



REVIEW

The chronobiology, etiology and pathophysiology of obesity

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The effect of CD on human health is an emerging issue. Many records link CD with diseases such as cancer, cardiovascular, cognitive impairment and obesity, all of them conducive to premature aging. The amount of sleep has declined by 1.5 h over the past century, accompanied by an important increase in obesity. Shift work, sleep deprivation and exposure to bright light at night increase the prevalence of adiposity. Animal models have shown that mice with Clock gene disruption are prone to developing obesity and MetS. This review summarizes the latest developments with regard to chronobiology and obesity, considering (1) how molecular clocks coordinate metabolism and the specific role of the adipocyte; (2) CD and its causes and pathological consequences; (3) the epidemiological evidence of obesity as a chronobiological illness; and (4) theories of circadian disruption and obesity. Energy intake and expenditure, relevance of sleep, fat intake from a circadian perspective and psychological and genetic aspects of obesity are examined. Finally, ideas about the use of chronobiology in the treatment of obesity are discussed. Such knowledge has the potential to become a valuable tool in the understanding of the relationship between the chronobiology, etiology and pathophysiology of obesity.

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Keywords: metabolic syndrome; chronobiology; circadian; clock genes

Introduction

Correct timing of the endogenous circadian clock enables organisms to predict and anticipate daily environmental changes, and temporally adjust behavioral and physiological functions accordingly. In humans, current societal habits, including high snacking frequency, a reduction in the time spent sleeping and increased exposure to bright light during the night, act on the brain to induce a loss of 'feeling' for internal and external rhythms. Consequently, the environment sensed by the brain has become metabolically flattened and arrhythmic. Among the well-known consequences of a disrupted circadian function are altered metabolism and even life span, which may be all adversely affected when the circadian time-keeping system is altered.¹

Obesity has emerged as one of the most serious public health concerns in the 21st century and the morbidity and

mortality associated with obesity continue to increase. Endogenous (that is, genetic) and exogenous factors (that is, diet and physical activity) have an important role in the assessment and management of obesity.² Recently, studies have suggested that disruption of the circadian system (chronodisruption (CD)) may lead to obesity.³ CD can also be produced by alteration of the core machinery of the molecular circadian clock. Brain- and muscle ARNT-like protein-1 (BMAL1), Period Circadian Protein-2 (PER2) and Circadian Locomotor Output Cycles Kaput (CLOCK), among others clock proteins, have a specific role in the organism's physiology in addition to their role in the circadian molecular clock. Animal models have shown that mice with Clock gene disruption are prone to developing obesity and a phenotype resembling metabolic syndrome (MetS).⁴

Complications of obesity include cardiovascular disease, hypertension, dyslipidemia, endothelial dysfunction, type-2 diabetes mellitus and impaired glucose tolerance, among others. Interestingly, chronobiology is implicated in most of these alterations.⁵ Circadian control of the cardiovascular function is firmly established. Furthermore, it is known that many hormones involved in metabolism, such as insulin, glucagon, growth hormone and cortisol, show circadian oscillation with different daily patterns. Current studies are

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