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NUTRITION AND THE CLOCK GENE

A.L.C. Figueroa[1], F. Hanzu[2,3,4,5], R. Gomis[1,3,4,5,*]

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), [1]Diabetes and Obesity Research Laboratory, [2]Group of Endocrine Disorders, [3]CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), [4]Hospital Clinic, Dept. of Endocrinology and Nutrition, [5]University of Barcelona, Barcelona, Spain

Abstract

A number of recent studies in animals and humans have linked energy regulation and the circadian clock at the molecular, physiological and behavioural levels, concluding that disruption of clock genes results in metabolic dysregulation. The search to understand the causes of obesity and diabetes and the development of new therapeutic strategies have mostly focused on caloric intake and energy balance. In this review, we present a global overview of the circadian clock as a critical interface between nutrition and homeostasis.

Key words: Nutrition, clock genes, circadian rhythms.

INTRODUCTION

The circadian system is composed of endogenous oscillators that generate daily rhythms of approximate 24h. In mammals, this biological clock controls different aspects of metabolism and physiology like body temperature, cycles of wakefulness and sleep, feeding habits and metabolism. The master clock is situated in the suprachiasmatic nucleus (SCN) in the hypothalamus which generates circadian rhythms throughout the body, conferring the body with the ability to adapt to variations in its environment (1-3).

The molecular clock

The circadian clock is composed of a transcriptional - translational feedback loop that generates these circadian rhythms through specific clock genes. Genes in this loop include CLOCK , Brain-muscle-Arnt like 1 (Bmal1), Period (PER1), Period2 (PER2), Period 3 (PER3), Cryptochrome1 (CRY1) and Cryptochrome2 (CRY2). CLOCK and BMAL1 form a heterodimer that binds to E-box sequences and activates the transcription of PER and CRY genes which drive a negative limb, dimerize and translocate into the nucleus to inhibit CLOCK and BMAL1 and reduce the transcription of their own genes. Another negative limb involves nuclear receptors ROR-alpha and REV-ERB-alpha, stimulating and repressing BMAL1 (4-7). The SCN is stimulated by light, which is the strongest entraining signal and coordinates peripheral clocks via autonomic innervations and neuroendocrine signals (8-10). These independent clocks are found in peripheral tissues such as the pancreas, muscles, the liver, the gut, and adipose tissue. Furthermore, feeding and specific nutrients are the main factors in entraining and help synchronize peripheral clocks (11-14).

Circadian rhythms and metabolism

The circadian clock has been reported to regulate metabolism and energy homeostasis by modulating the expression and activity of diverse metabolic enzymes and transport systems involved in glucose and lipid metabolism. In addition, several hormones implicated in metabolism exhibit circadian oscillations, such as insulin, glucagon, adiponectin, cortisol, leptin and ghrelin (15-17).

Circadian rhythms and metabolic diseases: obesity and diabetes

Obesity and type 2 diabetes have reached epidemic proportions. Obesity is an important factor that contributes to the onset and progression of T2DM (18, 19). In modern society, the human biological clock is commonly altered by changes in sleep patterns, nocturnal work shifts and exposure to artificial light at night, leading to metabolic anomalies associated with the etiology of obesity and type 2 diabetes (20, 21). Although genetic predisposition plays a relevant role in developing diabetes, environmental factors

*Correspondence to: Ramon Gomis MD, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Carrer del Rosselló, 149, 08036 Barcelona, Spain, E-mail: ramon.gomis@idibaps.org

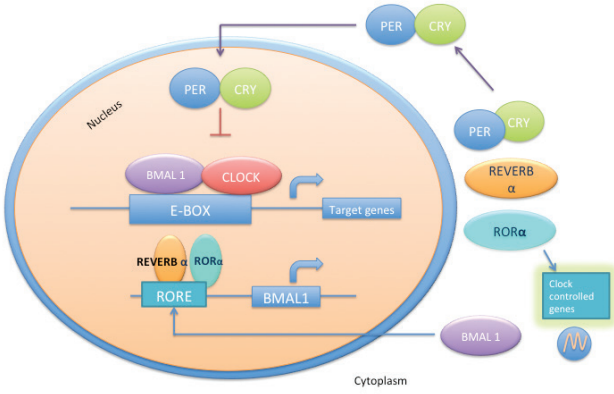

Figure 1. Molecular regulation of clock genes. CLOCK dimerizes with BMAL1 to activate the transcription of PER and Cry proteins that act as negative regulators of CLOCK:BMAL1.

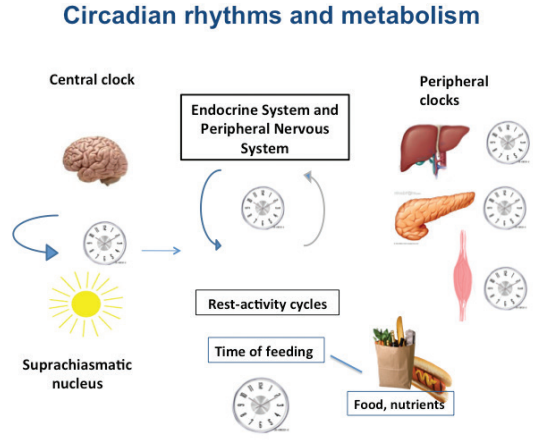

Figure 2. Signals of the central and peripheral clocks. Light is absorbed through the retina and is transmitted to the suprachiasmatic nuclei (SCN). Then the SCN dictates rhythms in rest-activity cycles, feeding, and entrainment of peripheral oscillators via the neuroendocrine and autonomic nervous systems. Some food components serve as resetting signals for the SCN or peripheral clocks.

have emerged as significantly higher predictors of this disease (22). Regulation of glucose homeostasis provides an excellent example of how the circadian system exerts metabolic control. In this sense, plasma glucose levels are tightly controlled throughout a 24-h period in mice and healthy individuals (23, 24). In animal models, mutations of clock genes in the pancreas lead to the loss of circadian rhythms of insulin secretion and glucose tolerance (25, 26). In humans, mutations and polymorphisms in clock genes are linked to obesity and metabolic syndrome (27, 28). *Ex vivo* analysis of the human peripheral visceral adipose tissue, the key endocrine tissue in insulin-resistance and type 2 diabetes, showed that peripheral clock genes oscillation is altered in the visceral obese adipose tissue, being the highest in metabolic syndrome (29).

Nutrients and feeding

Many studies have shown that changes in the patterns of feeding, food composition, and altered meal schedules can directly and indirectly affect the circadian clock.

Studies in animals consuming a hypercaloric diet during daylight hours showed a pronounced increase in weight gain in mice, disrupting both central and peripheral clocks (30, 31). On the other hand, restricting feeding time in mice on a high-fat diet resulted in lower body weight and improvements in glucose and lipid homeostasis by affecting only peripheral clocks (32, 33). As soon as food availability returned to normal, the SCN clock, whose phase remains unaffected, reset the peripheral oscillators (34). A high-fat diet, rather than the development of obesity, appears to initiate reprogramming of the circadian clock (35).

In this context, recently a new concept, chrononutrition, has been used to refer to the connection between the biological clock and feeding, by modulating the time of food ingestion and absorption, as a consequence, changing the entraining of the endogenous clock with different dietary components. (36).

In conclusion, accumulating evidence supports a role for the circadian clock in the development of metabolic disease. Environmental factors influence the circadian clock such as nutritional habits. Adapting the clock to nutrient status could be advantageous, as an understanding of the molecular mechanisms involved could help develop novel chronotheraputical approaches for the prevention and treatment of these pathologies.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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