AMERICAN COMMITTEE FOR THE WEIZMANN INSTITUTE OF SCIENCE

SCIENCE FOR THE BENEFIT OF HUMANITY

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TIME IS OF THE ESSENCE

REHOVOT, ISRAEL—February 5, 2014—New findings in mice suggest that merely changing meal times could have a significant effect on the levels of triglycerides in the liver. The results of this Weizmann Institute of Science study, recently published in *Cell Metabolism*, not only have important implications for the potential treatment of metabolic diseases, they may also have broader implications for most research areas in the life sciences.

Many biological processes follow a set timetable, with levels of activity rising and dipping at certain times of the day. Such fluctuations, known as circadian rhythms, are driven by internal "body clocks" based on an approximately 24-hour period – synchronized to light-dark cycles and other cues in an organism's environment. Disruption to this optimum timing system in both animal models and in humans can cause imbalances, leading to such diseases as obesity, metabolic syndrome, and fatty liver. Night-shift workers, for example, have been shown to have higher incidence of these diseases.

In studying the role of circadian rhythm in the accumulation of lipids in the liver, postdoctoral fellow Yaarit Adamovich and team in Dr. Gad Asher's lab at the Institute's Department of Biological Chemistry, together with scientists from Dr. Xianlin Han's lab at the Sanford-Burnham Medical Research Institute, Orlando, Florida, quantified hundreds of different lipids present in the mouse liver. They discovered that a certain group of lipids – namely, the triglycerides (TAG) – exhibit circadian behavior, with levels peaking about eight hours after sunrise. The scientists were astonished to find, however, that daily fluctuations in this group of lipids persist even in mice lacking a functional biological clock, albeit with levels cresting at a completely different time – 12 hours later than the natural schedule.

"These results came as a complete surprise: One would expect that if the inherent clock mechanism is 'dead,' TAG could not accumulate in a time-dependent

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fashion," says Dr. Adamovich. So what was making the fluctuating lipid levels "tick" if not the clocks? "One thing that came to mind was that, since food is a major source of lipids – particularly TAG – the eating habits of these mice might play a role." Usually, mice consume 20% of their food during the day and 80% at night. However, in mice lacking a functional clock, the team noted that they ingest food constantly throughout the day. This observation excluded the possibility that food is responsible for the fluctuating patterns seen in TAG levels in these mice.

When the scientists proceeded to check the effect of an imposed feeding regimen upon wild-type mice, however, they were in for another surprise: After they provided the same amount of food – but restricted 100% of the feeding to nighttime hours – the team observed a dramatic 50% decrease in overall liver TAG levels.

These results suggest that the time at which TAG accumulation occurs, as well as its levels, are determined by the clocks together with timing of meals. The details of the mechanism that drives the actual fluctuating behavior are yet to be discovered.

Says Dr. Asher: "The striking outcome of restricted nighttime feeding – lowering liver TAG levels in the very short time period of 10 days in the mice – is of clinical importance. Hyperlipidemia and hypertriglyceridemia are common diseases characterized by abnormally elevated levels of lipids in blood and liver cells, which lead to fatty liver and other metabolic diseases. Yet no currently available drugs have been shown to change lipid accumulation as efficiently and drastically as simply adjusting meal time – not to mention the possible side effects that may be associated with such drugs." Of course, mice are nocturnal animals, so in order to construe these results for humans, the timetable would need to be reversed.

Time is a crucial element in all biological systems, so these findings are likely to impact biological research in general: Circadian clock mechanisms function even in cultured cells, so research results could vary depending on the time at which samples are analyzed, or, with animals, their feeding regimen might significantly affect the experimental outcomes. In other words, when it comes to designing experiments, scientists should be aware that "timing is everything."

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