Circadian Rhythms in Gastrointestinal Health and Diseases

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Circadian clocks are present in most organisms and mediate the interplay between the environment and physiologic processes.[1] Normally, clocks adjust physiologic responses to anticipated stimuli times. Disruption of circadian clocks/rhythms exacerbates several chronic diseases. The "central" circadian pacemaker is in the suprachiasmatic nucleus in the hypothalamus and is responsible for biological rhythms regulated by the light/dark cycle (LDC). Peripheral tissues show circadian oscillations that are coordinated by the central pacemaker.[2] The LDC entrains circadian rhythms over a 24-hour cycle, enabling organisms to adapt to environmental changes. Peripheral tissues also possess self-sustaining, entrainable circadian timers not regulated by the LDC. In particular, the gastrointestinal (GI) tract and liver, which mediate food processing, are entrained by food and eating times.[3]

Circadian rhythms regulate a variety of GI processes including cell proliferation, immune homeostasis, gut permeability and microbial balance,[4] and metabolism. In May 2016, with support from the National Institutes of Health (NIH R13), we held the first symposium on Circadian Rhythms in GI Health and Disease in Chicago, in recognition of the emerging role of circadian disruption in diseases of modern life style (obesity; the metabolic syndrome[5]) and cancer.[6] as well as alcohol's effects on gut and liver.[7] This summary reviews the topics covered in this meeting (Figure 1).

Clocks and the Digestive System

In this section, Dr Turek covered the role of circadian clocks in the digestive tract. Clocks encompass transcriptional, translational feedback loops that keep time through several oscillating proteins in interwoven feedback loops. These clocks regulate ≤30% of genes expressed in a given tissue including gut and liver.[4] In modern societies, humans—when they are active, or when they sleep or eat out of synchrony with their suprachiasmatic nucleus clock—frequently experience disruption of the normal phase relationship between the central pacemaker and peripheral clocks. This circadian misalignment can contribute to GI and metabolic diseases.

Dr Brown reviewed how metabolism is governed by the clock, both systemically and locally via cell-autonomous circadian clocks.[5] Clock control of metabolism can be exerted via chromatin-level modifications of nuclear hormone receptors. Recent data suggest the clock can directly control, by post-translational mechanisms, cellular respiration and other mitochondrial functions, particularly in frequently-dividing cells such as GI epithelial cells.[5] This metabolic adaptation to circadian rhythms allows coordination of digestive-system physiology with the environment (e.g., food acquisition and consumption).[3]

Dr. Tischkau covered how this coordination is then orchestrated by sensors linking the environment to circadian machinery. One of these environmental sensors is PAS-domain-containing proteins. The aryl hydrocarbon receptor (AhR), a member of the PAS family, can directly affect transcriptional, translational feedback loops.[8] AhR, upon activation, forms a heterodimer with the circadian clock protein BMAL1, inhibiting CLOCK/BMAL1 activity. Multiple ligands in food can bind AhRs, which could mediate the effects of eating habits on circadian rhythms, and circadian-controlled genes. AhRs are intriguing targets for circadian-based interventions that strengthen intestinal–central circadian synchrony and control metabolism.

Circadian Dysrhythmia in GI Diseases

Intestinal barrier integrity is critical to health; barrier dysfunction contributes to development/progression of inflammation-mediated diseases both in and outside of the GI tract. Dr Keshavarzian showed that circadian disruption, in environmental models (shifting the daily LDC) or genetic models (*Clock*$^{\Delta 19}$) induced intestinal hyperpermeability (IHP), which was exaggerated by alcohol. Barrier dysfunction was associated with shifts toward proinflammatory profiles in intestinal microbiota and intestinal gene expression.[7] This finding suggests that circadian disruption contributes to IHP and a proinflammatory state, owing, at least in part, to perturbed relationships between intestinal microbiota and intestinal gene expression. Dr Swanson presented a recent human study on the effects of circadian disruption on alcohol-induced IHP (AIHP) comparing night shift with day shift workers for response to small doses of alcohol (0.5 g/kg = 2 glasses of wine per day for 7 days).[9] Night workers had increased AIHP, which was correlated with 24-hour area

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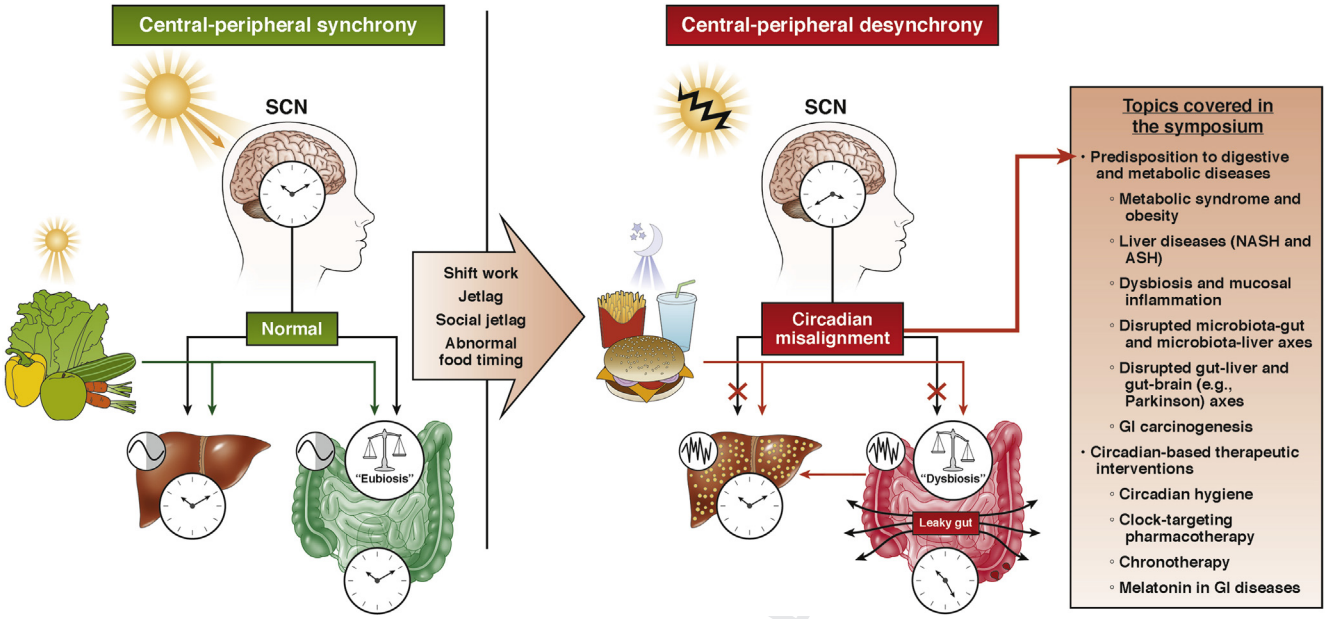

Figure 1. Under physiologic conditions, there is a synchrony between the central circadian clock in the suprachiasmatic nucleus (SCN) and the peripheral (hepatointestinal) circadian clock (*left panel*). Whereas the SCN is entrained by light, the latter, in addition to SCN signals, could respond to food. Disrupted light exposures (eg, shift work, jet lag) or dyssynchrony between food and light signals (eg, abnormal eating pattern) could cause central–peripheral misalignment, predisposing to a variety of digestive and metabolic pathologies (*right panel*). ASH, alcoholic steatohepatitis; GI, gastrointestinal; NASH, nonalcoholic steatohepatitis.

under the curve of serum melatonin, a measure of central circadian alignment. Alcohol, even in small amounts, can disrupt central circadian rhythms if combined with circadian misalignment (night shift workers). Also, alcohol disrupted peripheral circadian rhythms (expression of circadian genes in peripheral blood mononuclear cells). The interaction of alcohol and circadian disruption in disease states was confirmed by looking at serum inflammatory markers. Therefore, circadian disruption is a key cofactor in AIHP and vulnerable individuals (night workers) should be monitored more closely for conditions associated with AIHP (eg, liver injury).

Circadian disruption was recently implicated in pathologies associated with Westernized diets (eg, high fat). Dr Leone discussed the mediating role of microbiota in regulating circadian homeostasis and high-fat–induced obesity.[10] A high-fat diet could alter diurnal patterns of gut microbiota and microbial metabolites in mice. Butyrate modulated circadian clock gene expression (eg, in hepatic organoids) in vitro suggesting that microbe-derived metabolites directly affect circadian clocks within peripheral tissues involved in metabolic outcomes. Therefore, Westernized diets can alter diurnal patterns of gut microbiota and their metabolites, resetting peripheral circadian clocks and host metabolic responses.

Another new question arose at the meeting concerning how eating habits (eg, type and time of food) control and shift microbiome rhythms. A potential role for gut-secreted melatonin in passing circadian timing cues from host to commensal bacteria was presented by Jiffin Paulose from Dr Cassone's laboratory. Melatonin increased motility and swarming in *Enterobacter aerogenes*, an effect that is at least partially mediated by melatonin receptors.[11]

Circadian Rhythms, Obesity, and the Metabolic Syndrome

Metabolism is closely regulated by circadian rhythms; rhythm disruption is increasingly recognized in pathologies related to metabolism (obesity; the metabolic syndrome). Dr Bass discussed the link between the clock and glucose control. Blood glucose levels are tightly controlled by insulin, which is released by pancreatic β-cells in response to a meal. How does the intrinsic circadian clock of β-cells synchronize with cycling food intake and the body's demands? Oscillations of insulin secretion occur in synchrony with the expression of insulin regulatory genes. The cycling transcription of this metabolic gene network is regulated by CLOCK/BMAL1, co-localizing with the pancreatic transcription factor PDX1 within the active-enhancers region. Clock disruption (ie, via *Bmal1* ablation) causes diabetes in mice. This highlights the transcriptional mechanisms by which the circadian machinery controls peripheral metabolism.[12]

Circadian clocks control metabolism also through post-transcriptional effects as reviewed by Dr Green. *Nocturnin* is an output of the clock and a circadian-controlled gene that affects metabolism by removing the poly(A) tails from mRNAs, modulating mRNA stability or translatability. Nocturnin-deficient mice are resistant to obesity owing to inefficient utilization of dietary lipids in the intestine.[13] Nocturnin also affects lipid metabolism and mitochondrial functions outside the intestine, and links the clock to