Circadian Rhythms: From the Bench to the Bedside and Falling Asleep
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Abstract: The discovery of the molecular core machinery underlying the generation of circadian rhythms in mammals, and the ability to alter the genes and protein products that comprise the circadian clock, has led to a new appreciation of the role of the clock in regulating many parameters of the sleep-wake cycle, beyond just the timing of sleep. The journal, Sleep, with its mission of publishing papers on basic and translational research in the field of sleep, is in an ideal position to insure that advances in the field of circadian rhythms are used to improve human sleep and in the treatment of sleep-wake disorders.

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ANYONE EVEN MARGINALLY COGNIZANT OF RECENT RESEARCH ON CIRCADIAN RHYTHMS REALIZES THAT THIS FIELD HAS BEEN ONE OF THE HOTTEST ONES IN BIOMEDICAL RESEARCH OVER THE PAST FEW YEARS, AS NUMEROUS LABORATORIES HAVE CONTRIBUTED TO UNRAVELING THE CELLULAR AND MOLECULAR EVENTS UNDERLYING THE ENTRAINMENT AND GENERATION OF OUR 24-HOUR RHYTHMS. Indeed, in 3 of the last 7 years, the prestigious scientific journal Science has listed research in this area as 1 of the top-10 scientific breakthroughs of the year, including in 1998 when research on circadian rhythms was ranked as the number 1 biomedical breakthrough of the year.1 While surely there will be more exciting advances in our understanding of the basic mechanisms that allow organisms to remain synchronized to the 24-hour changes in the physical environment, equally exciting is the potential to use this information to improve human health, safety, and productivity. Indeed, in an era when more emphasis is being placed on taking new research findings from the bench to the bedside, it is noteworthy that the circadian field is poised to literally take its research to the bedside—via what people actually do in bed: SLEEP.

For many years the sleep-wake cycle was seen as just 1 of hundreds of “output” rhythms and thus of no special interest to circadian biologists. And in reverse, for sleep researchers, the circadian clock only regulated the timing of sleep and wake and was not part of the basic homeostatically regulated sleep-wake system, other than when the clock said “wake up” or “go to sleep.” However, recent studies in animals and humans have revealed that the sleep-wake and circadian clock systems are intimately linked to the other on the molecular and system’s levels. Regardless of how the circadian and sleep-wake systems are mechanistically related to each other, the 2 systems work together to regulate the overall temporal organization of the organism. While the “master circadian clock” in the hypothalamic suprachiasmatic nucleus (SCN) regulates many rhythms independent of the sleep-wake cycle, it also regulates other rhythms indirectly, via its control of the timing of the sleep-wake cycle, which in turn regulates the expression of rhythms dependent on the behavioral states of sleep and wake. Indeed, this indirect control of many rhythms dependent on the sleep-wake cycle has led to the notion that the sleep-wake cycle is the “master circadian rhythm.”2

Earlier I suggested that the field of circadian rhythms is “poised” to bridge basic and translational research via the sleep-wake cycle—poised, but not there yet. To date, research on the circadian control of the sleep-wake cycle in humans has tended to focus on how the clock controls the phase of the sleep-wake cycle relative to the light-dark cycle, and little attention has been given to how the clock controls the drive to sleep or be awake. Indeed, of the 3 articles in Sleep in 2003 that are primarily about the circadian control of the human sleep-wake cycle, all are focused on individuals with an altered phase relationship of the timing of sleep relative to the normal population: two papers examined delayed sleep-phase syndrome (DSPS) and one advanced sleep-phase syndrome (ASPS). Watanabe et al3 report for the first time that not only is the phase of sleep altered in DSPS patients, but there are also disturbances in sleep structure, including a decrease in sleep efficiency, as well as the amount and percentage of slow-wave sleep when compared to healthy normal-sleeping controls. Much of the focus on DSPS and ASPS is on the genetic basis of these disorders now that circadian biologists have identified many of the canonical circadian clock genes in flies and mice, which show remarkable homology in the genes and proteins that make up the core transcriptional-translational feedback loops of the circadian clock machinery.4 Archer et al5 report that a repeat region of 1 of the 3 Per genes (Per3) is associated with diurnal preference with the longer allele associated with morningness and the shorter allele with eveningness. With at least 10 (and counting) circadian clock core genes having been identified in mammals, it can be expected that many different genes/alleles will be involved in diurnal preference, as is suggested by the finding that ASPS in 2 Japanese families is not linked to the Per2 gene, as was recently found in a Caucasian family.6,7

The finding of a variety of changes in sleep-wake characteristics in individuals with DSPS supports the hypothesis proposed earlier in this review that alterations in circadian clock function will lead to more than just changes in the timing of sleep. Similarly, a recent study by Easton et al8 found that SCN-lesioned nocturnal mice sleep 1 to 2 hours more than controls.
indicating the presence of an SCN “alerting” factor, as originally proposed to explain a 4-hour increase in sleep time in diurnal monkeys after lesions of the SCN.9 Indeed, mutations or deletions of core clock genes, such as Clock or the cryptochromes, also leads to a variety of changes in sleep-wake architecture under baseline as well as sleep-deprivation conditions.10,11 There is now good evidence that the SCN is producing an alerting signal during normal wake time and a sleep-inducing signal during normal sleep time; such results indicate that the SCN controls to a large extent sleep and wake pressures. While the development of hypnotics has focused mainly on the GABA/benzodiazepine-receptor complex,12 the SCN outputs are an untapped target for drug discovery for the treatment of sleep disorders as well as for the development of wake-enhancing drugs. The circadian clock field is poised to have a major impact on the drives to sleep and wake; however, it is not there yet.

The maturity of a biomedical research field (and treatment for associated pathophysiologies) is often dependent on data from large epidemiology studies that define “healthy normal” in the population, and what deviations from the healthy normal underlie or are related to health and disease. For example, determining that a high cholesterol level was associated with heart disease fostered 1 of the largest pharmaceutical markets in the world. Three epidemiology-based studies in Sleep in 2003 make a start at defining (1) sleep parameters in premenopausal, perimenopausal, and postmenopausal women13; (2) the cost of poor sleep in different organizational levels in the individual, in the work place, and for society in general14; and (3) the effect of ethnicity on sleep.15 All 3 studies point to the importance of being able to define human sleep and circadian parameters in different populations in order to understand what is “healthy normal” and the impact of “unhealthy” sleep and circadian pathology for health and well being. However, monitoring sleep and circadian parameters is difficult, expensive, and time consuming. Thus, there is a great need to develop new analytical tools that can be used to define sleep and circadian characteristics in a quantitative and inexpensive fashion. Two papers appearing in Sleep in 2003 report on sleep questionnaires for tracking sleep-wake parameters more efficiently in adults16 and in adolescents.17 Wrist actigraphy, in place of expensive polysomnography, continues to hold promise as a highly accurate measure of some sleep-wake characteristics (with some limitations)18 that will be suitable for long-term populations-based studies.19 However, there is a clear need for new technologies to monitor circadian time and sleep-wake state, as well as to gauge levels of fatigue and alertness. Leinonen et al20 report on an automated system for detecting blinks in electroencephalograms, which can be used to monitor sleep in normal people, as well as in people with developmental disorders, a technology that may lead to new procedures to monitor levels of fatigue and alertness.

The need to perhaps chronically monitor on a day-to-day basis one’s overall circadian preference for sleep and wake, as well as one’s bank account for sleep loss (the so-called sleep debt) takes on added importance in view of the findings reported in what may become a classic paper in sleep research. Van Dongen et al21 demonstrated that chronic sleep restriction to 6 hours or less per night produces deficits in cognitive performance equivalent to 2 nights of total sleep deprivation. Importantly, many chronically sleep-deprived subjects were largely unaware of being increasingly cognitively impaired, raising the possibility that many individuals with APSS or DSPS, who can not adjust their work or social schedules to match their diurnal preference, may think their state of constant fatigue is normal. Just as we cannot measure our blood pressure without instrumentations, we may need objective measures to monitor our circadian ups and downs as well as our sleep debt. Since such a debt can have metabolic22 as well as neurobehavioral consequences,21 monitoring one’s sleep bank account may have long-term health benefits as well.

As noted at the beginning of this brief review, basic research on circadian rhythms in mammals has been advancing at a rapid pace. A major factor in the success has been the long-term “belief” in the field that the basic mechanisms underlying circadian rhythmicity have been highly conserved across species, and, even though the fruit fly or the molluscan brain does not contain an SCN, at the cellular or molecular core level, there could be similar genes and gene products. This belief, dating back prior to the discovery of any mammalian circadian clock genes, turned out to be remarkably accurate.4 Looking beyond the electroencephalogram and defining rest as sleep in electroencephalogram-lower organisms is opening up a new era for sleep research. Opening up more sleep research to genetically tractable organisms, such as the fruit fly and the mouse, holds promise for the discovery of basic sleep mechanisms at the genetic and molecular levels at a rapid pace, as has occurred over the last decade for research on circadian rhythms. As reported by Hendricks et al,23 not only does the fruit fly show many “rest characteristics” that are not modeled to define sleep in mammals, but it also responds to the alerting drug, Modafinil, in the same way as do rodents and humans. Linking research on the sleep-wake cycle with that of circadian clock research, particularly when core genetic or molecular elements linking the 2 systems can be identified, offers great promise for moving fundamental advances in circadian biology from the bench to the bedside and into the bed.

REFERENCES

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