# Impact of Shift Work on the Circadian Timing System and Health in Women

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**KEYWORDS**

• Shift work • Circadian clock • Sleep • Women • Sex differences • Circadian misalignment • Chronobiology

**KEY POINTS**

- Shift workers experience circadian misalignment, which leads to acute physiologic effects that may contribute to long-term health problems.
- Sex differences in the circadian timing system are present on molecular, physiologic, behavioral, and cognitive levels, which contribute to sex-specific health and safety concerns related to shift work.
- Recent epidemiologic evidence indicates that women who work night shifts have an increased risk of developing cancer, metabolic syndrome, cardiovascular disease, diabetes, and reproductive disturbances compared with women who work during traditional working hours.
- Night shift workers who have not adapted to their work schedule can experience the lowest alertness and performance during their work period and, importantly, during their commute home in the morning.

## INTRODUCTION

Shift work, commonly defined as work that is performed outside the conventional 9-to-5 working day, is a necessary product of the 24-7 society that requires many industries to be operational around the clock. Data from the 2010 National Health Interview Survey in the United States revealed that 29% of the workforce described their work time arrangement as different from a regular day shift.[1] The 2005 General Social Survey in Canada arrived at a similar percentage, with 28% of the workforce working in shifts.[2] In the European Union (EU), 21% of the workers report working in nonstandard shifts and 19% work at night at least once a month.[3] The percentages of men and women involved in shift work are equal in both North America and the EU.[1–3]

Shift work is associated with various adverse health effects[4,5] and is regarded as probably carcinogenic in humans by the International Agency for Research on Cancer (IARC).[6] Although there is

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increasing evidence that sex differences exist on all biological levels (see later discussion of chronobiology), women remain an underrepresented group in biomedical research. Therefore, it is crucial to address the specific challenges faced by female shift workers. This review provides a brief overview of the circadian timing system, the disruption of which is thought to contribute to the adverse health effects associated with shift work. Focusing on scientific literature involving actual shift workers or laboratory-based studies in healthy human subjects, we discuss sex differences in the regulation of the circadian timing system and the sleep–wake cycle that may underlie female-specific susceptibility to adverse effects of shift work. The health concerns for the female shift worker and countermeasures that might aid in the adaptation to the shifted work schedule and, possibly, in the prevention of the adverse health effects are described.

## CIRCADIAN TIMING SYSTEM

Daily variations have been found in many physiologic and behavioral processes in humans, such as hormone levels, sleep propensity, alertness, and organ function. These daily rhythms are generated by the circadian system (from the Latin *circa dies*: approximately 1 day), an endogenous timing system that emerged early in evolutionary history as an adaptation to predictable, cyclic changes in light, temperature, and food availability.[7]

Although sex differences in the period length for circadian rhythms have been identified (see later discussion), the endogenous circadian timing system in humans has an average period of 24.2 hours, and hence requires daily resetting to remain entrained to the 24-hour light–dark cycles on Earth.[8] Light, the most prominent synchronizer in humans and other mammals, is transmitted from the retina to the central clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus.[9] Within the SCN, photic input is integrated and conveyed to peripheral tissues (**Fig. 1**A). Cells in the SCN show self-sustained circadian rhythms, which are generated by a molecular transcriptional/translational feedback loop that autonomously sustains a rhythm with a period of approximately 24 hours in each neuron (**Fig. 1**B).[10]

The transcriptional–translational feedback loop is not unique to the cells of the SCN. In fact, most cell types in the body express a similar set of clock genes[11,12] that can oscillate autonomously.[13] In humans, 24-hour rhythms in the expression levels of clock genes have been found in many peripheral tissues, including peripheral blood mononuclear cells,[14] adipose tissue,[15,16] oral mucosa,[17] fibroblasts,[18] bone marrow,[19] and several brain regions.[20,21] The core clock genes not only regulate their own expression but also that of clock-controlled genes. Early microarray studies in mice revealed that up to 10% of genes in the SCN and the liver show circadian expression patterns.[22,23] In humans, genome-wide gene

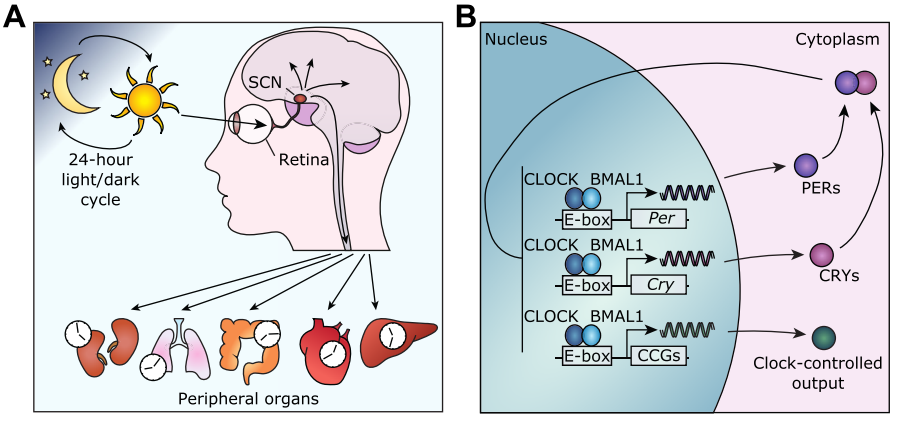


**Fig. 1.** Organization of the circadian timing system at (*A*) the level of the organism and (*B*) of the cell. (*A*) The biological clock is located in the SCN. Light information from the environment is transmitted from the retina to the SCN in the hypothalamus. Neuronal and humoral signals from the SCN synchronize the circadian oscillators in peripheral organs. (*B*) At the cellular level, a 24-hour rhythm is generated by a translational or transcriptional feedback loop. The transcription factors CLOCK and BMAL1 bind to E-box elements in the promotor of other clock genes (*period1, 2* and *cryptochrome1, 2*) and of clock-controlled genes (CCGs), thereby activating their transcription. After translation in the cytoplasm, PER and CRY dimerize and translocate to the nucleus, where they inhibit the transcriptional activity of CLOCK and BMAL1. Hereby, the 2 proteins down-regulate their own transcription. This (simplified) process creates oscillations in gene expression with a period of approximately 24 hours.