Editorial

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The double face of light effects: circadian adjustment or disruption

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Mammals are characterized by a temporal structure covering a broad frequency spectrum (infradian, circadian and ultradian) of biological rhythms which are present at all levels of organization, and are the object of multiple and highly complex interactions. Circadian rhythms with a periodicity ranging between 20 and 28 h are coordinated and regulated by an internal clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN generates circadian rhythms by means of a transcriptional-translational feedback loop. Circadian or clock genes, e.g. *clock*, *cry*, *per*, *Bmal1* comprise an autoregulatory transcriptional-translational feedback loop which demonstrates a cycle every 24 h. The period of the rhythms generated in the SCN is not precisely 24 h but close to 24.2 h. Therefore, the external synchronizers, with light as the major synchronizer in humans, allow for adjusting the daily 24-h cycle of the internal clock. The clock receives the light signal directly from the retina by way of the retinohypothalamic tract, then after several steps light signal reaches the pineal gland which produces melatonin, an hormone secreted almost exclusively at night.

Synchronization of biological rhythms is carried out through endogenous factors of genetic origin and by exogenous environmental factors called synchronizers or Zeitgebers, of a socio-ecological nature, such as the day-night alternation, the sleep-wake cycle, one's social life, etc. that entrain rhythms to 24 h. Clock desynchronization, also called disruption or misalignment, is therefore the expression of changes to the subject's normal synchronization, that is, the temporal dissociation of biological clock functioning from that of our watch (local time). Rhythm desynchronization occurs when synchronizers are altered under conditions in which the biological clock and the environment run counter to each other, such as during transmeridian flights (jet lag), night work and shift work where reversing or making major changes to the timing of our social life results in a dysfunctioning of the biological clock causing disorders known as shiftwork intolerance.

Light has different effects on the circadian system depending on its intensity, duration of exposure, spectral properties (the retinal photopigment melanopsin is sensitive to blue light, i.e. wavelengths of 460–480 nm) and time of exposure:morning light exposure advances (moves earlier) whereas evening light delays (moves later) the circadian system. This phenomenon is called a phase response curve (PRC) which represents the effects of the same stimulus (light) at different times of the day. As melatonin, a neurohormone produced by the pineal gland, has been shown to have oncostatic properties the decline in melatonin secretion by exposure to artificial light at night (ALAN) has therefore been put forward in some epidemiologic studies as a possible mechanism to explain the development of breast cancer in shift workers.

Shift work is defined as work outside the hours of about 7 a.m. to 6 p.m. It is a chronic situation with repeating conflicts with physical and social Zeitgebers that has been identified as a risk factor for breast and prostate cancers, diabetes, obesity, mood disorders. The main causes of these deleterious health effects is thought to be due to a complex combination of circadian disruption, chronic sleep loss, and long-term exposure to light at night resulting in the suppression of melatonin secretion. Exposure to ALAN results in a disruption of the circadian system, which is deleterious to health. About 20% of the working population in industrialized countries is engaged in shift work or night work which means that a large number of workers worldwide are exposed to unusual light-dark cycles which results in the most common type of misalignment that is misalignment of the sleep/wake cycle in relation to the biological night. Epidemiologic studies have pointed out an association between sustained night work and a 50%–100% higher incidence of breast cancer [1]. The potential and multifactorial mechanisms of the effects include the night time suppression of melatonin secretion by ALAN which results in an increase of estrogens, an important risk factor for breast cancer. Melatonin is also a potent antioxidant (as a free radical scavenger, and an activator of antioxidative enzymes), and may increase the capacity to repair DNA by affecting key genes involved in DNA damage response pathways. The role of this hormone in the epigenetic regulation of breast cancer cells through its antiestrogenic effects [interaction

with estrogen-receptor (ER)-α, aromatase and telomerase inhibition, effects on the cell cycle, and deregulation of *per2* which acts as a tumor suppressor gene] has also been raised [1, 2]. Interestingly, the paper by Zubidat and Haim published in this issue is a review on the association between ALAN and breast cancer with a focus on epigenetic modifications, i.e. DNA methylation and specific loci methylation in relation to cancer and obesity, and discuss the potential role of melatonin suppression and DNA methylation patterns as markers for early detection of metabolic disorders and breast cancer development [3].

The data in this area is sufficient enough such that in 2007 the International Agency for Research on Cancer (IARC) has classified shift work in group 2A of "probable carcinogens to humans" as "they involve a circadian disorganization". Though further studies are required to pinpoint the role of shift work in these disorders, the overall consensus, however, is that there is likely to be a negative impact of chronic circadian misalignment and sleep loss on health but more experimental data are needed to ascertain the causality for these effects. Well-controlled studies with more detailed aspects are needed to ascertain the relationship between exposure to light at night and the risk of cancer and to identify the underlying mechanisms. For that, it is essential to include in any study several parameters such as, and not exhaustively; the length of the shift, its direction, the number of nights worked per month and per year, the speed of rotation, the regularity or irregularity of the shift, among many other parameters [1]. The exposure threshold also remains to be clarified. Given the large number of night workers in the world, preventing the circadian disruption caused by light at night and its potential effects on health might become an important matter of public health.

Further research is needed to understand the mechanisms that contribute to the development of circadian misalignment, the links between misalignment to disease development and finally the role of taking care of the circadian time structure to alleviate the deleterious effects of ALAN and improve shift workers' conditions.

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