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**Attenuated effect of increased daylength on activity rhythm in the old mouse
lemur, a non-human primate**

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Running title: rhythms and daylength in an old primate

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ABSTRACT

Adaptation of physiological and behavioral functions to seasonal changes in daylength is of major relevance for optimal fitness and survival. Because aging is characterized by changes in biological rhythms, it may be hypothesized that old animals fall short of showing a full adaptation to prolonged changes in the duration of daily light exposure, as naturally occurring in relation to season in younger individuals. To test this hypothesis, we analyzed changes in the patterns of daily locomotor activity and body temperature rhythms of young and old mouse lemurs (*Microcebus murinus*, Primates) exposed to short and long daylengths. The effect of an increase in the duration of daily light exposure was attenuated in old animals, as compared to younger lemurs. Although some age-related differences in the locomotor activity rhythm could be seen under exposure to short daylength, they were predominant under long daylength. Some mechanisms allowing adaptation to changing day length thus seem to be impaired at old age. Changes in coupling of circadian oscillators to the light-dark cycle and disturbances in the physiological responses to change in light duration should be further investigated.

INTRODUCTION

Aging is associated with changes in circadian rhythmicity of endocrine, metabolic and behavioral parameters in humans (Weinert, 2000; Van Someren and Riemersma - Van Der Lek, 2007). It has been demonstrated for various circadian rhythms that aging is characterized by a decrease in amplitude, a phase advance and an impaired resynchronization following abrupt phase shifts in the light-dark cycle. In humans, aging modifies the daily rhythm of rest-activity. Aging is typically associated with (1) an increased fragmentation into shorter alternating periods of rest and activity; (2) an increased activity level during the major sleep period, (3) a decreased activity level during the major active period, and as a consequence (4) a decreased amplitude (Witting et al., 1990; Myers and Badia, 1995; Huang et al., 2002). The amplitude, pattern and phasing of the 24-hour profile of body temperature also changes with aging (Monk et al., 1995; Duffy et al., 1998; Gubin et al., 2006). However, some of the age-related changes can be ameliorated by increasing the exposure to artificial bright light (Van Someren et al., 2002). Moreover, there is now some evidence that human rhythms are influenced by season through changes in the duration of daylength (Bronson, 2004), and it appears of interest to experimentally test the effect of daylength changes on the circadian rhythms of young and old subjects. However, changes in the duration of light exposure have rarely been taken into account in studies on circadian rhythms of old humans.

The effects of age on the circadian clock system have also been extensively studied in rodents (e.g. (Zee et al., 1992; Penev et al., 1997; Valentinuzzi et al., 1997; Mailloux et al., 1999; Zhang et al., 2000)), confirming rhythm disturbances such as an increased fragmentation and decreased amplitude of the daily locomotor activity rhythm, as well as a decreased precision in the onset of activity phase. Previous work in rodents and primates indicates that the sensitivity of the circadian timing system to short-term manipulation of light

exposure may decrease with age (Zhang et al., 1996; Benloucif et al., 1997; Aujard et al., 2001). Taken together, these data suggest that age could have profound effects on the synchronization of circadian rhythms to changes in daylength. Rodent studies have shown that the effect of photoperiod on the temporal organization of daily rhythms is modulated by age (Scarborough et al., 1997; Benstaali et al., 2002). In primates, the importance of daylength in the expression of activity patterns (Hill et al., 2004) and reproductive function (Chik et al., 1992) has been demonstrated in young adults only. It remains to investigate whether circadian rhythms responses to long-term changes in the duration of light exposure are comparable between old and younger primates.

The mouse lemur (*Microcebus murinus*, Primates) is a small nocturnal primate (body weight: 60 – 90 g) originating from Madagascar. This primate exhibits photoperiod-dependent seasonal and daily rhythms in most of its biological functions. Daily exposure to light for longer than 12 h promotes sustained behavioral activity, whereas daily exposure to light for less than 12 h reduces behavioral activity and leads to an increase in fat deposits (Perret, 1992). The life span of this species is about 8 - 10 years in captivity (Perret, 1997). Old animals show a decrease in amplitude of the seasonal variations in body mass, sexual hormones (Aujard and Perret, 1998), melatonin (Aujard et al., 2001) and DHEA-S (Perret and Aujard, 2005, 2006). Moreover, a recent study demonstrated that thermoregulation differed according to photoperiod and age in this species (Aujard et al., 2006), see comments in (Van Someren, 2007). Several of these studies indicate that daily and seasonal biological rhythms are altered in old mouse lemurs in ways that are remarkably similar to what is observed in human aging (Huang et al., 2002; Cayetanot et al., 2005): a decrease in amplitude of the locomotor activity level, an increased activity during the resting diurnal phase and an increase in fragmentation. For these and other reasons, the mouse lemur can be regarded as a model of primary importance for human aging (Bons et al., 2006).

In the present study, we examined whether a prolonged exposure to an increased duration of daily light exposure would equally affect younger and older mouse lemurs with respect to their locomotor activity and body temperature rhythms. If a differential response to changes in the duration of daily light exposure exists, age-related differences in the expression of daily rhythms observed under one specific photoperiod may not surface under another photoperiod.

METHODS

Animals

All animals used in this study were born and kept in captivity in the laboratory breeding colony of the CNRS at Brunoy (MNHN, France, license approval N° A91.114.1). General conditions of captivity were maintained constant with respect to ambient temperature (24 – 26 °C) and relative humidity (55%), food and water available *ad libitum* (including fresh fruits, a milky mixture and meal worms). In captivity, seasonal variations of physiological functions can be entrained by alternating 6-month periods of long daylength (14 h of light/day) and short daylength (10 h of light/day) under artificial light. Nine young male mouse lemurs (mean age: 2.5 ± 0.5 years, range: 1 – 4 years) and 8 old male mouse lemurs (mean age: 7.3 ± 0.8 years, range: 6 – 10 years) were studied.

Body mass of animals was higher in short daylength than in long daylength (*t*-test, $t_{(16)} = 2.92$, $P < 0.01$). The body mass did not differ significantly between the 2 groups of mouse lemurs under each photoperiod (short days: young: 109 ± 4 g, old: 106 ± 5 g, *t*-test, $t_{(15)} = 0.5$, NS; long days: young: 93 ± 9 g, old: 91 ± 4 g, *t*-test, $t_{(15)} = 0.17$, NS). Thus, the age related differences observed in this study could not be attributed to differences in body mass.

All experiments were carried out in accordance with the European Communities council Directive (86/609/EEC). All efforts were made to minimize animal suffering throughout the experiments.

Procedures and lighting conditions

Locomotor activity and core body temperature (T_c) rhythms were recorded by telemetry (Dataquest LabPro System, Data Sciences, St Paul, Minnesota, USA) after implantation of a radio sensor-transmitter (TA10TA-F20 Data Sciences, St Paul, Minnesota, USA) in the visceral cavity under anesthesia (Valium 2mL/100g intra muscular, Imalgene 2mL/100g intra peritoneal). Mouse lemurs were housed individually in a cage containing a receiver board. Cages were placed in a chronobiological animal facility (Type A130-SP, Fisher Scientific Bioblock, Illkirch, France) with filtered air and controlled ambient temperature ($25 \pm 1^\circ\text{C}$). Each separated compartment was equipped with independent light-dark cycles, provided by cool fluorescent lamps (250 – 380 lux) during the light phase and with a dim red light (0.002 lux) during the dark phase. The lamps were placed on the side of the cage, at 10 cm from a wooden nest, where the animal could retire during the entire sleeping period, until it started its activity. All animals were tested after at least 1 month of exposure to a given photoperiod, a time lapse necessary for their complete physiological adaptation to the photoperiod (Perret, 1992). The recording period began at least 3 weeks after surgery. Locomotor activity and T_c were recorded simultaneously during 14 days after at least one month of exposure to a light-dark (LD) cycle of 10 h of light per day (short daylength), and then after at least one month of exposure to a LD cycle of 14 h of light per day (long daylength). The change in photoperiod was done by advancing the light onset by 4 h, as previously used in synchronization studies (Perret and Aujard, 2001).

Data analysis

Data were collected using a computerized data acquisition system (LabPro v.3.11, Data Sciences, St Paul, Minnesota, USA). T_c (in °C) was recorded for 10 s every 5 min and locomotor activity (in arbitrary units, AU) was recorded continuously. Actograms were performed using the Clocklab software (Actimetrics Inc., Evanston, IL). Quantitative characteristics of the locomotor activity rhythm were determined with non-parametric methods as previously described (Van Someren et al., 1999; Huang et al., 2002). Briefly, the following variables were calculated from the locomotor activity data. The interdaily stability quantifies the regularity of the timing of onset and offset of activity bouts and of the specific individual activity profile over days (increasing stability from 0 to 1). The intradaily variability quantifies the fragmentation of the period of rest and activity (increasing fragmentation from 0 to 2). L5 quantifies activity during the major sleep period as the average activity during the most restful 5-hour period of the activity profile. M10 similarly quantifies the average activity during the 10 most active hours. The amplitude of the locomotor activity rhythm was calculated as the difference between L5 and M10 values divided by their sum. Activity onset was defined as the first 6 successive bins where activity was greater than the mean locomotor activity during the light phase. T_c data were analyzed for average nocturnal T_c and both the level and timing of the daytime T_c minimum (expressed in minutes prior to the time of lights on). When the activity onset precedes lights off, this phase advance is expressed by a positive value. Inversely, a phase delay is expressed by a negative value.

All values are expressed as mean $\pm$ SEM and analyses were conducted using SYSTAT for Windows. Data were analyzed by two-way analysis of variance (ANOVA) on the effects of age, duration of light exposure and their interaction on repeated measures. One-way ANOVA was used to test the effect of duration of light exposure on activity onset in each age category. Differences in which $p < 0.05$ were considered to be significant.

RESULTS

Effect of the duration of daily light exposure on the locomotor activity rhythm of young and old mouse lemurs

Average 48h-profiles of locomotor activity and T_c of young and old mouse lemurs exposed to either short or long daylength are represented in Fig. 1. Whatever their age category, all animals exhibited a daily rhythm of both parameters. In all cases, the nocturnal period corresponded to the active phase of the day, where animals exhibited the highest level of locomotor activity and the highest T_c values. The profiles differed according to the duration of light exposure and age. Daylength-induced effects on the quantitative parameters of the daily locomotor activity rhythm in young and old mouse lemurs are represented in Fig. 2 and statistical results are indicated in Table 1. We found a significant effect of the duration of light exposure, no overall effect of age but a significant age x daylength effect on interdaily stability, indicating that an increase in the duration of light exposure enhanced interdaily stability less in old than in young lemurs (Fig. 2A). There was a significant effect of the duration of light exposure and a significant effect of age on intradaily variability (Fig. 2B). Young animals exposed to long daylength exhibited a lower level of intradaily variability of the locomotor activity rhythm compared to young mouse lemurs exposed to short photoperiod. The significant age x daylength effect indicated that the increase in the duration of light exposure attenuated intradaily variability in young, but not in old animals.

The activity rhythm amplitude was also significantly affected by the duration of light exposure (Fig. 2C). There was a main effect of age and a significant age x daylength effect: an increase in the duration of light exposure enhanced the amplitude of the locomotor activity

rhythm in young, but not in old animals. The activity level during the major sleep period (L5) was significantly affected by the duration of light exposure (Fig. 2D) as well. Due to high interindividual variability, the effect of age was only close to significance and no significant effect of age x daylength could be found. However, an increase in the duration of light exposure suppressed L5 in young mouse lemurs, but had no significant effect in old animals, which exhibited a high level of L5 whatever the duration of daily light exposure. The amount of activity during the major wakefulness period (M10) was significantly affected by the duration of light exposure, age and their interaction (Fig. 2E): when exposed to long daylength, young animals exhibited an increase of $43 \pm 7\%$ relative to their M10 level when exposed to short daylength, while the average increase in the age group was only $26 \pm 7\%$.

The onset phase of the major activity period always preceded lights off. There was no overall effect of the duration of daily light exposure on the onset of activity, but there was a significant effect of age (Fig. 2F). In all cases, animals started their activity period just shortly before lights off, except for old animals exposed to long daylength which exhibited a considerably earlier onset of their activity compared to their onset of activity under short daylength exposure. This effect of the duration of daily light exposure was significant in old animals, but not in younger ones (Table 2). Representative actograms of a young and an aged mouse lemurs exposed to long daylength are illustrated in Fig. 3.

Effect of the duration of daily light exposure on the core body temperature rhythm of young and old mouse lemurs

There was no age effect on the nocturnal level of T_c or on the minimum T_c value (Fig. 4A-B). A significant effect of the duration of daily light exposure was found for these two parameters that was due to an increase in average nocturnal T_c and in the minimum of T_c from short daylength to long daylength in both young and in old animals.

There was a significant effect of age on time of occurrence of the minimum of T_c (Fig. 4C). Whatever the duration of daily light exposure, the time of occurrence of the minimum of T_c was delayed in old animals compared to younger ones. The minimum of T_c occurred on average 174 ± 25 min after lights on in young and 280 ± 23 min after lights on in old animals, representing a delay of almost 2 h for old animals compared to younger ones.

DISCUSSION

An increase in the duration of daily light exposure had a more pronounced effect on the 24-h profile of locomotor activity rhythm in young than in old mouse lemurs. In old, as compared to short days, exposure to long days led to an increase in interdaily stability and activity level during the major period of wakefulness, yet in both cases less than the respective increases found in younger animals. Whether age affected the locomotor activity rhythm thus depended to a large extent on whether animals were observed during short days or long days: age-differences were much more pronounced during the period of longer daily light exposure. By contrast, no age difference could be detected in the response of the body temperature rhythm to changes in the duration of daily light exposure. Thus, although the activity rhythm response to an increase in the duration of daily light exposure was less in old animals, it was not completely absent, and even intact for the temperature rhythm response.

In young mouse lemurs, an increase in the duration of daily light exposure induced an increase in amplitude and activity during the major active period, and a decrease in activity during the major restful period, compared to exposure to short daylength. These effects do not match with the prediction of a potential masking effect of an increase in the duration of light exposure on the locomotor activity pattern of a nocturnal species, and rather suggest a full

adaptation to each daylength. In aged animals, the effects of an increase in the duration of daily light exposure on locomotor activity levels were attenuated.

Like in young mouse lemurs, old animals exhibited a higher interdaily stability of their locomotor activity rhythm when exposed to longer days. A similar finding was observed in the elderly, in demented patients only (Van Someren et al., 1996). The patients showed a relatively higher interdaily stability during the summer. This indicates that there is at least some preservation of functional plasticity of the circadian timing system at high age (for review see (Van Someren et al., 2002)). Moreover, it is noteworthy that old animals started at higher interdaily stability during the shorter days than young animals did. A higher interdaily stability has also been observed in elderly humans and has been proposed to reflect a more rigid schedule of activity as an adaptive response to overcome a circadian system that is more easily disrupted (Monk et al., 1992; Carvalho-Bos et al., 2007; Van Someren and Riemersma - Van Der Lek, 2007). ().

Whatever the duration of the daily light exposure, young mouse lemurs were tightly entrained to the onset of lights off. In old animals, a long photoperiod was associated with an advanced onset of activity. Under short days, no difference could be seen between young and old mouse lemurs, since all animals started their activity close to the time of lights off. In young mouse lemurs maintained in free running condition (constant dim red light), the subjective day lasted 9.5 ± 0.5 hr (Perret and Aujard, 2001). It could thus be argued that the endogenous architecture of the circadian system would more readily adapt to a light period of 10 than of 14 hr. According to this contention, a 10-hr light period would require only an additional extension of 0.5 hr on top of the endogenous 9.5 hr of subjective day, while a 14-hr light period would require an additional 4.5 hr extension for an efficient synchronization. A reduced strength of lights on and lights off as potential zeitgebers has been demonstrated in old mice (Weinert and Weinert, 2003). Although this remains to be demonstrated in the

mouse lemur, such an age-related alteration may also explain the photoperiod-dependent change in activity onset in old mouse lemurs.

In contrast to the activity rhythm response, the body temperature rhythm response to an increased duration of daily light exposure was preserved in old mouse lemur. The timing of minimal body temperature was delayed in old mouse lemurs compared to younger ones, irrespective of photoperiod. Of note, the delayed body temperature minimum in old mouse lemurs contrasts with the phase advance typical of old humans (Monk et al., 1995; Duffy et al., 1998). On the other hand, a delay in body temperature has been observed in demented elderly subjects (Harper et al., 2001), and Duffy *et al.* (Duffy et al., 1998) demonstrated that the body temperature nadir was actually delayed when expressed relative to the waking onset in the elderly. In mouse lemurs, the body temperature minimum was affected by photoperiod but not by age, while the timing of minimal body temperature changed according to age but not photoperiod. This corroborates the results of Benstaali *et al.* (Benstaali et al., 2002) in rats, showing that age and photoperiod acted independently on the daily rhythm of body temperature. The preservation of the body temperature rhythm response to daylength in old animals stands out as compared to the attenuated activity rhythm response, and also compared to previous findings in other rhythms. A decreased amplitude in seasonal variations of several other physiological parameters has also been demonstrated in old mouse lemurs, such as body weight (Aujard et al., 2001), behavioral thermoregulation (Aujard et al., 2006), testosterone (Aujard and Perret, 1998) and DHEA-S (Perret and Aujard, 2005).

In summary, although some age-related differences in the locomotor activity rhythm could be seen under exposure to short daylength, they were predominant under long daylength. Under short days, the patterns of old animals were close to those observed in young animals. Daylength effects on the rhythm parameters of young – but not old - animals led to the emergence of various age-related differences under exposure to long days. Some

adaptive mechanisms allowing synchronization and entrainment to changing day length seem to be impaired with aging. It may be that at high age, a higher intensity of environmental light is required in order to obtain a full behavioral circadian response. It is also possible that, by increasing daylength, the coupling of individual circadian oscillators to the LD cycle or to other circadian parameters is modified. Changes in coupling of circadian oscillators to the light-dark cycle and disturbances in the physiological responses to change in light duration should be further investigated.

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DISCLOSURE STATEMENT

There is no conflict of interest concerning this work. Full agreement was obtained to conduct this work on the breeding colony of Brunoy (agreement # A91.114.1).

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Figure captions

Fig. 1. Average ($\pm$ SEM) 48-h profiles of locomotor activity (A-B) and body temperature (C-D) obtained from the 14 days of recording in young (N = 9) and old mouse lemurs (N = 8) exposed to either short daylength (LD 10/14, left panels) or long daylength (LD 14/10, right panels). Locomotor activity is expressed in arbitrary unit (AU). Light and dark phases are represented by white and black bars, respectively. Light-dark transitions are indicated by dashed lines.

Fig. 2. Differences in quantitative parameters of the locomotor activity rhythm (A: interdaily stability, B: intradaily variability, C: amplitude, D: activity during the 5 most restful hours (L5), E: activity during the 10 most active hours (M10), and F: activity onset) according to the duration of light exposure (short daylength LD 10/14 or long daylength LD 14/10) in young or old mouse lemurs. AU: arbitrary unit; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Fig. 3. Representative actograms of the daily locomotor activity rhythm of a young and an old mouse lemurs exposed to LD 14:10. The red bar indicates the onset of lights off. Note the significant phase advance of the activity onset in the old animal.

Fig. 4. Differences in the daily body temperature (T_c) rhythm parameters (A: nocturnal T_c , B: minimum of T_c , and C: time of minimum of T_c) according to the duration of light exposure (short daylength LD 10/14 or long daylength LD 14/10) in young or old mouse lemurs. * $P < 0.05$; *** $P < 0.001$.

	Age effect		Daylength effect		Age x daylength effect	
	F	p	F	p	F	p
Interdaily stability	$F(1;15)=0.5$	NS	$F(1;15)=92.7$	$p<0.001$	$F(1;15)=7.8$	$p<0.05$
Intradaily variability	$F(1;15)=14.3$	$p<0.01$	$F(1;15)=11.4$	$p<0.01$	$F(1;15)=4.5$	$p<0.05$
Amplitude	$F(1;15)=9.2$	$p<0.01$	$F(1;15)=30.6$	$p<0.001$	$F(1;15)=39.8$	$p<0.01$
L5	$F(1;15)=4.5$	$p=0.05$	$F(1;15)=4.6$	$p<0.05$	$F(1;15)=2.0$	NS
M10	$F(1;15)=10.7$	$p<0.01$	$F(1;15)=67.3$	$p<0.001$	$F(1;15)=4.9$	$p<0.05$
Activity onset	$F(1;15)=5.2$	$p<0.05$	$F(1;15)=2.9$	NS	$F(1;15)=2.5$	NS
Nocturnal T_c	$F(1;15)=0.1$	NS	$F(1;15)=32.7$	$p<0.001$	$F(1;15)=0.0$	NS
Minimum T_c	$F(1;15)=0.1$	NS	$F(1;15)=11.6$	$p<0.01$	$F(1;15)=0.0$	NS
Time of minimum T_c	$F(1;15)=17.3$	$p<0.01$	$F(1;15)=0.4$	NS	$F(1;15)=0.2$	NS

Table 1. Two-way ANOVA results on the effect of age and daylength on the daily rhythms of locomotor activity and body temperature (T_c) in young and old mouse lemurs exposed to either short (LD 10:14) or long photoperiod (LD 14:10). L5: activity during the major resting period of the day; M10: activity during the major active period of the day.

	Photoperiod	Median	F	p
Young animals	LD 10:14	-25 mn	$F(1;8)=0.006$	NS
	LD 14:10	-10 mn		
Old animals	LD 10:14	-15 mn	$F(1;7)=5.98$	$p<0.05$
	LD 14:10	-50 mn		

Table 2. One-way ANOVA results on the effect of daylength on the onset of locomotor activity in each age category (young or old mouse lemurs), when exposed to either short (LD 10:14) or long photoperiod (LD 14:10).

Figure 1

Figure 2

FIG.3

Figure 4