Clock Genes, Chronodisruption, Nutrition and Obesity

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Abstract

The existence of biological clocks has been demonstrated in all living beings. Such clocks control the physio-metabolic activities of cells, organs and systems to warrantee efficacy in the process to obtain energy and metabolize nutrients under a homeostatic point of view. These ordered activities are known as circadian rhythms, occurring approximately every 24h, and depend on the activity of groups of neurons (oscillators) negatively interrelated. The oscillatory activity is related to gene expressions that implicate rhythms in the mRNA and protein production. However, alterations in such synchronism is frequently found because of many of human activities are performed in "unexpected" environmental conditions. Thus, light intensity and environmental temperature are normally rather constant; in addition light/darkness cycles are modified by working/leisure times, travels, meals and activities braking the ticking of the biological clocks producing chronodisruption. The aim of this mini review is to give some central information on most common chronodisruption aspects and their relationships with dietary habits and obesity. After a short and concise introduction explaining central aspects of biology clocks and disruptors, the role of some prevalent dietary behaviors (e.g. frequent snaking, late meals and large food consumption) acting at the level of CLOCK genes are described and discussed. This mini review far from to be exhaustive pretends to open discussion on the most accepted information, ending suggesting some future research to understand the role and importance of CLOCK genes and their polymorphisms in obesity.

Keywords: Chronodisruption; CLOCK genes; Dietary habits; Obesity

Abbreviations: CD: Chronodisruption; CRY: Cryptochrome; CCGs: Clock Controlled Genes; PER: Clock Genes Perio; SCN: Suprachiasmatic Nucleus

Introduction

Most living organisms have developed since millennium some mechanisms to improve response to daily or annually environmental changes. Thus, physiometabolic changes induced by light/dark, low/warm/high temperatures, could be more predictable during the season/day time, and consequently metabolic processes could be prepared in advance (e.g. migrations, reproduction, breeding) to improve their efficacy. The circadian system (from Latin circa that means approximately and diem meaning one day) has the aptitude to organize the internal temporal order of physiological processes according to predictable environmental cyclic signals. The circadian system is organized in a similar manner to a clock that ticking controls activities to optimize energy and nutrient utilization. It is accepted the existence of clocks in the different organs and systems of mammals controlling their activities that, in turn, are controlled by a master clock [1]. The central clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus where two groups of various neurons (ca., 20,000 each)-the ventrolateral and the dorsomedial areas-are negatively interrelated. The light/dark information analyzed in the retina arrives the SCN via the retino hypothalamic tract, inducing at a cellular level changes in the gene expression of those antagonic neuronal groups [1]. Thus, it can be accepted that circadiam system and, thus, rhythmicity is controlled by oscillatory -positive/negative mechanisms that at cellular levels implicate daily control of the mRNA and proteins. Although each neuron is able to act as an independent oscillator within a cell-autonomous period, each neuronal group acts as an oscillator that is synchronized to produce a circa 24h common periodicity [2,3]. GABAergic interneurons are responsible to inhibit one oscillator when the antagonic one is active and vice versa [4]. Thus, the ventrolateral area is the responsible for light synchronisation, while output regulation is mediated by dorsomedial area [5,6]. The BMAL1 and CLOCK transcription factors constitute a heterodimer, which activates the expression of the clock genes Perio (PER), Cryptochromes (CRY), REV-ERB, and ROR, as well as other clock controlled genes (CCGs) by binding to E-box augmentation elements [7]. PER and
CRY dimerize and inhibit their own expression by translocation into the nucleus and also acting as repressor of the CLOCK/ BMAL1 heterodimer with a delay of several hours [8]. A second loop also regulated by CLOCK:BMAL1 heterodimers activates the transcription of Rev-erb and ROR genes. Latter, REV-ERB and ROR transcription factors compete to bind response elements present on the Bmal1 promoter [1]. Thus, REV-ERB proteins repress Bmal1 transcription [9], while ROR proteins activate it [10] (Figure 1). In addition it has been described that ROR proteins are implicated in rhythmic Bmal1 expression [11] and that PER is lysed by the proteosome regulating the oscillatory loops. As the cellular processes implicated in the fine control of the master clock, and in turn, that of the different organ and tissue clocks is out from the aim of this mini review we will not insist more in these molecular aspects, although the reading of recent published reviews in chronicity is highly recommended.

Circadian system

In humans the circadian system is formed by a structural frame, ordered in a hierarchical manner, which is responsible for generating this rhythm and its synchronization with the environment. It consists of three main elements: circadian clocks, inputs tracks and outputs tracks [12].

Circadian clocks: As previously commented the central clock is located in the SCN of the hypothalamus. Its existence has been known since 1972, “resetting” daily by signals of light/darkness that come from the retina, through the optical pathways. Changes in the light/dark relationship are the main input to the SCN but there are other information produced by the interaction of the living being with the surrounding environment, such as proprioceptive, thermoactive, acoustic signals that reach the SCN or its connections with other brain areas contributing to the adjustment of this central clock. In addition, the schedule of meals and exercise seem to influence mainly the activity of other clocks located in different organs of the body. Thus, since 2001, it is known that the central alarm harmonizes the action of peripheral clocks located in organs and tissues such as lung, heart, liver, pancreas, kidney and adipose tissue, among others, through the activity of the vegetative nervous system and the secretion of hormones [12,13]. In addition the SCN has important connections with the adenohypophysis and pineal gland participating among other functions in the cortisol and melatonin production controls [13].

Inputs tracks: Our existence and behavior clearly depend on the signals from the environment and body organs. These signals have central importance in the circadian rhythms as the “Clock” must be adjusted periodically through the synchronizers which fluctuate rhythmically and integrate together these tracks [13].

Output tracks: The master “Clock” temporary transmit signals to the rest of the effectors by sending information to those brain areas involved in the regulation of body temperature, patterns of behavior and sleep-wake cycle, to neuroendocrine axes and peripheral organs. The SCN controls humoral mediators (e.g. melatonin and cortisol) and sends nerve projections and physical signs such as the pace of body temperature. From all mediators, the best known is the melatonin hormone, which is involved in the regulation of sleep and circadian rhythmicity. Melatonin its synthesis depends on subjects the SCN activity, the inhibitory action of light, with minimum and maximum levels at day and night, respectively [13]. With regard to the timing light, the pineal gland is responsible for regulating the sensitivity on the part of the SCN to various signals responsible for encoding the lighting of the environment [14]. That means, the lack of light would reduce the inputs to the system by inducing a lower production of melatonin, which in turn is sleep inducer, through implementing circuit inhibitors modulated by genes. Unlike, the presence of light energy would reduce the production of melatonin, which would delay or inhibit the induction of neurons involved in the initiation and maintenance of sleep. Therefore, melatonin, produced by the pineal, makes the different circadian oscillators located in the SCN act similarly to the object to operate as a circadian clock [14].

Chronodisruption

The alteration on the rhythmicity in any of the central or peripheral oscillators, the unstable wrong phase relationship between them, the uncoupling between inputs, pacemakers and outputs induces chronodisruption. Chronodisruption (CD) is every day more prevalent and favored by environmental factors that in turn are conditioned by the present living styles. Thus, working in rooms illuminated by artificial light, the almost permanent exposition to bright light at night (working with machines, computers, tablets) or dim lights during daytime, chronic and/or social jet-lag and shift-work can induce circadian system disruption [15]. However, other input alterations may also result in CD. Thus, warm and stable temperatures, irregular sleep time, low physical activity and frequent meals or constant snacking work as disruptors [16,17]. Ageing is a source of CD since it affects the circadian system and in some way can be related with the modification of some biomarkers involved in obesity. Three main factors are implicated in the frequent CD observed in aged people: a) decreasing inputs (e.g. reducing light reception and blue light transmission) [18], and those
other receptor signals (e.g., noise, odors); b) necrosis and/or apoptosis and loss of functionality of oscillators and their antagonists in the central clock [19,20] as well as of pineal and adenohypophysis neuroendocrine cells [21-23]; c) the reduction of day-night contrast due to losses in the rhythm amplitude [24,25].

**Chronodisruption, obesity and metabolic syndrome**

CD is associated to a predisposition to obesity, metabolic syndrome, cardiovascular diseases, cognitive and affective impairments, sleep disorders, premature age, prostatic, mammary and colorectal cancer and, in general, higher mortality [1,2,6,27]. This mini review will mainly focus on obesity, given the existing scientific evidence between obesity and CD, which contributes to negatively affect many functions involved in the metabolic regulation of lipids and carbohydrates as well as in the response to insulin [28].

Obesity is a chronic disease of multifactorial origin in which multiple factors of genetic, hormonal, metabolic, social and cultural type influence and, in a coordinated and interactive way, provoke an imbalance between energy income and expenditure, leading to fat mass and body weight gain. Obesity is characterized by an increase and content of adipose tissue, which causes morphological and metabolic alterations together with increase in several comorbidities [29]. Currently, a nearly unstoppable incidence and prevalence growth of obesity has been reported, representing a very important public health problem, and may lead to different degrees of insulin resistance, steatosis, metabolic syndrome and increased cardiovascular morbidity and mortality [12,29]. As already mentioned, a number of factors are involved in the etiology of obesity. Normally, obesity is treated modifying eating behavior and physical activity; however, in order to optimize results the impact and interaction of life style with genes should be considered (Figure 2 & Table 1). In relation to the topic of this mini review, two major factor groups can be defined.

![Figure 1: Molecular machinery of the circadian clock [32].](image)

**Table 1: Relationship between CLOCK and related gene polymorphisms and chronodisruption. Modified from López Minguez et al. [31]**

| SNP Associations and Interactions | Scientific Evidence | Recommendation | Reference |
|-----------------------------------|---------------------|----------------|-----------|
| **CLOCK** rs3749474 rs4580704 rs1801260 (3111 T>C) | Associated with BMI, energy intake and different variables related to be fat and are more obese | In minor alleles carriers: Decrease energy intake Decrease total fat intake | [33] |
| **CLOCK** rs1801260 (3111 T>C) | Associated with weight loss (C allele carriers were more resistant to weight loss) | In C allele carriers: Sleep at least 8 h/day Go to bed earlier Get up earlier in the morning Follow Mediterranean diet pattern | [34] |
| **CLOCK** rs1801260 (3111 T>C) | Interact with emotions for obesity (among C allele carriers, ‘emotional eaters’ lost significantly less weight than ‘non-emotional eaters’) and SFA for waist circumference (among C allele carriers when the SFA energy intake was more than 11.8% had higher waist circumference) | Among C allele carriers the ‘emotional eaters’: Try to have SFA energy intake lower than 11.8% Develop a stronger follow-up plan during dietary therapy | [33,34] |
| **REVERBα** rs2314339 | Associated with obesity due to a decrease in physical activity performed mostly in the afternoon/evening | In A allele carriers Increase physical activity Perform physical activity in the morning | [35] |
| **PER2** | Associated with several obesogenic behavior such as attrition of weight loss treatment, snacking, stress while dieting, eating while bored and skipping breakfast (allele minor carriers) | In G allele carriers Develop strong follow-up plan during dietary therapy Avoid snacking Avoid being around food when bored Have always breakfast | [36] |
Interact with melatonin intake for glucose resistance

The Clock, Bmal1 and Per2 proteins

It is clear that it is not only important what and how we eat

schedules, among others, act as relevant synchronizers. Thus, weight loss intervention

of CpG sites of carbohydrate intake [31]. Epigenetic modifications at the level with physical activity, and Mediterranean diet; (3111 T>C combined genotype) were related to adherence to

Eating behaviors (high frequency of snacking, eating quickly, eating when bored or eating from large packages) were all positively associated with the methylation levels of CLOCK CpG 1

Try to avoid snacking, eating quickly, eating when bored or eating from large packages

CpG sites of CLOCK

Eating behaviors (high frequency of snacking, eating quickly, eating when bored or eating from large packages) were all positively associated with the methylation levels of CLOCK CpG 1

Try to avoid snacking, eating quickly, eating when bored or eating from large packages

CpG sites of BMAL1

Evening type people presented more epigenetics modifications (high methylations in the CpG 5-9) due to weight loss intervention than morning types

Get up earlier in the morning

Endogenous factors: The Clock, Bmal1 and Per2 proteins play a very important role in this circadian functioning, so some failure in their synthesis and/or structure or in their associated CLOCK genes can induce CD. Polymorphisms of a single nucleotide (SNPs) are very common in a specific position of the genome and they are responsible, at least in part, of the inter individual differences in the vulnerability to certain diseases [28]. Although information is growing up very quick we have selected some SNP’s in the CLOCK genes whose importance on obesity and metabolic markers has been reported. (Table 1) includes general information about a selection of the most important gene polymorphisms implicated in the CD-obesity relationship.

Clock: SNPs rs3749474, rs4580704 and rs1801260 were associated with variables related to obesity, energy intake and BMI; SNP rs1801260 with weight loss, sleeping less, poor adherence to the Mediterranean diet. They carriers fit better within the evening type, and interact with saturated fatty acid intake for waist circumference and emotions. Also SNP rs4580704 interacted with monounsaturated fatty acid intake for blood glucose [31]. New evidences at epigenetic level of the CLOCK gene suggest association with erratic eating behaviors (eating quickly and/or hudge amounts, snacking and eating when bored) [31].

Other genes: PER2 SNP rs2304672 was associated with snacking, eating when bored, stress, etc; SIRT1 with CLOCK (3111 T>C combined genotype) were related to adherence to Mediterranean diet; REVERB rs2314339 appeared associated with physical activity, and CRY1 rs2287161 interacted with carbohydrate intake [31]. Epigenetic modifications at the level of CpG sites of BMAL1 have been reported to be associated with weight loss intervention [31].

Exogenous factors: Both the physical activity and the meal schedules, among others, act as relevant synchronizers. Thus, it is clear that it is not only important what and how we eat but also when we do it. In this regard, it has been found that a regular meal schedule contributes to the maintenance of the internal temporal order of the circadian system [13]. In addition, the response to energy dietary restriction differs in some individual with respect to others depending on the degree of CD. Therefore, to this aim, it has been proposed an index that based in some CD markers helps predicting weight loss [28]. Various determinations were made throughout the day, being the most predictive variables body temperature, blood pressure and the secretion of certain hormones such as melatonin and cortisol, since they present more precise rhythms [28,30]. From these, the so-called CD index was calculated permitting to classify patients with or without CD. Corbalán-Tutau et al. observed that the weighted mean of the first four factors explained the 53.8% of the total variance. These authors proposed the value 40.3 as CD index cut-off point as this value corresponded to the point that shows the best sensitivity along with the best specificity [30]. Therefore, individuals with moderate obesity who present a value for the already commented CD index above 40.3 will have CD. By the way, women with high CD score displayed higher BMI, waist perimeter, fasting glucose, total cholesterol and triglyceride concentrations and also higher systolic and diastolic blood pressure values; thus, were at risk for metabolic syndrome [28]. In agreement with others [31] and taking into account all already commented facts, some general nutritional and lifestyle suggestions should be taken into consideration in order to palliate the growing incidence and prevalence of obesity:

- Sleep during the night and be active during the day. Sleep in total darkness when possible.
- Avoid intense light exposition during night time.
- Make exercise during the morning.
- Avoid eating at night hours.
- Have adherence to Mediterranean diet
- Have lunch before 15:00hrs.

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Conclusion

Light/dark cycles are central in the control of the circadian system and that of several metabolic and physiological aspects in humans. However, environmental factors have drastically changed the daily inputs arriving to the master clock favoring its disruption and that of the other pacemakers. Among them, eating and sleeping times, light intensity exposition, noise, social jet-lag and shift works have been considered crucial in the understanding of CD. Nonetheless, taking into account the existence of interactions between way of living and presence of some CLOCK polymorphisms, active research is demanded to improve knowledge in such interaction. This effort should be performed to find out mechanisms and interactions occurring at critical life periods (fetal, lactation, childhood, aging) and also addressed in at risk people (e.g. over weighted, with type 1 obesity and familial antecedents) in order improve our knowledge and to decrease the growing tendency of both obesity and CD.

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