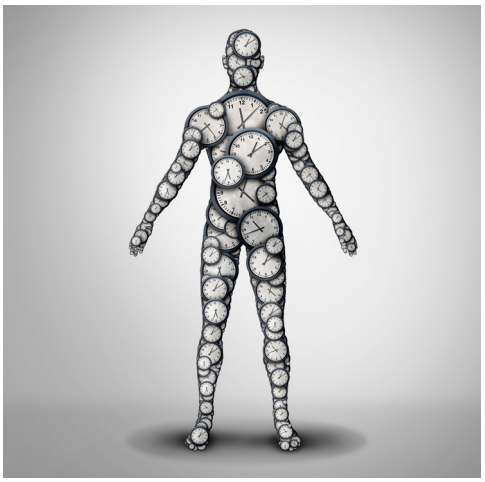
Circadian Rhythm and Obesity: The Role of the Body's Clocks in Metabolic Disorders

800 million people worldwide struggle with obesity, a disease poised to cost over $1 trillion in medical consequences by 2025. Over 40% of the US population is impacted, according to the Centers for Disease Control. Obesity is a major risk factor in the development of illnesses that lead to diabetes, such as insulin resistance, hypertension, and other metabolic disorders.

Long-term disruptions to circadian rhythm, the 24-hour cycle that governs most of the body's activities, are associated with many conditions including obesity, impaired glucose tolerance, and type 2 diabetes. Circadian rhythm has shown bidirectional interaction with almost all metabolic processes and with energy homeostasis.[1] Recent studies demonstrate that the circadian clock controls energy homeostasis by regulating the cyclical expression and activity of the enzymes, hormones, and transport systems involved in metabolism.[2]



Thousands of circadian clocks create a feedback loop and regulate physiological processes like energy homeostasis.

The Master and Peripheral Circadian Clocks

Circadian rhythms are inborn, 24-hour cycles that influence many behaviors and physiological processes such as the sleep-wake cycle and how organisms anticipate and adapt to their environments.[3] They are controlled centrally by the suprachiasmatic nucleus (SCN) located in the brain's hypothalamus. The SCN serves as the master clock, governing peripheral clocks throughout tissues including the liver, muscle, gut, heart, and pancreas.[4,5] Taken together, the central and local circadian systems form a feedback loop that regulates critical functions like energy homeostasis, hormone secretion, cardiovascular health, and body temperature. The SCN is the master synchronizer of this loop.

The SCN requires daily resetting to the external light-dark cycle to align the body's rhythm with its environment. Several external cues, called "zeitgebers," help. The word "zeitgeber" comes from German "zeit" meaning "time," and "geber" meaning "giver."[6] These "time givers" include light, temperature, timing of food intake, and exercise. Many changes can throw off the body's natural rhythms, including eating late, working at night, traveling across time zones, and taking medication. When the body's clocks are in sync, food intake, gastrointestinal activity, and metabolic function increase during the day and decrease at night in preparation for sleep.[7] Trouble arises when there are disruptions to the circadian cycle either at the central or local level.

Disruptions to the Central Clock Leading to Obesity

For the central clock, light is the most important trigger. When natural light fades and darkness sets in, production of the hormone melatonin increases. Melatonin helps regulate central and peripheral circadian expression.[3] For example, in adipose tissue, melatonin synchronizes metabolic and hormonal function by regulating the rhythm of genes involved in balancing carbohydrate and lipid metabolism.[8] A trigger like artificial light in the evening can disrupt the central clock, decrease melatonin production, and contribute to sleep issues that in turn alter the circadian rhythms of local processes like metabolism.

Long-term circadian disruptions induced by sleep deprivation are associated with excessive food intake and increased obesity risk.[9] In studies, sleep restriction impacts ghrelin and leptin levels, causing subjects to eat more. Ghrelin, the hunger hormone which signals the body to eat, increases, while leptin, the satiety hormone that gives the sensation of feeling full, decreases.[9]

The Wisconsin Sleep Cohort study found that 5 hours of habitual sleep time was associated with a 15% decrease in morning leptin levels and a similar increase in morning ghrelin levels.[10] Another study showed a 14% increase in caloric intake and a preference for carbohydrate-rich nutrients when subjects had full access to a buffet after four nights of 4.5 hours of sleep.[11] Taken together, these studies indicate that shorter sleep cycles not only increase how much food a person eats, but also lead them to choose high-calorie foods that are more likely to be stored as fat.

Losing sleep not only leads to eating more food, but also to choosing high-calorie foods.

Disruptions to Peripheral Clocks Leading to Obesity

Thousands of peripheral clocks work independently throughout the body in organs like the heart, pancreas, and liver, and re-synchronize continuously to the SCN.[3] In contrast to the central clock which responds to light, the major zeitgeber for peripheral clocks is timing of fasting and feeding.[5] While inducing obesity in humans, even for science, is not practical, many researchers have explored the impact of feeding and fasting times on weight gain in animal models. In studies, feeding mice when they would normally rest disrupted peripheral clocks and caused overeating that led to leptin resistance, physical inactivity, liver fat accumulation, and obesity.[12]

To understand the importance of circadian gene expression, researchers have altered or removed specific circadian genes in mice. The mutated mice exhibited excessive overeating which led to a 35% increase in fat mass compared with normal mice.[13] These studies reinforce how local circadian disturbances impact the entire system, leading to changes in eating behavior, weight gain, and, ultimately, obesity.

* Zeitgeber Impact on Human Clocks and Metabolism

Zeitgeber	Metabolic Impact
Circadian Disruption (Shift Work, Jet Lag, Sleep Disorder)	Abnormal glucose and lipid metabolism Insulin Sensitivity ↓ Inflammation ↑ Adverse Cardiovascular Consequences
Eating Patterns (Early meal, Intermittent fasting, Time-restricted feeding)	Fluctuations in: Plasma glucose, insulin, GLP-1, triglycerides, BMI, blood pressure, body weight, β-cell responsiveness, oxidative stress, fat oxidation, and cholesterol
Physical Activity (Timed exercise)	Changes to: Oxygen consumption, respiratory exchange ratio, heart rate, blood glucose levels, and body temperature

**Adapted from Guan and Lazar.[16]*

It's All about Timing: Exploring Circadian Interventions and Therapies

Researchers explore links between circadian rhythm and metabolic disorders to understand causes and effects and develop potential interventions. Zeitgebers like exercise, medication, and meals are clear targets. Researchers explore how purposeful timing of these cues may impact health.

The field of chronoexercise explores how to optimize the timing and length of exercise to an individual's specific circadian rhythm to positively impact health and conditions like metabolic disease and insulin sensitivity.[14] Chronopharmacology helps determine the best time to take certain medications to improve their efficacy.[15] To that end, researchers can establish a person's melatonin profile to help determine their Dim Light Melatonin Onset (DLMO), the time of day when their brain begins producing melatonin, which is important in therapeutic applications.

Many studies look at the impact of eating patterns on circadian rhythm and health. Timed meals are an approach to resetting the circadian clock and mitigating obesity. Based on animal studies, calorie restriction and intermittent fasting regimens may provide time cues that can reset the circadian clock, leading to potential health improvements.[2]

Summary

Obesity is a complex condition mediated through several pathways.[5] Direct impacts to either the central clock via disturbances like ambient light and shortened sleep, or through peripheral clocks by mistimed food consumption and fasting, alter circadian rhythms and have a cascade effect on hormone secretion and physiological processes. These lead to overeating and poor metabolic processing, among other problems, resulting in increased risk of obesity. There are many ways to positively impact the circadian clock and the physiological processes it controls through established routines that respect the body's natural rhythms. Fields like chronoexercise and chronopharmacology (also called chronotherapeutics) explore how to align external cues and activities to your body's natural rhythm, increasing the potential for positive health effects.

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