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Aging in the Circadian System: Considerations for Health, Disease Prevention, and Longevity

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Abstract

The circadian system orchestrates internal physiology on a daily schedule to promote optimal health and maximize disease prevention. Chronic disruptions in circadian function are associated with an increase in a variety of disease states including, heart disease, ulcers, and diabetes. With advanced age, the genes regulating circadian function at the cellar level become disorganized and the ability of the brain clock to entrain to local time diminishes. As a result, aged individuals exhibit a loss of temporal coordination among bodily systems, leading to deficits in homeostasis and sub-optimal functioning. Such disruptions in the circadian system appear to accelerate the aging process and contribute to senescence, with some systems being more vulnerable than others. This review explores aging-associated changes in circadian function and examines evidence linking such alterations to adverse health consequences in late life and promotion of the aging process.

Keywords

Senescence; clock gene; CCG; estrus; ovulation

I. Introduction: The Circadian System in Health, Disease, and Aging

In *The Wisdom of the Body*, Walter B. Cannon developed the concept of homeostasis to describe the exquisite precision in which countless bodily systems are maintained within finely-tuned operating limits to promote optimal health and avoid disease states. When we consider homeostasis, we often overlook the fact that the optimal limits for a given physiological or biochemical process vary by time of day. The circadian system orchestrates internal events on a daily schedule to ensure that bodily systems are coordinated with environmental time and with each other on a daily schedule (Figure 1). Disruptions in temporal homeostasis have pronounced impact on physiological functioning, overall health, and disease susceptibility. An endogenous, daily time-keeping system is necessary to anticipate environmental change, initiate internal adjustments in advance of the appropriate environmental time, and maintain proper phase relationships among internal systems.

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It is not difficult to imagine how physiological functioning would suffer without an internal circadian clock synchronized to the environment. Most of us have experienced this acutely, manifested by general feelings of malaise and other maladies following a long flight across time zones. This loss of synchrony between the circadian clock in the brain and the environment leads to pronounced clinical pathologies. One recent study found that elderly mice subjected to temporal disruptions equivalent to a flight from Washington to Paris, once a week for eight weeks, die as a result of their bodies being out of sync with local time (Davidson et al., 2006). Flight attendants frequently traveling across time zones exhibit cognitive deficits associated with reductions in temporal lobe structures (Cho, 2001; Cho et al., 2000). Numerous studies show that shift workers have a higher incidence of cancer (Conlon et al., 2007), diabetes (Morikawa et al., 2005), ulcers (Koda et al., 2000), hypertension and cardiovascular disease (Kivimaki et al., 2006), psychological disorders (Bildt and Michelsen, 2002), and a host of other clinical issues. These findings, although largely correlational, point to a critical role for internal circadian timing in maintaining normal brain functioning and peripheral physiology.

With advancing age, animals exhibit numerous circadian disruptions (Benloucif et al., 1997; Davidson et al., 2008; Li and Satinoff, 1995; Valentinuzzi et al., 1997; Weinert and Waterhouse, 1999) that contribute to poor health consequences and hastened senescence. In fact, longevity is diminished by circadian perturbations and decelerated by restoration of youthful circadian behavior by transplantation of a fetal clock into the brains of aged animals (Hurd and Ralph, 1998). The following review underscores the significance of two fundamental functions of the circadian system, internal organization and entrainment to the environment, in the aging process.

II. The Circadian System

Whereas a ‘master’ circadian clock has been localized to the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus in mammals (Moore and Eichler, 1972; Stephan and Zucker, 1972), it is now more appropriate to conceptualize the ‘circadian system’ as an assembly comprised not only of a master clock, but also a series of subordinate clocks whose phase and coordinated activity is set by the SCN. Numerous lines of converging evidence from a host of laboratories have confirmed the role of the SCN as a master pacemaker. For example, transplants of donor SCN tissue into the brains of arrhythmic, SCN-lesioned hosts restore circadian rhythmicity in behavior (Lehman et al., 1987; Ralph et al., 1990). Importantly, rhythms are restored with the period of the donor SCN, indicating that the transplanted tissue does not act by restoring host-brain function but that the “clock” is contained in the transplanted tissue. Furthermore, circadian rhythms in neural firing rate persist in isolated SCN tissue maintained in culture (Green and Gillette, 1982), demonstrating that input from extra-SCN brain sites is not necessary for circadian rhythms in this nucleus. As will be described in the following sections, the SCN has direct access to environmental time via retinal projections to the clock. Because subordinate central and peripheral clocks do not have access to such time cues, it is necessary for the SCN to communicate such information throughout the CNS and periphery. In addition to the core clock genes responsible for circadian function at the cellular level, subordinate clock-controlled genes (CCGs) represent important output and local coordination systems. The stability of this hierarchical arrangement is disrupted with advancing age (Davidson et al., 2008).

A. The Molecular Clock

Within a cell, circadian rhythms are produced by an autoregulatory transcriptional/translational negative feedback loop that takes approximately 24 hours. While the general mechanism for circadian oscillations at the cellular level is common among organisms, the components comprising the feedback loop differ. For the purpose of clarity, only the core mammalian feedback loop is described. Earlier work proposed a core feedback loop that begins when two

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proteins, CLOCK and BMAL1, bind to one another and drive the transcription of messenger RNA (mRNA) of the *Period* (*Per*) and *Cryptochrome* (*Cry*) genes by binding to the E-box (CACGTG) domain on these gene promoters. Three *Period* (*Per1*, *Per2*, and *Per3*) and two *Cryptochrome* (*Cry1* and *Cry2*) genes have been identified. The mRNA for these genes is translated into PER and CRY proteins in the cytoplasm of the cell over the course of the day. Throughout the day, these proteins build up within the cytoplasm, and when they reach high enough levels, they form hetero- and homo-dimers. These newly formed dimers then feed back to the nucleus where they bind to the CLOCK:BMAL1 protein complex to turn off their own transcription (reviewed in (Ko and Takahashi, 2006)) (Figure 2).

More recently, it has become clear that the cellular clockwork is more complex, with a number of integrated feedback loops whose regulators are often controlled by elements of the core clock mechanism. Two other promoter elements have emerged as important for circadian rhythm generation, DBP/E4BP4 binding elements (D boxes) and REV-ERBα/ROR binding elements (RREs) (Ueda et al., 2005). REV-ERBα, an orphan nuclear receptor, negatively regulates the activity of the CLOCK:BMAL1 complex and is also acted upon by PER and CRY. Transcription of REV-ERBα is controlled by the same mechanism controlling *Per* and *Cry* transcription. Similarly, the transcription factor DPB is positively regulated by the CLOCK:BMAL1 complex (Ripperger and Schibler, 2006) and acts as an important output mechanism by driving rhythmic transcription of other output genes via a PAR basic leucine zipper (PAR bZIP) (Lavery et al., 1999). Whereas most work to date has focused on transcriptional regulation as the key mechanism driving cellular rhythms, post-transcriptional and post-translational events are also critical for circadian coordination (Baggs and Green, 2003; Kramer et al., 2003; Reddy et al., 2006).

In addition to transcriptional/translational control of cellular clock function, regulatory kinases also play a pronounced role in regulation of circadian period. Over a decade ago, a circadian mutation named *tau* was identified that resulted in a shortened circadian period in Syrian hamsters (Ralph and Menaker, 1988). It is now known that the *tau* locus is encoded by casein kinase I epsilon (CKIε) (Lowrey et al., 2000; Wang et al., 2007). In normal rodents, CKIε phosphorylates PER and “tags” it for degradation throughout the day. Eventually, PER acts to overwhelm CKIε, and dimerizes with CRY to feed back to the cell nucleus. The mutant form of CKIε is unable to phosphorylate PER, leading to a short circadian period in *tau* mutants due to premature nuclear entry of PER:CRY dimers (Lowrey et al., 2000; Vielhaber et al., 2000).

B. Entrainment of the Circadian System

In addition to a direct visual pathway from retinal ganglion cells to the visual cortex, there is also a direct retinohypothalamic tract (RHT) projecting from the optic nerve to the SCN (Klein and Moore, 1979; Moore and Klein, 1974). This second visual pathway is necessary and sufficient to entrain (synchronize) the SCN to the environmental light:dark cycle. Early studies of circadian photoreception investigated the role of traditional rod and cone photoreceptors in entrainment. However, mice lacking both rod and cone photoreceptors (rd/rd) exhibit grossly normal entrainment even though they are visually blind (Foster et al., 1993; Freedman et al., 1999; Lucas et al., 1999; Van Gelder, 2001). These findings led to a search for a novel non-rod, non-cone photoreceptor necessary for photic entrainment. Several years of rapid discovery beginning in this millennium identified a subset of light-responsive ganglion cells containing the photopigment, melanopsin (Berson et al., 2002; Hannibal and Fahrenkrug, 2002). These ganglion cells project directly to the SCN and were initially thought to be the sole photoreceptors necessary for entrainment. However, melanopsin deficient mice exhibit only minor impairments in entrainment (Lucas et al., 2003; Panda et al., 2002; Ruby et al., 2002). This discrepancy was resolved by showing that entrainment is abolished in mice doubly mutant for both melanopsin and traditional rod/cone photoreceptors (Hattar et al., 2003; Panda et al.,

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2003). These findings suggest that traditional rod/cone photoreceptors project to specialized light-responsive ganglion cells that then transmit this integrated photic information directly to the SCN. Thus, these two types of receptors likely work together to entrain the circadian clock, and either receptor type can support entrainment in the absence of the other.

III. Age-Related Changes in the Circadian System

With advancing age, the circadian system exhibits loss of temporal precision (Benloucif et al., 1997; Davidson et al., 2008; Li and Satinoff, 1995; Valentinuzzi et al., 1997; Weinert and Waterhouse, 1999), contributing to a variety of age-related pathologies. Such age-related changes cannot be explained by cell death or atrophy in the SCN, as aging does not decrease cell size or numbers in the master pacemaker (Madeira et al., 1995). However, the aged SCN shows alterations in peptide expression (vasoactive intestinal polypeptide (VIP) (Kawakami et al., 1997); arginine vasopressin (AVP) (Roozendaal et al., 1987)), and a reduction in the amplitude of circadian rhythms of electrical activity (Satinoff et al., 1993; Watanabe et al., 1995). Transplantation of a 'young' SCN into aged animals yields improvements in numerous rhythmic functions, including the diurnal rhythm of corticortropin-releasing hormone (CRH) and behavioral rhythms in locomotion (Cai et al., 1997; Li and Satinoff, 1995). Together, these studies suggest that the SCN is an important locus for age-related changes in the rodent circadian system and treatments targeting this structure may act to ameliorate some of the deterioration seen in aged individuals.

A. Aged-Related Changes in Circadian Entrainment

When the circadian clock is not synchronized to the environment, temporal homeostasis is severely disrupted, comparable to some of the changes seen with aging. Consequently, one potential target of aging in the circadian system is the entrainment apparatus. Aged animals are about 20 times less sensitive to the entraining effects of light relative to young animals, despite the fact that they exhibit unaltered retinal innervation of the SCN (Zhang et al., 1998). This finding suggests that deficits in entrainment result from alterations at the level of the retina or the master clock. As aged mice do not exhibit gross morphological retinal abnormalities (Oster et al., 2003), most research has focused on the SCN as the site of entrainment alterations. Because *Per1* transcription is rapidly induced by light and is required for entrainment (Wakamatsu et al., 2001), the induction of *Per1* makes a convenient assay for investigating the response of the SCN to a phase-resetting light pulse. In aged animals, *Per1* expression following an entraining light stimulus is markedly reduced with a significantly longer delay to resynchronization (Davidson et al., 2008; Kolker et al., 2003). In young animals, disruption of the *Period* genes leads to aging-like declines in sensitivity to light (Asai et al., 2001; Weinert et al., 2001). These findings suggest that temporal disorganization with advancing age may result, in part, from reductions in the sensitivity of the SCN to retinal stimulation. Future studies using pharmacological approaches to examine the response of the SCN to neurochemical applications simulating retinal stimulation are necessary to rule out abnormal retinal signaling as a mechanism mediating age-related declines in entrainment.

B. Clock Genes and Aging

Given the pronounced decrements in rhythmic function seen in aged animals, several studies have investigated the impact of aging on the expression of the core clock genes. The amplitude of daily *Bmal1* expression is reduced in aged hamsters, with lower expression during the subjective night, when *Bmal1* expression is normally at its peak, compared to young animals (Kolker et al., 2003). *Bmal1* knockout animals are arrhythmic (Bunger et al., 2000), indicating the importance of this gene in normal circadian cycling, and lend support for the possibility that age-related changes in circadian rhythms may result from abnormal *Bmal1* expression. Interestingly, reductions in *Bmal1* expression are not associated with changes in *Per1*, *Per2*

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and *Cry1* amplitude in the aged SCN, indicating that the downstream targets of *Bmal1* responsible for circadian disruption with advanced age may be distinct from the core clock machinery (Asai et al., 2001). *Clock* expression is also reduced throughout the day in the SCN of aged animals although, importantly, mutation of the *Clock* gene and resulting arrhythmicity in constant conditions does not impact the aging process (Kolker et al., 2003). As a result, *Bmal1* has remained a focus for research exploring the role of clock genes in aging.

Additional evidence for a role of *Bmal1* in the aging process comes from studies of knockout mice. Mice deficient in *Bmal1* have a reduced lifespan and develop a number of age-related pathologies including sarcopenia, cataracts, and organ shrinkage significantly earlier than their wild-type counterparts (Kondratov et al., 2006). These age-related pathologies indicate that some circadian proteins are important for physiological processes that are not directly linked to circadian function. Since many peripheral tissues express clock genes endogenously (Reppert and Weaver, 2002), understanding the role of peripheral clock gene oscillations in maintaining organ homeostasis will aid in the development of strategies to treat age related pathologies. Future studies aimed at understanding the extent to which endogenous oscillations of peripheral clock genes versus synchronization of these peripheral tissues with the master pacemaker will reveal changes in the maintenance of organ and tissue homeostasis in aging animals.

IV. The Circadian System and Reproductive Aging

Age-related decline in reproductive axis function is common across species, with initiation of this decline typically occurring midway through life. Because females are affected earlier in life and to a greater extent than males, research to date has focused on female reproductive aging and the circadian system. In regularly cycling female rodents, a daily circadian signal from the SCN coinciding with a threshold level of estrogen initiates the gonadotropin-releasing hormone (GnRH) mediated luteinizing hormone (LH) surge required for ovulation (reviewed in (Kriegsfeld and Silver, 2006)). As female rodents age, the ability of the SCN to stimulate the surge weakens.

A delay in the timing, and attenuation of the amplitude, of the LH surge are hallmarks of reproductive aging. In middle-aged hamsters, for example, the peak level of LH is delayed by as many as three hours compared to the onset of the surge in young, reproductively healthy animals (Wise, 1982). The cadence seen in the timing and amplitude of the LH surge in middle-aged animals has been linked to changes in GnRH activation by SCN neuropeptidergic signals. The GnRH system represents the final pathway in control of the reproductive axis in most mammalian species. It would be reasonable to assume that the deficit in LH surge amplitude may be a direct consequence of a decrease in GnRH peptide release. However, concentrations of GnRH peptide do not show an age-related decline. Instead, the decline in reproductive capacity appears to be due to changes in the activation of the GnRH system by the circadian clockwork. In regularly cycling young females, 34–40% of GnRH neurons express immediate early genes on the afternoon of proestrus compared to 9–14% in middle-aged animals; the total number of GnRH-immunoreactive neurons does not differ between the two groups (Lloyd et al., 1994). This finding suggests that the SCN may not provide adequate stimulation to the GnRH system in aged animals. Two SCN peptides, VIP and AVP, have long been implicated in stimulation of the reproductive axis. VIP mRNA but not AVP mRNA becomes arrhythmic in the SCN of middle-aged female hamsters (Krajnak et al., 1998), and suppression of SCN VIP in young female hamsters results in accelerated deficits in GnRH activation and an LH surge that mimic that of an aged population (Gerhold et al., 2005; Harney et al., 1996). Together, these findings suggest that age-related deficits in the neuroendocrine mechanisms mediating ovulation may result from loss of function at the level of the SCN.

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V. Aging and Circadian Changes in Energetics

One of the most robust phenotypes associated with aging is change in energy utilization, including body fat stores. Increases in body fat mass and deteriorations in insulin sensitivity are associated with aging in many mammalian species as well as many clinical pathologies, including cardiovascular disease. Data from clock gene mutants demonstrate a strong circadian mechanism regulating adipose stores, as well as the release of insulin, a pancreatic hormone, and leptin, an adipose hormone, all of which activate the anorexigenic pathways of energy homeostasis and reduce food intake. The nocturnal rise in circulating leptin levels of younger animals is attenuated in older animals, including primates (Downs and Urbanski, 2006). The phases and amplitudes of rhythms of hormones associated with metabolic function, such as insulin, corticosterone, and prolactin, are disrupted in obese aged rodents and administration of these hormones at specific times of day mimicking the rhythms of the younger phenotype are able to re-establish metabolic characteristics of younger animals (Cincotta et al., 1993). Age-related alterations in corticosterone secretion are a direct result of the eradication of the diurnal rhythm of its hypothalamic releasing peptide, corticotropin-releasing hormone (CRH) (Cai and Wise, 1996). Fetal SCN grafts implanted into the brains of middle-aged rats restores the diurnal rhythm of CRH (Cai et al., 1997). The reinstatement of CRH rhythms in middle-aged rats by fetal SCN is unique, as other neuroendocrine rhythms are not restored by such grafts (Kriegsfeld and Silver, 2006). Future studies are needed to fully delineate if re-establishing temporal rhythms in aged populations through timed hormonal injections are able to re-set energetic processes to allow for minimization of metabolic deficits.

VI. Conclusions and Perspectives

With increased understanding of the mechanisms driving age-associated changes in the mammalian circadian clockwork, novel insight concerning the nature of age-related pathologies resulting from loss of temporal precision can be gained. Aged individuals exhibit pronounced deficits in the amplitude and timing of core molecular clock genes and entrainment of the master clock to local time. This deterioration in the circadian system manifests as disruptions in the sleep-wake cycle and system-wide physiology. Information on the role circadian abnormalities play in the aging process is limited and enormous opportunity exists for exploring these associations from gene to behavior. Further studies investigating the impact of aging on the master clock in the SCN and the mechanisms coupling the SCN to peripheral clocks will afford great insight into maximizing health with advancing age.

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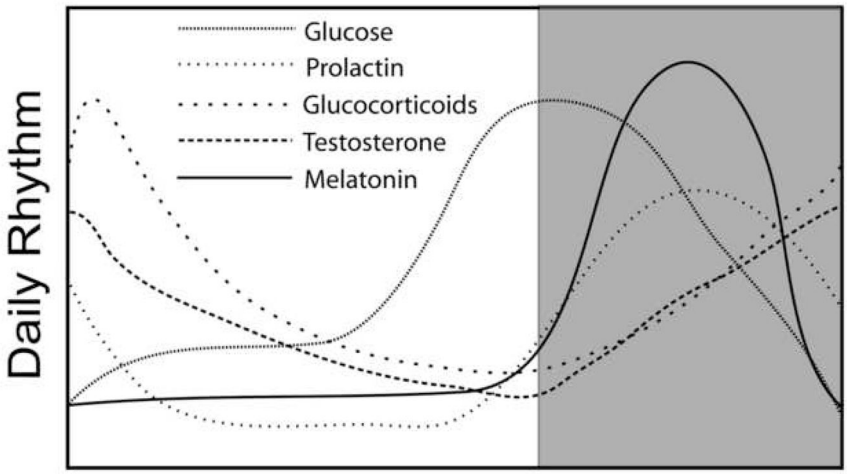

Figure 1.
Examples of circadian rhythms in humans. Shaded area represents times of sleep while the unshaded area represents times of activity. Note that all parameters exhibit unique peaks and troughs relative to each other. This phase relationship among individual rhythms is critical for optimal functioning and homeostasis.

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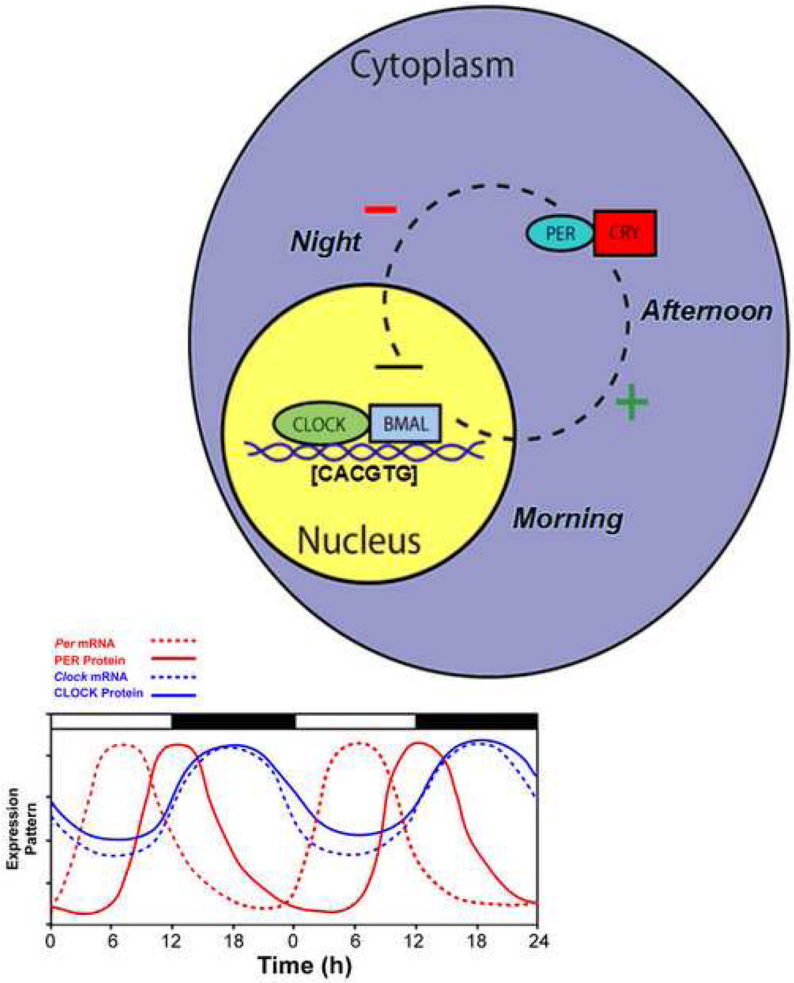

Figure 2.

A simplified model of the intracellular mechanisms responsible for mammalian circadian rhythm generation. The process begins when CLOCK and BMAL1 proteins dimerize to drive the transcription of the Per (Per1, Per2, and Per3) and Cry (Cry1 and Cry2) genes. In turn, Per and Cry are translocated to the cytoplasm and translated into their respective proteins. Throughout the day, PER and CRY proteins rise within the cell cytoplasm. When levels of PER and CRY reach a threshold, they form heterodimers, feed back to the cell nucleus and negatively regulate CLOCK:BMAL1 mediated transcription of their own genes. This feedback loop takes approximately 24 h, thereby leading to an intracellular circadian rhythm. (Adapted from Kriegsfeld and Silver, 2006).