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Photoresponsive properties of the retinohypothalamic tract

망막-시상하부 경로의 광반응 특성

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Abstract : Light is a synchronizing stimulus to regulate the circadian rhythms and neuroendocrine activities in both humans and animals. The retinohypothalamic tract is involved in the day/night cycle and neuroendocrine activities. In particular, melatonin secretion has been known to be affected by light and correlated with many aspects of health problems. This review introduces the role of the light in the biological rhythm and neuroendocrine activities, its relationship with health problems, and the characteristics of retinohypothalamic tract.

Key words : Light, biological rhythm, suprachiasmatic nucleus, paraventricular nucleus

요약 : 빛은 인간과 동물에서 일주 리듬과 신경내분비 활동을 조절하는 자극이다. 망막-시상하부 경로는 주/야 주기와 신경내분비 활동에 관여한다. 특히 멜라토닌 분비는 빛에 의해 영향을 받으며, 다양한 측면의 건강 문제와 관련이 있다는 것이 알려져 왔다. 본 논문은 생물학적 리듬과 신경내분비 활동에 있어서 빛이 수행하는 역할과, 빛과 건강 문제와의 관련성, 망막-시상하부 경로의 특성을 소개하고자 한다.

주제어 : 빛, 생물학적 리듬, 시교차상핵, 실방핵

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1. Introduction

Light can reset the biological clock and synchronize it within the environment. The clock affects various aspects of body function and synchronizes the body homeostasis into the daily rhythm. Light is the crucial stimulus in regulating circadian rhythms and neuroendocrine activities in human[22, 56]. In this review, we would like to introduce the role of light in the biological rhythm and neuroendocrine activities, its relationship with general health problems, and the characteristics of retinohypothalamic tract.

2. Circadian Rhythm

Light is known as a predominant stimulus in maintaining the circadian rhythm in humans as well as animals. The endogenous clock in the the suprachiasmatic nucleus(SCN) plays a central role in circadian timing system[34].

Melatonin is released much more during the night than during the day[3, 40]. Exposure to light can acutely suppress melatonin secretion in the pineal gland[25, 28]. Even a little hit of light during night may change the normal circadian rhythms and suppress nocturnal melatonin release in the pineal gland[12, 41]. Suppression of nocturnal melatonin secretion is affected by light in a dose-dependent manner: the brighter the photic stimulus, the greater the suppression of nocturnal melatonin secretion[7].

The SCN is known to be one of the most important physiologic determinants of alertness and performance, and it drives a circadian pacemaker in mammals, with an intrinsic period of 24 hours in average. Brainard et al.[6] constructed the action spectrum from human subjects and identified 446-477 nm as the most potent region of wavelength that provides circadian input to regulate melatonin secretion.

3. Circadian Rhythms and Health

3.1 Illumination and daily life

Too much light can disrupt or reset this pacemaker, which results in changes in melatonin rhythm. Light exposure at night may be related to a variety of behavioral changes and health problems.

Clinically, light therapy is proven to be effective in treating some affective disorders, sleep problems, circadian disruptions[15, 52]. Arvanitogiannis and Amir[2] found in rats that as few as five intense flashes can produce both phase shifts in free-running activity rhythms and Fos expression in the SCN. Therefore, daily function can be affected by light, which may be useful as one of effective therapeutics tools in treating disrupted biological rhythms associated with the day-night cycle.

3.2 Light at night and oncogenesis

Oncogenesis has been known to be correlated with the disruption of light-dark cycle. For example, Davis et al.[14] observed that the risk of breast cancer was increased among subjects sleep disturbance at night in which nocturnal melatonin level is typically highest, suggesting that indicators of exposure to light at night may be associated with the risk of developing breast cancer. There observed increased risk of among subjects living in the brightest bedrooms[14].

Stevens[47] has also proposed that work schedule with shift may increase the risk of breast cancer. The chance of breast cancer among women with a night shift is increased[20, 39, 54]. In addition, Hansen[20] and Tynes et al.[54] also reported that the risk can be increased depending on duration of the night job. Hahn[19] reported that the incidence of breast cancer may be reduced among women with profound bilateral blindness.

Similar phenomena were observed in experiments with animals. For example, Dauchy et al.[11] compared the effects of an alternating light:dark cycle(12L:12D), dim light(0.25lux) during the dark phase of a diurnal light cycle, and continuous light on growth and metabolism of fatty acid in hepatoma in rats 7288CTC. They observed dim light suppressed melatonin release by the pineal gland, increased uptake of tumor linoleic acid, and promoted growth of tumor as effectively as did the continuous light. In rats, exposure to constant light increases the incidence of mammary cancers[23] and pinealectomy increases the incidence of mammary cancers[24, 51].

The mechanisms involved in carcinogenesis by light exposure during the night may be directly related to melatonin release. Melatonin, “the hormone of the darkness,” has only recently gained substantial attention with regard to its potential oncostatic actions and its possible effect on breast cancer risk[4, 29].

Melatonin level in human serum decreases when people are exposed to light at night[25]. A reduced melatonin level might increases the likelihood of tumor [48]. An experimental evidence suggests that partial sleep deprivation during the time of peak melatonin release at night(1:30 AM) can result in an increased circulating estradiol concentration in the blood[5]. Light exposure during the night can shorten the length of menstrual cycle[26] and a shorter cycle are associated with an increased risk and a longer cycle with reduced breast cancer risk [21].

In addition, the dietary and other environmental factors influence cancer growth. Dietary linoleic acid and its lipoxygenase metabolite 13-hydroxyoctadecadienoic acid (13-HODE) stimulate the growth of a variety of tumors[43]. A typical lifestyle in developed countries shows that consumption of a high fat diet [8] and prolonged exposure to artificial light during the night[49] increase. Dauchy et al.[11] suggested that the overconsumption of diets high in linoleic acid, coupled with light-at-night suppression of melatonin, may create a new risk factor for the progression of cancer. However, exposure to others than light at night such as stress have played a role in hormonal changes associated with in the development of breast cancer.

4. Involvement in Cortical Activation

The paraventricular nuclceus(PVN) of the hypothalamus receives inputs from the SCN and is reported to be responsible for the occurrence of yawning. Stereotyped yawning response can be evoked by chemical stimulation of the PVN[32, 46]. The PVN may also play an important role in triggering cortical activation[46]. Generally, the PVN is known to play a role in stress reaction[50]. Therefore, the PVN may also be involved in cortical activation associated with stress. In relation to this phenomena, light stimulation induces cortical activation and yawning in rats[45].

5. Neural Pathways Involved in Circadian Rhythms

5.1 Retinal receptors

To date, there has been no reports an whether or not the retinal photoreceptors transduce light stimuli for circadian regulation. According to the studies using rodents with retinal degeneration, neither the rods nor cones are used to play a role in suppression of light-induced melatonin, circadian phase shifts, or photoperiodic responses [16, 37, 55].

To determine this, Freedman et al.[17] examined the effects of light on the regulation of circadian wheel-running behavior in mice lacking these photoreceptors. Mice with rod cells only or with none of rod and cone cells showed unattenuated phase-shifting responses to light. Removal of the eyes abolished this behavior. Similarly, Lucas et al. [27] found that mice lacking both rod and cone cells showed normal suppression of pineal melatonin in response to monochromatic light of wavelength 509 nm. Thus, these studies suggest that neither rods nor cones are required for photoentrainment and pineal melatonin production, and the murine eye contains additional photoreceptors that regulate the circadian clock and melatonin release. At present, the photoreceptors responding to light to regulate circadian rhythms are uncharacterized and remains an addressed.

In humans, light-induced melatonin suppression have been observed in the blind[10]. This study suggests that melatonin regulation is controlled by photoreceptors that differ from the photoreceptors involved in ordinary vision.

Therefore, the identity of the photoreceptors that mediate the responsiveness of the circadian system of rodents to light is still uncertain. It has been suggested that either a cone opsin-based mechanism or rhodopsin may be involved in transmitting a photic signal to the circadian system. Provencio & Foster[38] and David-Gray et al. [13] suggested that at least one photoreceptor with cone-like characteristics may have been involved. Freedman et al. [17] and Lucas et al. [27] proposed that non-rod, non-cone photoreceptors may be involved in regulation of mammalian circadian behavior and pineal melatonin. However, Thiele & Meissl[53] demonstrated an input via both retinal rod and cone pathways to the pineal gland of mammals, suggesting that more than one photoreceptor may have been involved in this system.

5.2 Neural pathways

The clock involved in circadian rhythm is located in the SCN. The retinohypothalamic tract that mediates circadian regulation by light projects from the retina to the SCN[33]. The SCN receives light stimuli directly via this pathway. The SCN shows an endogenous circadian activity with peak firing rates found during the light phase[31, 57]. The SCN transmits the light information to the PVN.

PVN neurons project to the intermediolateral cell column of the spinal cord containing cell bodies that innervate the superior cervical ganglion. Postganglionic sympathetic axons of the superior cervical ganglion then ascend along the internal carotid artery to enter the nervi conarii to the pineal gland to produce melatonin[34].

5.3 Physiological properties of the retino-hypothalamic tract

As shown above, a light and dark cycle is perceived through the retinohypothalamic pathway and is accompanied by SCN neural activity and the rhythmic secretion of melatonin from the pineal gland. The SCN is a functionally and anatomically heterogeneous nucleus and differences within some SCN neurons can lead to divergent patterns of rhythmicity[44]. Perreau-Lenz et al.[35] suggested that the SCN uses a combination of inhibitory and stimulatory signals towards the PVN for the control of circadian rhythms. According to Perreau-Lenz et al.[35], during the light period, the SCN sustains both an inhibitory and a stimulatory input to the PVN simultaneously. Recently, Perreau-Lenz et al. [36] demonstrated that glutamate is an essential neurotransmitter used by the SCN to stimulate the PVN for the melatonin synthesis in the pineal gland, suggesting direct glutamatergic SCN inputs to the preautonomic neurons of the PVN.

Electrophysiological studies have shown that the SCN neurons are affected by retinal illumination [18] and respond to changes in both duration and intensity of illumination[30]. Recently, Aggelopoulos & Meissl[1] examined the responses of neurones in the SCN in rats to retinal illumination to identify the types of photoreceptor input these found that the action spectrum conformed to the sensitivity of rhodopsin, with maximal sensitivity at around 505 nm, that the action spectra conformed to the spectrum of green cone opsin, and that a main sensitivity peak at 510 nm and a significant secondary peak in the near-ultraviolet region of the spectrum. In this case, the most common response under scotopic conditions was an 'on-excitation.'

In contrast to SCN neurons, the characteristics of PVN neurons are relatively uncertain. To our knowledge, there are few studies that recorded neuronal activities in the PVN. Recently, we observed that activities of PVN neurons increased, in response to specific wavelength of monochromatic light stimulation in rats[9]. These suggest that the PVN can respond to light stimuli to control biological rhythms or autonomic functions.

6. Conclusions

Light is a synchronizing stimulus in regulating circadian rhythms and neuroendocrine activities in both humans and animals. The retinohypothalamic tract is involved in the day/night cycle and neuroendocrine activities including nocturnal melatonin secretion. However, the characteristics of the retinohypothalamic tract are not simple. For example, Saeb-Parsy & Dyball[42] demonstrated that different cell groups in the rat SCN have different day/night rhythms of single-unit activity in vivo. Therefore, further studies will be necessary to identify the characteristics of the retinohypothalamic tract.

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