Distinguished Lecture highlights circadian rhythms

By Robin Arnette

The May NIEHS Distinguished Lecture focused on circadian rhythms, or the changes most animals, plants, and microbes undergo in response to the light and dark cycles in an environment. John Hogenesch, Ph.D., from the University of Pennsylvania, has spent the past 15 years trying to understand how these clocks influence the physiology and behavior of organisms, particularly mammals. He shared highlights of his work May 15 in a presentation titled, "The Circadian Clock Network: Implications for Biology, Medicine, and Toxicology."

Hogenesch is a professor of pharmacology and associate director of the Institute for Biomedical Informatics at the University of Pennsylvania Perelman School of Medicine. (Photo courtesy of Steve McCaw)

The rhythm of life

Hogenesch began by explaining that most mammalian genes, including those important in toxicology, are under the control of a circadian oscillator, also known as a master clock. In humans, this clock is located in a small part of the brain called the suprachiasmatic nuclei (SCN). Hogenesch explained that the human sleep pattern is the result of both the master clock, which controls the sleep and wake cycles, and the sleep homeostat, which measures the amount of sleep a person gets. This circadian network is reset each day by light striking special photoreceptor cells in the eye.

"Rods and cones are the two types of photoreceptor cells in the eye that form images, but melanopsin is a nonimaging photoreceptor that sends a light signal from the eye to the SCN," Hogenesch said. "Inside each of the SCN neurons is a cell-specific clock that keeps biological time."

NIEHS Deputy Scientific Director William Schrader, Ph.D., hosted the presentation. "By the end of the talk," Schrader said, "[Hogenesch] will hopefully convince you that you aren't the same in the morning as you are in the afternoon." (Photo courtesy of Steve McCaw)

Hogenesch emphasized the importance of these cycles. For instance, the majority of heart attacks occur between 8 a.m. and noon, and most people experience a drop in blood pressure of 15-30 percent during the night. Core body temperature, lung and muscle function, and other biological processes, including the dysfunction of cancer, depend on a working clock.

Members of the Hogenesch lab determined that approximately 55 percent of the mammalian genome is under clock control and will experience a surge in gene expression during a particular time within the 24-hour cycle. Surprisingly, they also found that tissues from the same animal may have different expression patterns. Most gene expression in the liver peaks around dawn, in anticipation of the next day, and lung genes peak in anticipation of the night phase. "In contrast," Hogenesch said, "the kidney has a morning and evening rush hour."

Improving treatment of disease with chronotherapy

According to Hogenesch, both the majority of genes associated with disease and the targets of medicines to treat those diseases are under clock control. Researchers have published hundreds of papers on chronotherapy, or the use of chemotherapeutics at various times of the day, to improve health treatments.

One example Hogenesch discussed was the use of statins to treat high cholesterol. Pioneers in the field discovered that cholesterol synthesis occurs at night in humans, so a pharmaceutical company ran clinical trials and told patients to take their medicine before bedtime. The statins had a short half-life, so they were still in the body and available to inhibit the target.

"We looked at the top 100 best-selling medicines in 2013, as well as the World Health Organization's (WHO) list of the top 250 essential medicines," Hogenesch said. "We found that 56 of the top 100 and a similar percentage of WHO drugs also had short half-lives and hit clock-regulated genes."

In an effort to help other researchers find out if their favorite gene is regulated by the circadian clock, Hogenesch developed the Circadian Expression Profiles Data Base. He encouraged everyone in the audience to use the database in studies on how the circadian clock influences disease.

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., said that Hogenesch's work on circadian rhythms has significant implications in the field of toxicology. (Photo courtesy of Steve McCaw)

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