Dietary restriction gives fruit flies a rhythm for a long life

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Drosophila sp fly. Credit: Muhammad Mahdi Karim / Wikipedia. GNU Free Documentation License, Version 1.2

Dietary restriction enhances the expression of the circadian clock genes in the peripheral tissue of fruit flies, according to research from the Kapahi lab at the Buck Institute. Publishing in *Cell Metabolism*, the researchers show that dietary restriction, induced by reducing protein in the diet, increased the amplitude of circadian clocks and enhanced the

cycles of fat breakdown and fat synthesis. This improvement in fat metabolism may be a key mechanism in explaining why dietary restriction extends lifespan in several species, including the flies in this study.

The research also presents a tantalizing possibility for humans eager to take a drug that would allow them to reap the health benefits of dietary restriction without going on an extreme diet. When scientists genetically altered the flies to boost clock function the animals lived longer, even when they ate whatever they wanted to. On the other hand, disrupting the clocks, either genetically or by keeping the flies under constant light, made the animals irresponsive to the beneficial effects of dietary restriction.

"More than 10-15% of the genome is under circadian control, especially genes which regulate processes involving cellular repair and metabolism," said senior scientist and Buck professor Pankaj Kapahi, PhD. "Every cell has a clock and the action of clocks in peripheral tissues, fat, intestines, kidneys—plays an important role in modulating metabolism and thereby mediating lifespan extension via dietary restriction."

Previous work from the Kapahi lab showed that flies on a lifespan-extending Spartan diet exhibited an enhanced turnover of triglycerides. This new work, also led by Buck assistant research professor Subhash D. Katewa, PhD, suggests a role for timeless, a circadian clock gene, in the cycling of specific medium chain triglycerides under dietary restriction. "The role of medium chain triglycerides in aging and regulation of clock functions is not clear, however dietary medium chain triglycerides have been associated with weight loss and improved healthspan in both humans and mice," said Katewa, noting current consumer interest in coconut oil which is rich in medium chain triglycerides. "Our work demonstrates for the first time that medium chain triglyceride synthesis

in animals is under nutritional and circadian control," he said. "If we want to modulate the effects of nutrient manipulation on fat metabolism and aging then targeting the activity of peripheral circadian clocks gives us a way to achieve that goal."

"Circadian rhythms, which impact many behaviors like sleep or cellular processes like metabolism, tend to dampen with age," said Kapahi. "The metabolic rhythms of flies on dietary restriction maintain a remarkable robustness as they age, which we think helps them live longer. It is exciting to contemplate how this mechanism might be exploited for human health."

More information: Peripheral circadian clocks mediate dietary restriction dependent changes in lifespan and fat metabolism in Drosophila, *Cell Metabolism*, CELL-METABOLISM-D-15-00087R3

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