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A mechanism to explain biological 'cross-talk' between 24-hour body cycle and metabolism

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It's well known that the body's energy levels cycle on a 24-hour, or circadian, schedule, and that this metabolic process is fueled by oxygen. Now, researchers at the University of Pennsylvania School of Medicine have found that a protein called Rev-erb coordinates the daily cycles of oxygen-carrying heme molecules to maintain the body's correct metabolism.

The research appears online this week in *Science Express* in advance of print publication in *Science*.

Many studies, including this one, point to a link between the human internal clock and such metabolic disorders as obesity and diabetes. Proteins such as Rev-erb are the gears of the clock and understanding their role is important for fighting these diseases.

"This is the next chapter on Rev-erb, a member of a family of cell-nucleus proteins that includes receptors for anti-diabetic drugs," explains senior author Mitchell A. Lazar, MD, PhD, Director of the Institute for Diabetes, Obesity, and Metabolism at Penn. About two years ago Lazar's group discovered that Rev-erb was a critical component of the circadian clock. In this paper, they found that the activity of Rev-erb is controlled by heme.

Heme represents the body's most important way of transporting and

using oxygen, which would simply bubble away in the body without being bound to heme. “In a molecular baton hand-off, oxygen is transferred from heme in the bloodstream to the heme molecules found inside a cell,” says Lazar, of how oxygen reaches cells to run their metabolic needs. One of the most important roles of heme inside cells is to facilitate the use of oxygen to generate energy in the process known as cellular respiration.

The findings further tie together the 24-hour cycle of the body with metabolic function. “Circadian rhythms are our sleep-wake cycle and metabolism is how we process food, so it makes sense that there would be biological cross-talk between the body’s 24-hour rhythm and metabolic function,” says Lazar. Indeed, scientists already recognize that getting too much or too little sleep increases the risk of diabetes. The newly discovered circadian/metabolic link could be the focus of a new generation of diabetes treatments.

The Penn group worked with scientists at GlaxoSmithKline, who demonstrated that the Rev-erb protein can physically bind to heme in the test tube. The Penn scientists then found that heme, by regulating the activity of Rev-erb, reduces the amount of glucose produced by liver cells.

“What’s exciting about this is that it puts heme in a central role in the metabolic regulation of the cell,” says Lazar. “Not only is it a key component in making energy, but also in the pathway for turning off glucose production.” Excessive glucose production by the liver is a major cause of high blood sugar in diabetes.

Source: University of Pennsylvania