Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease

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Penev, Plamen D., Daniel E. Kolker, Phyllis C. Zee, and Fred W. Turek. Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H2334–H2337, 1998.—Shift work is associated with increased cardiovascular morbidity and mortality. Whereas it has been suggested that continuous shifting of the circadian clock/sleep-wake cycle may have negative effects on health, there is very little experimental evidence to support such a hypothesis. Cardiomyopathic Syrian hamsters were either maintained on a fixed light-dark (LD) cycle (n = 31) or were subjected to a 12-h phase shift in the LD cycle on a weekly basis (n = 32). The duration of the life span was recorded for each animal. Chronic reversal of the external LD cycle at weekly intervals resulted in a significant decrease in the survival time in cardiomyopathic hamsters with the median life span being reduced by 11%. Disrupting normal circadian rhythmicity in an animal susceptible to early mortality due to cardiac disease results in a further decrease in longevity. The deleterious effects of the chronic phase shifts in the LD cycle in cardiomyopathic hamsters may be related to reports of increased cardiovascular morbidity and mortality in humans engaged in shift work.

rhythms; shift work; longevity; cardiac disease

A SALIENT CHARACTERISTIC of modern industrial societies is the fact that many jobs require individuals to work at times they would normally be asleep and to sleep at times they would normally be awake. Such “shift workers,” whether they rotate from one shift to another or work a fixed shift that results in them being active at times they sleep on their nonworking days, are constantly changing the times they are awake or asleep relative to the 24-h day. Thus there is repeated desynchronization or resynchronization between their internal 24-h, or circadian, clock with the external time of day. The increased frequency of night and shift (night/shift) work schedules in today’s industrial societies has resulted in a growing amount of epidemiological data on the health consequences of circadian maladaptation and disruption of sleep-wake cycles in night/shift workers. In particular, several reports have established a link between night/shift work and increased cardiovascular morbidity and mortality (7, 8, 12, 23).

Because of the myriad social, economic, and biological factors that are associated with shift work, the underlying causes for increased cardiovascular morbidity and mortality, as well as for other adverse medical problems associated with shift work (25), are not clear. One possibility is that the continuous shifting of the circadian clock/sleep-wake cycle has a negative effect on the health of the individual. However, there is little experimental evidence to support the hypothesis that the continuous disruption of normal temporal organization is in fact detrimental to the health of the organism (3).

Over the last several decades, the Syrian golden hamster has been one of the rodent species of choice in the field of circadian research, and a good deal of knowledge has been obtained about the structure and function of its circadian system (24). At the same time, cardiomyopathic Syrian hamsters have been widely used as a reproducible genetically transmitted model of muscular dystrophy with gradual cardiac hypertrophy, dilatation, and failure (5, 21) caused by a recently characterized autosomal recessive mutation (16). The availability of this background information makes the cardiomyopathic Syrian hamster a particularly attractive animal model to study the interactions between disrupted circadian rhythmicity and cardiovascular pathology. The specific aim of the present study was to examine the impact of experimentally induced circadian desynchronization and resynchronization to the light-dark (LD) cycle on the longevity of hamsters with progressive heart disease under controlled laboratory conditions.

MATERIALS AND METHODS

Experiment 1. A single cohort of 63 TO-2 cardiomyopathic male Syrian (Mesocricetus auratus) hamsters (subline of Bio 14.6) were purchased from Bio-Breeders (Fitchburg, MA) and arrived in the laboratory at 9 wk of age. All animals were housed in groups of 5–6 animals per cage in 24-h polypropylene cages (26 × 47 × 21 cm) with ad libitum access to food (Teklad rodent chow) and tap water. Thirty-two hamsters were assigned to the experimental group of the study, and the remaining thirty-one animals served as controls. The animals in each group were kept separately in two identical ventilated

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lightproof boxes (6 cages per box) stacked in a room with constant temperature (22 ± 1°C) and humidity (22 ± 2%). All hamsters in the control group were exposed to a fixed 14-h light/10-h dark (14:10 LD) cycle with lights on at 0700 (150–300 lux white fluorescent light at cage top). The animals in the experimental group were maintained on a 14:10 LD cycle with the timing of lights on alternating between 0700 and 1900 at weekly intervals. The reversal of the LD cycle at the end of each week was accomplished by extending the last light period by 12 h. Experimental and control hamsters had the same cage cleaning and changing schedules, and all maintenance procedures were done when the two groups were under identical LD cycles.

Hamsters were checked daily during the study period, and the date of each animal’s death was recorded. Four animals (two from each group) were autopsied postmortem, and heart, lung, liver, spleen, kidney, and small intestine tissue samples were collected for subsequent microscopic examination. After the experiment was completed, Kaplan-Meier estimates of the product-limit survival distribution in the two groups were calculated, and a log-rank test was used to compare the survival experience of the experimental and control animals (10).

Experiment 2. To determine whether the circadian timing system of this strain of hamster is responsive to shifts in the LD cycle, a second cohort of 12 animals was subjected to a similar protocol. Animals were housed individually in clear polycarbonate cages (26 × 47 × 21 cm) equipped with a running wheel (17-cm diameter) in two ventilated light proof boxes. A microswitch connected to a personal computer running the Chronobiology Kit software (Stanford Software Systems, Stanford, CA) continually recorded wheel-running activity. Animals were randomly assigned to either experimental (n = 6) or control (n = 6) groups. As in experiment 1, animals in the control group were exposed to a constant 14:10 LD cycle. Animals in the experimental group were subjected to weekly reversals of the LD cycle in such a manner that the total duration of light seen by each group over any 2-wk interval was the same (i.e., the reversal was accomplished by lengthening the light period 1 wk and by lengthening the dark period the next week).

RESULTS

Experiment 1. The pathological changes detected at autopsy and the histological findings confirmed the presence of cardiomyopathic heart disease and congestive heart failure in both experimental and control hamsters. Comparable findings of ventricular dilatation, dystrophic mineralization, and scarring of the myocardium were present in both groups of animals. These findings were further accompanied by pleural effusion and congestion of the lungs, liver, and kidneys, along with areas of hepatic and renal hemorrhagic-ischemic necrosis.

Plots of the Kaplan-Meier estimates of conditional probability of survival to a given age in the experimental and control groups of hamsters are shown in Fig. 1. The median (±SE) life spans of control and experimental animals were 371 ± 4 and 329 ± 11 days, respectively. The log-rank test revealed that weekly reversal of the external LD cycle was associated with a significant decrease in survival time (P < 0.05) of the cardiomyopathic hamsters in the experimental group in comparison with that of the control animals.

Experiment 2. The entrained rhythm of locomotor activity is sensitive to shifts in the LD cycle. Actograms of one animal from both the control and experimental
groups are presented in Fig. 2. Actograms are representative of all animals’ circadian patterns of wheel running; there were few qualitative differences between animals in a given group (data not shown). The actograms indicate the stability of the cardiomyopathic hamsters’ pattern of entrainment in a constant LD cycle and their ability to respond to shifts in the LD cycle.

DISCUSSION

The results of the present study indicate that chronic reversal of the external LD cycle at weekly intervals resulted in a reentrainment of the activity rhythm to the new LD cycle and, most importantly, has adverse effects on the survival of cardiomyopathic hamsters and leads to an 11% reduction in the median life span of these animals. Previous studies indicate that similar experimental interventions can cause both internal and external desynchronization (and even disruption) of multiple biochemical, physiological, and behavioral circadian profiles (1, 15, 24). The existence of well-characterized 24-h rhythms of blood pressure, heart rate, hemodynamic, hemostatic, and other cardiovascular variables (4, 20) raises the possibility that repeated interference with the 24-h temporal homeostasis of the cardiovascular system may underlie the adverse effects of chronic reversal of the external LD cycle on longevity of cardiomyopathic hamsters. The presence of a characteristic 24-h pattern in the occurrence of sudden cardiac death in patients with hypertrophic cardiomyopathy also suggests that circadian factors play an important role for the increased cardiac vulnerability in this disorder (11). Approximately one-half of the deaths in cardiomyopathic hamsters are sudden and appear related to cardiac arrhythmias, whereas the remainder of the animals die of congestive heart failure (21). The experimental intervention used to induce repeated circadian maladaptation in the present study might have accelerated the development and occurrence of both of these pathological mechanisms.

Weekly reversal of the external LD cycle is also regarded as a form of chronic stress for the organism, because it is associated with suppression of the cellular immune response, lower body weight, and decreased adrenal gland mass in rats (9). A separate line of evidence indicates that exposure of young cardiomyopathic hamsters to repeated stress results in hyperactivity of their coronary microcirculation to endogenous vasoconstrictors and vascular spasms (14), which may exacerbate the lesion-forming processes during the necrotic stage of the disease. Additional data also indicate a negative impact of stress on the ventricular function in older animals with cardiomyopathy (17). Thus, in addition to the potential role of deficits in the temporal homeostasis of the cardiovascular system for the adverse effects of repeated LD cycle reversal on survival of cardiomyopathic hamsters, the results of the present study raise the possibility that chronic circadian maladaptation may be a physiologically meaningful and deleterious stressor for the organism with progressive heart disease.

The lifelong increase in the total light exposure of the experimental group by 12 h per week represents another environmental factor that might have contributed to the decreased survival of these animals. However, this possibility seems unlikely, since several earlier studies have demonstrated that exposure to constant light is not associated with adverse effects on the life span of cardiomyopathic hamsters (13, 22).

The weekly reversal of the external LD cycle used to induce circadian maladaptation in the present study resembles the repeated and frequent changes in the daily routines of shift/night workers. More importantly, the deleterious effects of this experimental intervention on the survival of cardiomyopathic hamsters may be related to reports of increased cardiovascular morbidity and mortality in shift workers (7, 8, 23). Future studies will be necessary to explore the broad spectrum of potential implications of the present findings for human health and disease.

Internal 24-h temporal organization is thought to be of considerable importance for the survival of the organism (3, 18, 24). However, surprisingly few direct attempts have been made to determine whether repeated disruption of normal circadian rhythmicity would be detrimental to health and survival. Whereas early work indicated that use of non-24-h LD cycles and repeated phase shifts of the external periodic environment to disturb normal circadian organization could decrease the life span of several invertebrate species (2, 19), a limited number of more recent studies on invertebrates and rodents have provided conflicting results (3, 6, 15). Use of the cardiomyopathic hamster enabled us to examine the effects of disrupted circadian rhythmicity on the rate of mortality caused by a defined pathological condition in a relatively short period of time in a mammalian species.

In summary, the results of this study indicate that repeated circadian desynchronization has deleterious effects on the survival of cardiomyopathic Syrian hamsters. These findings suggest that temporal synchronization has a measurable impact on the course and outcome of chronic cardiovascular disease and support the hypothesis that experimental or voluntary disruption of the 24-h temporal homeostasis may have adverse effects on the health, well-being, and longevity of the organism.

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