Available online at www.sciencedirect.com
ScienceDirect
Frontiers in Neuroendocrinology 28 (2007) 61–71
Frontiers in Neuroendocrinology
www.elsevier.com/locate/yfrne

Review

The relationship between nutrition and circadian rhythms in mammals

Oren Froy *

Institute of Biochemistry, Food Science and Nutrition, Faculty of Agricultural, Food and Environmental Quality, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel

Available online 24 March 2007

Abstract

The master clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus regulates circadian rhythms in mammals. The clock is an intracellular, transcriptional mechanism sharing the same molecular components in SCN neurons and in peripheral cells, such as the liver, intestine, and retina. The circadian clock controls food processing and energy homeostasis by regulating the expression and/or activity of enzymes involved in cholesterol, amino acid, lipid, glycogen, and glucose metabolism. In addition, many hormones involved in metabolism, such as insulin, glucagon, adiponectin, corticosterone, leptin, and ghrelin, exhibit circadian oscillation. Furthermore, disruption of circadian rhythms is involved in the development of cancer, metabolic syndrome, and obesity. Metabolism and food intake also feed back to influence the biological clock. Calorie restriction (CR) entrains the SCN clock, whereas timed meals entrain peripheral oscillators. Furthermore, the cellular redox state, dictated by food metabolism, and several nutrients, such as glucose, ethanol, adenosine, caffeine, thiamine, and retinoic acid, can phase-shift circadian rhythms. In conclusion, there is a large body of evidence that links feeding regimens, food components, and the biological clock.

Keywords: Clock; Caloric restriction; Restricted feeding; Nutrition; Metabolism; Circadian rhythms

1. Introduction

The rotation of earth around its axis imparts light and dark cycles of 24 h. Organisms on earth developed the ability to predict these cycles and evolved to restrict their activity to the night or day. By developing an endogenous circadian (*circa*—about and *dies*—day) clock, which is entrained to external time cues, animals and plants ensure that physiological processes are carried out at the appropriate, optimal time of day or night [103]. In mammals, the circadian clock influences nearly all aspects of physiology and behavior, including sleep–wake cycles, cardiovascular activity, endocrine system, body temperature, renal activity, physiology of the gastrointestinal tract, hepatic metabolism, etc. [103,109]. Disruption of circadian coordination may be manifested by hormone imbalance, psychological and sleep disorders, cancer proneness, and reduced life span [31,40,48,70,105,109]. In contrast, resetting of circadian rhythms has led to well-being and increased longevity [61,65,67].

The control of the biological clock over feeding behavior has been well established. In addition, molecularly, the biological clock regulates the expression and/or activity of enzymes and hormones involved in metabolism. However, recently, there is a growing body of evidence that metabolism, food consumption, timed meals, and some nutrients feed back to entrain the clock. This review will summarize the recent findings concerning the relationship between feeding regimens, food components, metabolism, and circadian rhythms.

2. The mammalian biological clock

In mammals, the central circadian clock is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus in the brain. The SCN clock is composed of multiple, single-cell circadian oscillators, which, when synchronized,

* Fax: +972 8 936 3208.
E-mail address: froy@agri.huji.ac.il

0091-3022/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.yfrne.2007.03.001

generate coordinated circadian outputs that regulate overt rhythms [56,84,108,146]. Similar clock oscillators have been found in peripheral tissues, such as the liver, intestine, and retina. Thus, the central circadian clock (often termed the master clock) is located within the SCN [83,88], whereas peripheral clocks are found within non-SCN cells of the organism, including other regions of the central nervous system (CNS) [46,47,82,109,156]. The SCN must periodically send signals to peripheral oscillators in order to prevent the dampening of circadian rhythms in these tissues. The mechanisms by which the SCN accomplishes this task are not well understood [81]. Complete destruction of the SCN abolishes circadian rhythmicity in the periphery, as it leads to a loss of synchrony among individual cells and damping of the rhythm at the population level [147,154].

SCN oscillation is not exactly 24 h, therefore, it is necessary to entrain the circadian pacemaker each day to the external light–dark cycle to prevent drifting (or free-running) out of phase. Light is the most potent synchronizer for the SCN [107]. Light is perceived by the retina and the signal is transmitted *via* the retinohypothalamic tract (RHT) leading to the SCN [51,85,109]. The SCN receives the information, interprets it, and transmits it further to peripheral oscillators located outside the SCN, apparently *via* neuronal connections or circulating humoral factors. The SCN provides its most intense output to the subparaventricular zone (SPZ) and dorsomedial nucleus of the hypothalamus (DMH) that are necessary for organizing circadian rhythms of body temperature, sleep and wake cycles, locomotor activity, feeding, and corticosteroid production [121]. Several humoral factors expressed cyclically by the SCN, transforming growth factor α (TGFα) [73], prokineticin 2 (PK2) [22], and cardiotrophin-like cytokine (CLC) [74] have been shown to inhibit nocturnal locomotor activity when injected into the cerebral ventricle. In turn, SCN rhythms can be altered by neuronal and endocrine inputs [119].

3. The biological clock at the molecular level

Transcriptional–translational feedback loops lie at the very heart of the core clock mechanism of animals, plants, and fungi. Generation of circadian rhythms is dependent on the concerted co-expression of specific clock genes. Genetic analysis of mutations affecting the clock in organisms, such as *Neurospora*, *Drosophila*, Cyanobacteria, *Arabidopsis*, and, most recently, the mouse, have paved the way for the identification of these clock genes. In mammals, the clock is an intracellular, transcriptional–translational mechanism sharing the same molecular components in SCN neurons and peripheral cells [124]. Many clock gene products function as transcription factors, which possess PAS (PER, ARNT, SIM) and basic helix–loop–helix (bHLH) domains involved, respectively, in protein–protein and protein–DNA interactions. These factors ultimately activate or repress their own expression and, thus, constitute a self-sustained transcriptional feedback loop. Changes in concentration, subcellular localization, posttranslational modifications, and delays between transcription and translation lead to the achieved 24-h cycle [35,103,109].

The core clock mechanism involves *Clock*, brain–muscle-Arnt-like 1 (*Bmal1*), *Period1* (*Per1*), *Period2* (*Per2*), *Period3* (*Per3*), *Cryptochrome1* (*Cry1*), and *Cryptochrome2* (*Cry2*) (Fig. 1). In the mouse, the first clock gene identified, encodes the transcription factor CLOCK [144], which dimerizes with BMAL1 to activate transcription. CLOCK and BMAL1, two PAS-bHLH transcription factors, are capable of activating transcription upon binding to E-box (5′-CACGTG-3′) and E-box-like promoter elements [109]. BMAL1 can also dimerize with other CLOCK homologs, such as neuronal PAS domain protein 2 (NPAS2), to activate transcription and sustain rhythmicity [8,33]. The PERIOD proteins (PER1, PER2, and PER3) and the two CRYPTOCHROMEs (CRY1 and CRY2) operate as negative regulators [45,108,158]. Thus, CLOCK:BMAL1 heterodimers bind to E-box sequences and mediate transcription of a large number of genes including those of the negative feedback loop *Per*s and *Cry*s. When PERs and CRYs are produced in the cytoplasm, they dimerize and translocate to the nucleus to inhibit CLOCK:BMAL1-mediated transcription (Fig. 1). *Per*s and *Bmal1* have robust oscillation in opposite phases correlating with their opposing functions [46]. All the aforementioned clock genes exhibit a 24-h rhythm in cells (Fig. 1). In addition, casein kinase I epsilon (CKIε) is thought to phosphorylate the PER proteins and, thereby, enhance their instability and degradation [35–37,148]. CKI ε also phosphorylates and partially activates the transcription factor BMAL1 [37]. *Bmal1* expression is negatively regulated by the transcription factor reverse erythroblastosis virus α (REV-ERBα) [106] and positively regulated by retinoic acid receptor-related orphan receptor α (RORα) [122] *via* the RORα response element (RORE) [142] (Fig. 1).

4. Effect of the biological clock on metabolism

The fraction of cyclically expressed transcripts in each peripheral tissue ranges between 5% and 10% of the total population and the vast majority of these genes are tissue-specific [3,34,71,103,124,137]. Many hormones involved in metabolism, such as insulin [76], glucagon [116], adiponectin [4], corticosterone [32], leptin, and ghrelin [11], have been shown to exhibit circadian oscillation. In addition to the endocrine control, the circadian clock has been reported to regulate metabolism and energy homeostasis in the liver and other peripheral tissues, by mediating the expression and/or activity of certain metabolic enzymes and transport systems [59,69] involved in cholesterol metabolism, amino acid regulation, drug and toxin metabolism, the citric acid cycle, and glycogen and glucose metabolism [28,76,77]. Some examples are glycogen