

Impact of circadian disruption on energy balance and diabetes risk

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We are impressed but passive observers of the "metabolic big bang", resulting in the dual explosion of Obesity and type 2 Diabetes Mellitus throughout the developed and even the developing world. Diabetesity, the new epidemic, has risen as a major public health problem since it greatly increases chronic diseases with huge human and socioeconomic burdens. Further comprehension of the underlying pathophysiology is an urgent need for the development of novel preventive and therapeutic strategies. Behavioral and environmental changes in modern societies act as circadian disruptors with detrimental effects on energy balance, body weight, wellbeing and overall health. Circadian disruption and sleep disorders emerged as new players in the field of Diabetes.

During the past decade, numerous data from experimental and epidemiological studies have suggested that delayed feeding, prolonged nocturnal activity and exposure to artificial light, excess use of self-luminous devices at nighttime, long-term and frequent shift work, reduced sleep duration and abnormal sleep architecture cause circadian misalignment. This, in turn, promotes central obesity, inflammation, insulin resistance, hypertension, cancer, depression and/or anxiety, neurodegenerative diseases, immunological disorders, hypertension, cardiovascular diseases and T2DM. Chronobiology was thrust into the spotlight with the 2017 Nobel Prize in Physiology or Medicine awarded to Jeffrey Hall, Michael Rosbash and Michael Young for the discoveries over the past 15 years of the genetic and molecular mechanisms of circadian rhythms and of their fundamental role in the regulation of cellular metabolism. In addition to recognizing their groundbreaking work, the Prize also served as: a) a call for further molecular and epidemiological research about the impact of sleep quantity and quality on health, b) a "social alarm" for humans neglecting their circadian clock and pushing their bodies beyond internal borders, since a disturbed clock becomes a potential ticking time bomb and c) a Roadmap to Metabolic Therapeutics, Chronopharmacology, Chronotherapy, Chrononutrition and other emerging applications. Living organisms, spanning from cyanobacteria to humans, are governed by common daily cycles known as circadian rhythms. They represent an evolutionarily conserved adaptation of cellular processes, physi-

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ological functions and behavioral patterns to the predictable cycle of light and dark on Earth in order to optimize energy homeostasis. The word “circadian”, introduced by Franz Halberg, is derived from Latin words *circa*=about and *diem*=day and literally means “about a day”. Thus, circadian rhythms are endogenous, self- sustained oscillations of ~24h in the biological and biochemical landscape (tissue, cell, subcellular compartment as mitochondria, body temperature, blood pressure, levels of circulating hormones and metabolites, CNS outputs, gut microbiome, etc).

In mammals and humans, the circadian timing system is organized into a hierarchical manner with a central pacemaker or master circadian clock, located in the suprachiasmatic nuclei (SCN) of anterior hypothalamus and formed by a net of ~20,000 neurons. Light/Dark cycle is the most important timing cue (Zeitgeber) that sets SCN at a periodicity of ~24h. Transmission of light signals via the retinohypothalamic tract facilitates adaptation to the geographical location and daytime. In turn, SCN interacts with peripheral clocks, consisted of oscillators in various brain regions and peripheral organs including heart, lungs, liver, pancreas, kidneys, adipose tissue and endocrine glands. The SCN acts as the hypothalamic link between the retina and peripheral oscillators, entraining them to the Light/Dark cycle. Physical activity, nutrient availability, meal timing and GLP-1 release can reset peripheral clocks and crosstalk with SCN. Glucocorticoids, melatonin, neuroendocrine outputs and direct autonomic innervation are the main endogenous signalling mechanisms by which the SCN maintains alignment of central and peripheral oscillators. A main SCN–CRH–ACTH output drives a rise in adrenal glucocorticoids just before activity onset. This promotes arousal and alertness by enhancing liver gluconeogenesis. Melatonin is an endogenous hormone produced by the pineal gland exclusively at night (21.00-4.00) and responsible for initiation and maintenance of sleep and circadian rhythmicity. Recent data support that it affects the insulin secretory activity of the pancreatic beta cells, hepatic glucose metabolism and insulin sensitivity. Additionally, melatonin exerts potent antioxidant, anti-inflammatory and oncostatic properties, especially in breast cancer. Reduced melatonin levels, mutations and/or genetic polymorphisms of the melatonin receptors

MTNR1B are associated with an increased risk of developing type 2 DM.

Chronic exposure to artificial light at night (ALAN) in work, home and social life result in melatonin synthesis suppression, circadian misalignment and sleep/wake cycle disruption with sleep deprivation. The widely used electric lights, like Daylight White Fluorescent and energy-saving Compact Fluorescent ones, are richer in blue λ and suppress melatonin release when used within 1h of bedtime. A new source of ALAN is nighttime use of personal computers, mobile phones, electronic tablets, televisions, and internet world "surfing", a behavioral epidemic in adults, adolescents and school-aged children. ALAN pollution of urban areas is a modern threat for ecosystems and humans. Unfortunately, ALAN exposure occurs concomitantly with severe decrease of exposure to sunlight, whose blue-violet (446-484 nm) spectrum synchronizes the circadian clocks and whose UV-B (290-315 nm) spectrum stimulates vitamin D synthesis. Vitamin D insufficiency or deficiency in combination with melatonin suppression is a dual deleterious factor for health. The association of exposure to ALAN and higher BMI has been found statistically significant in both adults and paediatric populations.

At the cellular level, circadian oscillation is encoded by a transcription-translation feedback loop (TTFL) of interacting transcriptional factors known as clock genes. This family includes CLOCK, Bmal1, Per1, Per 2, Per 3, Cry1 and Cry2, ROR α and REV-ERB α . The positive limb of the loop contains a heterodimer complex of CLOCK: BMAL1 which binds to E-box motifs and upregulates the transcription of circadian genes, including those from the cryptochrome family (Cry1 and Cry2) and the period family (Per1, Per2 and Per3). The negative limb of the loop contains protein products of the Per and Cry genes which heterodimerise to form PER–CRY and repress BMAL1: CLOCK activity. REV-ERB α and ROR α control the timing and amplitude of BMAL1 expression and provide additional stability to the molecular oscillator. The CLOCK: BMAL1 complex stimulates mitochondrial biogenesis and mitophagy through activation of SIRT1 and plays a critical role in mediating the transcription of coactivators that regulate the synthesis of 25% of genes and most of the enzymes and hormones involved in glucose homeostasis, i.e., regulation of hepatic glu-

coneogenesis and pancreatic β -cell insulin secretion. Elegant studies demonstrate that the molecular circadian clock is coupled to metabolism at the cellular level, and that circadian mutant animals develop metabolic dysregulation, obesity, impaired glucose tolerance/diabetes and reduced lifespan. Obvious circadian disruption is found in shift workers (eg, airline crews, truck drivers, medical doctors, nurses, scientific technical staff, law enforcement and the military) and has been correlated with increased risk of breast and prostate cancer, increased BMI, IGT, DM2 and cardiovascular morbidity and mortality. However, the general public is exposed to ALAN, work schedules that conflict with an individual's chronotype (endogenous circadian preference) and "social jet lag" (changes in sleep patterns from the

work days to nonwork days such as weekends).

Chronic sleep restriction is associated to increase of ghrelin levels, decrease of leptin levels and constantly increased cortisol levels resulting in unhealthy snacking, emotional overeating, less physical activity, central obesity and increased cardiometabolic risk.

There is a general belief, according to experimental data, that calorie intake throughout the day is preferable to late in the evening, but RCTs are lacking. The phrase "It is not only what and how much you eat, but also when you eat" sends a simple but important message to clinicians and patients. Another message is "more sleep and less blue light at night", as a clinical translation of circadian rhythms disruption.