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Review

Sex differences in circadian timing systems: Implications for disease

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ABSTRACT

Virtually every eukaryotic cell has an endogenous circadian *clock* and a biological *sex*. These cell-based clocks have been conceptualized as oscillators whose phase can be reset by internal signals such as hormones, and external cues such as light. The present review highlights the inter-relationship between circadian clocks and sex differences. In mammals, the suprachiasmatic nucleus (SCN) serves as a master clock synchronizing the phase of clocks throughout the body. Gonadal steroid receptors are expressed in almost every site that receives direct SCN input. Here we review sex differences in the circadian timing system in the hypothalamic–pituitary–gonadal axis (HPG), the hypothalamic–adrenal–pituitary (HPA) axis, and sleep–arousal systems. We also point to ways in which disruption of circadian rhythms within these systems differs in the sexes and is associated with dysfunction and disease. Understanding sex differentiated circadian timing systems can lead to improved treatment strategies for these conditions.

1. Introduction and rationale

Evidence of the inter-relationships between the circadian timing system and sex differences cannot be ignored. Virtually every cell in the body has a circadian *clock* and a biological *sex*. It appears that no matter what one studies, the measured response is likely influenced by the circadian timing system, and many of these variables differ between the sexes. As noted by Simerly (2005), "The same basic neural pathways are present in each sex, but they are represented differentially (e.g. differing numbers of neurons, projections, dendritic spines, and differing synapse densities); thus, the transmission and processing of sensory information through sexually dimorphic neural networks are likely to be distinct in males and females." Moreover, there is substantial evidence that sex differences in the circadian timing system are important in determining responses to both endogenous and exogenous factors. This *not so* inconvenient truth (McCarthy et al., 2012) has implications for understanding behavior and physiology at many different levels of analysis, including: genes, cells, tissues, and whole organisms.

Female–male differences in regulatory events at the level of individual brain cells can arise from many factors, including: sex chromosome differences, specializations in receptor expression, ion channels, or as a result of differences in circulating hormones.

Abbreviations: 5-FU, 5-fluorouracil; 5-HT, serotonergic; E_2, 17β-estradiol; ACTH, adrenocorticotropic hormone; AMY, amygdala; ANS, autonomic nervous system; AP, action potential; AR, androgen receptors; ARC, arcuate nucleus; AVP, arginine vasopressin; AVPV, anterolateral paraventricular nucleus; BMAL1, brain and muscle ARNT-like protein1; BNST, bed nucleus of the stria terminalis; c-fos, denoting the gene or mRNA; C-FOS, denoting the protein; CRH, corticotropin releasing hormone; DD, constant darkness; DHT, dihydrotestosterone; DMH, dorsomedial hypothalamus; DR, dorsal raphe; DSPS, Delayed Sleep Phase Syndrome; EEG, electroencephalography; EP, estradiol plus progesterone; ER, estrogen receptors; ERα, estrogen receptor alpha; FASPS, Familial Advanced Sleep Phase Syndrome; GC, glucocortocoids; GDX, gonadectomy; GHT, geniculo-hypothalamic tract; GnIH, gonadotropin inhibiting hormone; GnRH, gonadotropin releasing hormone; GR, glucocortocoid receptor; GRP, gastrin-releasing peptide; HA, histamine; HB, habenula; HPA, hypothalamic–adrenal; HPG, hypothalamic–pituitary–gonadal; IGL, intergeniculate leaflet; IML, intermediolateral column; Kiss1, kisspeptin; Kiss1 R, Kiss1 receptor; KO, knock out; LC, locus coeruleus; LD, light-dark; LH, luteinizing hormone; LHA, lateral hypothalamic area; LS, lateral septum; MnPO, median preoptic area; mPOA, medial preoptic area; mpPVN, medial parvocellular PVN; MR, medial raphe; MUA, multi-unit neural activity; NA, norandrenergic; Npas2, Neuronal PAS domain-containing protein 2; OVX, ovariectomized; P, progesterone; PER1, Period1 protein; *Per1*, Period1 gene or mRNA; PER2, Period2 protein; *Per2*, Period2 gene or mRNA; POA, preoptic area; PVA, anterior paraventricular thalamic nuclei; PVN, paraventricular nucleus of the hypothalamus; Rch, retrochiasmatic area; RHT, retinohypothalamic tract; SCN, suprachiasmatic nuclei; SD, sleep deprivation; sPVZ, sub paraventricular zone SWA, slow wave activity; T, testosterone; TH, tyrosine hydroxylase; TMN, tuberomammillary nucleus; VIP, vasoactive intestinal polypeptide; VMH, ventromedial nucleus of the hypothalamus; VNTR, variable nucleotide tandem repeat; VLPO, ventrolateral preoptic area; WT, wild type.

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In turn, these cell based sex differences can give rise to male–female differences in brain networks, organs, and behavior. Such effects have substantial implications for the application of basic research findings to practical problems and investigating the causes of sex differences in disease incidence. The former can lead to optimizing the timing of drug delivery; the latter can provide clues to both protective and susceptibility mechanisms that differ between the sexes (IOM [Institute of Medicine], 2011). As noted in a series of papers in Nature magazine on sex differences in 2010 (Zucker and Beery, 2010; Kim et al., 2010), there is a dearth of research with female animals, and in some instances the sex of the subject is not even reported. This is especially relevant to circadian rhythms research where a small fraction of work (<20%) includes females (Kuljis et al., 2013).

Daily rhythms exist in virtually every behavioral and physiological response that one can measure. These are orchestrated by a *brain clock* located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Three distinct components are involved in the SCN's ability to function as a brain clock (Fig. 1). These include: input from the environment via a direct retinohypothalamic tract (RHT), an oscillating clock in the SCN, and output pathways to various target areas in nearby hypothalamic regions. Important in the present context is the fact that brain nuclei at each stage in this system – namely input, clock and targets, all bear estrogen receptors (ER), androgen receptors (AR), or both. This allows for feedback from circulating hormones to act on each of these components of the circadian timing system. Sex differences in the steroid receptor expressing brain regions set the stage for the present review of sex differences in the circadian timing system. Such differences can arise from organizational actions of hormones in the pre- and perinatal period, and/or from activational effects of hormones during the pubertal period and adulthood. Furthermore, as noted by Arnold (2012), some sex differences antecede gonadal differentiation and are determined by non-gonadal effects such as the number and type of sex chromosomes. These influences on sex differences in circadian timing have not been examined.

To explore sex differences in the circadian timing system and resulting neuroendocrine consequences, we first characterize circadian phenomena and define terminology used in the field of chronobiology. In turning to the current literature, we focus on the SCN and its organization, the history of research in circadian timing, and some of the terminology and experimental paradigms used in the field. We next provide a brief overview of the literature on sex differences in circadian timing. We then focus attention on sex differences and the relationships between circadian rhythms and several physiological and behavioral systems. In the hypothalamic–pituitary–gonadal axis (HPG) the differences between the sexes are highly salient; the hypothalamic–adrenal axis (HPA) has broad impact on circadian regulation of cells and clock genes throughout the body. Next, we examine sleep–wake cycles, which constitute the most salient circadian phenomena experienced by most people and discuss their importance in understanding environmental disturbances related to jet lag and shift work which can increase one's susceptibility for numerous disease states. Finally, we consider a very practical issue: the critical importance of sex differences in circadian rhythmicity in disease and drug administration using findings from the treatment of cancer as a case in point.

2. Overview of the circadian timing system

2.1. Circadian terminology and experimental paradigms

To explore research on circadian rhythms we review some of the terminology, key concepts, and experimental paradigms used by chronobiologists. Circadian rhythms are biological processes which have an endogenous oscillation of about (circa) a day (diem) and persist in the absence of any external temporal cues. In fact, the body's circadian clocks are generally viewed as oscillators with a period of approximately 24 h.

In order to distinguish endogenous circadian rhythms from daily variations that are driven by external cues, chronobiologists study responses in the presence and absence of external signals. Proof that a given response is under endogenous circadian control requires that it can be detected in the complete absence of time cues from the environment. In contrast, some daily rhythms which are not circadian in nature occur in the presence of environmental

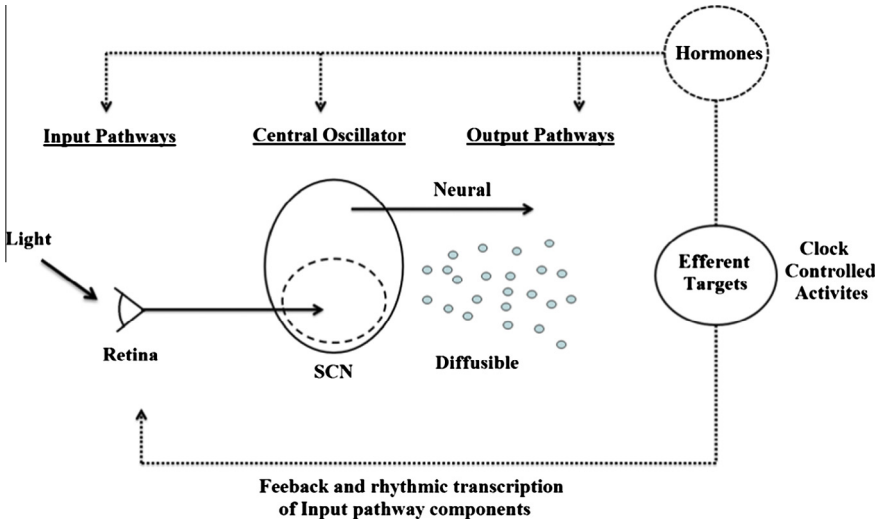

Fig. 1. Representation of circadian timing system. The circadian clock has been represented as having three components: input pathways, a central oscillator (or pacemaker), and output pathways. Input pathways such as photic signals from the retina, or temperature, can influence the master oscillator in the suprachiasmatic nucleui (SCN) of the hypothalamus which produces the endogenous biological rhythm that synchronize the rest of the body. Output pathways to target sites entail both neural connections and diffusible signals, and these regulate clock-controlled biological processes. Additional pathways (shown as dotted lines) include multiple interlocking positive or negative feedback from clock controlled activities. One prominent feedback mechanism are the systemically secreted hormones which can then influence the circadian system at all levels, including input pathways, the central oscillator, and output pathways. Adapted from Kriegsfeld et al. (2002a).