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Disrupted circadian rhythm may cause triglycerides to rise

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When the circadian rhythm gets thrown off, it could come with an unexpected side effect: high triglycerides. The discovery, based on studies in mice with a "broken clock," helps to explain the normal rise and fall in triglycerides, which happens at about the same time each day, according to researchers who report their findings in the August issue of *Cell Metabolism*.

"We show that the normal up and down [of triglycerides] is lost in clock mutants," said M. Mahmood Hussain of SUNY Downstate Medical Center. "They have high triglycerides all the time." An elevated triglyceride level is a risk factor for atherosclerosis and heart disease.

Several biological, physiological, and behavioral activities show a characteristic recurrence with 24-hour intervals attuned to sunrise and sunset, the researchers explained. That circadian rhythm is driven by the interaction of so-called clock genes.

In normal mice, plasma triglycerides double or triple over the course of the day, reaching their lowest point at night when the nocturnal animals eat and are most active, the new report shows. In clock mutants, triglyceride levels don't change; rather, they stay high all the time.

The researchers delved further into the mechanism linking the animal's internal clocks to triglycerides. They found that a core component of the circadian circuitry—a protein known as CLOCK—controls levels of another protein (called microsomal triglyceride transfer protein, or

MTP) that helps to ferry triglycerides through the bloodstream. That control takes place via yet another transcription factor.

"Metabolic syndrome and obesity are major metabolic disorders characterized by high plasma lipid concentrations," the researchers conclude. "Plasma lipids are tightly controlled by mechanisms regulating their production and clearance. Here, we show that light-entrained mechanisms involving clock genes also play a role in regulating plasma triglyceride."

If the findings in mice can be extrapolated to humans, it suggests that the effects of drugs designed to lower triglyceride levels by acting on MTP might depend on when they are taken each day, the researchers said.

"The dose needed may vary depending on the time of day," Hussain said. "Now we can start to think about [the role of] drug timing in controlling disease states."

The findings also suggest that activities that disrupt the circadian rhythm—staying up until 2:00 a.m. or traveling overseas—might come with real consequences for lipid metabolism, he added.

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