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EFFECT OF EXPOSURE TO LIGHT-AT-NIGHT ON LIFE SPAN AND SPONTANEOUS CARCINOGENESIS IN FEMALE CBA MICE

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The effect of constant illumination on the development of spontaneous tumors in female CBA mice was investigated. Fifty female CBA mice starting from the age of 2 months were kept under standard light/dark regimen (12 hr light: 12hr dark; LD) and 50 CBA mice of similar age were kept under constant illumination (24 hr a day, 2,500 Lux, LL). Exposure to the LL regimen decreased food consumption but did not influence body weight, significantly accelerated age-related disturbances in estrous function, and was followed by a significant increase in spontaneous tumor incidence in female CBA mice. Tumor incidence as well as the number of total or malignant tumors was significantly increased in the LL group compared to the LD group ($p < 0.001$). The incidence of lung adenocarcinomas, leukemias and hepatocarcinomas was 7/50; 6/50 and 4/50 in the LL group and 1/50; 0/50 and 0/50 in the LD group. Mice from the LL groups had shorter life spans then those from the LD group. The data demonstrate, for the first time, that exposure to constant illumination was followed by increases in the incidence of spontaneous lung carcinoma, leukemias and hepatocarcinoma in female CBA mice.

Key words: *light-at-night; spontaneous tumors; life span; CBA mice*

Alternation of the day and night circadian cycle is an important regulator of a wide variety of physiological rhythms in organisms. Light exposure at night has been found to be related to a number of serious behavioral and health problems including cancer. In rodents, light-at-night leads to disruption of the ovulatory cycle followed by hyperplastic processes and tumor development in mammary gland, ovaries and uteri.[1,2] A tumor-promoting effect of exposure to the LL regimen was shown on chemical carcinogenesis in the mammary gland of rats.[3–6] Prolonged light exposure suppresses the night peak of melatonin, the 'hormone of the night.'[7,8] Melatonin is the principal hormone of the pineal gland, the small neuroendocrine gland connected with the brain that mediates information on light from the retina to the organism.[7,8]

A significant increase in the risk of breast and colorectal cancers was shown in women who frequently did not sleep during the period of the night, about 1:30 a.m., when melatonin levels are typically the highest.[9–12] The 'Melatonin hypothesis' suggests reduced pineal melatonin production might increase human breast cancer risk because lower melatonin output would lead to an increase in female sex hormones and stimulate proliferation of breast tissue.[13] Data on the enhancing effect of constant illuminations on spontaneous endometrial carcinogenesis in BDII/Han rats[14] agree with this suggestion. There are data on the promoting effect of the LL regimen on hepatocarcinogenesis induced by *N*-nitrosodimethylamine (DENA) in rats[15] and on the development of neurogenic and kidney tumors in progeny of rats exposed to *N*-nitrosomethylurea *in utero*.[16] We report, for the first time, that exposure to constant illumination increased the incidence of spontaneous lung carcinoma, leukemias and hepatocarcinoma in female CBA mice.

MATERIAL AND METHODS

Animals

One hundred 2-month-old female CBA mice were purchased from the "Rappolovo" Animal Farm of the Russian Academy of Medical Sciences. There are data on synthesis and secretion of melatonin by pineal gland of CBA mice.[17] Mice were randomly subdivided into 2 groups and kept 5 per polypropylene cages (30 × 21 × 10 cm) under standard light/dark regimen (12 hr light:12 hr darkness; LD) or constant light regimen (LL) at a temperature of 22 ± 2°C and received standard laboratory chow[18] and tap water *ad lib*.

Experimental design

In the LD regimen mice were exposed from 08:00–20:00 hr to electric lamps (75 W, 200 V, Russia) with the illumination of 300 Lux at the bottom of cages at a distance of 1.7 m. In the LL regimen mice were exposed to 2 luminescent lamps LB-40-2 (Russia) with illumination of 2,500 Lux at the bottom of cages at a distance of 1.5 m. It was shown earlier in our experiments that the constant exposure to 2,500 Lux more effective induced disturbances in estrus function and promoted spontaneous carcinogenesis in HER-2/neu mice as compared to the exposure to 300 Lux.[19] Control of the illumination was carried out weekly with the luxmeter U-116 (GOST-14841, Russia). The weekly measure of air temperature at the level of the cages with animals failed to show any significant changes in the room temperature at the constant illumination conditions as compared to the room at the LD regimen. Once a week, all mice were palpated to detect mammary tumors. Once every 3 months, 5 times daily for 2 weeks, vaginal smears were cytologically examined to determine estrus function. Animals were kept under LD or LL regimens until their natural death.

Pathomorphological examination

All dead 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 haematoxylin and eosin and microscopically examined. Tumors were classified according to the International Agency for Research on Cancer recommendations.[20]

Statistics

Experimental results were analyzed using STATGRAPH. The significance of discrepancies was defined by the Student's *t*-criterion, Fischer's exact method, χ^2 and non-parametric Wilcoxon-

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Mann-Whitney. Student-Newman-Keuls method was used for pairwise comparisons.[21] For discrepancies in neoplasm incidence to be estimated, an IARC method of combined contingency tables calculated individually for the fatal and incidental tumors.[22] For survival analysis, Cox's method[23] was used for testing 2 groups. Taron's life table test[24] was used. All test values reported for survival analyses are 2-sided.

Mathematical models and estimations

Survival is described using the Gompertz hazard with the survival function,

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

where α and β are parameters associated with age and the initial mortality rate, respectively. Parameters were estimated using the maximum likelihood method implemented in the Gauss statistical system.[25]

RESULTS

Daily observations have shown that, under constant illumination mice were more active, had increased locomotor activity, aggressiveness and depilation (baldness) compared to mice from the LD group. The cases of cataract never were registered in groups kept at the LD or LL regimens.

Food consumption of the LL group was significantly less (on average 30%) compared to LD groups from the 6–16 months of age (Table I). The body weight of mice in both groups increased with age but did not significantly differ (Table II). There were no significant differences in the length of estrous cycles between groups exposed to LD or LL regimen (Table III). At 6 months of age the relative number of days with estrus was increased in the LL group. In the LD group, the age-related decrease of the incidence of short estrous cycles (<5 days) and increase of long cycles (5–7 days) as well as increase in the rate of irregular estrous cycles was observed (Table III). Exposure to the LL regimen significantly accelerated age-related disturbances in estrous in CBA mice. At 6 months of age no mouse had short estrous cycles; 80% had irregular estrous cycles.

The mean life span of mice was similar in both groups, however the mean life span of last 10% survivors was reduced in the LL group ($P < 0.001$). The population aging rate estimated as α in the Gompertz equation was increased, and MRDT decreased, in the LL group in comparison to the LD group ($P < 0.05$) (Table IV, Fig. 2*a*).

Exposure to constant illumination was followed by a significant increase in spontaneous tumor incidence in female CBA mice (Table V). The 1st tumor in the LL group (leukemia) was detected 10 months earlier than in the LD group. At autopsy enlargement of the spleen, liver, thymus and mesenterial lymph nodes was observed. Microscopically significant infiltration of the liver and some other organs with atypical lymphocytes was revealed (Fig. 1). Total tumor incidence as well as the total number of malignant tumors was significantly greater in the LL compared to the LD group ($p < 0.001$). Cumulative tumor yield curves for the LD and LL mice were significantly different (Fig. 2*b*). The incidence of lung adenocarcinomas, hepatocarcinomas and leukemias was higher in the LL group than the LD group. There were no significant differences in the incidence of other spontaneous tumors between LD and LL groups.

Survival in mice exposed to the LD or the LL regimen is presented in Figure 2. Survival was similar in both groups. The curves crossed at age 27 months. At age 32 months survival was 2 times higher for mice from group LD than group LL ($p < 0.05$; Fischer exact test). The last mouse from the group LL died at age

TABLE I – FOOD CONSUMPTION DYNAMICS IN FEMALE CBA MICE EXPOSED TO VARIOUS LIGHT/DARK REGIMENS

Light/dark regimen	Daily food consumption (g/mouse)				
	3 months	6 months	8 months	12 months	16 months
LD	2.6 ± 0.2	3.8 ± 0.3	3.9 ± 0.1	3.4 ± 0.4	3.5 ± 0.4
LL	3.1 ± 0.2	2.5 ± 0.3[1]	2.7 ± 0.2[2]	2.4 ± 0.1[3]	2.4 ± 0.1[3]

[1]Significant difference with LD ($p < 0.01$).–[2]Significant difference with LD ($p < 0.001$).–[3]Significant difference with LD ($p < 0.02$).

TABLE II – BODY WEIGHT GAIN DYNAMICS IN FEMALE CBA MICE EXPOSED TO VARIOUS LIGHT/DARK REGIMENS

Light/dark regimen	Body weight (g)					
	3 months	6 months	8 months	11 months	16 months	19 months
LD	22.3 ± 0.2[1]	25.9 ± 0.3	28.7 ± 0.5	29.5 ± 0.8	30.1 ± 0.8	30.2 ± 0.8
LL	22.2 ± 0.2[1]	26.2 ± 0.5	28.9 ± 0.5	28.8 ± 0.7	29.0 ± 0.8	31.6 ± 1.1

[1]The difference of all ages with the age of 3 months is significant at $p < 0.05$ using Student's *t*-test.

TABLE III – AGE-RELATED DYNAMICS OF ESTROUS FUNCTIONAL PARAMETERS IN CBA MICE EXPOSED TO VARIOUS LIGHT/DARK REGIMENS

Age (months)	Mice (*n*)	Length of estrous cycle (days)	Rate of separate phases of estrous cycle (%)		Rate of estrous cycles (%)			Number of mice with regular cycles (%)	Number of mice with irregular cycles (%)
			Estrus	Diestrus	<5 days	5–7 days	> 7 days		
LD regimen									
3	29	6.0 ± 0.3	45.8	49.4	29.0	47.0	24.0	88.4	11.6
6	22	6.9 ± 0.4	34.0	64.7	27.0	37.0	36.0	85.0	15.0
9	18	7.2 ± 0.4	60.0	37.7	14.0	72.0	14.0	67.0	33.0
12	18	7.9 ± 0.6	52.0	46.0	11.0	67.0	22.0	43.0	57.0
LL regimen									
3	30	6.7 ± 0.5	46.7	52.8	24.0	40.0	36.0	67.6[1]	32.4[1]
6	30	9.2 ± 0.8	54.5[1]	43.7	0	17.0	83.0[3]	20.0[3]	80.0[3]
9	27	5.6 ± 0.4	50.0	50.0	0	100	0	7.2	92.8
12	26	6.7 ± 0.5	42.4	54.6	0	50.0	50.0[1]	4.0[3]	96.0[2]

[1]$p < 0.05$ compared with corresponding LD group using Fischer's exact test.–[2]$p < 0.002$ compared with corresponding LD group using Fischer's exact test.–[3]$p < 0.001$ compared with corresponding LD group using Fischer's exact test.

TABLE IV – PARAMETERS OF LIFE SPAN IN FEMALE CBA MICE EXPOSED TO DIFFERENT LIGHT/DARK REGIMENS[1]

Parameters	Light/dark regimen	
	LD	LL
Number of mice	50	50
Mean life span, days (mean ± SE)	665 ± 45.3	694 ± 34.3
Median	713	741
Mean life span of last 10% of survivors	1020 ± 4.5	965 ± 1.8[3]
Maximum life span	1036	971
α (days-1)[1]	3.42 (3.37–3.46)	5.42 (5.36–5.47)[4]
MRDT, days[2]	203 (200.2–205.5)	128 (126.7–129.3)[4]

[1]Constant α in the Gompertz equation: $R = R_0 (\exp) \alpha t$, where R_0 = mortality at t = 0–[2]MRDT, mortality rate doubling time, days. 95% confidence limits are given in parentheses.–[3]$p < 0.001$ compared with LD group using Student's *t*-test.–[4]$p < 0.05$ compared with LD group using Cox's method.

TABLE V – TUMOR INCIDENCE, LOCALIZATION AND TYPE IN FEMALE CBA MICE EXPOSED TO DIFFERENT LIGHT/DARK REGIMENS

Parameters	Light/dark regimen	
	LD	LL
Number of mice	50	50
The time of the 1st tumor detection, days	610	312
Mean life span of tumor-bearing animals, days	700 ± 39.4	699 ± 48.9
Tumor-bearing mice, *n* (%)	4 (10)	15 (35)[1]
Total tumors, *n*	5	22
Malignant tumors, *n*	3	19
Tumor, incidence, localization and type		
Lungs		
Adenoma	1	1
Adenocarcinoma	1	7[2]
Liver		
Hemangioma	—	1
Hepatocellular carcinoma	—	4
Malingnant lymphoma/leukemia	—	6[3]
Mammary gland, adenocarcinoma	1	2[4]
Soft tissues, histiocytic fibrous sarcoma	1	—
Skin, basalioma	1	
Forestomach, papilloma	—	1

[1]$p < 0.001$ compared with LD group using Fischer's exact test.–[2]$p < 0.05$ compared with LD group using Fischer's exact test.–[3]$p < 0.02$ compared with LD group using Fischer's exact test.–[4]One mouse had a metastasis into the lungs.

971 days. At this age 30% of mice in the LD group were alive. The last died 2 months later.

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 every 24 hr.[7,8] When introduced during the dark phase, bright light inhibits melatonin production.[7,8]

Artificially increasing the length of light phase of day (by 2–4 hr) was followed by increases in the duration of estrous cycle and in some cases to disturbances. If the light is on 24 hr/day the majority of female mice and rats in a short period showed a persistent estrus syndrome. In physiological circumstances, this

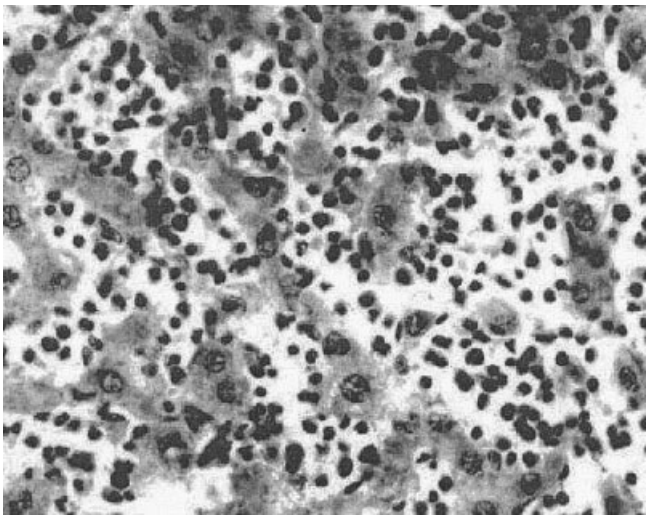

FIGURE 1 – Lympholeukemia in CBA mice exposed to constant light regimen. There is a significant lymphatic infiltration of liver (H&E, ×320).

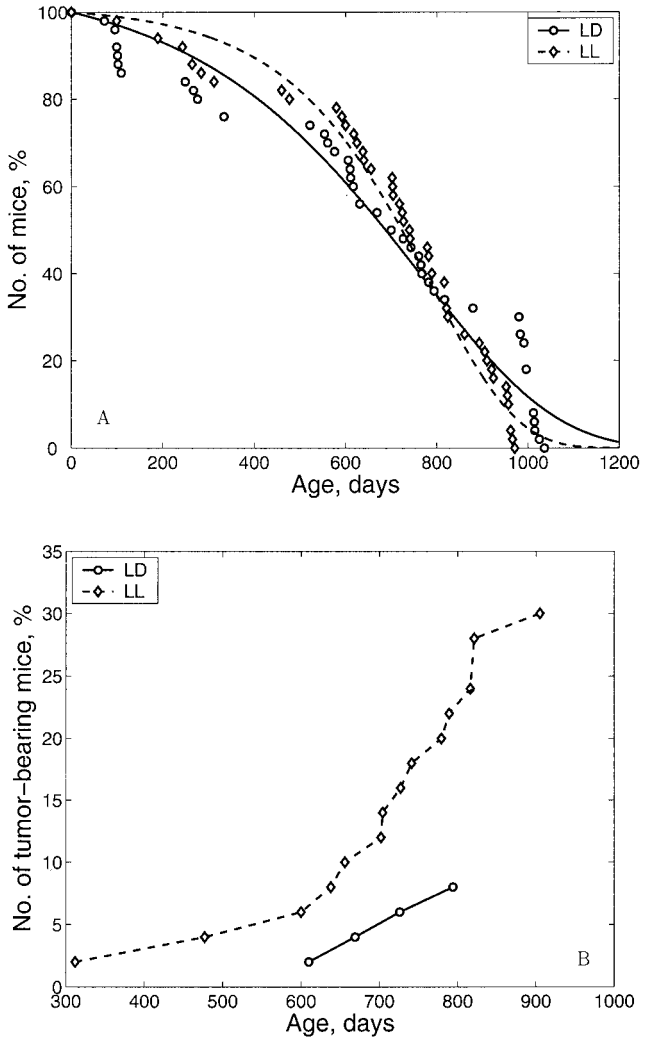

FIGURE 2 – Effect of the exposure to the constant illumination (LL) on survival and tumorigenesis in female CBA mice. Abscissa, age, days. (*a*) Survival. Ordinate, number of mice, %. The difference in the survival of mice kept at the LD and the LL regimen was significant ($p < 0.05$) at the age of 900–1050 days. (*b*) Age-dependent tumor rate curves. Ordinate, number of tumor-bearing mice, %.

syndrome naturally develops at some age (in rats, usually between 15th and 18th months) and precedes anestrus,[26] 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 *corpora lutea* are absent.[1,2,26] Instead of cyclic production of gonadotropins, prolactin, estrogens and progesterone characteristic for the normal reproductive period of life, their production was acyclic with hyperplastic processes in mammary gland, ovaries and uterus.[1,2,26,27] Decrease in glucose tolerance and of sensitivity to insulin have been observed in rats with persistent-estrus.[2] We have found that exposure to the LL regimen leads to increases in the threshold of sensitivity of the hypothalamus to feedback inhibition by estrogens in female rats.[28] This is crucial in the aging of reproductive system in female rats as well as in women.[28–30] Disturbances in estrous function developed earlier in CBA mice from the LL group.

Exposure to the LL regimen promoted spontaneous mammary carcinogenesis in female C3H and transgenic HER-2/neu FVB/N mice[31,32] and mammary carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) or *N*-nitrosomethylurea (NMU) in female rats.[2–6,33] Exposure to the LL regimen accelerated spontaneous uterine carcinogenesis in BDII rats.[14] In our experiments constant light illumination promoted development of spontaneous hepatocarcinomas, lymphomas/leukemias and lung adenocarcinomas. Blask *et al.*[33] reported that when male rats bearing tissue-isolated hepatoma 7288CTC and ER+ adenocarcinoma of the liver were exposed to constant bright light during the dark phase of 12L:12D photoperiod, the latency to onset was significantly reduced whereas the growth of tumors was markedly increased over a 4-week period as compared to control tumors in the LD group. There is evidence of the promoting effect of the LL regimen on DENA-induced hepatocarcinogenesis in rats.[15] On the other hand, treatment with melatonin inhibited the growth of mouse hepatoma cell line HEPA 1-6,[34] inhibited cellular proliferation, doubled mean life-time and increased survival of rats inoculated with hepatoma AH 130[35] and inhibited induction of preneoplastic liver lesions in rats exposed to DENA.[36] A low serum melatonin level was observed in hepatic porphyria patients with hepatocellular carcinoma.[37]

Spontaneous malignant tumors of liver, lung and hematopoietic tissues are common in male CBA mice,[38] whereas lung adenomas, ovarian hemangiomas and low incidence of mammary carcinomas are typical for female CBA.[38,39] Disturbances in estrous function due to constant illumination can be a key factor in development of liver tumors in female CBA mice. An increased production of aromatized (nonclassic) phenol steroids was found in ovaries of rats exposed to the LL regimen.[40,41] The persistent estrus syndrome induced by orthotopic ovarian transplantation after ovariectomy or X-ray irradiation was characterized by similar changes in ovarian steroidogenesis and masculinization in female rats.[26,30]

We failed to find any references to the effect of the LL regimen on hematopoietic tissue and lung tumor development. There is evidence of the oncostatic effect of melatonin on mammary tumor growth *in vitro* and *in vivo* experiments.[2–6,18,33,42] There are data on the inhibitory effect of melatonin on DMBA-induced cervicovaginal carcinogenesis in mice[43] and 1,2-dimethylhydrazine-induced colon carcinogenesis in rats.[44,45]

Mechanisms of the inhibitory effect of melatonin on carcinogenesis include a variety of possibilities, discussed in several comprehensive reviews and include antioxidant and antiproliferative effects, increase in apoptosis and inhibitory effect on telomerase activity in tumor cells *in vivo* and *in vitro*, antiestrogenic effects, decreased IGF-1 and insulin levels, *etc*.[2,3,46–49]

In conclusion, the data in our study demonstrates that exposure to light-at-night may have an important role in the development of not only mammary tumors but also a wide spectrum of tumors of different localization.

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