HUMAN BRAIN PERFORMANCE in realms no less important than judgment, problem solving, creativity, memory, and mood is powerfully modulated by brain state, particularly the underlying level of alertness. The latter varies in a predictable way across the 24-h day under the influence of both circadian (biological clock) and homeostatic (sleep deprivation or satiety) regulatory factors (2). Other influences such as motivational, physical environmental, and pharmacological or dietary factors can also contribute but are more situational than innate.

The circadian (Process “C”) and sleep deprivation (Process “S”) influences on sleep drive and alerting mechanisms seem to be integrated by the brain in as yet poorly understood ways to produce the manifest level of sleep or alertness. In both nocturnal and diurnal mammals, Process S is thought to gradually build up during one wake period of the solar day-night cycle. The gradual paying off of this “sleep debt” is then disinhibited or actively promoted during the circadian sleep period. This two-process model has been important because of the conceptual framework it provides to begin to explain the general time course of the normal sleep-wake rhythm as well as the response to temporal (C) and sleep-deprivation (S) stress. For example, sufficiently sleep-deprived mammals may generate sleep during some part of the normal circadian wake time. Similarly, even significantly sleep-deprived animals may not be able to “catch up” on missed sleep when sleep opportunities are provided at the peak of circadian alertness.

The neuroanatomic substrate of the rhythmic circadian (~24 h) component is in the anterior hypothalamus (7). The paired suprachiasmatic nuclei constitute a true clock in the sense that the circadian rhythm of most or all physiological functions persists even in constant environmental conditions. The anatomic substrate of the tonic sleep-deprivation component was less clear until recently. Studies in mice, rats, and cats suggest that waking accumulation of intercellular adenosine stimulated by prostaglandin D2 in a small region of periventricular lateral basal forebrain is a critical signal for sleep deprivation (6, 9).

Regardless of how Processes S and C are “added up” or integrated to generate a state of sleepiness or alertness, it has been assumed, at least in rodents [based on surgical lesions of the suprachiasmatic region (8)], that Processes C and S are regulated independently. However, surgical lesions could alter other neuronal circuits involved in hypothalamic sleep-wake regulation, leaving the conclusion of independent regulation of these two processes in some doubt. There is also evidence from humans that the intensity of waking activity (which could modulate Process S) feeds back on the circadian clock (13). Therefore, given the brain’s proclivity to reciprocal interaction as a strategy for physiological regulation, it remains quite possible that the circadian component feeds back on Process S. In addition, recent rodent work suggests that a “circadian mutation” in the cryptochrome gene increases sleep drive even during the circadian wake time (15).

In this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, Shiromani and colleagues (10a) use another genetic lesion of the circadian clock to explore the regulatory interaction between these two processes by eliminating Process C and measuring how much sleep and wakefulness (Process S) are left.

The authors used inbred lines of mice differing only in the presence or absence of normal Period genes (mPer1 and mPer2) known to be critical for circadian clock function (10). Wake time, sleep time, and depth of sleep were measured by means of chronically implanted brain electrodes in conditions of photic entrainment of the circadian rhythm to a light-dark cycle in so-called “free-running” conditions of constant darkness and after sleep deprivation. Sample sizes reported were less than 10 for each genotype. Some differences in the kinetics of recovery sleep were found between wild-type and arrhythmic mutants, but this was in the expected direction of intact circadian wake promotion in the wild-type animals. The main finding was that sleep depth and duration were similar in wild-type and mutant animals in all three conditions, demonstrating that, to a first approximation, Process S is regulated independently of Process C.

It remains to be seen whether these findings in nocturnal rodents will be replicated in diurnal primates. As noted by the authors, circadian lesion studies in squirrel monkeys suggest that the primate circadian system does have a net stimulatory effect on wakefulness. However, that does not prove that the primate circadian system changes the regulation of Process S per se; it only demonstrates that the circadian factor could oppose sleep-deprivation sleepiness in the intact animal.

Proving the absence of physiological interaction is logically impossible and in practice is approached by failing to find statistical differences with large sample sizes. The small sample sizes used in this study are understandable given the necessity for labor-intensive data-acquisition and analysis techniques but still leave open the possibility of some small level of coordinated regulation of Processes C and S. It is the convergent evidence from two fundamentally different ways of eliminating the circadian component (one surgical, the other genetic) that adds strength to the conclusion that Processes C and S are regulated more or less independently.

Separating the circadian and homeostatic influences on sleep is likely to have a significant impact on animal studies of mammalian sleep-wake regulation. Eliminating the circadian component may expedite elucidation of the neuroanatomic, neurotransmitter, and genetic substrates of Process S. The mechanisms of the direct (masking) effects of light on wake and sleep may likewise unravel sooner. Arrhythmic mice with additional mutations in circadian-related (clock output) genes might be used to identify “downstream” interactions of these other genes with Process S. The basic notion of separating Processes S and C may stimulate an analogous attempt to clarify the circadian influence on sleep and wake by creating...
animals deficient in Process S. A surgical lesion or pharmacological impairment of Process S may be possible but the work of Shiromani et al. (10a) will also encourage consideration of genetic approaches such as the adenosine A2 receptor-deficient mouse (12).

While acknowledging the inherent worth of animal studies, the ability to explore the separate contributions of sleep deprivation and circadian factors in animal models of temporal stress is of potentially great significance to human temporaladaptation. Do individual differences in Process S affect ad-

vention and circadian factors in animal models of temporal stress is of potentially great significance to human temporal adaptation. Do individual differences in Process S affect adaptation to shift work, jet lag, and sleep deprivation as has been demonstrated for differences in Process C (4)? There are also significant individual differences in napping and “catch-up sleep” ability, habitual duration and depth of sleep, and predilection to sedative and stimulant drug effects. There is currently much interest in changes in Process S in elderly humans (3). The mouse model of aging (14) might be combined with an arrhythmic genotype and manipulations of Process S to generate hypotheses about sleep loss in the elderly.

Many other questions will be raised by the work reported here. Do the apparent differences in Process S between Cry-decient and Per-decient rodents predict differences in Process S between different human circadian (11) phenotypes (e.g., “morning people” vs. “night people”)? Will arrhythmic animal studies suggest the extent and mechanisms by which factors such as daytime activity level and intensity of ambient light influence human sleepiness in the subsequent night? Does Process C contribute to short-period (15–90 min “ultradian”) rhythms of performance and alertness that have been demonstrated in humans? How do Processes S and C interact to produce the normal “siesta time?” Several authors have proposed that interactions between the sleep-wake rhythm and circadian time could underlie mood disorders (1, 5). Would comparison of rhythmic- and circadian-deficient mouse models of learned helplessness studied in short vs. long photoperiods shed light on seasonal depression?

REFERENCES

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