Study provides neuronal mechanism for the benefits of fasting

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A study from the Buck Institute offers for the first time an explanation for the benefits of fasting at the neuronal level, providing a possible mechanism for how fasting can afford health benefits. Publishing on December 1st in *Neuron*, researchers used fruit fly larvae to uncover the presence of a molecular pathway that responds to nutrient scarcity and lowers synapse activity at the junctions between neurons and muscle cells. Specific effects in response to changing nutrient availability at the level of the synapse has not been reported before.

"On the one hand, our findings might sound counter-intuitive because we always think of fasting as being beneficial and here we have found blockage of a natural neuronal activity," said senior author and Buck Institute professor Pejmun Haghighi, PhD. "On the other hand, we think that we might actually be answering the question of why fasting is beneficial. Perhaps it's a good thing that when nutrients are unavailable, an organism reduces neurotransmitter release and thus saves a good proportion of its overall energy expenditure."

Additionally, Haghighi added, neurotransmission requires continuous orchestration of signal transmission steps and this stress could lead to accumulated damage in neurons. "Our findings suggest that one of the reasons that fasting is beneficial is that it gives the nervous system a break and calms things down," he said.

Dampening of synaptic activity occurred within three hours of removing nutrients from the larval food. The inhibition was pronounced, reducing

activity by half. "It's really amazing that a change in nutrient intake can have such dramatic influences on neuron activity on such a short time scale," said the study's co-lead author Grant Kauwe, PhD, a postdoctoral research fellow in the Haghighi lab. "It demonstrates how quickly changes caused by fasting can occur."

Researchers have long wondered exactly how caloric restriction extends lifespan and slows age-related disease in a range of species, but the impetus for the current study actually stemmed from Haghighi's decades-long interest in understanding the molecular mechanisms that regulate neurotransmitter release at synapses. In particular, he has focused on a phenomenon called synaptic homeostasis, which is a way that neuronal circuits maintain activity within a set range to ensure stable and reliable communication.

In 2012, Haghighi's team published a paper showing synaptic homeostasis was controlled by an enzyme, the target of rapamycin (TOR), which plays a critical role in regulating lifespan in a wide range of organisms from yeast to mice. This finding connected on a molecular level how nervous system function and lifespan regulation are intertwined.

TOR plays many roles, but one of its primary tasks is to function like a wrench loosening and tightening the control of protein synthesis in response to nutrients, specifically amino acid availability. While previous evidence had suggested that fasting influences neuronal activity and neurotransmitter release, Haghighi realized that no research had linked TOR's known ability to regulate nutrients and lifespan with TOR's role in synaptic homeostasis.

To determine the molecular details about how nutrient reduction affects synapse function, Haghighi's team combined their genetic and molecular tools with imaging and electrophysiological techniques to see what

happened when they changed the food composition of Drosophila larvae. At the basic level, their experiments were recording neuron activity in muscle, Kauwe explained. The synapse between a neuron and a muscle - the neuromuscular junction - of a fruit fly larva turns out to be a good model for studying how the nervous system works in general, which can be applied to other organisms, including humans.

The team started by restricting protein in the larvae's diet, since protein restriction was already known to reduce TOR activity. Surprisingly, they discovered that synaptic homeostasis was unaffected by dietary restriction, despite lower TOR activity. However, transient removal of food, called acute fasting, completely suppressed synaptic homeostasis within a few hours.

The team's further experiments delved into what else beyond TOR was involved to evoke the suppression. They showed genetically that there was an additional response coming from the transcription factor - Forkhead box O (Foxo) - which in turn enhances the transcription of one of the translational regulators: eukaryotic initiation factor 4E binding protein (4E-BP). Furthermore, it is the balance between TOR and 4E-BP that controls synapse stability.

Stability is a hallmark of healthy neuronal circuits and disruption of this stability in the form of increased activity at the synapse may lead to neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, schizophrenia or epilepsy.

"We might have some real insight into the advantages of dampening of synaptic activity that is caused by fasting," said Haghighi, for example, how fasting can be beneficial for epileptic patients, who can experience reduced seizures when restricting calories.

Kauwe and others in Haghighi's lab are exploring why such a change in

the set point of synaptic transmission occurs so rapidly, and how dampening neuron activity might be beneficial in treating, or even preventing, neurodegenerative diseases. "I think uncovering this mechanism is an important basic discovery that could lead to tangible ways of thinking about design of therapeutic approaches for neurodegenerative diseases in the near future," said Haghighi.

More information: Acute Fasting Regulates Retrograde Synaptic Enhancement through a 4E-BP-Dependent Mechanism, *Neuron*, DOI: 10.1016/j.neuron.2016.10.063

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