

Liver-Brain Communication Affects Eating Patterns and Obesity

Disrupting the liver's circadian clock genetically or with a high-fat diet altered eating patterns in mice.

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Various processes in the body oscillate on a 24-hour cycle called the circadian rhythm. These rhythms are controlled by coordinated activation of specific “clock” genes, which depends on environmental cues such as light and food intake. The suprachiasmatic nucleus in the brain functions as the preeminent circadian clock, but most tissues and organs have their own molecular clocks.

Past studies have shown that metabolic function and health depend on synchronization between circadian rhythms in the brain and the liver. Shiftwork or chronic jet lag can disrupt this synchronization and increase the risk of obesity and metabolic disease. But how these clocks interact with each other is not well understood.

A research team led by Dr. Mitchell Lazar at the University of Pennsylvania School of Medicine sought to better understand how the liver circadian clock affects circadian control of behavior in the brain. To do so, they engineered mice lacking the genes for two key clock components, REV-ERB α and REV-ERB β , in the liver. Results of their study, which was funded in part by NIH, [appeared in Science](#) on November 7, 2024.

The “double knockout” mice had altered eating patterns. Compared with control mice, they did more of their eating in the daytime, when mice are normally less active. They also ate more total food in a day than the control mice. Deleting the gene for a different clock component, BMAL1, in the liver had the same effect as the double knockout.

Deleting the clock genes also disrupted the timing of gene activation in the hepatic vagus nerve (HVN). This nerve relays information from the liver to the brain. To explore the role of the HVN in eating patterns, the researchers surgically severed the nerve. This prevented the changes in eating patterns caused by removing the liver clock genes. Selectively killing HVN neurons also prevented these changes.

A high-fat diet has been shown to disrupt activation of liver clock genes in mice and cause shifts in eating patterns like those seen in the engineered mice. Severing the HVN prevented these

changes in mice fed a high-fat diet. Mice on a high-fat diet also gained less weight when the HVN was severed.

The findings suggest that feedback from the liver to the brain via the HVN helps control circadian eating patterns. Disruption of the liver's circadian clock, through diet or other means, leads to disrupted and unhealthy eating patterns.

"These findings open the door to future therapies that can target specific neural pathways to help those struggling with metabolic disorders caused by irregular eating schedules," Lazar says.

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