

Effects of Light on Human Circadian Rhythms
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Human physiology and behavior is dominated by near-24-hour rhythms that have a major impact on our health and well-being. For example, sleep-wake cycles, alertness and performance patterns, core body temperature rhythms and the production of hormones such as melatonin and cortisol are all regulated by an endogenous near-24-hour oscillator in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. In order for the circadian pacemaker to ensure that physiology and behavior are timed appropriately with the outside world, environmental time cues must be able to reset this internal clock. The major environmental time cue able to reset these rhythms is the 24-hour light-dark cycle (Czeisler and Wright, 1999). Light information is captured by specialized retinal photoreceptors and transduced directly to the SCN via a dedicated neural pathway, the retinohypothalamic tract (RHT) (Foster and Hankins, 2002). The daily light-dark cycle resets the internal clock on a daily basis which in turn resets the physiology and behavior controlled by the clock.

The vital importance of light input to the pacemaker is readily observed when the circadian rhythms of totally blind individuals, particularly those who are bilaterally enucleated, are examined (Miles et al., 1977; Lewy and Newsome, 1983; Sack et al., 1992; Klein et al., 1993; Lockley et al., 1997a; Skene et al., 1999a). In such people, the sleep-wake cycle, alertness and performance patterns, and the rhythms of temperature and some hormones become desynchronized from the 24-hour day as a result of light information failing to reach the brain to synchronize the clock and its outputs (Lockley et al., 1997a; Lockley et al., 1999; Skene et al., 1999b). The resulting clinical condition – non-24-hour sleep-wake disorder – is observed in the majority of totally blind people and is characterized by a cyclic sleep disorder with episodes of good sleep followed by episodes of bad sleep and excessive day-time naps as the internal pacemaker runs in and out of synchrony with the 24-hour day (Lockley et al., 1997b; Lockley et al., 1999). The disorder can be treated by melatonin administration (Lockley et al., 2000; Sack et al., 2000; Lewy et al., 2001; Lewy et al., 2002; Hack et al., 2003) provided it is appropriately timed to each individual's circadian phase (Lockley et al., 2000; Hack et al., 2003).

Properties of light that have been shown to relate to circadian resetting include the intensity, number, duration, pattern and timing of exposures, and more recently, the wavelength of light used. The human circadian pacemaker is extremely sensitive to dim light, with a light intensity equivalent to indoor room light able to significantly shift the timing of the circadian system (Boivin et al., 1996; Zeitzer et al., 2000). More recent work has shown that light as dim as candlelight can maintain synchronization to the 24-hour day (Wright et al., 2001). Another important aspect of light exposure is its timing which determines whether light shifts the clock to an earlier time (advance) or a later time (delay). Under normal conditions, light exposure in the late evening will delay the circadian system to a later phase and light in the early morning will advance the circadian system to an earlier phase (Khalsa et al., 2003). This property of photic resetting is the underlying cause of sleep and other rhythmic disorders associated with 'jet-lag' and shiftwork.

The impact of wavelength on light-induced resetting of circadian rhythms is only recently emerging in humans. We and others have recently shown that the circadian system is most sensitive to short wavelength light and has a spectral sensitivity different to that from

conventional scotopic and photopic vision (Lockley et al., 2003; Warman et al., 2003). These findings, and others in both animals (Hattar et al., 2003) and humans (Brainard et al., 2001; Thapan et al., 2001; Hankins and Lucas, 2002), suggest that a novel photoreception system exists in the eye that has evolved to detect light for the circadian system separate from that used for sight. Moreover, mutations of the visual system do not appear to attenuate circadian responses to light; a small number of totally blind people with eyes have intact circadian responses to white light exposure despite a complete lack of vision (Czeisler et al., 1995; Klerman et al., 2002), and individuals with red-green color-blindness do not differ from controls in the ability of white or green light to suppress their melatonin production (Ruberg et al., 1996).

The longer term effects on health of inappropriate light exposure are under investigation. Misalignment between the internal circadian pacemaker and the external environment is thought to contribute to health problems such as cardiovascular disease, diabetes, sleep disorders, and gastro-intestinal disorders (Rajaratnam and Arendt, 2001; Dijk and Lockley, 2002). As more is learned about the properties of light exposure that affect the circadian system (Czeisler and Wright, 1999), such information can be used to optimize light exposure regimes to ensure proper synchronization. These regimes can be used to reset the pacemaker after extreme desynchronization, for example following long-haul flights (e.g., Boulos et al., 2002), space flight (e.g., Dijk et al., 2001), and the transition from day shift to night shift (e.g., Horowitz et al., 2001), or to correct less obvious, but still possibly damaging misalignment, for example during ageing (Duffy et al., 1998; Duffy and Czeisler, 2002; Duffy et al., 2002) or in relation to diurnal preference ('owls' vs 'larks') (Duffy et al., 2001). In conjunction with parallel advances in understanding how light affects the pacemaker at a molecular level, physiological studies can be used to develop and optimize therapies to treat not only clinical disorders of the circadian system, but also to help maintain normal circadian synchronization in our 24/7 society.

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