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Exposure to light at night accelerates aging and spontaneous uterine carcinogenesis in female 129/Sv mice

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The effect of the constant illumination on the development of spontaneous tumors in female 129/Sv mice was investigated. Forty-six female 129/Sv mice starting from the age of 2 mo were kept under standard light/dark regimen [12 h light (70 lx):12 hr dark; LD, control group], and 46 of 129/Sv mice were kept under constant illumination (24 h a day, 2,500 lx, LL) from the age of 5 mo until to natural death. The exposure to the LL regimen significantly accelerated body weight gain, increased body temperature as well as acceleration of age-related disturbances in estrous function, followed by significant acceleration of the development of the spontaneous uterine tumors in female 129/Sv mice. Total tumor incidence as well as a total number of total or malignant tumors was similar in LL and LD group ($p > 0.05$). The mice from the LL groups survived less than those from the LD group ($\chi^2 = 8.5$; $p = 0.00351$, log-rank test). According to the estimated parameters of the Cox's regression model, constant light regimen increased the relative risk of death in female mice compared with the control (LD) group ($p = 0.0041$). The data demonstrate in the first time that the exposure to constant illumination was followed by the acceleration of aging and spontaneous uterine tumorigenesis in female 129/Sv mice.

Introduction

The alternation of the day and night seems is a most important regulator of a wide variety of physiological rhythms in living organisms. Exposure to the bright light during the night suppresses the night peak of melatonin—the "hormone of the night."[1] Melatonin is a principal hormone of the pineal gland—the small neuroendocrine gland connected with the brain that mediates information on light from the retina of the eyes to the organism.[1,2]

Light exposure at night has been found to be related to a number of serious behavior as well as health problems, including cancer. Significant increase in the risk of breast and colorectal cancers was found among women who frequently did not sleep during the period of the night, about 1:30 a.m., when melatonin levels are typically at their highest.[3-7] "Melatonin hypothesis" suggests that reduced pineal melatonin production might increase human breast cancer risk, because lower melatonin output would lead to an increase in the level of female sex hormones and would stimulate proliferation of breast tissue.[7] Global co-distribution of light at night and cancers of breast, prostate and some others was demonstrated in humans.[8-10] Constant illumination probably exerts its detrimental effects on health, tumorigenesis as well as survival via disturbances of the female reproductive cycle.[11] The mechanisms involved can be assumed to include the pineal hormone melatonin as well, which, as chemical signal of darkness and controlled by the central circadian clock in *N. suprachiasmatici,* may play a very central part, since it is suppressed by constant exposure to light and participates in the neuroendocrine control of the female reproductive system. Latest data from experiments in model organisms, gene expression studies and clinical trials imply that dysfunctions of the circadian clock contribute to aging and age-associated pathologies, thereby suggesting a functional link between the circadian clock and age-associated decline of brain functions.[12-18] Potential molecular mechanisms underlying this link include the circadian control of physiological processes such as brain metabolism, reactive oxygen species homeostasis, hormone secretion, autophagy and stem cell proliferation.[11,16,17]

On the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves night work" and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)," the International Agency for Research on Cancer (IARC) Working Group concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Group 2A).[18-20]

In rodents, light at night leads to disruption of the ovulatory cycles followed by hyperplastic processes and tumor development in mammary gland, ovarian and uterine.[11,19] The tumor-promoting effect of exposure to the constant illumination regimen was

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Table 1. Body weight gain dynamics in female 129/Sv mice exposed to various light regimens

	Body weight (g) at the age of:						
Light/dark regimen	5 mo	9 mo	13 mo	18 mo	20 mo	23 mo	25 mo
LD	23.4 ± 0.3	24.8 ± 0.4	24.7 ± 0.1	26.0 ± 0.5	26.6 ± 0.3	27.0 ± 0.3	28.7 ± 0.4
LL	23.3 ± 0.3	23.1 ± 0.13[b]	25.5 ± 0.3[a]	29.8 ± 0.3[b]	31.6 ± 0.5[b]	32.6 ± 0.5[b]	35.4 ± 0.8[b]

The difference with the LD is significant, [a]$p < 0.05$; [b]$p < 0.01$, the Student's t-test.

Table 2. Parameters of estrous function in female 129/Sv mice exposed to various light regimens

			Rate of estrous cycles of various length, %			
Age (months)	**Number of mice**	**Length of estrous cycles (days)**	**< 5 d**	**5–7 d**	**> 7 d**	**Fraction of mice with irregular estrous cycles (%)**
			LD			
6	46	6.4 ± 0.14	0	76.7	23.3	8.7
10	46	6.5 ± 0.13	0	76.7	23.3	10.9
13	45	6.3 ± 0.24	3	73.5	23.5	20.0
20	36	6.1 ± 0.31	7.1	78.6	14.3	8.3
			LL			
6	46	6.7 ± 0.15	0	82.0	18.0	15.2
10	46	6.8 ± 0.23	3.7	77.8	18.5	45.7[a]
13	44	6.6 ± 0.39	5.6	83.5	11.1	54.5[a]
20	38	7.3 ± 0.44	0	58.3	41.7	68.4[a,b]

[a]The difference with the LD is significant, $p < 0.05$; the Fischer exact test. [b]The difference with the LL age of 6 mo is significant, $p < 0.05$.

shown on chemical carcinogenesis of mammary gland, liver and nervous system in rats and spontaneous endometrial carcinogenesis in rats.[21-27]

In this paper, we report for the first time that the exposure to constant illumination was followed by the acceleration of the development of spontaneous uterine hemangiomas and sarcomas in female 129/Sv mice.

Results

The body weight of mice both in groups increased with age, but the body weight gain between the age of 5 and 25 mo was higher in mice of the LL group (51.9%) than that in the LD group (22.6%; $p < 0.05$) and was significantly higher in the LL regimen as compared with LD regimen from the age of 13 mo to the age of 25 mo (**Table 1**).

The body temperature was not changed significantly with age in mice of the LD group, being 37.07 ± 0.066, 37.09 ± 0.05 and 37.66 ± 0.07°C at the ages 6, 10 and 20 mo, respectively. In LL mice, the body temperature was significantly ($p < 0.001$) higher than these in the control (LD) mice: 37.55 ± 0.036, 38.03 ± 0.07 and 38.15 ± 0.06°C, respectively.

There was no significant difference in the length of estrous cycles between groups exposed to LD or LL regimen since sixth to thirteenth month of life. At the age of 20 mo, the estrous cycle was longer in the LL mice as compared with the LD mice (**Table 2**). At the age of the 20 mo, the relative number of mice with long estrous cycles (> 7 d) was significantly higher in the LL group as compared with the LD group. In the LD group, there was not significant age-related increase the rate of mice with irregular estrous cycles (**Table 2**). The exposure to the LL regimen significantly accelerated the age-related disturbances in the estrous function in 129/Sv mice. At the age of 20 mo, 68.4% mice in the LL group had irregular estrous cycles, whereas in the LD group only 8.3% ($p < 0.05$).

The estimation in the "open field" test of parameters of locomotor activity revealed the age-related decrease of its indices in 20-mo-old LD mice as compared with the 6-mo-old ones. Thus, relative number of crossed squares decreased by 3.7 times, duration of grooming reaction increased by 8.8 times, duration of feeble reaction increased by 19 times ($p < 0.01$). The exposure to the LL regimen practically did not modify these parameters (data are not shown).

The mortality of LD in LL mice was similar until the age of 2 y; however, after this age, mice maintained at LL have increased rate of death (**Table 3** and **Fig. 2**). The longest surviving mouse from the group LL died at the age of 902 d. At this age, 21.7% of mice in the LD groups were alive, and the oldest mouse died 3 mo later.

The mean lifespan of mice, as well as the mean lifespan of the last 10% survivors median and maximum lifespan were reduced by 8.1–10.3% in the LL group as compared with the LD group ($p < 0.001$). The aging rate calculated as α in the Gompertz equation was increased, and MRDT was decreased in the LL group in comparison to these parameters for the LD group ($p < 0.05$) (**Table 4**). According to the log-rank test, the conditional lifespan distributions of 129/Sv mice (given the animals survived the age of 300 d) subjected to the constant light regimen (LL) differed significantly from the control (LD) group: $\chi^2 = 8.5$, $p = 0.00351$. According to the estimated parameters of the Cox's regression

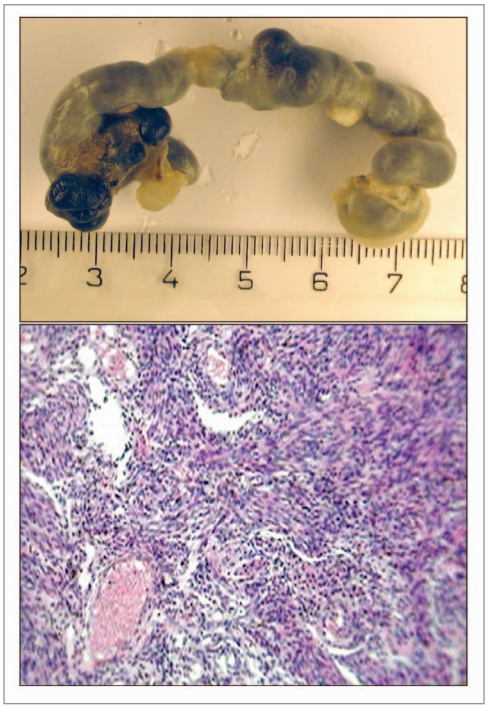

Figure 1. Macro- and microphotograph of uterine sarcoma in 129/Sv mice exposed to constant light regimen (H and E, ×320).

model, constant light regimen increased the relative risk of death in female mice compared with the control group. Cox's regression model parameters were β = 0.656; exp(β) = 1.93; se(β) = 0.228; p = 0.0041.

The exposure to constant illumination failed to significantly change the total or fatal spontaneous tumor incidence in female 129/Sv mice (**Table 4**). However, the first tumor in the LL group was detected 2 mo earlier than that in the LD group. At the autopsy, the enlargement of uteri have been observed in the majority of mice (**Fig. 2B**). Microscopically tumors were classified as hemangionas and sarcomas (**Fig. 1**).

According to the log-rank test the tumor-bearing female mice subjected to the constant light regimen (LL) differed significantly from the respective control (LD) group: group: $\chi^2 = 7.7$, p = 0.0055 and for fatal tumor-bearing mice: $\chi^2 = 5.6$, p = 0.0183, respectively. According to the estimated parameters of the Cox's regression model constant light regimen increased the relative risk of death in female tumor-bearing mice compared with the control group. Cox's regression model parameters were: β = 0.719; exp(β) = 2.05; se(β) = 0.264; p = 0.0065 for total tumor-bearing mice and β = 0.71; exp(β) = 2.03; se(β) = 0.306; p = 0.02.

Discussion

In mammals, exposure to bright constant illumination alters the central circadian pacemaker activity of the suprachiasmatic nucleus in the hypothalamus. Constant light exposure or pinealectomy blocks the circadian melatonin signal emanating from the mammalian pineal gland during every 24 h dark period. When introduced during the dark phase, bright light inhibits

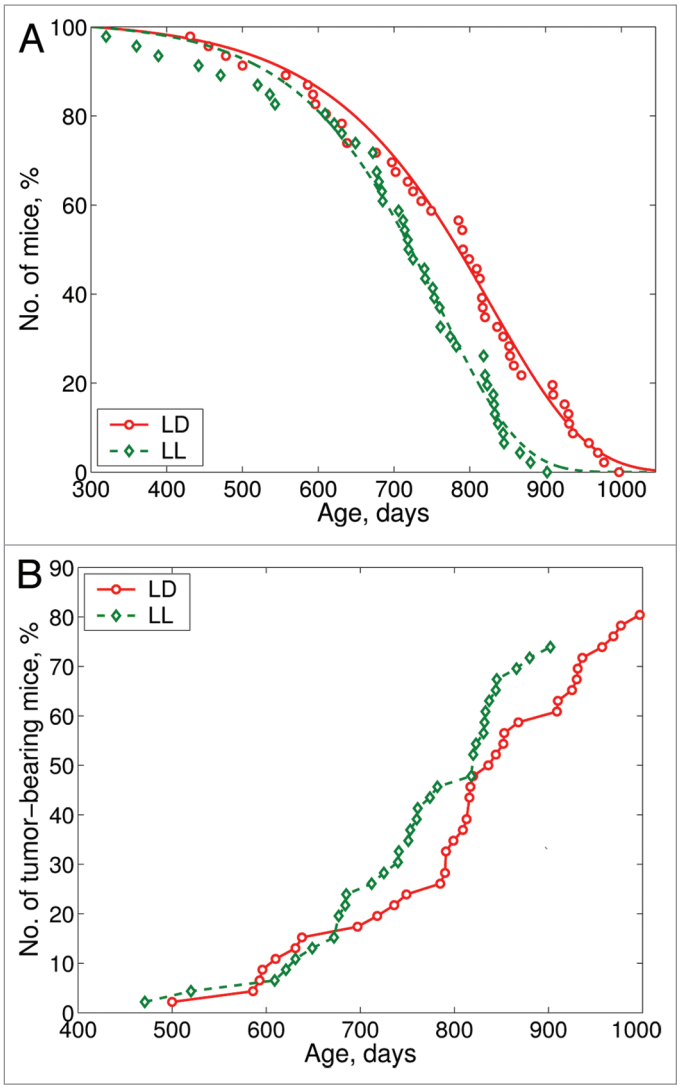

Figure 2. Effect of the exposure to the constant illumination (LL) on survival and tumorigenesis in female 129/Sv mice. Abscissa, age, days. (**A**) Survival. Ordinate, number of mice, %. (**B**) Age-dependent tumor rate curves. Ordinate, number of tumor-bearing mice, %.

melatonin production.[1,2,11] Artificial increase of the length of light phase of the day (by 2–4 h) was typically followed by the increase in the duration of estrous cycle and in some cases to its disturbances. If the light will be switched on for 24 h per day, the majority of female mice and rats in a short period revealed the persistent estrus syndrome. In physiological circumstances, this syndrome naturally develops at some age (in rats, as usual between 15th and 18th months) and precedes to the anestrus,[28-31] being the physiological equivalent of climacteric syndrome and climacteric in women. The ovary of persistent-estrus rats contains follicular cysts, hyperplasia of theca-tissue, whereas the corpora lutea are absent.[30,31] Instead of cyclic production of gonadotropins, prolactin, estrogens and progesterone characteristic for normal reproductive period of life, their acyclic production is followed by hyperplastic processes in mammary gland, ovaries and uterus.[29,30] We have found that the exposure to the

Table 3. Survival distribution in female 129/Sv mice exposed to various light regimens

	Number of survivors at the age of: (days)												
Group	300	400	500[a]	550	600	650	700	750	800	850	900	950	1000
LD	46	46	43	42	38	34	32	27	22	14	10	2	0
LL	46	43	41	38	38	34	28[b]	20[b]	13[b]	3[b]	1[a]	0	0

[a]The first tumor detected in this interval. [b]The difference with the controls of corresponding age is significant, $p < 0.05$; Fischer's exact test.

Table 4. Parameters of the lifespan and tumorigenesis in female 129/Sv mice exposed to various light regimens

	Light regimen		
Parameters	**LD**	**LL**	**Ratio**
Number of mice	46	46	
Mean lifespan (LS), days	763 ± 21.8	701 ± 20.7[a]	–8.1%
Median	795	722	–9.2%
Mean LS of last 10% survivors	967 ± 10.2	867 ± 11.0[b]	–10.3%
Maximum lifespan, days	997	902	–9.5%
Aging rate (α), days^{-3}	7.97 (6.74; 8.23)	9.39[a] (8.83; 10.9)	+1.2 times
MRDT, days	87 (84; 103)	74[a] (63; 79)	–1.2 times
The age of the 1st tumor detection, days	500	442	
Effective number of mice	45	43	
Number of tumor-bearing mice	37 (86.7%)	35 (81.4%)	
Number of fatal tumor-bearing mice	31 (68.9%)	23 (53.5%)	
Mean LS of tumor-bearing mice, days	800 ± 20.6	745 ± 17. 4[a]	–6.9%
Localization and type of tumors			
Uterus:			
hemangioma	6	12	$p = 0.065$
sarcoma	30	20	$p = 0.079$
Malignant lymphoma	1	2	
Lung:			
adenoma	-	2	
adenocarcinoma	1	1	
Stomach: adenocarcinoma	1	-	
Bladder: papilloma	-	1	

The difference with the control of the LL: [a]$p < 0.05$; [b]$p < 0.001$.

LL regimen leads to the increase in the threshold of sensitivity of the hypothalamus to the feedback inhibition by estrogens in female rats.[31] This mechanism is a key mechanism in the aging of reproductive system in female rats as well as in women.[31,32] The disturbances in the estrous function developed much more early in 129/Sv mice in the LL group than that in the LD group.

We have observed excess of the body weight in the old female 129/Sv mice maintained at LL regimen as compared with the control LD mice. The obesity, decrease of tolerance to glucose and of the sensitivity to insulin have been observed in rats with persistent estrus.[11,33,34] Metabolic syndrome characterized by obesity, hypertriglyceridemia and hypercholesterinemia is observed to decrease the level of high density lipoproteins, blood fibrinolytic activity, arterial hypertension, tolerance to glucose and insulin resistance more frequently.[35] The metabolic syndrome is a risk factor not only for cardiovascular diseases but for cancer too.[36-38] The inhibition of pineal function due to exposure to continuous light probably facilitates the metabolic syndrome development. The exposure to the LL regimen promoted spontaneous mammary carcinogenesis in female LIO rats[33] and in transgenic HER-2/neu FVB/N mice,[24] mammary carcinogenesis induced by 7,12-dimethylbenz(a)anthracene or N-nitrosomethylurea in female rats[21,22] and colon carcinogenesis induced by 1,2-dimethylhydrazine in rats.[39] The exposure to the LL regimen accelerated spontaneous uterine carcinogenesis in BDII rats.[25] It was first shown in our present experiments that the constant light illumination promotes the spontaneous development of uterine tumors in 129/Sv mice.

The mechanisms of the protective effect of melatonin on carcinogenesis include the variety of possibilities discussed in several comprehensive reviews and include antioxidant and antiproliferative effects, the increase in apoptosis and inhibitory

effect on telomerase activity in tumor cells both in vivo and in vitro, antiestrogenic effect, the decrease IGF-1 and insulin levels, etc.[3,19,23,40-45]

In conclusion, the results presented in this article demonstrate that exposure to light at night may have an important role in development of not only mammary tumors, but also a wide spectrum of tumors at different localization.

Materials and Methods

Animals. Ninety-two 2-mo-old female 129/Sv mice originally provided by The Jackson Laboratory and bred at the animal facility at our Department were randomly subdivided into two groups and kept five per cage in polypropylene cages (30 × 21 × 10 cm) under standard light/dark regimen (12 h light:12 h darkness; LD, control group) of constant light regimen (LL) at a temperature of 22 ± 2°C and received standard laboratory chow[47] and tap water ad libitum.

Experimental design. At the LD regimen, mice were exposed from 08:00 to 20:00 h to electric lamps (75 W, 200 V) with the illumination of 70 lx at the bottom of cages at the distance 1.7 min. At the LL regimen mice were exposed to two luminescent lumps LB-40-2 with illumination of 2,600 lx at the bottom of cages at the distance of 1.5 min. The control of the illumination was performed weekly with the luxmeter TKA PKM. Once a week, all mice were palpated to detect any tumors. All animals were weighed monthly with an electronic balance. Once every 3 mo, vaginal smears taken daily for 2 wk from the animals were cytologically examined to estimate the phases of their estrous functions. In the same period, rectal body temperatures of the mice were measured with an electronic thermometer, TPEM (KMIZ) Once every 3 mo, vaginal smears taken daily for 2 wk from the animals were cytologically examined to estimate the phases of their estrous functions. In the same period, rectal body temperatures of the mice were measured with an electronic thermometer, TPEM (KMIZ). For behavior anomalies parameters of locomotor activity were estimated by the "open field" test in mice of both groups at the age of 6 and 20 mo.[47]

Pathomorphological examination. All animals were autopsied. All tumors, as well as tissues and organs with suspected tumor development, were excised and fixed in 10% neutral formalin. After routine histological processing, tissues were embedded in paraffin; 5–7 μm thin histological sections were stained with hematoxylin and eosin and were microscopically examined. Tumors were classified according to the "International Agency for Research on Cancer" recommendations.[48]

Statistics. Experimental results were statistically processed using STATGRAPH. The significance of discrepancies was defined according to the Student's t-criterion, Fischer's exact method, χ^2 and non-parametric Wilkoxon-Mann-Whitney. Student-Newman-Keuls method was used for all pairwise comparisons. For survival analysis, Cox's method[49] was used for testing two groups. Taron's life table test[50] was used. All reported test values for survival analyses are two-sided.

Mathematical models and estimations. The mathematical model used to describe survival is the Gompertz model with the survival function:

$$S(x) = \exp\left\{-\frac{\beta}{\alpha}\left[\exp(\alpha x) - 1\right]\right\}$$

where parameters α and β are associated with the aging and initial mortality rate, respectively. Parameters for the model were estimated from data using the maximum likelihood method implemented in the Gauss statistical system.[51]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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