Researchers discover sex-specific differences in neural mechanisms for glucose regulation

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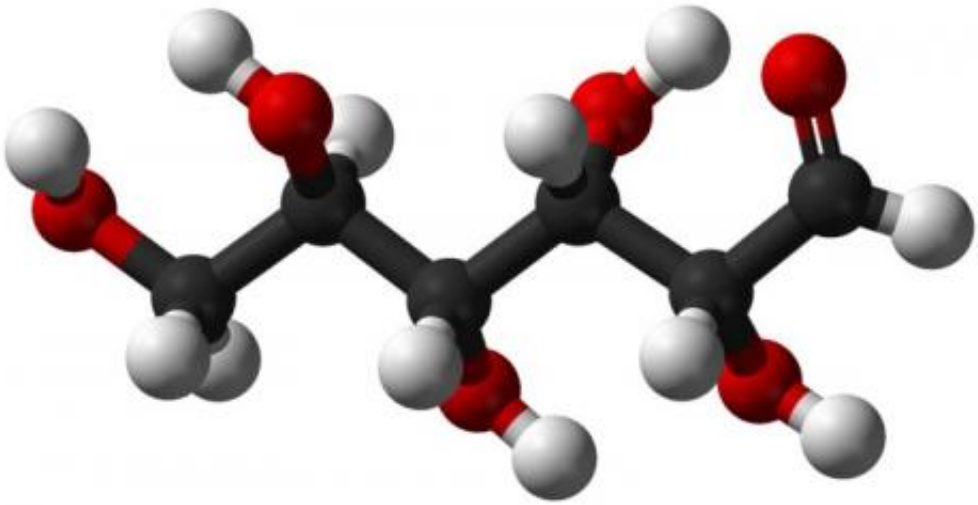

Glucose C6H12O6. Credit: Wikipedia.

Researchers at Tufts University School of Medicine and Tufts Graduate School of Biomedical Sciences have discovered neural mechanisms in mice specific to females that can shift estrogen from playing a protective role in glucose metabolism to one that is disruptive. The authors of the study, published online in the *Proceedings of the National Academies of Sciences (PNAS)*, hypothesize that the metabolic 'switch' mediated by estrogen may provide clues to the increased risk of insulin resistance and diabetes among post-menopausal women.

The study focused on a region of the brain called the ventromedial hypothalamus (VMH) and found that the removal of the metabotropic glutamate receptor 5 (mGluR5) in that area caused estrogen to reduce the activity of neurons important for glycemic control, leading to insulin resistance and glucose intolerance. These effects were opposite to the increased neuronal activity and enhanced glucose metabolism observed in mice with the receptor following estrogen delivery. The paradoxical outcome on glucose metabolism was seen in female, but not male, mice.

Prior research by others had indicated that the VMH region of the brain plays a role in managing appropriate levels of glucose production in the liver and utilization of circulating glucose by cells and tissues. Within the VMH, steroidogenic factor 1 (SF1) neurons are responsible for helping to regulate glucose as well as lipid levels, e.g. cholesterol and triglycerides. However, less was known about exactly how the VMH regulates glucose metabolism. Similarly, while the beneficial effects of estrogen have long been recognized, the mechanisms driving these effects remain poorly understood.

mGluR5 is highly expressed in the VMH and is known to regulate neuron activity in other parts of the brain. When the researchers knocked out the expression of mGluR5 specifically in the VMH using gene editing methods, they observed a reduction of SF1 neuron activity and a disruption of normal glucose regulation, but only in the female mice.

Knocking out mGluR5 in male mice did not have these effects and their glucose metabolism remained normal.

Noting different effects on glucose metabolism between male and female mice, the researchers examined the potential involvement of sex hormones. They discovered that estrogen, which normally promotes metabolic health in females, supports glycemic control only when

mGluR5 is present in the VMH. Without mGluR5, estrogen actually suppresses the neurons responsible for regulating glucose—it becomes a metabolic liability.

"Our findings show that the glutamate receptor is essential for the effects of estrogen regulating proper glucose levels and utilization in females, whereas it does not appear to play that regulatory role in males. This could give us insight into many of the differences between men and women in their risk of diabetes and disease progression throughout life," said senior author Maribel Rios, researcher in neuroscience at Tufts School of Medicine and a member of the neuroscience and cell, molecular and developmental biology program faculties at Tufts Graduate School of Biomedical Sciences.

More information: Micaella P. Fagan et al, Essential and sex-specific effects of mGluR5 in ventromedial hypothalamus regulating estrogen signaling and glucose balance, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2011228117

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