Sugar alters compounds that impact brain health in fruit flies

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When fruit flies are exposed to a high sugar diet, key metabolites associated with brain health become depleted, according to a University

of Michigan study.

This finding could tell researchers why behaviors that change with the internal energy state, such as food intake, learning and memory, and sleep, change on high-nutrient diets.

When our bodies metabolize food, that food is broken down into metabolites—small molecules that perform many functions in the body, including providing fuel to cells and activating or inhibiting enzyme production. The study, published in *Nature Communications*, examines how metabolites in the brains and bodies of fruit flies change as the flies transition between hunger and satiety.

Through the study, the researchers found that the flies' metabolic profiles change rapidly during the quick transition from hunger to satiety, with the flies' brains showing a larger change than their bodies. In particular, the high sugar diet lowered the levels the brain metabolites N-acetyl aspartate, or NAA, and kynurenine.

The alteration of metabolites could impact how quickly the fly senses satiety, causing it to eat more. In fact, U-M researchers previously found that an increase in a specific metabolite with a high sugar diet caused overeating and weight gain.

Although scientists aren't clear on the role of NAA in the brain, it appears to provide fuel for brain cells and balances osmolarity—or regulates cell volume—in the brain. Lower levels of another metabolite, kynurenine, which is produced in high levels during exercise, is associated with depression.

"What we found was a metabolic remodeling," said senior author Monica Dus, U-M assistant professor of molecular, cellular and developmental biology. "It wasn't just a gradual accumulation from an

early to longer exposure, but by the seventh day on a high sugar diet, these fruit flies had a completely different metabolic profile."

Cancer cells also undergo this type of metabolic remodeling in order to fuel their growth, which is why diet may play a role in cancer treatment and a reason the Dus lab wanted to examine the shift of metabolites in the brain.

To examine how a high sugar diet affects the brains and bodies of fruit flies, the research team compared a group of fasting flies to a group of fed flies. In the fed flies, the researchers skipped giving them dinner, then fed them a breakfast of moderately sweet glucose jelly the next day.

The researchers mix the sugar jelly with blue or green dye, and after an hour, check the belly of the fly to make sure it's eaten. To make sure the animals have eaten their fill, the researchers put the flies on a lickometer covered with the glucose jelly. A lickometer is exactly what it sounds like: A meter that counts the number of times it has been licked.

Then, inside separate tubes, researchers freeze the sated flies as well as the group of fasting flies. This stops the metabolic process, so that researchers can look at what's going on in the flies' brains at the moment of satiety. The researchers shake the tubes, which shatters the fly. A sieve separates the fly's head, thorax, abdomen and legs. These parts were then sent to a company that uses mass spectrometry to measure the metabolites within the fly.

To help refine the list of metabolites in the flies, Alla Karnovsky, a research associate professor of computational medicine and bioinformatics at Michigan Medicine, created a tool called FlyScape. She based it on a previous tool she created for the analysis of human metabolomics data called MetScape. Like Metscape, Flyscape is open access: any researcher studying metabolites in fruit flies can use the

software.

These tools help researchers look for patterns in metabolomics data. A researcher like Daniel Wilinski, a postdoctoral fellow in the Dus lab and first author of the manuscript, can input a list of metabolites found in her fruit fly subjects, as well as a list of genes from fruit flies, into Flyscape. The tool will produce visualizations of the metabolic networks of fruit flies.

"You can view the metabolites and genes that are changing between different conditions," Karnovsky said. "This helps us understand what biological processes are happening."

Co-author Peter Freddolino, assistant professor of biological chemistry and computational medicine and bioinformatics at Michigan Medicine, has worked with Dus on previous papers to study how a high sugar diet dulls the sense of taste in fruit flies.

"We examined what the changes in metabolites are that could be fundamentally perturbing the way that these cells were working," Freddolino said. "What this study tells us is what metabolomic pathways might be involved."

Ultimately, the study found that 20 metabolites, in addition to NAA and kynurenine, were impacted by sugar consumption. Next, says Dus, the research team plans to dial down into how changes in these metabolites impact the brain, altering food intake and affecting other conditions such as sleep, learning and memory.

Provided by University of Michigan

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