

GUEST EDITORIAL – SUMMARY EVALUATION

## Light, endocrine systems, and cancer – A view from circadian biologists

Till Roenneberg<sup>1</sup> & Robert J. Lucas<sup>2</sup>

1. Centre for Chronobiology, Institute for Medical Psychology, Munich, Germany.
2. Centre for Chronobiology, Division of Neuroscience and Psychological Medicine, Faculty of Medicine, Imperial College London W6 8RF, UK.

*Correspondence to:* Dr. Till Roenneberg  
Centre for Chronobiology  
Institute for Medical Psychology,  
Goethestr. 31  
D-80336 München, GERMANY.  
E-MAIL: till.roenneberg@imp.med.uni-muenchen.de

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A multidisciplinary panel of scientists got together in Cologne to discuss the relationships between light, the endocrine system, and cancer. The basis for this discussion is grounded as follows.

- (1) There is evidence from human epidemiology and animal experiments that alterations in the normal diurnal light:dark cycle are associated with increased risk of cancer.
- (2) The production of melatonin is controlled by light.
- (3) Melatonin has the potential to modulate cancer rates, both by acting as a free-radical scavenger and through activation of melatonin receptors on tumor cells.

Based on these three facts, melatonin levels have been postulated to affect cancer rates (the melatonin hypothesis). Specifically, light at night (LAN) is hypothesised to increase cancer rates via an inhibition of pineal melatonin production. What is the experimental evidence that there is a direct causal link?

There is no doubt that LAN is a feature of modern society. The most important question is, therefore, whether this factor is detrimental to our health in general and, more specifically, whether it is a risk factor for cancer. Superficially straight-

forward, this question is enormously difficult to answer and has to be addressed both epidemiologically and experimentally. To scrutinise the effects of nocturnal light on the endocrine system, systematic measurements must establish the exact quantity and quality of LAN and its variation over different more or less industrialised communities. There are surely non-trivial technical difficulties inherent in such an assessment, but in view of verifying/falsifying the melatonin hypothesis, these difficulties must be overcome. These light measures will need to be related to detailed examinations of the quantity and quality of light required to suppress melatonin under field conditions. An important challenge is the question of adaptation. Most experiments that show suppression of melatonin levels by acute light are performed with dark adapted subjects. The question remains how effective LAN is in the context of the light history of the preceding day. Is a bedside light of 100 lux capable of suppressing melatonin when a subject has spent the last 8 hours exposed to 20,000 lux or more?

Epidemiology has examined the association between LAN and a variety of cancers (especially breast cancer). The great difficulty in establishing the proposed causality lies in identifying the appropriate control groups. It will be difficult, for example, to find comparable groups of subjects/patients

who have a similar lifestyle but do not experience LAN. For this reason, several other group comparisons have been made: for example, between those who work shifts (more LAN?) and those who don't (less LAN?), or between blind (no LAN?) and sighted people (more LAN?).

There are severe complications inherent in these group comparisons because they all differ in the quality of entraining the circadian clock, a fundamental system responsible for optimal temporal coordination of physiology. Light at night, in most cases, goes together with dim light during the day. The invention of electrical light, and electricity in general, has not only enabled us to read and work into the small hours of the day, it has also created infinite possibilities to constantly work indoors. Modern workers suffer from a greatly reduced zeitgeber strength (the amplitude of the light:dark-cycle which entrains the circadian system). As a consequence, the biological clocks of office workers will be entrained differently than those of farmers. In the case of shift workers, entrainment of the circadian system is even worse. While the central clock in the suprachiasmatic nucleus of the brain does not adjust to the (night-)shifted activity, the clock in the liver might. The reason for this lies in the fact that shift workers tend to expose themselves to more light during the normal day time than those who do not work shifts. While the latter spend all day inside, the former have the opportunity to spend more of their free time outside in broad daylight. In addition, the clock in the liver can be entrained by the food which shift workers will consume during their nightly work hours.

Electrified society is an enormous challenge for circadian coordination and internal synchrony of different parts of our body. Weak entrainment and internal desynchrony may, thus, create numerous reasons for increased cancer rates that would be reflected in epidemiological studies quite apart from any effect of melatonin suppression. Another challenge for the melatonin hypothesis is to distinguish between the specific effect of light on melatonin production and its effects on other aspects of physiology. Quite apart from the retinal projection to the suprachiasmatic nuclei (through which circadian entrainment and melatonin suppression are thought to be affected), direct connections to other parts of the hypothalamus have also been described. These are thought to provide photic regulation of a variety of behavioural and physiological parameters distinct from effects on the pineal. Thus, detrimental effects of LAN may be a result of circadian disruption, melatonin suppression and/or the regulation of other physiological parameters.

In fact, the relationship between light and melatonin levels is not straightforward due to the additional regulation of the pineal by the circadian clock. When animals are kept in constant darkness, melatonin production continues to be rhythmic with a period of about one day due to the endogenous rhythm produced by the circadian clock in the suprachiasmatic nucleus. Under these constant conditions, melatonin is produced at the beginning of the "subjective" night, reaches a peak around subjective midnight and declines to baseline levels around subjective morning. Melatonin levels are also decreased by

acute light exposure. In the early night, light can prevent, or rather delay its production, while, in the second half of the night, light irreversibly decreases melatonin levels. Thus, clock-controlled melatonin production is restricted to the night and can be rapidly inhibited by exposure to light. As a false condensation of these kinetics, melatonin is often referred to as an internal representation of darkness. In fact, because clock-controlled melatonin production is limited only to a portion of the circadian cycle, and cannot acutely be induced by darkness at other phases, the presence of melatonin is a rather limited indication of darkness.

Many experimental approaches to test the relationship between light and cancer in nocturnal animals, concentrate on constant light conditions. Yet, it is uncontroversial that nocturnal laboratory rodents do not thrive under these conditions. In addition, constant light is very disruptive to circadian rhythms, most mice strains become arrhythmic under these conditions. Again, it is impossible to distinguish the effects of circadian disruption, melatonin suppression and other effects of LAN. Finally, great caution has to be taken when the physiology and behaviour of nocturnal rodents are being compared to those of day active creatures like humans.

The Mel-LAN hypothesis is strengthened by the fact that administered melatonin (though at much higher dosage than physiologically measured) appears to counteract the progression of cancerous growth. The mechanisms underlying these effects remain to be fully elucidated. One possibility is that they rely on the radical-scavenging capacity of the indolamine. Yet, many tissues possess specific melatonin receptors and, as yet, little is known about the role of melatonin as a hormone. Melatonin receptors are G protein-coupled receptors (GPCRs) that are widespread, in particular in many tumours (see excellent contribution of David Blask to this conference). There appears to be good evidence that at least some of anti-tumor effects of melatonin arise from activation of these receptors. When organisms, tissues, or cells are exposed to millimolar concentrations of melatonin, many questions have to be answered about the effects eventually measured. These questions concern the pharmacokinetics of melatonin at this dosage, possible effects on many other anabolic and catabolic biochemical pathways, its role as a hormone versus a potential radical scavenger, and many more. Even in administering melatonin as a drug against cancer, the circadian question has to be considered, because the biological clock controls most biochemical pathways and enzymes, possibly including all the mechanisms of the cell that keep free radicals from damaging macromolecules. In summary, while the melatonin hypothesis has provided a useful framework for investigations in a fascinating field, the hypothesis as a whole and many of its components remain to be scrutinised extensively before a direct connection between light → melatonin → cancer rate can be concluded.