Long-Term Fitness Training Improves the Circadian Rest-Activity Rhythm in Healthy Elderly Males

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Abstract In old age, the circadian timing system loses optimal functioning. This process is even accelerated in Alzheimer's disease. Because pharmacological treatment of day-night rhythm disturbances usually is not very effective and may have considerable side effects, nonpharmacological treatments deserve attention. Bright light therapy has been shown to be effective. It is known from animal studies that increased activity, or an associated process, also strongly affects the circadian timing system, and the present study addresses the question of whether an increased level of physical activity may improve circadian rhythms in elderly. In the study, 10 healthy elderly males were admitted to a fitness training program for 3 months. The circadian rest-activity rhythm was assessed by means of actigraphy before and after the training period and again 1 year after discontinuation. As a control for possible seasonal effects, repeated actigraphic recordings were performed during the same times of the year as were the pre and post measurements in a control group of 8 healthy elderly males. Fitness training induced a significant reduction in the fragmentation of the rest-activity rhythm. Moreover, the fragmentation of the rhythm was negatively correlated with the level of fitness achieved after the training. No seasonal effect was found. Previous findings in human and animal studies are reviewed, and several possible mechanisms involved in the effect of fitness training on circadian rhythms are discussed. The results suggest that fitness training may be helpful in elderly people suffering from sleep problems related to circadian rhythm disturbances.

Key words activity, exercise, fitness, physical activity, circadian rhythm, actigraphy, aging, sleep

INTRODUCTION

Circadian rhythms (i.e., rhythms of approximately 24 h) are present in many physiological and behavioral

phenomena including rest activity, sleep-wakefulness, body temperature, and hormone levels. Several studies have shown circadian rhythm changes in elderly people (reviewed in Bliwise, 1993; Mirmiran et al.,

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1992; Myers and Badia, 1995; Van Someren et al., 1993a). Deterioration of circadian rhythms in elderly is thought to contribute to sleep disturbances and reduced daytime functioning, and finding ways in which to improve the circadian timing system may therefore be of interest for the well-being of elderly (Van Someren et al., 1993a). Bright light, the primary modulator of the circadian timing system, is indeed effective both in increasing vigilance (Badia et al., 1991; Campbell and Dawson, 1990) and in improving subsequent sleep (Bunnell et al., 1992; Campbell et al., 1993).

In the present study, we investigated another way in which to improve the circadian timing system. Animal studies have shown that increased levels of physical activity are associated with changes in the period (Aschoff et al., 1973; Edgar et al., 1991; Gnaedinger and Rosenberg, 1992; Honma et al., 1991; Joy et al., 1989; Mrosovsky, 1993), phase (Janik and Mrosovsky, 1993; Joy et al., 1989; Mrosovsky, 1991; Mrosovsky and Biello, 1994; Turek et al., 1995; Van Reeth et al., 1992), and entrainment (Mrosovsky and Salmon, 1987; Reeb and Mrosovsky, 1989; Turek et al., 1995; Van Reeth et al., 1993) of circadian rhythms. In humans, a large number of studies suggests that increased physical fitness improves both daytime performance and nighttime sleep, but its effect on circadian rhythms has received very little attention (Van Someren et al., 1994). Decreasing physical activity by means of forced bed rest disturbed sleep and depressed the amplitude of body temperature (Campbell, 1984; Winget et al., 1972), whereas increased physical activity induced phase shifts (Piercy and Lack, 1988; Van Reeth et al., 1994a) and accelerated reentrainment after phase shifts (Schmidt et al., 1990). Although it is well known that the levels of activity decrease with aging (Dalloso et al., 1988; Renfrew et al., 1987; Van Hilten et al., 1994; Van Someren et al., 1996b), the effect of increased physical fitness on circadian rhythms has, as far as we are aware of, not been investigated previously in elderly subjects. The present study, therefore, investigated whether the circadian rest-activity rhythm in healthy elderly people improved after long-term fitness training.

METHODS

Subjects

A total of 10 healthy elderly males, age 73 ± 1.5 years (mean $\pm$ SEM), completed the study protocol. Subjects

gave informed consent and were included only after approval of their physicians. None had major heart or respiratory problems. Repeated actigraphic measurements of another 8 healthy elderly males, age 69 ± 1.3 years, were used to check for possible seasonal effects on rest-activity rhythms.

Fitness Training

A total of 10 subjects participated in supervised indoor aerobic activities such as running, jogging, and ball games for 3 months (from the end of March to the beginning of June), three times 1.5 h a week, at around noon. In the middle of each training session, the subject's heart rate were measured, and the training was intensified when the heart rate was less than 60% of the pre-experimentally assessed maximal heart rate in the fitness test.

Aerobic Power

To quantify the effectiveness of the training, $\text{VO}_{2\text{max}}$ was assessed using a maximal test on a bicycle ergometer both before and after the 3-month training period.

Rest-Activity Rhythm Assessment

In the experimental group, the rest-activity rhythm was assessed by means of actigraphy on three occasions: within 2 weeks of the start of the training period, within 1 month following the training period, and once again 1 year after this post assessment. None of the assessments were made during the actual weeks of exercise so as to exclude possible masking effects of the exercise on actigraphic recordings. To evaluate possible changes in light exposure during or after the training period, subjects were interviewed on the extent to which the training period changed their outdoor activities. To investigate possible seasonal effects, we evaluated repeated actigraphic recordings that were made during the same times of the year (i.e., corresponding to the pre and post/follow-up assessments in the experimental subjects) in control subjects not involved in the training protocol. No third assessment was performed in the control subjects. On each occasion, subjects wore a small ($57 \times 46 \times 22$ mm) and lightweight (70 g) actigraph—a miniaturized version of the actigraph described by Mirmiran et al. (1988)—on the wrist. The actigraph registered movement-

induced accelerations, and the resulting series of hourly summed movement counts were plotted and analyzed. Analysis was performed after visual inspection of the plots and removal of periods during which the plots and/or a log that was kept by the subjects indicated that the actigraph was not worn or that the actigraph had failed to register. This resulted in an actigraphic recording of, on average, 5½ days duration.

Three variables were calculated. First, the Interdaily Stability (IS) is the 24-h value from the chi-square periodogram (Sokolove and Bushell, 1978; Witting et al., 1990), normalized for the number of data, and gives an indication of the strength of coupling between the rest-activity rhythm and zeitgebers. The IS is calculated as the ratio between the variance of the average 24-h pattern around the mean and the overall variance:

$$IS = \frac{n \sum_{h=1}^p (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^n (x_i - \bar{x})^2}$$

where n is the total number of data, p is the number of data per day (24 in this study), $\bar{x}_h$ are the hourly means, $\bar{x}$ is the mean of all data, and x_i represents the individual data points. Second, the Intradaily Variability (IV) gives an indication of the fragmentation of the rhythm (i.e., the frequency and extent of transitions between rest and activity) and is calculated as the ratio of the mean squares of the difference between successive hours (first derivative) and the mean squares around the grand mean (overall variance) (Witting et al., 1990):

$$IV = \frac{n \sum_{i=2}^n (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^n (x_i - \bar{x})^2}$$

Third, in addition to these measures describing signal-to-noise ratios, a Relative Amplitude (RA) measure was calculated as follows. First, the average 24-h pattern was determined by averaging over the registration days. From this pattern, the average hourly movement duration was calculated for the uninterrupted least active 5-h period (L5) and most active 10-h period (M10). The RA was calculated by subtracting L5 from M10 and dividing the result by their sum.

Statistics

A Student's t test was used to evaluate changes in the VO_2 max levels before and after training. The effect of the training period on the circadian variables (IS, IV, RA) in the experimental group was tested using repeated-measures analyses of variance (ANOVAs) with one within factor (pre, post, and follow-up). ANOVAs with one between factor (experimental and control groups) and one within factor (pre and post) were used to evaluate differences between experimental and control subjects on the circadian variables, and to evaluate possible seasonal effects. To further explore the relation between fitness and circadian organization of the rest-activity rhythm, correlations between the VO_2 max levels and the circadian variables were calculated for the pretraining levels, the percentage changes on the variables, and the posttraining levels. In all tests, the two-tailed critical significance level was .05.

RESULTS

Interviews with the subjects indicated that they all liked the fitness training, and regretted that no further training was given after 3 months. During and after the fitness training period, none of the subjects changed his lifestyle with regard to the general engagement in activities or time spent outdoors.

Aerobic Fitness

The fitness training resulted in a significant ($t = 3.21$, $p = .01$) increase in VO_2 max from 21.99 ± 1.45 to 23.71 ± 1.76 ml $O_2 \times \text{min}^{-1} \times \text{kg}^{-1}$.

Rest-Activity Rhythm

Figure 1 gives an example of the raw and double-plotted actigraphy data at pre, post, and follow-up assessments in a subject included in the fitness group. All means and standard errors can be found in Table 1 and are plotted in Fig. 2. The ANOVAs for the experimental group indicated a significant effect only for the IV ($F = 4.95$, $p = .02$), which showed a decrease after the training and a relapse at follow-up. Contrasts indicated that the difference between the pre- and post-training levels ($F = 9.86$, $p = .01$), as well as the difference between the posttraining and the pooled pre and follow-up levels ($F = 8.00$, $p = .01$), reached significance. The ANOVAs for the pre and post levels

Figure 1. Raw activity data (left panels) of a subject in the experimental group assessed three times: before training (upper left panel), after discontinuation of training (middle left panel), and 1 year after discontinuation of training (lower left panel). The right panels show double plots of the average 24-h activity level (solid line) and 1 standard deviation above this level (dashed line). Note the decreased fragmentation following the 3-month training period.

in experimental and control groups indicated significant effects only for the IV: a group effect ($F = 4.62, p = .05$) and an interaction effect of group and time (pre and post) ($F = 7.27, p = .02$). The mean values indicate that the groups did not differ initially but that the IV was lower at the post assessment in the experimental group only. The lack of change in the RA indicates that the improvement in the IV did not result from an increase in the circadian amplitude (i.e., more daytime activity and/or less nighttime activity); rather, it resulted from a reduction of variability or noise.

Correlation of Fitness and Rhythm Variables

Before the training period, $VO_{2\max}$ levels showed no significant correlation with circadian variables. The percentage changes in $VO_{2\max}$ levels also were not significantly correlated with percentage changes on the circadian variables, although trends were found for an association of the increase in fitness with both

the IS ($r = .59, p = .07$) and the RA ($r = .61, p = .06$). The posttraining $VO_{2\max}$ levels were significantly correlated with the posttraining IV levels ($r = -.67, p = .03$), indicating that a high fitness level was associated with a low IV.

DISCUSSION

Although the rest-activity rhythm gives only a limited view on the circadian timing system, its actigraphic assessment is well tolerated even by otherwise noncomplying subjects (Van Someren et al., 1996a), whereas the long-term ambulatory assessment with larger devices and wiring is difficult in many elderly (Pollak et al., 1992). Given this fact, as well as the fact that locomotor activity probably is the circadian function most often measured in animal studies (Aschoff et al., 1973; Morin and Blanchard, 1991b), surprisingly few human studies make use of actigra-

Table 1. Mean values and standard errors of the mean on the variables Interdaily Stability, Intradaily Variability, and Relative Amplitude for both the exercise group and the control group.

	<i>Pre</i>	<i>Post</i>	<i>Follow-Up</i>
Training group (<i>n</i> = 10)			
Interdaily Stability	0.68 ± 0.03	0.72 ± 0.03	0.72 ± 0.04
Intradaily Variability	0.74 ± 0.06	0.56 ± 0.04	0.66 ± 0.04
Relative Amplitude	0.86 ± 0.02	0.84 ± 0.02	0.82 ± 0.03
Control group (<i>n</i> = 8)			
Interdaily Stability	0.70 ± 0.05	0.68 ± 0.02	
Intradaily Variability	0.72 ± 0.06	0.74 ± 0.05	
Relative Amplitude	0.83 ± 0.01	0.82 ± 0.01	

NOTE: In the exercise group, three assessments have been done: before a 3-month training period (pre), after discontinuation of this period (post), and again 1 year after this second assessment (follow-up). To control for possible seasonal influences, the pre and post assessments also were done in a control group not involved in any training.

phy for this purpose. In the present study, actigraphy has been used to assess the circadian rest-activity profile of elderly males before and after a 3-month period of increased physical activity. Fragmentation of the rest-activity profile improved after the training period. Thus high levels of physical activity appear to affect the circadian timing system in humans, as has been reported previously in animal studies. Because interviews indicated that none of the subjects increased his outdoor activities, and given the strong negative correlation of fitness and fragmentation, it is highly unlikely that the effect has been mediated by altered exposure to light.

In this section, we first discuss the results—variable by variable—and give an interpretation of the findings. Subsequently, mechanisms involved in the immediate effects of increased activity on circadian rhythms are discussed. Finally, because the effect has actually been found to exist after discontinuation of fitness training, we discuss a possible mechanism for the sustaining effects of exercise on the circadian timing system.

Intradaily Variability

The present study showed that fitness training reduced the fragmentation of the rest-activity rhythm in healthy elderly males. The findings cannot be attributed to seasonal fluctuations in the rest-activity rhythm, because the IV did not change in the control group. The involvement of physical fitness in the IV also is supported by the finding of a correlation be-

Figure 2. Mean values and standard errors of the mean on the variables Interdaily Stability (IS, upper panel), Intradaily Variability (IV, middle panel), and Relative Amplitude (RA, lower panel) for both the exercise group (circles) and the control group (squares). Analyses of variance indicated that only the postexercise IV was significantly less. See text and legend of Table 1 for further explanation.

tween posttraining IV and VO_2max levels, indicating that higher fitness levels were associated with less fragmentation in the circadian rest-activity rhythm. No correlations were found for the pretraining IV and VO_2max levels, and only trends for an associated increase in VO_2max , IS, and RA were found. These findings indicate that the relation of the IV and VO_2max

surface only at higher individual "maximal" fitness levels and that this relation is obscured by variance due to other influences on the IV at suboptimal fitness levels. Possibly related effects previously have been found in animal and human studies. In hamsters, Mrosovsky and colleagues (Janik and Mrosovsky, 1993; Reebbs and Mrosovsky, 1989) showed that the phase-shifting effect of wheel running was correlated with the amount of wheel running only at higher levels of activity but not at lower levels of activity. In humans, Theron et al. (1984) found a correlation between the pulse rate during exercise and the melatonin level following that exercise; they suggested that a threshold level of energy output has to be reached before activity affects melatonin secretion. Trinder et al. (1982) demonstrated an effect of fitness but not of acute exercise on sleep structure. Horne (1981) and Horne and Staff (1983) showed that a critical level of sustained exercise should be reached to induce effects on subsequent sleep. In sum, these studies all suggest a relation of physical activity and circadian rhythms at high or maximal levels of physical activity but not at low levels of activity.

The IV by definition reflects the presence of ultradian rhythms with a period of approximately 120 min in states of activity and rest. Since Kleitman (1963) suggested the existence of "basic rest activity cycles," ultradian rhythms with a period of 70-150 min have been found in several indicators of the level of arousal of the central nervous system (reviewed in Lavie, 1989). We suggest that the actigraphy variable IV reflects an ultradian component, of which the relative contribution increases in a circadian timing system that is losing stability with aging. It should be noted here that the emergence of ultradian patterns in the rest-activity rhythms has been noted in several suprachiasmatic nucleus (SCN) lesion studies (Edgar et al., 1993a; Ibuka and Kawamura, 1975; Johnson et al., 1988a; Mistlberger et al., 1987). Our results suggest that increased physical fitness in healthy elderly males improves the stability of arousal states and, consequently, the ability to withstand periodic drops in the level of arousal. Interestingly, it has been shown that highly fit subjects also show less fragmentation of sleep stages (Edinger et al., 1993).

Interdaily Stability

Increased physical fitness did not improve the IS. Physical fitness may not be involved in the coupling

of the rest-activity rhythm to zeitgeber, but, on the other hand, it also may imply that the IS in elderly is already at such a high level that further improvement by exercise is unlikely. In fact, Monk et al. (1992) have shown that healthy elderly have a significantly greater regularity in daily lifestyle than do the young, possibly developed as an adaptive response to age-related changes in the circadian system. Our study cannot exclude the possibility that subjects with low IS might profit from exercise.

Relative Amplitude

The training also failed to increase the RA of the rest-activity rhythm. In fact, we have not been able to show changes in the amplitude of the rest-activity rhythm in any of our intervention studies (Van Someren et al., 1995, 1996c). This may be related to the design of presently available actigraphs that count movement activities regardless of their intensity. The inclusion of both time and amplitude in formation may result in actigraphs that better discriminate "quiet" activity from activity of high intensity (Van Someren et al., 1993b). Given the restriction of the actigraphs used, it appears that variables describing the variability of the rest-activity rhythm are more sensitive to changes than are amplitude measures.

Possible Mechanisms Mediating Immediate Effects of Increased Activity on Circadian Rhythms

Environmental light, the primary source of information for the circadian timing system, is conveyed to the SCN—the biological clock of the brain—directly through the retinohypothalamic tract and indirectly via the thalamic intergeniculate leaflet (IGL), although the presence of the latter tract has not yet been verified in humans (Moore, 1992). Lesion studies show that an intact IGL, which at least in rodents is the second major input to the SCN, is of essential importance to the mechanism by which increased activity influences circadian rhythms (Janik and Mrosovsky, 1994; Johnson et al., 1988b; Wickland and Turek, 1994). Interestingly, Van Reeth et al (1992, 1993) showed that entraining effects of increased activity were less pronounced in old hamsters but were restored after grafting fetal SCN in old animals (Van Reeth et al., 1994b), suggesting an age-related reduction in sensitivity of the SCN to activity-related synchronizing signals. Indeed, age-related changes are present in the human SCN (Swaab

et al., 1985). However, Mrosovsky and Biello (1994) showed that old hamsters did show activity-induced phase shifts when the level of activity was further increased by means of additional stimuli, indicating a relative preservation of the nonphotic phase-shifting mechanism in aging. The results of our study also support the idea that the age-related reduction in SCN functionality can be overcome by means of increased activity levels but, of course, cannot distinguish between IGL and SCN components in the mechanism of this effect.

Another structure that may be involved in activity-related changes in the circadian rhythm is formed by the raphe nuclei. Locomotor activity is strongly correlated with raphe discharge (cf. Edgar et al., 1993b). Increased brain 5-Hydroxytryptamine (5-HT or serotonin) levels are indeed found after exercise (Chaouloff, 1989); more specifically, the activity level is correlated with the 5-HT level in the SCN (Shioiri et al., 1991). The median raphe nuclei are a third major input to the SCN (Meyer-Bernstein and Morin, 1996; Smaile et al., 1990; Takahashi et al., 1986; Van de Kar and Lorens, 1979), where the highest 5-HT receptor density of all hypothalamic nuclei is found (Saavedra et al., 1974). The dorsal raphe nuclei further project to the IGL (Meyer-Bernstein and Morin, 1996; Morin, 1991; Papadopoulos and Parnavelas, 1990; Van De Kar and Lorens, 1979). Destruction of the dorsal raphe 5-HT cells induces a loss of circadian rhythmicity (Morin and Blanchard, 1991a). These findings strongly suggest an increased serotonergic input to the SCN and IGL during exercise, and may thus be another pathway of increased input to the circadian timing system.

Three other mechanisms may further be involved in the effect of increased activity on the circadian timing system. First, plasma levels of melatonin, a hormone involved in circadian timekeeping (Krause and Dubocovich, 1990) and showing an age-related decline in both level and rhythmicity (Skene et al., 1990), increase after daytime exercise and decrease after nighttime exercise (Carr et al., 1981; L'Hermite-Balériaux et al., 1986; Monteleone et al., 1990, 1992; Ronkainen et al., 1986; Strassman et al., 1989; Theron et al., 1984; Van Reeth et al., 1994a). Functional melatonin receptors have been demonstrated in the SCN (McArthur et al., 1991; Starkey et al., 1995; Weaver et al., 1993). Second, a temperature increase during daytime and the subsequent decline during the evening may be involved in the effect of high levels of activity on circadian rhythms. In healthy adults, long-term fitness training affects daytime and nighttime

metabolic rate in an opposed way; whereas the daytime metabolic rate increases, the nighttime metabolic rate decreases (Meijer et al., 1991; Westerterp et al., 1994). Although no temperature recordings were reported, these findings strongly suggest that the amplitude of the circadian temperature rhythm increases after long-term fitness training. Thermosensitivity of SCN neurons recently has been demonstrated (Ruby and Heller, 1996). Furthermore, lowering of environmental temperature reduces the effect of activity on sleep and circadian rhythms (Horne and Staff, 1983; Janik and Mrosovsky, 1993; Mrosovsky and Biello, 1994). Third, increased sensory feedback during exercise has been suggested to be involved in circadian effects of physical activity (cf. Morin, 1991). Exercise has indeed been shown to increase stimulus sensitivity in humans (cf. Bashore, 1989). In rats, it has been shown that light-evoked activity of the IGL can be enhanced by simultaneous somatic stimuli (Davidowa and Albrecht, 1992; Wickland and Turek, 1994). Furthermore, it recently has been shown that transcutaneous electrical nerve stimulation, also increasing somatic input, improves the coupling of the rest-activity rhythm to zeitgeber in Alzheimer's patients (Van Someren et al., 1996c).

In sum, increased input to the circadian timing system appears to be a final common path of all suggested mechanisms by which increased physical activity influences circadian rhythms.

A Possible Mechanism Mediating the Sustained Effect of Increased Activity on Circadian Rhythms

As described in the Methods section, none of the subjects trained at the time of the posttraining assessment. Therefore, the decrease in fragmentation cannot be attributed to effects of acute exercise and must have been mediated by some medium long-term effect of the repeated training. However, the effect did not last for a year. How can rhythm effects persist for some weeks after discontinuation of the stimuli, as found in the present experiment? We suggest that the repeated activity-induced increase in input to the circadian timing system, a final common path of all mechanisms proposed, may induce long-term changes in SCN and/or projecting areas (raphe, IGL) by a mechanism that has been paraphrased as "use it or lose it" (Swaab, 1991). This model states that activation of nerve cells within the physiological range by internal stimuli such as hormones, growth factors, and transmitters or by environmental stimuli prevents their degeneration

and may even restore to some degree their function in aging and neurodegenerative diseases. In support of the idea of plasticity of the SCN, Amir and Stewart (1996) recently have demonstrated learning effects in SCN Fos expression, behavioral phase shifting, and temperature rhythms. Effects of conditioning also have been demonstrated in the IGL (Albrecht and Davidowa, 1993; Davidowa and Albrecht, 1992).

CONCLUSION

We have shown that repeated engagement in high levels of physical activity counteracts the age-related fragmentation of the circadian rhythm. Although actigraphic assessment is of limited value in the evaluation of sleep quality in the elderly (Chambers, 1994; Hume et al., 1996), it is tempting to conclude that the training-induced improvement of the circadian timing system may be helpful in elderly suffering from those sleep problems that result from underlying circadian rhythm disturbances.

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