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Review

Neuroendocrine underpinnings of sex differences in circadian timing systems

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ABSTRACT

There are compelling reasons to study the role of steroids and sex differences in the circadian timing system. A solid history of research demonstrates the ubiquity of circadian changes that impact virtually all behavioral and biological responses. Furthermore, steroid hormones can modulate every attribute of circadian responses including the period, amplitude and phase. Finally, desynchronization of circadian rhythmicity, and either enhancing or damping amplitude of various circadian responses can produce different effects in the sexes.

Studies of the neuroendocrine underpinnings of circadian timing systems and underlying sex differences have paralleled the overall development of the field as a whole. Early experimental studies established the ubiquity of circadian rhythms by cataloging daily and seasonal changes in whole organism responses. The next generation of experiments demonstrated that daily changes are not a result of environmental synchronizing cues, and are internally orchestrated, and that these differ in the sexes. This work was followed by the revelation of molecular circadian rhythms within individual cells. At present, there is a proliferation of work on the consequences of these daily oscillations in health and in disease, and awareness that these may differ in the sexes.

In the present discourse we describe the paradigms used to examine circadian oscillation, to characterize how these internal timing signals are synchronized to local environmental conditions, and how hormones of gonadal and/or adrenal origin modulate circadian responses. Evidence pointing to endocrinologically and genetically mediated sex differences in circadian timing systems can be seen at many levels of the neuroendocrine and endocrine systems, from the cell, the gland and organ, and to whole animal behavior, including sleep/wake or rest/activity cycles, responses to external stimuli, and responses to drugs. We review evidence indicating that the analysis of the circadian timing system is amenable to experimental analysis at many levels of the neuraxis, and on several different time scales, rendering it especially useful for the exploration of mechanisms associated with sex differences.

Contents

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1. Introduction and background

While sex differences[1] are best known in relation to reproduction and reproductive behaviors, they in fact occur in phenomena completely unrelated to reproductive processes. Given that each cell of the body contains copies of the sex chromosomes identifying the animal as male or female, it is to be expected that bodily functions unrelated to reproduction also differ between the sexes. One such example is seen in the circadian system and the mechanisms underlying these differences.

In general, we are acutely aware of the regular alternation between activity and rest, and we are especially aware of the daily need for sleep. Less salient are the multitudes of regularly recurring changes in endocrine and metabolic responses that accompany these regular rest-activity cycles. These changes are not externally driven by the light–dark cycle or our alarm clocks, but are orchestrated by a plethora of clocks within the body. The internally organized daily rhythms are termed “circadian rhythms”. In the absence of all external temporal cues, circadian rhythms persist under constant conditions, with a period (cycle duration) close to 24 h. This is an important piece of evidence supporting the notion that circadian rhythms are indeed driven by internal clocks, rather than external stimuli.

Internally orchestrated circadian rhythms can be distinguished from daily rhythms (changes that are driven by signals from the environment). This is achieved by testing for rhythmicity in the absence of external cues, thereby distinguishing internally timed from externally driven responses. Circadian rhythms also differ from “masked” responses, which can influence behavior but do not entrain or phase shift the body clock. Rhythms can be measured by their amplitude, frequency and phase relationship to other markers of time. The tools and terms used by chrono-researchers to explore these aspects of circadian rhythms are described in Box 1.

The circadian timing system has the dual functions of enabling the anticipation of upcoming events and determining the time of maximal and minimal expression times of a multitude of responses. These two functions, anticipation and modulation of expression, can be seen in both behavioral and physiological responses. Thus, circadian timing system enables organisms to anticipate the daily fluctuations in light, temperature, food availability or predator activity, and prepare the body to meet the physical and cognitive demands that are essential for survival. This system also ensures that the peak activity time of individual cells, and of each behavioral and physiological activity, occurs at an optimal time of the day.

As will be discussed, virtually each cell in the body has a “circadian clock”. Furthermore, the secretions of gonadal hormones differ in males and females, and these sex-typical hormones circulate in the blood and act back on many sites in the body, thereby affecting circadian processes at the cellular level. Male–female differences in the circadian timing system range from the localization of steroid receptors of the master brain clock within the suprachiasmatic nucleus (SCN), to daily rhythms of hormone secretion. The sexual dimorphism in the circadian timing system derives in part from the diverse effects of steroid hormones in regulating physiological and neurological processes. The two major sources of steroids involved in modulating clock functions are the adrenal and gonadal glands, each of which influences circadian rhythmicity in unique and often sex-specific ways.

In the present review, we introduce the basic organization of circadian system. Next we discuss the reciprocal regulation of circadian clocks and steroid hormone effects, and then explore the sex differences in circadian system and the potential underlying mechanisms.

2. Overview of the circadian timing system

One of the advantages of studying the circadian timing system is that it is experimentally tractable at multiple levels of analysis including rhythmic changes in genes and proteins within cells, in electrical and metabolic responses, rhythmic responses in specific tissues and organs, and in the behavior of the organism as a whole. Sex differences have been described at each level of the neuraxis regulating circadian rhythms, from genes to behavior. We discuss this system using a bottom-up approach, first describing the timing system at a cellular/molecular level, then discussing the master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and then delineating the ways in which the SCN orchestrates the phase relationships of oscillation in clock bearing cells in the rest of the body, including extra-SCN brain regions and peripheral organs.

2.1. Molecular and cellular clocks

Individual cells are capable of self-sustained circadian oscillation in gene expression [1,2]. The cellular-molecular clock entails a set of transcriptional modulators and their protein products, constituting interlocked transcriptional/translational feedback loops (reviewed in [3,4]). In this molecular clock (Fig. 1), CLOCK and BMAL1 are two transcriptional factors that bind to the highly conserved E-box (sequence CACGTG) in the promoter region of

[1] This paper focuses on sex differences in the circadian timing system. We follow the convention of distinguishing between sex and gender. Sex differences refer to the biological sex as it occurs in normal development with concordance between genetic, gonadal and hormonal sex. Gender, gender role and gender identity refer to the subjective experience of being a man or a woman, consisting primarily of the acceptance of membership into a category of people such as male or female. The latter topic is outside the domain of this review.

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