Light, Endocrine Systems and Cancer

–

A Meeting Report

Vladimir N. Anisimov[1], Johnni Hansen[2]

1. Department of Carcinogenesis and Oncogerontology, N.N. Petrov Research Institute of Oncology, Pesochny-2, St. Petersburg, 197758, Russia, E-mail: aging@ mail.ru
2. Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen, Denmark, E-mail: johnni@cancer.dk

The International Symposium “Light, Endocrine Systems and Cancer” was held on May 2-3 at Cologne University, Germany. The symposium was organized by Professor Claus Piekarski and Dr. Thomas C. Erren, Institute and Polyclinic for Occupational and Social Medicine. The main goal of the symposium was to evaluate the epidemiological and experimental data on the effect of the exposure to light-at-night on cancer risk and to indicate the main directions of future research in the field. The symposium covered also the mechanisms and epidemiology of skin cancer which, however, are not included in the present summary.

The alternation of the day and night circadian cycle is a very important regulator of a wide variety of physiological rhythms in living organisms, including humans. Due to the introduction of electricity and artificial light about hundred years ago the pattern and duration of human exposure to light has changed dramatically, and thus light-at-night has become an increasing and essential part of modern lifestyle. Light exposure at night seems associated with a number of serious behavioral as well as health problems, including cancer. The meeting gave unique possibilities to discuss the available data on this issue and to evaluate the strength of evidence for carcinogenic risks arising from epidemiological studies, experimental animal data, etc..

In the opening lecture of Professor Russel J. Reiter (University of Texas Health Science Center, San Antonio, U.S.A.) “Excessive light exposure: Endocrine influences particularly as they relate to cancer initiation and progression” it was stressed that oxygen and light regimen are two of the main regulators of physiological functions of the organisms living on the Earth. Circadian organization of these functions have over eons basically been a function of the rising and setting of the sun. The suprachiasmatic nucleus of the hypothalamus and the pineal gland are key structures maintaining the circadian rhythms in the body. The particular role in this process belongs to the pineal indole hormon melatonin. Being lipid and water soluble, melatonin reaches each organ and each cell which reads the melatonin signal, i.e., that it has become night. Melatonin is a very potent endogeneous protector of DNA from damage and has a high capacity

for scavenging oxygen and nitrogen-based reactants which are capable to damage DNA and thereby potentially initiate cancer development. Since the pineal production and release of melatonin normally vary inversely with the intensity of light on the retina, the antioxidant activity of the serum is maximal at the night time and minimal during the light phase of the day. Light pollution at night reduces melatonin synthesis and secretion and hence increases the rate of oxidative damage and, possibly, cancer. Melatonin reduces DNA damage, inhibits growth of some tumors, reduces degree of malignancy, lowers toxicity of cancer chemotherapy and improves wellbeing of cancer patients. In conclusion, R.J. Reiter stressed that the integrity of the daily dark period should be maintaned to reduce light inhibition of melatonin synthesis.

The very important background data on the physics of light and sunlight was presented in the lecture of Professor Sidney Perkowitz (Emory University, Atlanta, U.S.A.). He stressed that the light is the oldest thing in the universe which gave birth to matter and now light sustaines life and sets its rythms. On the other hand light can, especially in the short wavelengths (blue to white), break chemical bindings, and thus disturb biological processes and life. Artificial light is a growing part of our night environment and the light pollution is the reality today in the majority of the world perhaps except in certain areas in Africa. The very impressive pictures of Los Angeles at night in 1908 and in 1988 demonstrated clearly the expansion of light polution.

Professor George C. Brainard (Thomas Jefferson University, Philadelphia, U.S.A.) presented an excellent lecture on ocular input for human melatonin regulation. It was initially believed that light of at least 2500 lux was needed to reguate melatonin secretion from the human pineal gland. Carefully designed studies have shown, however, that illumination as low as 1.3 lux of monochromatic blue light at 460 nm or 100 lux of broadband white light can significantly suppress melatonin production in humans. A white light illumination of 119 lux or lower can phase shift the human melatonin rhythm. Light exposure can induce acute suppression of nocturnal melatonin, entrain daily melatonin rythm and adjust melatonin secretion duration. It is both from a scientific and a clinical view important to understand the meaning of how so

relatively small illuminances can regulate melatonin production in humans. Physiological studies on the transduction of light stimuli from eyes to suprachiasmatic nucleus and to pineal gland seem thus important for understanding the role of light in the development of pathology in humans exposed to light pollution.

A comprehensive report on the role of light in regulation of biological rhythms was given by Professor Alexander Lerchl (International University Bremen, Germany). He stressed that in mammals, including human, the most important 'zeitgeber' for endogenous rhythms is the environmental light/dark cycle. Examples of season effects on bith rate, mortality and longevity have been observed, but are not clearly understood. There are two main hypotheses on the origin of circadian rhythms during evolution: 1) an escape from light, and 2) a coordiantion of biochemical processes in the organism. It seems important that light intensity for entrainment needs to be more intense than for visual function. The speaker reviewed contemporary data on physiological mechanisms of photoreception and focussed attention on a new type of retinal photoreceptors, melanopsin, located in ganglion cells, which may be responsible for entraining the suprachisamatic nucleus, and seems to be the major regulator for malatonin and thereby the circadian rythms.

In his second lecture "Light, melatonin and aging", Professor Russel J. Reiter presented his own and literature data related to the role of melatonin as a potent endogenous antiaging substance. The free radical theory of aging proposed by D. Harman in 1956, is at present one of the most fruitful and developing theories of aging. Humans, as well as rodents and other animals, have a relative balance of reactive oxygen species (ROS) formation and efficacy of an antioxidative defence system in the organism. Total antioxidant activity of serum in humans is maximal at night time and minimal at day time in humans and correlated with the rhythm of melatonin production. But production of melatonin decreases with age which leads to the decrease in diurnal rhythm and amplitude of total antioxidative activity in the serum. This phenomenon alongside with age-related increases in ROS formation, the decrease in efficacy of

antioxidant systems and the decrease in DNA repair fidelity can be a cause of age-related oxidative damage of DNA. Melatonin as a most potent scavenger of free radicals, mainly hydoxyl radicals (?OH) and thus protects the organism from ROS-induced damages. R. Reiter stressed that light exposure during the normal dark period inhibits melatonin production and the loss of this antioxidant may be consequential free radical-mediated, age-associated diseases, including neurodegenerative disesases and cancer.

Professor Vladimir N. Anisimov (N.N. Petrov Research Institute of Oncology, St. Petersburg, Russia) presented a review on the role of light-dark regimen and cancer development based mainly on experimental studies from his and other laboratories. Light-at-night inhibits melatonin synthesis and secretion, increases the synthesis and secretion of prolactin, decreases hypothalamic threshold sensitivity to feedback inhibition by estrogens and glucocorticoids (one of the leading mechanisms of age-related switching-off of reproductive function and age-related decrease of the resistance to stress), induces an anovulation and ovarian follicular cysts, stimulates the arteriosclerosis and shortens the life span. These disturbances can lead to promotion of spontaneous and chemically induced carcinogenesis in rodents. Thus, the constant light exposure induces persistent estrus syndrome, ovarian cysts, mastopathy, mammary, ovarian and uterine tumors in outbreed rats; promotes spontaneous mammary carcinogenesis in C3H mice and spontaneous endometrial carcinogenesis in BDII/Han rats; promotes 7,12-dimethylbenz[a]anthracene (DMBA)-induced and N-nitrosomethylurea (NMU)-induced mammary carcinogenesis in rats; promotes N-nitrosodiethylamine-induced hepatocarcinogenesis in rats and the growth of transplantable hepatoma in rats; N-nitrosoethylurea (NEU)-induced transplacental carcinogenesis in rats. In contrast, light deprivation inhibits DMBA-induced mammary carcinogenesis in rats; the growth of transplanted RMK-1 mammary carcinoma in rats; NMU-induced mammary carcinogenesis and NEU-induced transplacental carcinogenesis in rats. The recent results on the effect of light regimens on the estrus function development of mammary tumors in inbred CBA and HER2/neu transgenic mice were also discussed. It was

shown that the exposure to light-at-night promotes mammary carcinogenesis in transgenic HER-2/neu mice, whereas the treatment with melatonin given with drinking water at night time inhibited the effect of the light exposure and down-regulated the expression of HER-2/neu mRNA in mammary tumors from HER-2/neu transgenic mice. In conclusion, effects were shown of melatonin on expression of a number of genes in mouse heart, mainly genes regulating cell cycle, adherence, membrane transport and mitochondrial genes.

Professor Günter Vollmer (Technical University Dresden, Germany) reported on endocrine modulation and the fragile balance of homeostasis. A contemporary view on the potential pathways leading to interference of environmental hormones with homeostasis and eventually resulting health effects was presented.

Dr. Christopher J. Portier (National Institute of Environmental Health Sciences, Research Triangle Park, NC, U.S.A.) gave with "Endocrine dismodulation and cancer" a critical analysis of methodological issues of the evaluation of cancer risks of hormones as well as some other agents, including light-at-night. Among new tools for research in these directions, the use of transgenic, knockout and mutant mice, study of gene-environmental interactions, microarray technology and computer modeling, in-life imaging could be very important for understanding the mechanisms of carcinogenesis induced by environmental factors. The need for stronger evidence of influence of small intensity factors on cancer development was stressed.

In the lecture of David E. Blask (Bassett Research Institute, Cooperstown, U.S.A.), R.T. Dauchi, L. A.Sauer, J.A. Krause and G. C.Brainard "Light during darkness, melatonin suppression and cancer progression" results were presented on the biochemical and molecular inhibitory effects of melatonin on the growth of tumors in vitro (MCF-7 model) and in vivo (transplantable rat hepatoma 7288CTC and NMU-induced rat mammary cancer). An important role has been established of receptor-mediated suppression of tumor cAMP production which leads to a suppression of the tumor uptake of linoleic acid and subsequently blocks the production of 13-hydroxyoctadecadienoic acid (13-HODE). The exposure to light-at-night seems

to reduce the latency time and to increase the tumor growth rate. These findings provide the definitive experimental evidence that light-at-night increases the risk of cancer progression via elimination of the nocturnal melatonin signal and its suppression of tumor linoleic acid uptake and metabolism to 13-HODE.

Two lectures were given by Dr. Richard G. Stevens (University of Connecticut, Farmington, USA) – "Epidemiological studies of light and breast cancer" and "Novel mechanistic research". During a reltively short recent time span human exposure to light regarding instensity, timing, spectrum and duration has changed dramatically due to the introduction of electrical light and the built environment. It is, however, difficult on an epidemiological basis to measure potential health effects on humans accurately, e.g. the size of breast cancer risk as predicted from the "melatonin hypothesis". This is especially due to the fact that in epidemiological studies an appropriate (unexposed) comparison group is necessary in order to estimate risks precisely. In defiance of predictable limitations three independent studies on night and shift workers from Denmark and the United States have recently been published based on the hypothesis that such workers are exposed to more light during the night than other people, why their diurnal melatonin production may be lower, and thereby the risk of the estrogen sensitive tumors such as breast cancer may be increased. The results from all three studies were quite similar pointing to an increased breast cancer risk among long-term night and shift workers after adjustment for known risk factors for breast cancer. Studies from the United States, Sweden, Finland and Norway on blind women, who to a different extent are not prone to light exposure via retina, have shown a decreased risk of breast cancer in the range of 20-40%. Therefore, if this observation is caused biologically by the absence of light at night, such exposure may be responsible for a high proportion of the breast cancers and possibly other cancers in the industrialized world. Finally, it was suggested, in order to expand the epidemiological evidence for the "melatonin-hypothesis", to study potential circadian disrupting cancers among larger groups who live without electricity, e.g. among the Amish people.

In the second lecture “Novel mechanistic research” Dr. Stevens discussed possible mechanisms involved in breast cancer development related to the light-at-night conditions. He stressed the role of environmental input, in particular, photo transduction to entrain the circadian clock, and molecular input, in particular, clock genes in feedback regulation of circadian rhythms. It was shown, that the inhibitory effect of light on melatonin inversely depends on the wave length. Alcohol consumption can promote breast cancer by increasing the level of serum estradiol and decreasing melatonin level. Diet enriched with polyunsaturated fatty acids increases the level of estradiol that also promotes breast cancer. These factors together with light-at-night can play an important role in the increased breast cancer rates in industrialized countries. One of the problems needed to be solved is an exposure to light-at-night or alcohol during the pregnancy since such exposures may increase the occurence of mammary tumors in the female offspring.

In the final lecture ”Does light cause internal cancers? – The problem and challenge of an ubiquitous exposure” by Dr. Thomas C. Erren (University of Cologne, Germany) the focus was particularily on a third avenue of giving epidemiological evidence for the “melatonin hypothesis”, i.e. the risk of hormone dependent cancers among residents in the Arctic with extended winter darkness periods and thereby, as measured in several investigations, an increase in the yearly average melatonin level. So far, ecological studies on residents from the Arctic have, despite the built in limitations, observed a uniformly low risk of hormone- dependent cancers which may not be explained from (unmeasured) confounders. However, epidemiological studies with more detailed individual information on exposure to light are needed in order to confirm this association.

In conclusion, Dr. Charles Poole (University of North Caroline, Chapel Hill, NC, USA) made an overview of the main issues of the symposium. He concluded that here seems to be a tendency of a consensus that ligh-at-night may increase the risk of certain cancers, whereas light deprivation may decrease the risk, but, at the same time “more research is needed” for understanding the mechanisms of the effects observed both in humans and in rodents. It was

noticed that light/dark regimen may also influence carcinogenesis in other organs than the female breast, and it seems clear that not all effects of light–at-night and light deprivation are mediated by melatonin only. The generation of testable inter-diciplinary hypotheses could be important in promoting our understanding of the interrelation between light-at-night exposure and cancer. Finally, attributable risks for realistic interventions may be taken into considerations.

During the Symposium the participants had a possibility to discuss a number of poster presentations. H.C. Roemer and B. Griefahn (Dortmund, Germany) have shown that bright light inhibited melatonin synthesis completely in any of young healthy volonteers and delayed the nadirs of rectal temperature and of heart rate. It was further found that melatonin synthesis increased after light exposure to reach a significant higher maximum, thus revealing a rebound. E. Peschke *et al.* (Halle, Germany) have shown the increased susceptibility to insulin under the influence of melatonin. M.F. Borisenkov (Syktivkar, Russia) has found a non-linear negative correlation between estrogen and progesterone receptor levels in some of breast cancer tissues obtained from patients subjected to surgery in the spring and the fall that may indicate transient dysregulation of sex hormone receptors biosynthesis and/or gene expression in breast cancer tissues at that time of year. The changes in sex hormone receptor gene expression in the spring and fall may be stimulated by external factors (such as light regimen and/or electromagnetic fields) through the changes in melatonin production. In the poster of D. S. Beniashvili (Holon, Israel) *et al.* it was shown that exposure to constant light during pregnancy and lactation potentiates the realisation of the transplacental carcinogenesis induced by NEU in rats whereas the exposure to contant darkness inhibits it. C. Bartsch (Tubingen, Germany) presented data on the susceptibility to melatonin in earlier and later passages of DMBA-induced mammary carcinomas.

Before closing the symposium, a round table discussion was performed. A common opinion was that this issue on light, endocrine systems and cancer needs an international collaboration with involvement of specialists both in epidemiology and basic research from countries with different level of light pollution and geographically located not only on the North but in different latitude zones.