What makes the heart 'tick-tock'

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Researchers have new evidence to show that the heart beats to its own drummer, according to a report in the December issue of the journal *Cell Metabolism*. They've uncovered some of the molecular circuitry within the cardiovascular system itself that controls the daily rise and fall of blood pressure and heart rate. The findings might also explain why commonly used diabetes drugs come with cardiovascular benefits, according to the researchers.

"This is the first study to demonstrate that a peripheral clock plays a role in the circadian rhythm of blood pressure and heart rate," said Tianxin Yang of the University of Utah and Salt Lake Veterans Affairs Medical Center.

While much progress has been made over the years in understanding the body's master clock in the brain, the new study offers one of the first glimpses into the biological function of peripheral clocks in maintaining the circadian rhythms of tissues throughout the body, the researchers said.

Circadian variations in blood pressure and heart rate are among the best-recognized circadian rhythms of physiology, Yang explained. In humans, there is a sharp rise in blood pressure before awakening, with the highest values around midmorning. Many cardiovascular events, such as sudden cardiac death, heart attack, and stroke display daily variations with an increased incidence in the early morning hours. It is suspected that those trends correlate with the morning surge in blood pressure.

On the other hand, researchers have suggested that a reduction in the normal decline of blood pressure at night may be a strong predictor of cardiovascular events and end-organ damage. As in many other peripheral tissues, such as the liver and kidneys, the circadian oscillation of clock gene activity had been well demonstrated in the cardiovascular system, but the biological significance of those oscillations had remained unclear.

Earlier studies suggested a role for the nuclear receptor called peroxisome proliferator-activated receptor-g (PPARg) in clock function. PPARg is perhaps best known as the molecular target for a class of widely prescribed and effective diabetes drugs called thiazolidinediones (TZDs), including rosiglitazone (trade name Avandia) and pioglitazone (trade name Actos). Those diabetes drugs are known to come with a side benefit: they have protective effects on the cardiovascular system.

To further explore in the new study, the researchers examined two strains of mice, each lacking PPARg only in cardiovascular cells. The researchers found that both knockout strains showed a significant reduction of circadian variations in blood pressure and heart rate. (Since mice are nocturnal, their rise and fall in blood pressure occurs at opposite times to those of humans). The mice also showed declines in variation of norepinephrine/epinephrine in their urine—a measure of activity of the sympathetic nervous system, which plays a key role in heart rate and blood pressure.

The animals had impairments in the rhythmicity of the major clock genes, including Bmal1, a transcription factor that controls the activity of other core clock components, they report.
By treating the mice with the diabetes drug rosiglitazone, they were able to increase the activity of Bmal1 in the animals' aortas, the largest artery of the body that issues blood from the heart, and further study showed that the core clock gene is directly controlled by PPARg.

"Our major finding is that PPARg has a circadian function in the vasculature," Yang said. The data also suggest that TZDs' benefits for the cardiovascular system may stem from their ability to restore circadian rhythms.

Indeed, he added, PPARg may have circadian functions in many other metabolic tissues throughout the body. If so, then many of the benefits of TZDs may result from its ability to "help correct the function of the clock."

While the new findings confirm a critical role for the heart's own clock, they don't rule out the possibility that this peripheral clock relies on the master clock seated in the suprachiasmatic nucleus (SCN) of the brain, Yang said. "It's possible there is communication between the SCN and the peripheral clock."

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