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Review

Circadian aspects of energy metabolism and aging

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ABSTRACT

Life span extension has been a goal of research for several decades. Resetting circadian rhythms leads to well being and increased life span, while clock disruption is associated with increased morbidity accelerated aging. Increased longevity and improved health can be achieved by different feeding regimens that reset circadian rhythms and may lead to better synchrony in metabolism and physiology. This review focuses on the circadian aspects of energy metabolism and their relationship with aging in mammals.

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1. Circadian rhythms, health and life span

Organisms on Earth evolved to predict the day-night cycle by developing an endogenous circadian clock synchronized by light (Panda et al., 2002a,b). The clock machinery is self-sustained, but in the absence of light, the primary time giver, the endogenous clock free-runs, generating cycles of approximately 24 h, hence the term circadian (circadian, circa = about dies = day). The circadian clock controls a wide array of physiological and behavioral systems, such as energy metabolism, gastrointestinal tract motility, sleep-wake cycles, cardiovascular activity, endocrine secretion, body temperature and locomotor activity (Panda et al., 2002a,b; Reppert and Weaver, 2002; Urbanski, 2011). Misalignment between the endogenous clock and the environment leads to symptoms of fatigue, disorientation, and insomnia as seen in jet lagged travelers and shift workers (Davis and Mirick, 2006; Gibson et al., 2009; Hofman and Swaab, 2006). Disruption of circadian rhythms can seriously impact overall health, increase cancer proneness and shorten the organism's life span (Anea et al., 2009; Davis and Mirick, 2006; Filipski et al., 2003; Froy, 2011; Fu et al., 2002; Jung-Hynes et al., 2010; Montagnana et al., 2009; Penev et al., 1998; Reppert and Weaver, 2002). Even disruption of circadian rhythms by continuous reversal of the light-dark cycle results in decreased survival time of cardiomyopathic hamsters (Penev et al., 1998). Moreover, changes in the light/dark cycle induced significant mortality in aged animals (Davidson et al., 2006). In contrast, aged animals given fetal suprachiasmatic implants lived longer as higher amplitude rhythms were restored (Hurd and Ralph, 1998; Hurd et al., 1995; Li and Satinoff, 1998). Thus, circadian disruption is associated with increased morbidity and mortality, whereas robust and reset circadian rhythms could lead to better health and increased longevity.

2. The mammalian circadian clock

The mammalian central circadian clock is a cellular mechanism found within a bilateral nucleus in the anterior hypothalamus called suprachiasmatic nuclei (SCN). Photic information reaches the SCN from the retina via the retinohypothalamic tract (RHT) (Fig. 1). Synchronization of SCN cells leads to a coordinated circadian output that regulates peripheral rhythms (Herzog et al., 1998; Liu et al., 1997; Reppert and Weaver, 2001; Welsh et al., 1995) (Fig. 1). Clocks, similar, but not identical, to those found in SCN cells, are found in peripheral tissues, such as the liver, intestine and adipose tissue (Froy and Chapnik, 2007; Lee et al., 2001; Reppert and Weaver, 2002). The percentage of cyclically expressed transcripts in each peripheral tissue ranges between 5 and 20%, with the vast majority being tissue-specific (Akhtar et al., 2002; Duffield et al., 2002; Kita et al., 2002; Kornmann et al., 2001; Lemos et al., 2006; McCarthy et al., 2007; Panda et al., 2002a,b; Reddy et al., 2006; Storch et al., 2002; Young, 2006; Zvonic et al., 2006), emphasizing the circadian control over peripheral function. Several humoral factors expressed cyclically by the SCN, such as transforming growth factor α (TGFα) (Kramer et al., 2001), prokineticin 2 (PK2) (Cheng et al., 2002), and cardiotrophin-like cytokine (CLC) (Kraves and Weitz, 2006), have been shown to affect peripheral clocks, as their intracerebroventricular injection inhibited nocturnal locomotor activity. Thus, the control of the SCN over the periphery is achieved through the autonomic nervous system, secretion of factors (Cheng et al., 2002; Kramer et al., 2001; Kraves and Weitz, 2006), or indirectly by driving rhythmic feeding, locomotion and/or body temperature rhythms (Asher and Schibler, 2011; Froy et al., 2008; Kornmann et al., 2007).

3. The mammalian clock at the molecular level

The molecular clock in SCN neurons and peripheral cells is an intracellular mechanism composed of transcription-translation feedback loops (Schibler et al., 2003) (Fig. 2). CLOCK (Circadian Locomotor Output Cycles Kaput) (Vitaterna et al., 1994) dimerizes with BMAL1 (brain and muscle ARNT-like protein 1) to activate transcription by binding to E-box promoter sequences (Reppert and Weaver, 2002). BMAL1 can also dimerize with other CLOCK homologs, such as neuronal PAS (PER, ARNT, SIM) domain protein 2 (NPAS2), to activate transcription and sustain rhythmicity (Asher and Schibler, 2006; Debruyne et al., 2006). Amongst the targets of the CLOCK:BMAL1 heterodimer are the *Period* (*Per1*, *Per2* and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) genes (Fig. 2). Nuclear translocation of the PERs:CRYs oligomers and binding to the CLOCK:BMAL1 heterodimer lead to transcriptional inhibition (Froy et al., 2002; Reppert and Weaver, 2002). Several other transcription-translation loops also play a role in sustaining clock function. For example, *Bmal1* expression is negatively regulated by the transcription factor REV-ERBα (Preitner et al., 2002), but positively regulated by

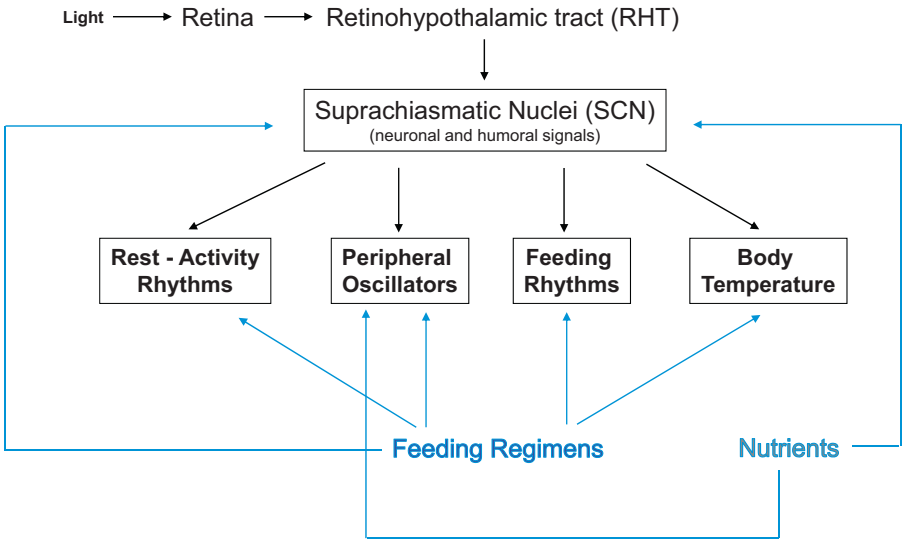

Fig. 1. Resetting signals for central and peripheral clocks. The SCN dictates rhythms in peripheral tissues and physiological activities. Light, nutrients and feeding regimens affect either the central clock in the SCN or peripheral clocks.