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Age-dependent changes in the stability of the daily activity rythms of laboratory mice

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Abstract

The aim of the present study was to investigate age-dependent changes in the daily activity rhythm of laboratory mice with special reference to its stability and synchronization with the light-dark (LD)-cycle. Attempts were made under laboratory conditions to reverse changes by means of Zeitgeber-strengthening and social factors.

Investigations were carried out on female laboratory mice. Animals were kept under standardized environmental conditions (L : D = 12 : 12; Light-on: 7.00; 100 : 0 lx, T = 21 +/– 2 °C; food and water ad libitum). Locomotor activity was measured by passive infrared detectors. The percentage of total activity per 24 h accounting for the dark period was used as a measure for the synchronization with the LD-cycle. To characterize the stability of the rhythms an ANOVA and a correlation analysis were performed.

The daily activity rhythms were investigated from weaning to death of the animals. Using these results four age groups were chosen for a more detailed analysis (24, 56, 65, and 88 weeks). The total activity per 24 h and the magnitude of the daily changes were found to be statistically lower than in adult mice (24 weeks) only in the oldest group. The percentage of total activity per 24 h accounting for the dark period was already decreased in 56-week-old mice, the stability of the daily patterns in 65-week-old ones. Further investigations were performed simultaneously on adult and presenile mice (24 and 65 weeks old). In an initial experiment the magnitude of the LD-cycle was changed. Following an increase (200 : 0 lx) the interdaily variability decreased to a greater extent in presenile mice. A decrease in the magnitude (5 : 0 lx) caused a higher variability mainly in adult animals. As a result the differences between the age groups were not longer significant. In a second experiment the animals were transferred to groups with 3 individuals. The rhythm stability of presenile mice increased and was not further different from those in adult mice.

The results provide evidence that it is possible to stabilize the circadian system of aged organisms by strengthening of the LD-Zeitgeber and/or additional Zeitgebers.

Key words: *Mus musculus* f. dom., circadian rhythm, age, stability

Introduction

Changes in circadian/daily activity rhythms in aged animals have been frequently described (Aschoff 1994; Turek et al. 1995). These reports concerned characters of rhythm such as the circadian amplitude, the percentage of ultradian components, the period length, and the phase position under entrained conditions. In addition, differences in the phase response to photic and nonphotic stimuli and the resynchronization rate following a Zeitgeber-shift have been obtained.

In our own investigations on laboratory mice we found decreased circadian ampli-

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tudes, while the percentage of ultradian components was elevated. The acrophases were progressively advanced. The rate of resynchronization following Zeitgeber-shift was lower as compared to adult mice. Altogether our results indicated a deteriorating ability of old mice to synchronize their rhythms with periodic environment and its complete loss during the last days before death. The circadian rhythmicity remained as long as the animals realized a certain amount of activity (Schuh et al. 1991; Weinert and Weiss 1997; Weinert and Weinert 1998).

Established circadian rhythms, their stable synchronization with the periodic environment and physiological phase relationships between different rhythmic functions are characteristics of the internal and external temporal order of adult organisms. As a consequence of the age-dependent changes in the circadian rhythmicity this temporal order is disturbed in old organisms; this in turn may diminish health and performance. The aim of the present investigation was to analyze age-dependent changes in the daily activity rhythm, and to attempt to improve the interdaily stability and the synchronization with the LD-periodicity by means of Zeitgeber-strengthening.

Materials and methods

Experiments were carried out on female laboratory mice of our own outbred stock (Haz:ICR). This has been very well investigated chronobiologically during the last few years (for review, see Weinert and Weinert 1998). Female animals were chosen because most of our former studies were performed on female mice. Also their daily rhythms are more stable compared to male mice (Weinert 1996). Animals were housed in air-conditioned rooms at an ambient temperature of 21+/–2 °C and a relative humidity of 55–65%. They were exposed to an artificial light-dark (LD) cycle of 12:12 h with light from 07:00 to 19.00 h Central European Time. The mean illumination intensity during light time was 100 lux. Standardized food (Altromin®) an water were available ad libitum. These conditions will further be called "standard conditions".

At an age of 21 days the mice were weaned. Those animals that were investigated at juvenile age were singly housed. The other mice were housed in groups of 10 individuals until two weeks before the experiments started. Then, they were singly housed and exposed to experimental conditions.

To obtain a complete picture of the ontogenetic development of the daily activity rhythm from weaning until the physiological death of the animals, results of several experiments have been summarized. They have all been performed under standard conditions on singly housed mice. Several additional experiments were conducted to fill some gaps of data or to increase the number of animals. On the basis of these results the age groups for the experiments were selected. Adult mice with a stable and well synchronized activity rhythm were chosen as control. In an older group (presenile mice) the activity rhythm was still present but with a deteriorated stability and synchronization (for details, see "Results").

In a first set of experiments the Zeitgeber-strength of the LD-cycle was modified. Compared to standard conditions, the magnitude was decreased (5:0 lx) or increased (200:0 lx). To investigate the influence of social factors two experiments were performed. In the first one, adult and presenile mice were investigated for two weeks individually and thereafter in groups of 3 animals of the same age. In a second experiment, mixed groups with 1 adult and 2 presenile mice or with 2 adult and 1 presenile mouse were studied.

The locomotor activity was recorded continuously using passive infrared motion sensors. They were mounted 5 cm above the cage roof in such a way that they detected motions of the mice in all sectors of the cage. The impulses were stored and partly analysed using the "Chronobiological Kit" (Stanford University). The activity counts were summarized to hourly values, and mean value chronograms of seven consecutive days were calculated for each mouse. The difference between the lowest and the highest values was taken as the magnitude of the oscillation. The activity rhythm was also characterized by the total activity per day (counts/24 h) and the percentage of total activity per 24 h accounted for the dark time. The latter characterizes the synchronization of the daily rhythm with the LD-cycle.

Interdaily variability or stability of the daily activity patterns was investigated by means, of ANO-

VA and correlation analysis (Weinert 1996). The intra-individual variance was used as a measure for the differences between consecutive days. On the other hand, the coefficient of correlation charcaterized the coincidence between consecutive days.

To verify the obtained differences statistically the Mann-Whithey u-test was used.

Results

The daily activity rhythm was investigated starting immediately after weaning until the death of the mice. Figure 1 shows the mean values of some rhythm characters depending on age. Prominent changes were obtained mainly in juvenile and senile mice. The total activity per 24 h showed a steep increase up to an age of 11–12 weeks and then decreased slightly. From about 24 weeks of age the changes were comparatively small (adult stage). Between the 70th and 80th weeks of age activity decreased to 25% of the value measured in young adults. The magnitude of the daily rhythm changed in the same way as the total activity. Adult mice realized more than 70% of their activity during the dark period. In about one-year-old mice the percentage of total activity per 24 h accounting for the dark period started to decrease. At the beginning, the decrease was slow. About 5 weeks following the steep decrease in the total activity and the magnitude of the activity rhythm, which was observed between the 70th and 80th weeks, the dark period activity decreased considerably. Animals older than 80 weeks realized only about 50% of their total daily activity during the dark period.

Using results depicted in figure 1 four age-groups have been chosen for a more detailed analysis. 24-week-old mice were used as control. Beginning from this age the daily rhythms changed only slightly in the course of several months. 56-week-old mice were chosen because former studies revealed the first age-dependent changes in daily rhythms at an age of one year (Weinert and Schuh 1988). Finally, two groups were chosen immediately before (65 weeks) and after (88 weeks) the steep decrease in total activity, rhythm magnitude, and dark-period activity.

The daily patterns of the four age groups are shown in figure 2. They were all bimodal with a main maximum in the dark period and a secondary one following lights-on. The magnitude of the main maximum decreased, whereas the secondary one became more pronounced, becoming higher and broader. Together with the phase advance in the main maximum this caused a shortening of the resting period during the light period. The total activity/24 h decreased with advancing age (Tab. 1). In the younger groups the differences were not yet significant. However, the activity of the oldest animals was only 20–25% from that of adult mice (24 weeks). The daily magnitudes changed similarly. Considerable changes were found for the dark-period activity. It was significantly lower already in 56-week-old animals and decreased further with increasing age. This was a result of the phase advance of the main maximum, but also of the larger secondary maximum.

Age-dependent changes were found also concerning the stability of the daily rhythms (Tab. 1). With increasing age the coefficients of correlation decreased, reflecting a worse coincidence of the activity patterns of consecutive days. ANOVA revealed an increasing percentage of total variance which accounted for the variability between consecutive days. Thus, both analyses confirm a lower stability of the activity rhythm in senile mice, being significantly different from adult mice already in 65-week-old animals.

The experiments investigating possibilities to stabilize the circadian rhythm were carried out simultaneously on adult (24 weeks) and presenile (65 weeks) animals. The 65-week-old mice were chosen, because at this age the stability of the rhythm and its synchronization with the LD-Zeitgeber were already decreased, whereas the activity rhythm itself (shape, daily mean, magnitude) was not yet significantly change.

The differences between the activity patterns of adult and presenile mice obtained un-

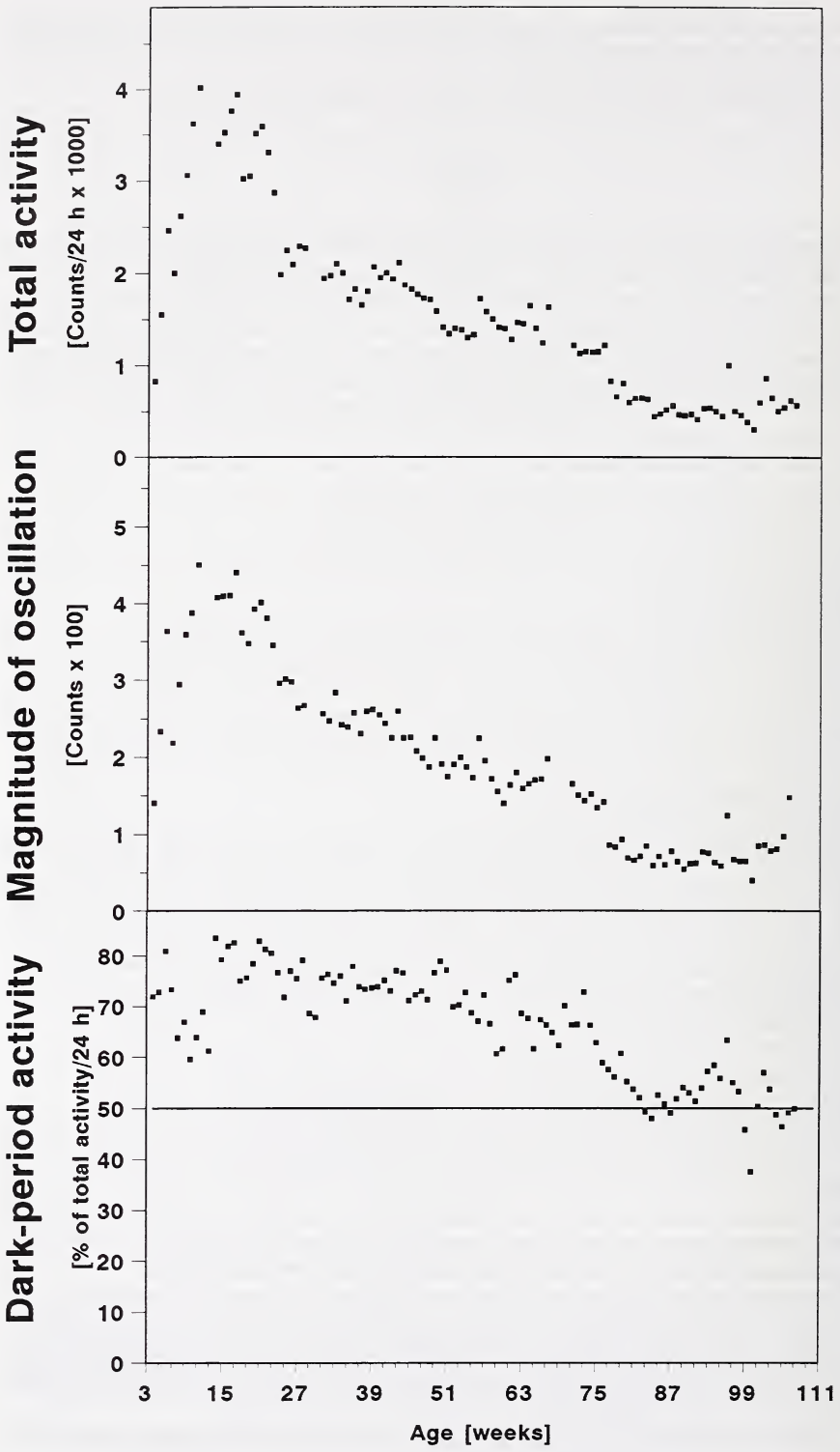

Fig. 1. Changes in some characters of the daily activity rhythm in the course of the postnatal development (weekly mean values of ≥5 female mice, from the 96th weeks of life n = 3).

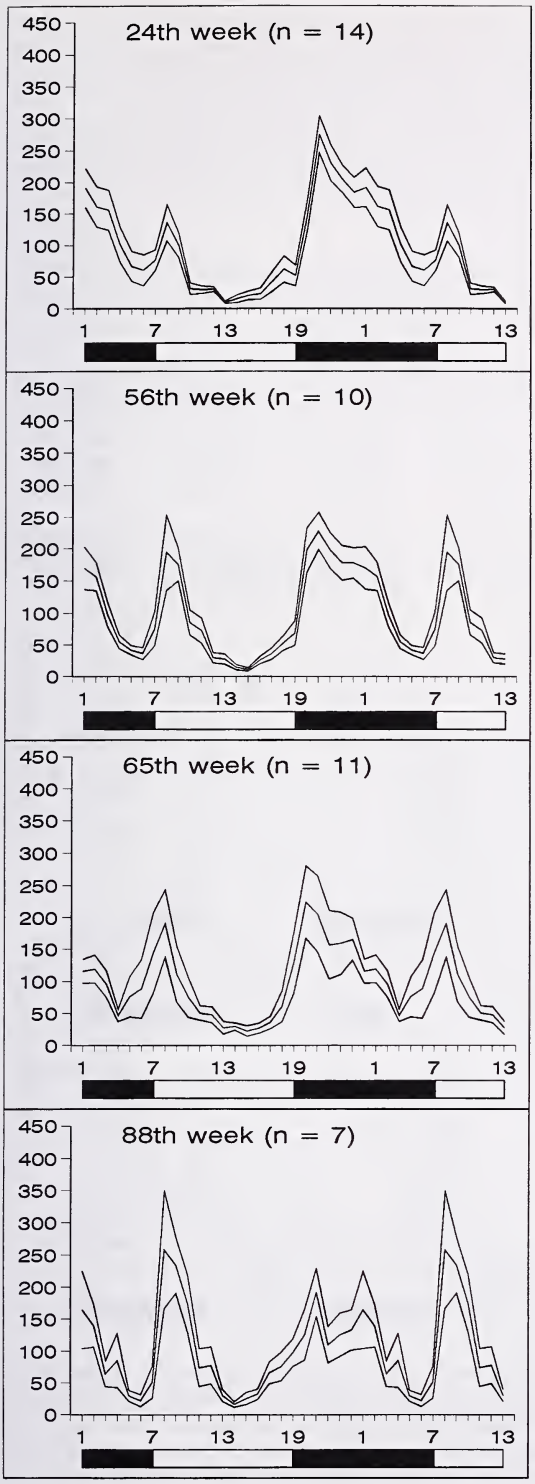

Fig. 2. Daily rhythms of locomotor activity depending on age. Mean values (± SEM) of 7–14 female mice investigated over 7 days. For better visualization $1\,^1/_2$ periods were shown, i. e., the last twelve values of the curves are identical to the first twelve. Abscissa: Time of day, the bars below indicate the lighting regimen. Ordinate: Locomotor activity (deviation from the daily mean in %).

der standard conditions (Fig. 2) were no longer significant following an increase or a decrease in the LD-magnitude (Fig. 3). However, differences have been obtained depending on the LD-magnitude. Under 200 : 0 lx the activity increased steeply following lights-off, whereas under 5 : 0 lx it started to increase already at the end of the light period.

The percentage of total activity accounting for the dark period and the rhythm stability were not significantly different under both LD-magnitudes but increased with increasing light intensity (Tab. 2). Considering the results obtained under standard conditions re-

Table 1. Age-dependent changes of the daily activity rythm. (The data set depicted in Fig. 2 has been used.) Mean values ± SEM (* – for ANOVA and correlation analyses the data of the subsequent week were included.) Bold: Significant different from 24 weeks old mice: [a] – $p \leq 0.05$, [b] – $p \leq 0.01$, [c] – $p \leq 0.001$ (Mann-Whitney u-test)

	24 weeks	56 weeks	65 weeks	88 weeks
Total activity (counts/24)	1 986 ± 168	1 723 ± 202	1 398 ± 382	**463 ± 84**[c]
Magnitude of oscillation (counts/h)	296 ± 26	224 ± 34	170 ± 52	**65 ± 15**[c]
Dark-period activity (% of total activity/24 h)	76.7 ± 1.8	**67.1 ± 3.5**[a]	**61.7 ± 3.4**[b]	**51.8 ± 2.6**[c]
Correlation between consecutive days (r)*	0.62 ± 0.50	0.54 ± 0.03	**0.45 ± 0.04**[a]	**0.42 ± 0.04**[b]
Interdaily veriance (% of total variance)*	41.5 ± 4.6	50.1 ± 3.5	**56.5 ± 3.8**[a]	**62.8 ± 4.6**[b]

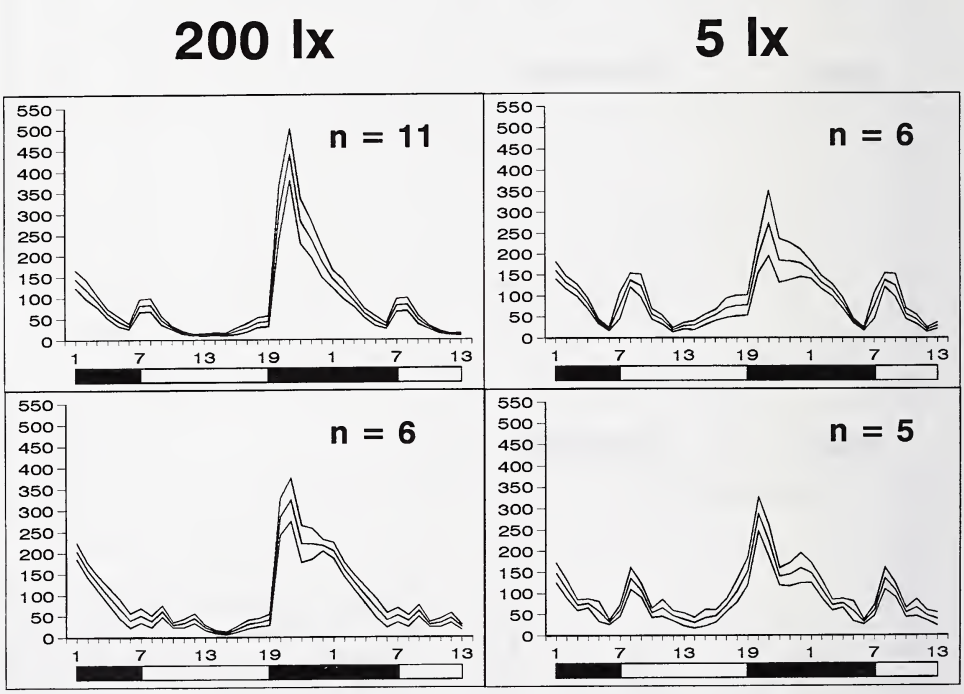

Fig. 3. Daily rhythms of locomotor activity of adult (top) and presenile (bottom) mice under L : D =12 h : 12 h with 200 lx (left side) or 5 lx (right side) during the light period. Mean values (± SEM) of 5 to 11 female mice investigated over 7 days. For better visualization $1\,^1/_2$ periods were shown, i. e., the last twelve values of the curves are identical to the first twelve. Abscissa: Time of day, the bars below indicate the lighting regimen. Ordinate: Locomotor activity (deviation from the daily mean in %).

Table 2. Synchronization and stability of the daily activity rythm depending on age and Zeitgeber strength. (The Data sets depicted in Fig. 2 (100 lx) and Fig. 3 (5 and 200 lx) have been analysed. Mean values ± SEM (* – for ANOVA and correlation analyses the data of the subsequent week were included) ** – the same values as in Tab. 1 (all differences between adult (24 weeks old) and presenile (65 weeks old) mice are significant). [a] – significantly different from the value under 5 lx ($p \leq 0.05$, Mann-Whitney u-test)

	Age	200 lx	100 lx**	5 lx
Dark-period activity	adult	82.1 ± 2.7	76.7 ± 1.8[a]	66.8 ± 2.4
(% of total activity/24 h)	presenile	83.6 ± 3.4[a]	61.7 ± 3.4	61.8 ± 3.6
Correlation between	adult	0.69 ± 0.04	0.62 ± 0.05[a]	0.43 ± 0.03
consecutive days (r)*	presenile	0.68 ± 0.04[a]	0.45 ± 0.04	0.41 ± 0.05
Interdaily variance	adult	36.4 ± 4.3	41.5 ± 4.6[a]	56.7 ± 2.9
(% of total variance)*	presenile	38.0 ± 5.0[a]	56.5 ± 3.8	61.4 ± 3.0

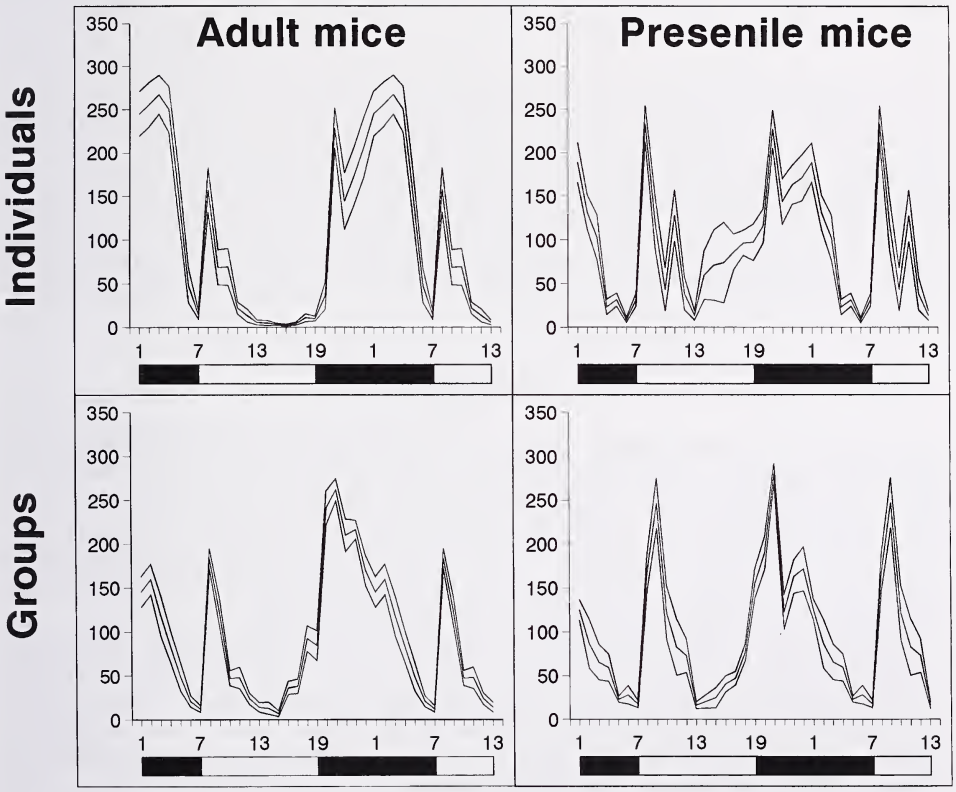

Fig. 4. Representative examples of daily activity rhythms of adult (left side) and presenile (right side) mice housed individually or in groups (n = 3). Mean values (± SEM) over 14 days. For better visualization 1 $^1/_2$ periods were shown, i. e., the last twelve values of the curves are identical to the first twelve. Abscissa: Time of day, the bars below indicate the lighting regimen. Ordinate: Locomotor activity (deviation from the daily mean in %)

Table 3. Stability of the daily activity rhythm depending on age and housing conditions. (The same data set as for Fig. 4 has been analysed.) * – results of all investigated mice were summarized; [a,bç] – significant differences ($p \leq 0.05$, Mann-Whitney u-test); I – individual mice; G – groups

		Adult mice*	Presenile mice*
Correlation between consecutive days (r)	I	0.62 ± 0.05^{a} (n = 14)	$0.45 \pm 0.04^{a,b}$ (n = 11)
	G	0.65 ± 0.03 (n = 6)	0.59 ± 0.03^{b} (n = 6)
Interdaily variance (% of total variance)	I	41.5 ± 4.7^{c} (n = 14)	56.5 ± 3.8^{c} (n = 11)
	G	37.2 ± 4.2 (n = 6)	45.5 ± 3.3 (n = 6)

veals age-dependent differences. The stability and synchronization of the activity rhythm of adult mice were significantly improved under 100 : 0 lx. The coefficient of correlation was higher, the percentage of total variance accountable for intra-individual variance was lower, and the percentage of total activity accountable for the dark period was higher. For presenile mice, the same result was obtained only under the highest LD-magnitude, which indicates a lower susceptibility to light.

Figure 4 shows representative activity rhythms of mice housed singly or in groups. While the patterns of adult mice were similar independent of the housing conditions, the daily pattern of presenile mice was clearer when kept in groups. The stability of the activity rhythm was also influenced by the housing conditions (Tab. 3). The coefficient of correlation was significantly higher, the percentage of total variance accounting for intra-individual variance was significantly lower in individual adult mice as compared to presenile ones. When adult animals were transferred to groups both values remained nearly unchanged. On the contrary, in presenile mice the coefficient of correlation increased and the intra-individual variance decreased significantly. Thus, when animals were kept in groups, the rhythm stability was no longer different with respect to age. Also in mixed groups (2 adult + 1 presenile or 1 adult + 2 presenile animals) the coefficient of correlation and the intra-individual variance were the same as in groups of only adult or only senile mice.

Discussion

The results of the present study are consistent with data in the literature (Aschoff 1994; Turek et al. 1995; Valentinuzzi et al. 1997) as well as with our own earlier investigations (Weinert and Weinert 1998). They showed that with advancing age all characters of the daily activity rhythm change. However, they also showed a decreased rhythm stability and a deteriorated ability to synchronize with external Zeitgebers at comparatively early age when regarding the mean life span of our mice (85 weeks). In contrast, the daily rhythm was present as long as the animals were locomotoric active.

Several reasons might be responsible for the lower rhythm stability and the impaired synchronization in presenile mice. This is mainly due to the high complexity of the circadian system, which includes oscillator(s), mechanisms of external synchronization, and internal coupling. Deterioration in the function of any of these components may result in changes of circadian rhythms in old age. In addition, one must bear in mind that not all changes in the overt rhythm – consisting of endogenous, due to the body clock, and exogenous (masking) components – are caused by changes in the circadian system.

The main component of the circadian pacemaker system is the nucleus suprachiasmaticus (SCN) of the hypothalamus, which consists of a number of mutually synchronized pacemaker cells (Miller 1998). If the number of functioning neurons decreases with advancing age, and if this were linked to a weaker coupling between them, it is probable

that only unstable rhythms could be generated. A lower stability of the free-running activity rhythm was found in old mice (Weinert and Kompauerova 1998; Weinert and Weiss 1997), hamsters (Aschoff 1994), and humans (Wever 1992).

The total number of neurons does not change in the SCN of aging rats (Madeira et al. 1995). However, the number of neurons expressing neuropeptides, which are believed to be involved in circadian time-keeping (AVP, VIP), decreased in old rats (Lucassen et al. 1995; Li and Satinoff 1998) and humans (Hofmann et al. 1996). Van der Zee et al. (1999) found a decrease in the number of AVP-immunopositive cells in aging common voles which coincided with a loss of precision of circadian rhythmicity.

The LD periodicity has been accepted for rodents and other mammalian species as the most potent Zeitgeber, exerting a stable phase control over circadian rhythms. With respect to the problem of impaired synchronization, one might expect a decreased sensitivity of the circadian system to light in old organisms. There is evidence in favour of this supposition. Sutin et al. (1993), Zhang et al. (1996) and Benloucif et al. (1997) found a decreased sensitivity to light in rats, hamsters, and mice. The response of immediate early genes (IEG), which are part of the entrainment pathway, was less in the SCN of old animals, as was the phase-shifting effect of the light pulses. There are further studies on hamsters (Aschoff 1994; Pohl 1984; Rosenberg et al. 1991) and mice (Provencio et al. 1994; Weinert and Kompauerova 1998) investigating only the phase response of the activity rhythm. Despite some inconsistency, all results indicate an altered susceptibility to light with increasing age.

An altered response of the circadian system to photic stimuli in advanced age may be caused by changes in the retina, in the afferent, neuronal pathways to the SCN, or in the SCN itself. With respect to photoreceptors there is currently a debate as to what receptors are relevant for the circadian system (Freedman et al. 1999; Provencio et al. 1994). No differences were found in the retinal innervation of the SCN (Zhang et al. 1998). Concerning the SCN, Cai and Wise (1996) were able to restore the decreased response to light in old rats by transplantation of fetal SCN tissue.

Finally, analysing the stability and synchronization of daily rhythms one must take into account also non-photic factors. These are effective via motor activity or the associated arousal. Some evidence exists that photic and non-photic events interact to produce entrainment (Hastings et al. 1998). The impact of non-photic Zeitgebers is decreased in old animals not only due to their lower activity level but also due to deficits in the monoaminergic neurotransmission (Penev et al. 1995).

Age-dependent changes initially concern only the stability of the circadian rhythms and their ability to synchronize to the environment. Both are diminished, whereas the rhythms themselves continue to be pronounced. Therefore, it seems possible to treat disturbances. As for old organisms, a decreased susceptibility to external cues, particularly Zeitgebers, becomes characteristic, this might be realized by increasing the strength of the main Zeitgeber and/or additional, synergistic Zeitgebers, as a temperature cycle, a restricted or scheduled feeding regimen, or social Zeitgebers. Another possibility might be to strengthen feedback effects, by increasing the daily amount of motor activity, for example, and to improve the synchronization and stability of circadian rhythms by this means. The LD-cycle, the main Zeitgeber for mammals, may be strengthened by increasing its magnitude. By this means, Witting et al. (1993) were able to reverse some of the age-related changes in the sleep-wake cycle of rats, particularly the damped amplitude. Similarly, Labyak et al. (1998) reduced the fragmentation of the activity rhythm, increased the general activity level, and increased its amplitude in old hamsters. The present study on old mice revealed an improvement of the rhythm stability; the percentage of activity during the dark period was increased. All these results might reflect an improved synchronization of the circadian rhythm; however, masking effects due to the high level of illumination during the light phase must be considered as well (Aschoff 1988).

In the present study we also found age-dependent differences in the circadian rhythm of activity between mice kept individually or in groups. Whereas in adult animals the rhythm stability was not different regardless of whether the animals were kept in groups or individually, in senile mice, the inter-daily variability decreased significantly when they were transferred to groups, and then did not differ from adult mice. As mice are social animals, the decreased stability of the activity rhythm of animals kept individually might be a consequence of isolation stress, and it is possible that old mice are more susceptible to this condition. Another possible explanation might be that housing animals in groups stabilizes the circadian rhythm by means of social Zeitgebers. However, the problem of whether social factors are effective as Zeitgebers is controversial, and has recently been discussed (Gattermann and Weinandy 1997).

In summary, the present results provide evidence that it is possible to stabilize daily rhythms by means of Zeitgeber strengthening and/or additional Zeitgebers.

Acknowledgements

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Zusammenfassung

Altersabhängige Änderungen in der Stabilität von Tagesrhythmen der Aktivität bei Labormäusen

Ziel der vorliegenden Untersuchung war die Erfassung altersabhängiger Änderungen des Tagesrhythmus der Aktivität, insbesondere unter dem Aspekt der Stabilität sowie der Synchronisation mit dem Licht-Dunkel (LD) -Wechsel. Desweiteren sollte unter Laborbedingungen versucht werden, altersbedingte Änderungen rückgängig zu machen. Die Untersuchungen erfolgten an einzeln gehaltenen weiblichen Labormäusen in klimatisierten Räumen ($T = 21 \pm 2\,°C$, relative Luftfeuchte – 55–65%, Licht-Dunkel-Zyklus von L : D = 12 : 12 h, 100 : 0 lx, Licht von 07 : 00 bis 19.00 h, Futter und Wasser ad libitum). Die lokomotorische Aktivität wurde mit PIR-Bewegungsdetektoren registriert. Die Beurteilung der Stabilität der Tagesmuster erfolgte mittels Varianz- und Korrelationsanalysen.

Tagesrhythmen der Aktivität wurden vom Absetzen (21. Lebenstag) bis zum Alterstod erfaßt. Auf dieser Grundlage wurden vier Altersgruppen (24, 56, 65 und 88 Wochen) ausgewählt und genauer untersucht. Die Tagesmuster waren erst bei der ältesten Gruppe deutlich unterschiedlich. Auch die Gesamtaktivität/24 h sowie die Schwingungsbreite im Tagesgang waren hier signifikant geringer als bei den adulten Mäusen (24 Wochen). Der Anteil der Aktivität in der Dunkelzeit an der Gesamtaktivität/24 h, als ein Maß für die Synchronisation mit dem LD-Wechsel, war bereits bei den 56 Wochen alten Tieren signifikant geringer, die Stabilität der Tagesmuster im Alter von 65 Wochen.

Da sich zunächst nur die Synchronisation sowie die Stabilität verschlechterten, der Rhythmus jedoch erhalten blieb, schien es möglich zu sein, den Rhythmus zu stabilisieren. Diese Untersuchungen erfolgten parallel an 24 und 65 Wochen alten Tieren. Zunächst wurde die Zeitgeberstärke des LD-Wechsels modifiziert. Durch eine Erhöhung der LD-Amplitude auf 200 : 0 lx verminderte sich die Variabilität der Muster aufeinanderfolgender Tage vorwiegend bei den senilen Tieren. Wurde die LD-Amplitude verringert (5 : 0 lx) nahm die Variabilität zu und zwar in stärkerem Maße bei den adulten Tieren. In beiden Fällen bestanden keine Unterschiede zwischen den Altersgruppen mehr. Der Anteil der Aktivität in der Dunkelzeit an der Gesamtaktivität/24 h erhöhte sich mit zunehmender LD-Amplitude vorwiegend bei den senilen Mäusen und verminderte sich bei Verringerung der Amplitude vorwiegend bei den adulten. Eine Stabilisierung des Aktivitätsrhythmus konnte auch durch eine Gruppenhaltung erreicht werden. Bei einzeln gehaltenen senilen Tieren war die Stabilität signifikant geringer als bei adulten. Wurden die Tiere in Gruppen umgesetzt, erhöhte sich die Stabilität bei den senilen Mäusen deutlich und unterschied sich nicht mehr von der adulter.

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