

From mouse to man: Circadian nitrogen balance impacts survival and susceptibility to common diseases

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Researchers at Case Western Reserve University School of Medicine demonstrated that nitrogen balance, the process of utilizing amino acids and disposing of their toxic byproducts, occurs with a precise 24-hour rhythm – also known as circadian rhythm – in mammals. Disruption of this cycle has a direct impact on survival of organisms, and may predispose one to life altering diseases including diabetes and cardiovascular disease.

The study led by Darwin Jeyaraj, MD, MRCP, assistant professor of medicine at Case Western Reserve School of Medicine and cardiologist at Harrington Heart & Vascular Institute at University Hospitals Case Medical Center, who works in the laboratory of Mukesh Jain, MD, FAHA, professor of medicine, Ellery Sedgwick Jr. Chair, and director, Case Cardiovascular Research Institute at Case Western Reserve School of Medicine and the chief research officer, Harrington Heart & Vascular Institute at University Hospitals Case Medical Center, discovered that the KLF15 gene as a singular factor could control the entire process of nitrogen balance in mammals. This discovery was published in [Cell Metabolism](#).

In mammals, the nutrient that is at a premium is glucose. This is because the brain and red blood cells can only burn glucose to sustain their energy, whereas the capacity of the organisms to store glucose is limited to a few hours. Thus, during periods of fasting, like daily sleep,

mammals need an alternative way to synthesize glucose to keep the brain functioning properly.

To overcome this daily challenge, glucose is generated by the breakdown of amino acids stored in skeletal muscles, and then transported to the liver. Another component of amino acids, not required for glucose production, is nitrogen. Excess nitrogen can be toxic and thus the byproduct must be disposed of by the liver.

"If mammals did not have the ability to adapt in this way, the very survival of the species would be threatened," Dr. Jain says.

The investigators found that levels of KLF15, short for Kruppel-like factor 15, change during the day, with peaks during periods of starvation. The team also found that KLF15 cyclically regulated expression of key enzymes involved in amino acid consumption, glucose production, and nitrogen disposal in the skeletal muscle and liver.

Animals lacking KLF15 developed low blood glucose levels and high ammonia levels. Over time, the abnormal levels in KLF15-deficient animals led to alterations in brain function.

"Current literature portrays amino acids as nutrients that are in a constant state in mammalian organisms," Dr. Jeyaraj, the lead author of this work, notes. "In contrast, our work in mice and humans identify nitrogen balance is a dynamic process and follows circadian variation."

"Importantly, we identify KLF15 as the missing molecular link between the biological clock and this process. The cyclical variations in [nitrogen balance](#) discovered by our team have far-reaching implications for many fields in medicine. For example in current medical practice we are frequently measuring glucose and lipid levels. Should we be measuring amino acids to guide clinical diagnosis or predict prognosis is an

important question that is currently in evaluation" Jeyaraj continues .

Indeed, these findings dovetail well with recent observations in human subjects. "Over the past several years, there has been an explosion of data from investigators at Duke and Harvard University suggesting that dys-regulation of amino acids (especially branched chain [amino acids](#)) and urea metabolites, byproducts of nitrogen detoxification, are associated with cardiovascular and metabolic disease," Dr. Jain explains.

These observations in humans are particularly interesting in light of a 2010 study in Science Translational Medicine from the Jain laboratory revealing that KLF15-deficient mice are susceptible to cardiovascular disease and heart failure. Furthermore, in a recent paper published in Nature, the same group reported that deficiency or excess of KLF15 causes electrical instability in the heart.

These findings, along with the observations in human subjects, suggest that disruptions in the circadian cycle of nitrogen homeostasis may predispose patients to cardiovascular disease and metabolic anomalies.

Dr. Jain adds, "Remember that people with altered circadian rhythms, such as nightshift workers, are also predisposed to diabetes and cardiovascular disease. We do not know if KLF15 is involved but it is an intriguing possibility."

As a continuation of this research, Dr. Jain developed a method to detect mutations in KLF15 that may contribute to patients with metabolic or cardiovascular diseases. He is currently initiating efforts to identify chemical compounds for gene therapy that will allow one to manipulate KLF15 levels.

Provided by Case Western Reserve University

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