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Review

The trouble with circadian clock dysfunction: Multiple deleterious effects on the brain and body

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ABSTRACT

This review consolidates research employing human correlational and experimental work across brain and body with experimental animal models to provide a more complete representation of how circadian rhythms influence almost all aspects of life. In doing so, we will cover the morphological and biochemical pathways responsible for rhythm generation as well as interactions between these systems and others (*e.g.*, stress, feeding, reproduction). The effects of circadian disruption on the health of humans, including time of day effects, cognitive sequelae, dementia, Alzheimer's disease, diet, obesity, food preferences, mood disorders, and cancer will also be discussed. Subsequently, experimental support for these largely correlational human studies conducted in non-human animal models will be described.

Contents

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Most English speakers are familiar with the phase: *the early bird gets the worm.* One strategy for getting the worm is to predict when it will be available. Thus, the possession of a clock, particularly an alarm clock, would be highly advantageous. Conveniently, endogenous timekeepers are present in virtually all living things (Young and Kay, 2001). Relatively simple, single cell organisms exhibit circadian rhythmicity, but individual oscillators in multicellular organisms must be coordinated. This master clock is the suprachiasmatic nucleus (SCN) of the anterior hypothalamus in animal species that possess complex central nervous systems (CNS, Reppert and Weaver, 2001). The SCN is capable of maintaining rhythmicity in the absence of environmental inputs, but cues like sunrise, sunset, and fluctuations in temperature increase its temporal fidelity (Dibner et al., 2010).

The first section of this review provides a description of the machinery that underlies circadian rhythms. The expression of various genes and associated protein products vary throughout the day in the SCN and these variations are associated with changes in the synthesis, sensitivity, efficacy, and concentrations of various neurotransmitters, neuropeptides, and hormones throughout the brain and body (Hirota and Fukada, 2004). Many of these same agents regulate gene expression and activity within the SCN (Antle et al., 2005; Choi et al., 2008; Liu et al., 1997; Morin, 1999). Further, the dependence of the SCN on exogenous cues for anchoring its activity to real world events means that the presence or absence of cues such as light at particular phases of circadian cycle elicit different effects in the activity of the circadian network (Antle et al., 2009).

The second section describes the relationship between circadian rhythms and health. If the presence of circadian rhythmicity is advantageous, the absence of circadian rhythmicity should be detrimental. Shift work, jetlag, obesity, diabetes, affective disorders, dementia, and cardiovascular diseases have all been linked to circadian rhythmicity or the disruption thereof in epidemiological studies and in experimental animal models (Dallmann et al., 2012; Pan et al., 2011; Parkes, 2002; Tranah et al., 2011). Regardless of whether a particular study focuses on the effects of circadian disruption or correlates of poor health, the association between the two is routinely identified. Further, many treatment outcomes for disease states also elicit partial reparation of circadian rhythmicity and *vice versa* providing additional support for the links between circadian rhythms and health.

The final section of this review describes experimental queries of the impacts of circadian rhythm disruption in animal models. The localization of the master clock to the SCN provides the opportunity for experimental manipulations of circadian rhythmicity. Elimination of circadian rhythms has been elicited via techniques such as physical ablation of the SCN (Lesauter and Silver, 1998), molecular knockouts (KOs; Husse et al., 2011; Okamura et al., 1999) or mutant rodent strains (Ralph and Menaker, 1988). The reliance of the system on environmental inputs make it possible to manipulate circadian rhythms by altering the timing of relevant events (*e.g.*, light onset) without physical manipulation of the brain (Moore, 1996). Various illumination paradigms have been developed for studying circadian rhythmicity including constant illumination paradigms (Yan et al., 2005), the administration of light pulses at conflicting times of day (Antle et al., 2009), or altering light schedules to elicit shifts in the light-dark (LD) cycle (*i.e.*, LD shifts; Devan et al., 2001). Each of these manipulations elicits differential responses, but they provide the opportunity to examine the impacts of circadian disruption on different types of learning and memory (*e.g.*, spatial memory, stimulus–response associations, time-place learning) as well as the structures (*e.g.*, hippocampus) that underlie these abilities.

1. Anatomy and gross morphology of the suprachiasmatic nucleus

The CNS of all vertebrates contains a group of bilaterally distributed nuclei, the SCN. The SCN are located in the periventricular zone of the anterior hypothalamus dorsal to the optic chiasm and, as is true for so many nuclei located within the hypothalamus, serve a homeostatic or physiological regulatory function. Each SCN is comprised of two distinguishable regions, a core and a shell (Abrahamson and Moore, 2001; Antle and Silver, 2005; Leak and Moore, 2001) and while some arguments can be made against this oversimplification, it will suffice for the purposes of this discussion (Morin, 2007). Please see Morin and Allen (2006) for a complete description of this debate and in depth discussion of neuronal phenotypes, anatomy, and connectivity within SCN.

The SCN exhibits cyclical patterns of electrical activity and responsiveness to input over an approximate 24 h cycle (Inouye and Kawamura, 1979). These rhythmic patterns of activity, which occur with a frequency of an approximate solar day, are called circadian oscillations (from Latin: "circa" = approximately and "diem" = day). The SCN interprets information about time of day that it receives from various sensory and homeostatic afferents including inputs from the geniculohypothalamic tract and median raphe (Morin and Allen, 2006). The geniculohypothalamic tract provides various inputs to the SCN including GABAergic and neuropeptide Y (NPY), although the molecular profiles differ by species (Morin and Allen, 2006). The serotonergic projections from raphe nucleus are thought to affect the responsiveness of the SCN to other inputs (*e.g.*, light) (Abrahamson and Moore, 2001; Challet, 2007; Selim et al., 1993). Of the inputs received by the SCN, light, arriving at the SCN via the retinohypothalamic tract (RHT) from intrinsically photosensitive melanopsin expressing retinal ganglion cells (pRGCs) elicits the most robust effects within the SCN (Ruby et al., 2002; Hattar et al., 2002; Provencio et al., 1998). When combined, these multimodal inputs inform daily cycles of SCN activity (Abrahamson and Moore, 2001; Leak and Moore, 2001) which then feed into the transcriptional and translational machinery of each neuron. Although the RHT is the major photic input in mammals (Cassone et al., 1988), this can differ by taxa. For example, Tuatara (Sphenodon) possess light sensitive cells in the pineal gland (Tosini et al., 2001) which may act to synchronize certain rhythmic processes, bypassing the eye altogether.

The SCN also receives information about internal physiological state (Leak and Moore, 2001). These inputs include humoral signals and thus involve various brainstem and medial hypothalamic nuclei (Kalsbeek and Buijs, 2002), along with other components of the autonomic nervous system (Krout et al., 2002). For example, melatonin, released from the pineal gland, affects transcription rates in SCN in a multistep cascade that ultimately targets the SCN shell (Reppert and Weaver, 2001). In addition to timing cues derived from light, blood pressure, insulin, sex hormones and other neuropeptides, various homeostatic processes exhibit their own circadian oscillations that, in turn, may feed-back into the SCN to tune the circadian clock. The loci responsible for generating these rhythms have been categorized as *peripheral oscillators* due to their