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Internal rhythms in humans

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Human physiology and behavior are characterized by a daily internal temporal dimension. This so-called circadian rhythmicity is present for almost all variables studied to date, persists in the absence of external cycles, and is synchronized to the external 24-h world by an internally generated circadian rhythm of light sensitivity. The light-sensitive circadian pacemaker, presumably also in humans located in the suprachiasmatic nucleus of the hypothalamus, drives the endogenous circadian component of rhythmicity for a number of variables including plasma melatonin, alertness, sleep propensity and sleep structure. Overt rhythmicity and the consolidation of vigilance states are generated by a fine-tuned interaction of this circadian process with other regulatory processes such as sleep homeostasis.

Key words: circadian pacemaker / light / phase response curve / sleep / sleep homeostasis

REMARKABLE PROGRESS has been made in the understanding of the neurophysiological and neuropharmacological characteristics and identification of the neuroanatomical localization of an endogenous circadian pacemaker in mammals.[1] This pacemaker, localized in the suprachiasmatic nucleus (SCN) of the hypothalamus, has been shown to continue to oscillate *in vitro*. Actually, it was recently reported that the firing rate of dispersed individual SCN neurons exhibits a near 24-h periodicity, which continues for many weeks *in vitro*, suggesting that many if not all neurons of this structure can act as a circadian pacemaker.[2] Previously, transplantation studies, in which fetal SCN tissue was transplanted into the third ventricle of an SCN-lesioned and thus arrhythmic hamster, had demonstrated that the phenotype of the restored rhythm is determined by the genotype of the donor without any evidence of interaction of the genotype of donor and host.[3] This demonstrates that the SCN is both necessary and sufficient for the generation of circadian rhythmicity.

In humans, the SCN is unaccessible, except in postmortem studies, and its role in the regulation of human circadian physiology has been inferred primarily from comparative neuroanatomical studies which demonstrated that key pathways, such as the retino-hypothalamic tract (RHT), which conveys photic information from the retina to the SCN, are present in humans.[4,5] In addition, circadian rhythm abnormalities in a small number of cases in which tumors or lesions in or near the SCN were present support the notion that in humans the SCN also plays a key role in the generation of circadian rhythmicity.[6]

Whereas animal researchers used a variety of invasive and in-vitro techniques to study the localization, neuroanatomy as well as neurophysiological and neuropharmacological characteristics of mammalian circadian systems, the characteristics of the human circadian system have been studied primarily in the intact organism. Analyses of the properties of the human circadian system and experimental protocols aimed at describing the role of the human central circadian pacemaker in the absence of direct access to this pacemaker have revealed new aspects of the role of this structure in the organization of human physiology and behavior. These aspects, which have not been emphasized in animal studies, will be described briefly.

Assessment of internal rhythms in humans

Endogenous and exogenous components

Human subjects isolated from the external 24-h cycle of light and darkness, with or without access to information on the time of day, continue to exhibit near 24-h rhythms for a variety of variables including body temperature, urine flow, cortisol, melatonin and the sleep–wake cycle.[7,8] These observations under free-running conditions indicate that an endogenous mechanism is involved in the generation of the 24-h periodicity as we observe and experience it when we

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are living in society and are exposed to a 24-h light–dark cycle. A conspicuous difference between the entrained state, i.e. when humans are synchronized to the 24-h light–dark cycle, and the free running situation, is the timing of the major sleep episode relative to the trough of the core temperature rhythm. Whereas during the free run the preferred phase of sleep onset is located close to the minimum of the body temperature rhythm and subjects typically wake up 6–8 hours after the minimum of the core body temperature rhythm, in the entrained situation young healthy subjects go to sleep approximately 6 hours before the temperature minimum and wake up 1–2 hours after the temperature nadir.[9]

Contribution of circadian pacemaker to internal rhythms

Internal rhythms are generated by a complex interplay of many physiological systems. For instance, the daily rhythm of core body temperature, one of the most widely used markers of the human circadian timing system, results from rhythmic activity in heat loss and heat production mechanisms. Heat loss and heat production vary with activity levels, vigilance state, posture, food intake, etc. This implies that the rhythm of body temperature — as observed under normal conditions in which food intake, vigilance state, posture and activity levels all exhibit near 24-h periodicity and additional non-rhythmic variation- — does more than reflect the direct influence of the circadian pacemaker on these heat loss and heat production mechanisms. Thus, under normal conditions — in which a variety of external and internal factors influence food intake, vigilance state, posture and activity — the observed rhythm of body temperature is comprised of components driven by exogenous factors ('external masking'), by periodic variations in behavior ('internal masking', which in part depends on the pacemaker) and by components driven directly by the clock.

To obtain more accurate information on the direct contribution of the circadian pacemaker to these processes, protocols have been developed in which the rhythmic components of activity, food intake and vigilance state were removed.[10] In these so-called constant routine protocols subjects typically remain awake for 24–60 h while in bed in a semi-recumbent position. Food and fluid is given frequently in evenly spaced intervals, light intensity is kept at low and constant levels, and variations in activity levels are minimized.

Under these conditions circadian variations in heat production, heat loss and core body temperature do persist, albeit with an amplitude which on average is only half of that observed under non-constant routine conditions.[11] Similar observations have been made for other variables, although the extent to which the rhythmic components of these variables are affected by such factors as activity, food, posture, etc., varies widely. For instance, the amplitude of the robust rhythm of plasma melatonin is only marginally affected by posture, activity, vigilance state, etc., although variations in light intensity have a profound effect on melatonin synthesis.[12-14] On the other end of the spectrum, the overt 24-h component in the plasma levels of human prolactin, as observed under normal conditions of 16-h wakefulness and 8 hours of sleep, is markedly reduced when human subjects are studied under constant routine conditions.[15] Interestingly, under these constant routine conditions several hormonal rhythms, such as for growth hormone and prolactin, have been shown to differ between the sexes.[15,16]

During constant routine protocols in which subjects are kept awake for prolonged periods of time, the time course of some variables, such as subjective alertness, exhibit linear trends superimposed on the near 24-h rhythmicity. These trends reflect the accumulation of sleep debt and indicate that another process, i.e. the history of sleep and wakefuless, contributes to overt rythmicity.[17,18]

The main implications of these observations are that it is very difficult to obtain accurate information on the status of the human circadian pacemaker, because many processes distinct from the circadian pacemaker contribute to overt rhythmicity. In the constant-routine measurements, characteristics of the role of the circadian pacemaker that are concealed during normal conditions become evident.

An internal circadian rhythm of light sensitivity

One of the main characteristics of circadian systems, in organisms ranging from prokaryotes to mammals, is that they can be synchronized to geophysical cycles, of which the light–dark cycle is the most potent synchronizer. A prerequisite for entrainment, i.e. control of the period and phase angle of internal rhythms relative to the external synchronizing cycle, is that the pacemaker exhibits a circadian rhythm of light sensitivity. Originally this rhythm of light sensitivity has been assessed by assaying the effect of light

pulses on free-running rhythms. These experiments have demonstrated that in both nocturnal and diurnal animals, light induces phase delay shifts when applied during the early subjective night and phase advances when applied in the late subject night.[19] During the subjective day light pulses do not induce major phase shifts.

In vitro, the SCN exhibits a circadian rhythm in sensitivity to glutamate, the putative neurotransmitter of the RHT.[20] In addition, the light-induced expression of the immediate early gene c-fos in the SCN exhibits a circadian rhythm.[21] In the intact animal endogenous circadian rhythms in retinal function may also play a role in the entrainment process.[22,23]

An internal rhythm of light sensitivity in humans has been assessed in free-running experiments and in constant-routine protocols.[24,25] Both approaches have shown that phase delays can be induced when light pulses are applied before the temperature minimum and advances are induced by light pulses given after the temperature minimum. Repetitive exposure to bright light centered at the temperature minimum initially induces a reduction of circadian amplitude followed by large phase shifts.[26] This observation is consistent with so-called strong or Type 0 phase resetting, which implies that the sensitivity to light is determined by both phase and amplitude of the human circadian system and that during phase shifts the amplitude of the circadian system may change. Under entrained conditions, the consolidated nocturnal sleep episode, which is initiated on average 6 hours before the temperature minimum and is terminated approximately 2 hours after it, covers the circadian phase of maximum sensitivity to light. This indicates that the timing of the sleep–wake cycle, relative to the rhythm of core body temperature and light sensitivity, is a major determinant of entrained phase.

In animals, changes in day length associated with the seasons are internalized in the SCN, as demonstrated by the effects of photoperiod on the duration of the episode during which light can induce c-fos expression.[27] These changes are thought to be associated with the role of the SCN in seasonal regulation of a variety of physiological functions of which seasonal changes in reproductive status are probably the most important. In humans, seasonal changes in circadian rhythmicity have not been investigated extensively; with the advent of artificial light they may have become less pronounced.[28] Recent evidence suggests that exposure to different day lengths in the laboratory markedly affects the internal circadian rhythmicity of a number of variables including body temperature and plasma melatonin, suggesting that the photoperiodic response has been preserved in humans.[29] Furthermore, seasonal changes in sleep structure and the phase angle between the sleep–wake cycle and the endogenous circadian rhythm of core body temperature have been observed in some field studies.[30] It thus appears that the human circadian system can track seasonal changes in day length, and there is some evidence to suggest that these changes are present at the level of peptidergic rhythmicity in the human SCN.[31]

A main issue in the research on the role of light in the entrainment of the human circadian system has been the assessment of the minimum intensity of light that exerts a significant effect. Although early research suggested that only light of an intensity higher than 1500 lux exerted a significant biological effect,[12] recent research has demonstrated that ordinary room light exerts a significant effect and that the dose–response relationship for light and circadian effects follows a cube root function,[32] similar to the dose–response relationship described in algae and hamsters. The main implication of these recent observations is that the artificial light present in our living rooms during the evening and early night is of an intensity sufficient to affect the phase of the light-sensitive pacemaker in humans. In addition this high light sensitivity also implies that previous assessments of the intrinsic period of the human circadian pacemaker, while subjects were exposed to a self-selected cycle of room light and darkness, were flawed.[33] Assessment of the intrinsic period of the human circadian pacemaker in the absence of this obscurity by light exposure has revealed that the period is on average only 10–20 minutes longer than 24 hours,[8,34] which is considerably shorter than the period of 25 hours once thought to be typical for humans. The discovery of the pivotal role of light in the synchronization of the human circadian system has also led to the recognition that many blind people suffer from chronic desynchrony between their circadian system, which is free running with a period slightly longer than 24 h, and the 24-h cycle of rest and activity imposed upon them in a 24-h society.[35,36] The documentation of free-running circadian rhythms in blind subjects living in society, and associated sleep disturbances[37] — despite the fact that they adhere to a 24-h rest–activity cycle — questions the effectiveness of motor activity as a feedback signal to the circadian pacemaker. Such an effect of motor activity has been demonstrated conclusively in some

rodents.[38] Some positive evidence for such an effect of activity in humans has been reported recently[39] although in another publication an inversion of the sleep–wake cycle appeared to have no effect on the phase of endogenous circadian rhythms.[40]

Internal rhythms driven by the light sensitivity pacemaker

In some experiments the effects of light on the pacemaker have been assayed by monitoring multiple variables, ranging from behavioral measures such as subjective alertness[41] and sleep termination[42,43] and sleep initiation[44] to hormonal measures such as the rhythm of plasma melatonin;[45] and the most widely used marker of circadian rhythmicity in humans: core body temperature.[25] A key observation is that all of these rhythms appear to be shifted by light in a similar way, despite the fact that the brain areas involved in the regulation of these rhythmic variables are very different. This suggests that the light-sensitive pacemaker is indeed a 'master clock', which imposes circadian organization on all of these brain areas and all of these variables. Because the SCN is the only known light-sensitive pacemaker in mammals — besides the retinal pacemaker driving the rhythms of rod outer segment disk shedding[22] and retinal melatonin[23] — it seems reasonable to assume that these effects of light on overt circadian rhythmicity in humans are mediated by this small structure located just above the optic chiasm.

An internal circadian rhythm of sleep propensity

Under entrained conditions the internal rhythm of sleep propensity has been assessed by the so-called multiple sleep latency test, in which the latency to sleep onset is assessed multiple times during the habitual waking day; and, in some studies, during the habitual sleep episode by assessing the latency to return to sleep after induced awakenings from the nocturnal sleep episode.[46] The essentials of this pattern of sleep propensity are that sleep propensity is low in the first few hours after awakening. In the afternoon hours sleep propensity exhibits a modest and temporary increase, i.e. sleep latencies become shorter. Thereafter sleep propensity decreases to reach a minimum at around 10 pm. In the hours coinciding with the nocturnal sleep episode and the nocturnal rise of plasma melatonin, sleep propensity increases suddenly and progressively to reach a maximum at around 4–6 am.

During this standard assessment of the internal rhythm of sleep propensity during the daytime hours, the elapsed time since awakening from the nocturnal sleep episode increases progressively, while at the same time the endogenous circadian phase changes. Therefore, the relative contribution of these two processes to the overt internal rhythm of sleep propensity cannot be assessed from these multiple sleep latency tests. A number of protocols have been developed to assess the contribution of the circadian pacemaker and the sleep–wake-dependent process to sleep propensity. A common characteristic of these protocols is that sleep and wakefulness are experimentally distributed uniformly across the endogenous circadian cycle by the induction of desynchronies between the sleep–wake cycle and the endogenous circadian cycles of body temperature, etc. Two of such protocols are the 90-min day[47,48] and the 28-h day.[18,49,50] In the 90-min-day protocol, subjects are instructed to sleep 30 min out of each 90-min episode; this protocol is continued for a number of days. In the 28-h day, subjects are instructed to sleep for 9 h and 20 min out of each 28-h day; this protocol is continued for up to one month. In both protocols the sleep-dependent component can be assumed to reach a near steady state. The results from both protocols demonstrate that the circadian drive for sleep is strongest at or shortly after the minimum of the core body temperature rhythm; it gradually declines on the rising limb of the body temperature rhythm to reach its nadir (i.e. crest of the circadian drive for wakefulness) approximately 8 hours before the temperature minimum. This implies that during entrainment — when the minimum core body temperature is located at approximately 6 am — we go to sleep just after the crest of the circadian drive for wakefulness and wake up just after the circadian peak drive for sleep. The putative functional significance of this paradoxical phase relationship between the sleep–wake cycle and the circadian rhythm of sleep propensity is that, by providing a drive for wakefulness which becomes progressively stronger in the course of the waking day, the circadian pacemaker counteracts the progressive drive for sleep associated with sustained wakefulness. Likewise the progressive increase in the circadian drive for sleep in the course of a nocturnal sleep episode counteracts the dissipation of sleep drive associated with consolidated sleep. By this mechanism of opposition[51] the circadian pacemaker

facilitates consolidation of wakefulness and sleep. When this paradoxical phase relationship between the sleep–wake cycle and the endogenous circadian rhythm of sleep propensity changes, sleep consolidation deteriorates, and high levels of alertness and performance cannot be maintained during the waking episode.[18,49,50] Furthermore, in SCN-lesioned squirrel monkeys, which have consolidated bouts of wakefulness and sleep when intact, sleep and wakefulness become highly fragmented.[51]

Concluding remarks

Despite the limited number of techniques that can be applied in human circadian research, the efforts in understanding human circadian organization have established that the light-sensitive pacemaker plays a major role in the temporal organization of human physiology and behavior. In addition, these experiments have provided new insights in the interaction of circadian and sleep–wake-dependent processes in the regulation of the consolidation of sleep and wakefulness. These new insights, in combination with established and new methodologies — such as constant routines and forced desynchrony protocols[52,53] — are now being applied to research on the mechanisms involved in the marked changes in the timing and consolidation of sleep and age-related changes in subjective sleep quality that are observed in older humans (reviewed in ref 54).

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