



Circadian Cycle and Metabolic Dysfunction

Speakers: Pere Puigserver (Dana-Farber Cancer Institute), Carla Green (University of Texas Southwestern Medical Center), Joe Bass (Northwestern University), Robert Levitan (Centre for Addiction and Mental Health, University of Toronto), Michael Terman (Columbia University)

Organizers: John G. Kral (SUNY Downstate Medical Center), Andrew Swick Presented by the [Diabetes and Obesity Discussion Group](#)

Reported by Alan Dove | Posted April 22, 2010

Overview

Ever since the first life forms developed, evolution has confronted the problem of timing: when should the organism eat, when should it reproduce, when should it rest? Across a span of nearly four billion years, our ancestors evolved to rise at dawn, sleep at dusk, feast in fall and fast in the winter.

That ancient schedule is still programmed into our genes, and we ignore it at our peril. Indeed, a growing body of evidence shows that the modern habits of waking to an alarm clock, sleeping after the "Tonight Show", and feasting all year round are largely responsible for some of the worst health problems of modern humans. The Academy's Diabetes and Obesity Discussion Group met on February 9, 2010 to discuss this interaction, in a meeting that featured presentations and a lively panel discussion by four leading researchers in the field.

Use the tabs above to find a meeting report and multimedia from this event.

Meeting Report

Feeding time

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Regulation of the nutrient cycle

Pere Puigserver started the session with an overview of the nutrient cycle, the system that his laboratory studies. The purpose of the nutrient cycle is to keep glucose and lipid levels in the bloodstream in balance, and to store excess food calories for future use. In mammals, the central regulator of this cycle is insulin.

After a meal, insulin levels in the bloodstream rise, stimulating the fat cells to take up glucose and synthesize lipids. Fasting shifts the balance in the other direction, causing insulin to drop and fat deposits to break down into glucose again. The liver mediates both sides of this cycle. "It's kind of a buffer tissue that basically supplies or reorganizes these nutrients," said Puigserver.

Traditional nutrition studies often treated the liver's response as a binary phenomenon, where eating triggers one set of responses and fasting triggers an opposing set. More recently, though, researchers have found that the nutrient cycle is more nuanced. In particular, the feeding response occurs in at least two phases.

The liver is the central regulator of the nutrient cycle.

In the first phase, insulin levels rise along with the activity of an enzyme called Akt, which carries some insulin-triggered signals inside different types of cells. As the meal progresses, insulin levels remain high, but Akt activity declines. Puigserver and his colleagues wanted to know how this change affects the nutrient cycle. "A lot is known about this first phase, but little was known about this second phase," said Puigserver.

To address that, the investigators put mice on a regimen of one meal a day, which synchronized their metabolisms to a 24-hour cycle of fasting and feeding. During the feeding, a transcription factor called PGC-1 α becomes significantly less active. PGC-1 α activity then rises during the fasting period. Looking more closely, the researchers uncovered a signaling cascade in which Akt phosphorylates another kinase called Clk2, which in turn inactivates PGC-1 α . The high Akt levels of the first feeding phase therefore explain the decline in PGC-1 α activity.

Expressing Clk2 constantly in the liver causes the mice to develop very high liver triglyceride levels, showing that in addition to suppressing glucose output, Clk2 also stimulates lipid synthesis. The investigators are now studying the effects of Clk2 in other tissues, such as fat, to determine how general its effects are. Because Clk2 acts through PGC-1 α , which is also regulated by circadian cycles, the same pathway could link diet, insulin sensitivity, and sleep patterns.

Nocturnin's effects on body weight

Carla Green has found another component of the system that links sleep cycles to diet and weight. Several years ago, Green and her colleagues set out to find circadian genes in the frog *Xenopus laevis*, by looking for changes in messenger RNA expression over the course of the normal day/night cycle. The screen uncovered Nocturnin, which the frog's retina expresses at high levels in the early part of the night. The team subsequently found that the *Nocturnin* gene encodes a deadenylase, an enzyme that can destabilize other messenger RNAs.

In mice, Nocturnin shows up in several tissues, including the suprachiasmatic nucleus of the brain, an area long linked to circadian cycles. However, deleting the *Nocturnin* gene had no effect on the animals' normal circadian patterns. "We do not think that Nocturnin is influencing the central clock or its ability to keep time," said Green, adding that "we instead think that ... Nocturnin is downstream of the clock, part of the output of the clock."

To test that hypothesis, Green and her colleagues put the Nocturnin-lacking mice through a series of tests, including a high-fat diet regimen. The diet makes wild-type mice obese and fills their livers with fat deposits, but it only stimulates modest weight gain and liver changes in animals without Nocturnin.

Switching the mice to a once-daily feeding pattern causes gradual weight loss in wild-type mice, but makes the *Nocturnin*-knockout mice lose weight much faster. Indeed, the knockout mice had to be removed from this experiment early, because they were beginning to starve to death. "This restricted feeding paradigm had really profound effects on the body weight and health of the knockout mice, they couldn't deal with the restricted food," said Green.

Besides the brain, *Nocturnin* is also expressed in the villi that line the intestine. Looking at this tissue, the researchers found large lipid droplets accumulating at the upper part of the villi. Feeding the mice radiolabeled lipids revealed that these molecules accumulate in the intestines of the knockout animals.

Nocturnin may link circadian cycles to fat absorption.

The data support the idea that Nocturnin is serving as an output of the central circadian clock, particularly in the digestive tract.

"We think that Nocturnin controls messenger RNA expression profiles post-transcriptionally, and ... we believe that it's also perhaps playing a role in the down-regulation of messenger RNAs that are under circadian control," said Green.

In the gut, Nocturnin may break down specific messenger RNA molecules to ensure that intestinal cells are ready to digest food at particular times of the day. In the absence of Nocturnin, the intestine absorbs much less fat, allowing more of the energy in the food to pass into the feces. Green and her colleagues are now testing that model, and trying to identify the messenger RNAs downstream of Nocturnin.

A "seasonal thrifty" phenotype?

Robert Levitan studies a slower type of circadian cycle: the seasonal clock. One of the best-described pathologies of this clock is seasonal affective disorder, or SAD, a condition in which patients develop depression, weight gain, oversleeping, and fatigue on a predictable annual cycle. In most cases, the depression and overeating begins in early winter and ends in the spring.

Because SAD affects mostly pre-menopausal women, Levitan wondered whether there was an evolutionary selective pressure that favored this pattern of behavior. "Are there fundamental seasonal mechanisms in humans that we share with other organisms living at northern latitudes that used to be very beneficial to our ancestors, but perhaps in modern day have become maladaptive and lead to obesity?" asked Levitan.

In this view, SAD could be an evolutionary remnant of a "seasonal thrifty" phenotype, which drove child-bearing women in northern latitudes to put on weight in the winter, give birth in the spring, and mate again in summer in order to capitalize on the seasonal availability of food. Consistent with this, the incidence of SAD increases with increasing latitude.

Was seasonal affective disorder originally a survival strategy?

To probe the biology of SAD, Levitan and his colleagues focused on the dopamine response, which is linked to pleasure-seeking as well as appetite. One type of dopamine receptor, called DRD4, shows a particularly interesting genetic pattern. One variant allele of DRD4, called the 7R allele, seems to have arisen about 40,000 years ago. "The most interesting thing to me about this gene, though ... is that it's been positively selected for over the last 40,000 years of human evolution," said Levitan.

In a sample of 182 patients with SAD, the researchers found that those with the 7R variant of DRD4 had higher body mass indices (BMIs) than patients with other versions of the gene. The patients with the 7R variant also had higher rates of binge eating.

Meanwhile, another group found that patients with SAD were more likely to have been born in the spring or early summer than in other seasons. Levitan's team then looked at both birth season and DRD4 alleles, and discovered that SAD patients who had the 7R allele and were born in the spring had maximum lifetime BMIs near 34. Patients with the 7R allele born at other times of the year had maximum BMIs below 30. A BMI of more than 30 is considered obese.

Spring birth and the 7R allele correlate with weight gain.

"That's quite an effect size for people born in the spring and having the high-risk allele," said Levitan. The results suggest that the 7R allele and a spring birth combine to drive the diet-related aspects of SAD.

Historical records show a dominant peak of births in springtime in northern European and Canadian populations, so many developing fetuses in those latitudes would have been in their second or third trimester during the fall and winter. If their mothers had SAD and carried the 7R allele, those fetuses would have been exposed to dopamine and melatonin cycles that could have forewarned them of a life of seasonal feasts and famines.

"It's entirely possible that a fetus knows its latitude even before it's born. Presumably if that's the case, there may be epigenetic mechanisms that are triggered influencing the dopamine system that later in life will sensitize that individual to develop seasonal depression and overeating," said Levitan.

Light therapy for circadian phase disorders

Michael Terman brought the discussion into the clinic with a presentation about his own work in the burgeoning field of chronotherapeutics. Because researchers are still trying to figure out all of the components of human biological clocks, Terman argued that it is too early to target specific molecules in these systems clinically. "The focus at this point cannot be on manipulation of the mechanics of peripheral oscillators—we wouldn't dare interfere or interject ourselves into that system at this point," said Terman.

Fortunately, much simpler interventions can already reset patients' biological clocks, using triggers such as bright lights and melatonin pills to stimulate the suprachiasmatic nucleus of the brain. Indeed, most people in modern societies are already manipulating their brains' central clocks with light, or the lack of it. "When you measure indoor light levels, we live perennially under twilight illumination," said Terman.

Living in perpetual twilight can have serious medical consequences.

Individual responses to this perpetual twilight vary dramatically. In one study, Terman and his colleagues found that the evening rise in melatonin levels, a crucial hormonal cue for bedtime, occurred across a six-hour time span in a group of patients. When a clock on the wall indicates midnight, some people's body clocks are set only at 6:00 pm. The consequences of this temporal misalignment can range from mild insomnia to debilitating depression.

A 30-minute exposure to bright, broad-spectrum white light can resynchronize a patient's body clock, but only if it's delivered at the right time. A simple morningness-eveningness test called the Horne-Östberg test, originally developed for industry, can read a person's biological clock quite accurately; Terman and his colleagues found that Horne-Östberg chronotype scores correlate tightly with evening melatonin levels. "On the basis of a ten minute questionnaire, we can estimate where your melatonin onset is going to be ... and therefore we can schedule the light to maximally deliver a phase shift at the appropriate time," said Terman.

Based on their results, researchers have developed and tested a clinical protocol for treating clock-related disorders. For example, they may treat severely depressed patients by depriving them of sleep for one night,

then administering light therapy and melatonin at precise intervals to gradually reset the patients' body clocks. Such chronotherapeutic combination treatment appears to work well, and while it is compatible with drug treatment, it brings far more rapid results than drug monotherapy, even reducing the duration of hospital stays.

A panel discussion after the talks ranged as widely as the presentations themselves, touching on everything from the molecular mechanisms of clock regulation in the mouse intestine to the role of architecture in human chronobiology. The field still has many questions to answer, but one thing is clear: it's a good time to be studying clocks.

Open Questions

How does Clk2 affect both gluconeogenesis and lipogenesis?

Does the central circadian clock control Clk2 activity directly or indirectly?

Where does the excess food energy go in mice lacking Nocturnin?

What environmental signals normally induce Nocturnin activity?

Does season of birth correlate with other circadian disorders besides SAD?

How does the 7R allele of the dopamine DRD4 receptor affect appetite and mood?

Can light therapy treat disorders that are not directly linked to the circadian clock?

To what extent does the disruption of natural day/night cycles account for the global obesity pandemic?

Media



Slides & Audio

[Nutrient Cycles Coupled to Insulin Signaling and Transcription](#)

Pere Puigserver (Dana-Farber Cancer Institute)



Slides & Audio

[Loss of Nocturnin, a Circadian Deadenylase, Confers Resistance to Diet-induced Obesity](#)

Carla Green (University of Texas Southwestern Medical Center)



Slides & Audio

[Is There a Seasonal Thrifty Phenotype?](#)

Robert Levitan (Centre for Addiction and Mental Health)



Slides & Audio

[Clinical Control of Circadian Phase with Light Therapy](#)

Michael Terman (Columbia University)

Abstracts

Nutrient Cycles Coupled to Insulin Signaling and Transcription

Speaker: **Pere Puigserver**

Dana-Farber Cancer Institute

Changes in expression of genes encoding for proteins that control metabolic pathways is essential to maintain nutrient and energy homeostasis in individual cells as well as in organisms. A hallmark for metabolic diseases is an inability to respond adequately to nutrient levels and fluctuations. In this context, the PGC-1s transcriptional coactivator complexes participate in a large array of glucose and lipid metabolic adaptations in mammals. Using skeletal muscle cells as a metabolic model system we have found two different nutrient sensing pathways that control nutrient utilization. The first pathway involves a response to low nutrients and glucose that in a cell-autonomous manner switches from glucose to fatty acid oxidation via an increase in a specific subset of mitochondrial genes. This coordination switch to fatty acid oxidation and full respiration activities is controlled through PGC-1a and PGC-1b lysine acetylation. This reversible chemical modification is controlled by the deacetylase SIRT1 and the acetyltransferase GCN5. The second pathway involves the nutrient-dependent mTOR kinase that is activated by growth factors and high nutrients such as glucose and amino acids. mTOR positively controls mitochondrial oxidative function through regulation of PGC-1s and other mitochondrial transcriptional regulators. Mechanistically, we found mTOR in transcriptional complexes bound to the chromatin of genes controlling the expression rates. In vivo, mice treated with the mTOR inhibitor rapamycin develop several symptoms of type 2 diabetes including reduction of skeletal muscle mitochondrial oxidation. Gene expression analysis indicates that genes involved in glucose and lipid metabolic pathways are altered in mice treated with rapamycin. Interestingly, the severity of glucose intolerance is dramatically exacerbated in mice fed with high-fat diet. In conclusion, we have identified two nutrient-dependent molecular mechanisms that involve regulation of PGC-1 pathway and mediate control of skeletal muscle mitochondrial nutrient oxidation activities. Our results suggest the possibility to target the enzymes that control this pathway in metabolic diseases.

Loss of Nocturnin, a Circadian Deadenylase, Confers Resistance to Diet-induced Obesity

Speaker: **Carla B. Green**

University of Texas Southwestern Medical Center

Nocturnin is a deadenylase that controls mRNA expression in a circadian manner by degrading the poly-A tails of target mRNAs, leading to mRNA turnover or translational silencing. Previously we reported that a mouse lacking Nocturnin was resistant to diet-induced obesity and hepatic steatosis. The lean phenotype

was not due to increased activity, decreased food intake or a higher metabolic rate. Transcript analysis in liver showed alterations in genes associated with lipid uptake and utilization. Through a subsequent series of in vivo and in vitro studies, we demonstrated that the Nocturnin KO mice are deficient in their ability to take up lipids. These animals have significantly disrupted lipid trafficking in the enterocytes, resulting in decreased absorption via apoB-containing non-HDL lipoproteins. We propose that Nocturnin has a role in the absorption of dietary lipid in bowel, presumably by altering genes necessary for metabolism or digestion through circadian post-transcriptional modifications of targeted transcripts.

Circadian Clock Gene Disruption in Obesity and Metabolic Disease

Speaker: **Joe Bass**

Northwestern University

Circadian rhythms of physiology and behavior represent a conserved organizing mechanism to optimize internal systems involved in energy storage and utilization in synchrony with the daily rotation of the Earth. Like the metabolic system, the circadian system involves a complex network of feedback loops involved in both transcriptional and post-transcriptional regulatory pathways in brain and peripheral tissues. In mammals, the core clock in the suprachiasmatic nucleus functions to entrain extra-SCN and peripheral clocks to the light-dark cycle, including regions central to energy homeostasis and sleep, as well as peripheral tissues involved in carbohydrate and lipid turnover. Recent evidence indicates that genetic and environmental disruption of circadian cycles results in impairment of both sleep and metabolism, and may contribute to risk of obesity, diabetes and cardiovascular disease. Our goal is to exploit genetic models of circadian disruption in rodents in order to identify targets and mechanisms coordinating biological timing with feeding, energy expenditure and metabolism.

Is There a Seasonal Thrifty Phenotype?

Speaker: **Robert Levitan**

Centre for Addiction and Mental Health

The classic thrifty hypothesis of Barker and Hales is based on the notion that maternal-fetal signaling of an impoverished food environment can trigger a thrifty response in her offspring intended to enhance survival if food supplies remain scarce. In modern developed countries, this otherwise adaptive process becomes a risk factor for obesity and diabetes due to the resulting mis-match between predicted caloric conditions and actual food resources. Over the last 40,000 years of human evolution, which has included several extended periods of glaciation across North America and Europe, it is likely that seasonal changes were a highly predictable signal of low food availability. If so, there ought to be one or more "seasonal thrifty phenotypes" encoded in our genes intended to optimize survival and reproduction in the face of predictable seasonal famines. This talk will provide epidemiological and genetic evidence for at least one putative "seasonal thrifty phenotype", focusing on a hypo-functional variant of a dopamine receptor gene. This variant, the 7-repeat allele of the dopamine-4 receptor gene, has been shown to influence food intake and has been positively selected over recent human evolution.

Clinical Control of Circadian Phase with Light Therapy

Speaker: **Michael Terman**

Columbia University

Disruption, phase shifts and dampening of circadian rhythms, and abnormal internal phase relationships among rhythms are thought to underlie a range of medical and psychiatric disorders. The paradigmatic examples are seasonal affective disorder and delayed sleep phase disorder. Timed light exposure provides the primary corrective measure. The circadian phase-response curve to light is bipolar, with light in the evening and throughout most of the night eliciting phase delays of the internal clock, and light toward the end of the night and the morning eliciting advances. Physiological day and night, however, differs markedly between individuals and is often poorly synchronized with the outdoor day-night cycle. Successful clinical administration of light therapy must therefore be timed individually, in distinction from the dictates of the clock on the wall.

Books and Web Site

[Automated Morningness-Eveningness Questionnaire](#)

This questionnaire was developed by Michael Terman and others at the [Center for Environmental Therapeutics](#).

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Pere Puigserver

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Speakers



Joe Bass, MD, PhD

Northwestern University

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Joseph Bass is an associate professor in the Department of Medicine, Division of Molecular Medicine and Endocrinology, at the Northwestern University Feinberg School of Medicine, and in the Department of Neurobiology and Physiology. The major research focus of his group is on the molecular integration of circuits coordinating feeding, sleep, and wakefulness with systems controlling energy balance and nutrient utilization. This work stems from recent discoveries on the role of the circadian clock gene network in the integration of both brain and peripheral tissue energy sensing and metabolism. The Bass lab exploits approaches ranging from cell biology, to whole animal physiology, experimental genetics and behavioral analyses in order to elucidate the pathophysiology of diabetes, obesity, and metabolic syndrome in states of circadian and sleep disruption, and the reciprocal interplay between metabolic disease states and circadian disorders.



Carla Green, PhD

University of Texas Southwestern Medical Center

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Carla Green is a professor of neuroscience at the University of Texas Southwestern Medical Center. She received her PhD from the Department of Biochemistry and Molecular Biology at the University of Kansas Medical Center where she worked on the structure and function of a human prostate-specific gene with Simon Kwok. Her postdoctoral research with Joseph Besharse in the Department of Anatomy and Cell Biology at the University of Kansas Medical Center marked the beginning of her interest in circadian biology. While in the Besharse lab she identified a number of circadian clock-controlled genes, including a novel rhythmic gene *Nocturnin*, in the *Xenopus* retina

After starting her own lab at the University of Virginia in 1997, she continued to use that model system to study molecular mechanisms of retinal clock function, developing tools to perturb clock function molecularly

in transgenic *Xenopus*. She also continued her studies on the Nocturnin gene and demonstrated that this gene encodes a deadenylase—a polyA-specific ribonuclease that removes the polyA tails from mRNAs. More recently, her lab has begun to focus on mammalian model systems and, in addition to a continued focus on Nocturnin and its role in clock control of metabolism, also works on the role of the Cryptochrome proteins in the central circadian mechanism.

In September of 2009, she moved to the University of Texas Southwestern Medical Center to join the Department of Neuroscience. Carla Green is a fellow of the American Association for the Advancement of Science.



Robert Levitan, MD

Centre for Addiction and Mental Health

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Robert Levitan is an expert on atypical subtypes of mood disorders characterized by depressed mood and increased eating behavior, including atypical depression, seasonal affective disorder, and eating disorders such as binge eating disorder and bulimia nervosa. In many cases, these various disorders co-exist in the same individual, suggesting that one or more vulnerability factors are shared among them. Levitan integrates clinical research in adults with developmental research focused on the early origins of disease. This includes both genetic association studies and novel methodologies emerging from the rapidly evolving field of socio-biology, which focuses on the interplay of nature and nurture. A better understanding of the complexity inherent in these disorders will lead to new prevention strategies and treatment approaches.

Levitan is a senior clinical investigator in the mood disorders clinic at the Centre for Addiction and Mental Health, Toronto and is a full professor in the Department of Psychiatry at the University of Toronto. Levitan is also the immediate past-president of the Society for Light Treatment and Biological Rhythms (SLTBR).



Pere Puigserver, PhD

Dana-Farber Cancer Institute

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Pere Puigserver received his PhD in biochemistry from the University of Illes Balears, Spain, in 1992. He did postdoctoral research with Bruce Spiegelman at DFCI before joining the faculty as an assistant professor of cell biology at Johns Hopkins University School of Medicine in 2002. In 2006, Puigserver rejoined the faculty of Harvard Medical School and DFCI to continue his research on the genetic and biochemical mechanisms underlying the control of intermediary metabolism by nutrients and hormonal signals in mammals. In 2008 Puigserver was promoted to associate professor of cell biology at Harvard Medical School and Dana-Farber Cancer Institute.



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Michael Terman is professor of clinical psychology in Psychiatry at Columbia University, research scientist VI at the New York State Psychiatric Institute, director of the Center for Light Treatment and Biological Rhythms at New York-Presbyterian Hospital / Columbia University Medical Center (www.columbia-chronotherapy.org), and president of the Center for Environmental Therapeutics () an independent 501(c)(3) nonprofit consortium of mental health clinicians and chronobiologists. His animal research has focused on circadian rhythmicity in visual sensory and retinal function, circadian entrainment by feeding schedules, and the zeitgeber properties of naturalistic dawn-dusk transitions. His clinical research has led to the development of 10,000 lux light therapy, dawn simulation therapy, and negative air ionization therapy for depressive disorders. He is a co-author of the first treatment manual in the field, "Chronotherapeutics for Affective Disorders" (Karger, 2009).

Alan Dove

Alan Dove is a science writer and reporter for *Nature Medicine*, *Nature Biotechnology*, and *Bioscience Technology*. He also teaches at the NYU School of Journalism, and blogs at <http://dovdox.com>.