On the other hand, the uptake of glucose by astrocytes remained relatively constant regardless of brain activity.

On the cellular level, the researchers observed that the neurons were doing their own job of converting glucose to lactate and that an enzyme that plays a key role in the creation lactate, called hexokinase, was present in greater amounts in neurons compared to astrocytes.

These findings have significant implications for understanding a host of diseases. The overproduction of lactate can result in lactic acidosis, which can damage nerve cells and cause confusion, delirium, and seizures. In stroke, lactate accumulation contributes to the loss of brain tissue and can impact recovery. Neuronal metabolism also plays an important role in conditions such as Alzheimer's and other neurodegenerative diseases.

Recent research has shown that inhibiting the transport of lactate between cells can reduce seizure activity in mice. However, much of this prior work has assumed that lactate was produced by astrocytes and that neurons were passive bystanders. The new study brings into question these assumptions by showing that neurons consume glucose directly and do not depend on astrocytic production and delivery of lactate.

"Understanding the precise and complex biological mechanisms of the brain is a critical first step in disease-based research," said Nedergaard.

"Any misconception about biological functions - such as metabolism - will ultimately impact how scientists form hypothesize and analyze their findings. If we are looking in the wrong place, we won't be able to find the right answers."

Provided by University of Rochester Medical Center