

Functional Interdependency between Intestinal Microbiota and Biological Clock.

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Abstract

In the human body practically all organs work in coordination in co-operation with other organs since they are regulated by neurological, hormonal, environmental signals. Scientists have lately found out another regulatory factor the intestinal micro biota. The quality and the quantity of micro biota are also dependent on many internal and external factors. The composition of the intestinal micro biota also affects those systems which are regulated by circadian rhythms, in other words circadian rhythms and micro biota is a two-way street. In this review we have discussed cross talk between these two regulators.

Key words: sleep-wake cycle; genes; sexual dimorphism; metabolism; night shift workers; melatonin dependent cancers; micro biota

Introduction

Small deviation in our life style makes a big impact on health issues. The pineal and micro biota both are situated deep inside the body but are regulated by light [1, 2]. The pineal is a master regulator, produces melatonin in the absence of light. Serotonin is converted to melatonin in the pineal gland in the absence of light; this master regulator of the clock is light dependent. There is a close relationship between the pineal cycle and biological rhythms. The biological clock controls the timing of several activities and functions of the body, including when one goes to sleep and wakes up. This internal mechanism is rhythmic and cycles about every 24 hours. The biological clock controls the synchronization of several vital activities in our body including the gut micro biota.

Recent researches show that biological clock even influences the contents of the gut organisms (bacteria, fungi and other microorganisms)—commonly referred to as the micro biota inside human host [3]. These organisms play a vital role in maintaining our health. The bacteria in the micro biota help in digesting the food regulate the immune system, protect against other bacteria that cause disease, and produce vitamins including B vitamins B12, thiamine, riboflavin, and Vitamin K, which are essential for blood coagulation [4]. However if there is any imbalance between beneficial and pathogenic species it may become a causal factor for cancer development [5].

Circadian Rhythms and Micro biota: A Two-Way Street

The human microbiota appears to follow daily rhythms influenced by timing of eating and the types of foods consumed and to exert effects over circadian rhythms. Research has also found that the relationship between

these different biological rhythms works both ways. Scientists have discovered that disruptions of circadian rhythms also disrupts microbial rhythms and the health of the microbial ecosystem due to which people suffer metabolic imbalance, glucose intolerance, and weight gain [6]. It has also been suggested that gender may play some role in the relationship of gut microbial health, metabolism, and circadian function.

Functional cooperation between micro biota and biorhythms in:

A. Genes: Clock genes control the circadian rhythm [7]. Similarly, host genes influence and is influenced by the gut micro biota as shown in the recent studies [7, 8].

B. Sleep-wake cycle: When to sleep and when to wake up is control by light in all organisms. For example, diurnal animals wake up with the sun rise where as nocturnal animals rise when sunsets. Due to artificial light during night desynchronises the sleep-wake cycle, diurnal mammals have difficulty in sleeping, and the quality of sleep is also poor. Improper sleep interferes with daily activities which are controlled by circadian rhythms [9]. The sleep-wake cycle goes out of gear albeit, temporary may be due to external factors such as the sleep habits, job, and/or travel. However long term disorder in circadian rhythm can be caused by internal factors such as age, genetics, and/or medical conditions. These factors also control the production of key hormones in the endocrine glands. For example, the production of melatonin in pineal gland is controlled by light, which in turn controls sex cycle in females and males. Disruption of circadian rhythms, notably the circadian sleep-wake rhythm, increases Alzheimer's disease (AD) neuro pathological changes such as brain amyloid-beta accumulation [10]. Aging and low levels of

daytime light exposure leads to gradual attenuation and disruption of circadian rhythms. Both aging and circadian rhythm disruption increase the risk of AD, further disrupting of circadian rhythms.

Both human and animal models have shown the gender dependent generation of circadian rhythm and its potential consequences for health and resilience to changes in sleep pattern.

A study of chronotype, or day-night preference, in more than 53,000 individuals (diurnals) highlighted how age and sex both substantially affect the timing of circadian rhythms [5]. Whereas children are typically morning types regardless of sex, after puberty males tend to become more evening oriented than females, mirroring the findings in animal models. Chronotypes converge during middle age as both sexes become more morning oriented, however, the hormonal changes associated with menopause add extra complexity nevertheless, physiological readouts that will clarify the array of sexually dimorphic rhythms in humans [7].

It seems both the key regulators (pineal and micro biota) are in turn regulated by light. The photobiomodulation (PBM) can alter the ratio between beneficial and pathogenic gut micro biota. This operation that is (red and near infra red light) delivered to the abdomen in mice, is in a potentially beneficial way. The known effects of PMB on the micro biota and circadian rhythms as well other effects of light which are modulating activities of both the regulatory factors a new term "photobiomics" was introduced [11].

C. Sexual dimorphism: Physiologically, sexual dimorphism is a result of genetic and hormonal differences between females and males. Circulating estrogen and testosterone are also likely to affect the suprachiasmatic nucleus (SCN) of the brain in a different rhythmic fashion between the two genders this dimorphism is manifested in females at the behavioural level through higher-amplitude rhythms compared with that of males.

Circadian rhythms, or the body clock, confer temporal structure on human physiology to align homeostatic processes with anticipated changes in the environment. The few studies that do consider how these rhythms differ between sexes. Recent findings from both humans and animal models illustrate how the systems that generate circadian rhythms diverge between the sexes [12], which have potential consequences for health and resilience to changes in sleep pattern. This change in sleep pattern may influence the diversity, composition, and function of gut bacterial micro biota, although the results are inconsistent. Several studies

have reported that men have lower microbial diversity than women [13-16]. The change in gut micro biota composition and functions according to sex and menopausal status [17] has also been studied.

D. Metabolic health: Disrupted sleep and misaligned circadian rhythms have been strongly tied to higher rates of obesity and to metabolic disorders including Type 2 diabetes. Our emerging knowledge of the micro biota and its relationship with circadian function may in time deliver a deeper understanding of how health is influenced by sleep and circadian activity. Science has just begun to delve into the world of the micro biota and its relationship to sleep as well as health more broadly, a significant area of further research.

We are fully convinced that host metabolism is regulated by gut micro biota influenced by environment. Drastic life style changes as well as environmental shifts were observed to be the contributing factors for the pathogenesis of metabolic diseases though the underlying mechanism is still an enigma. It is anticipated that host immune system may play a role to provide homeostatic signals to maintain overall metabolic health [6].

E. Immune system: The immune system is indispensable for the life of the host as well as gut biotome and biorhythm coordinates to regulate the immune system. In turn, the function of the circadian clock, right density and right time of availability of the micro biota is needed for the development of immune system [18]. Perfect coordination is essential for the function of immune system both during steady-state and in response to infectious threats. The circadian clock is responsible for daily rhythms of immune cell functions, including timing of leukocyte trafficking and inflammatory signalling. This regulation aids in the coordination of effective inflammatory responses at times of increased environmental exposure to pathogens [19-21].

F. Shift workers: Short sleep duration is associated with metabolic diseases and shift workers typically have shorter sleep durations [5,7,11]. Short sleep durations have been shown to elicit a physiological stress response, and both physiological and psychological stress disrupt the healthy functioning of the intestinal gut micro biota. Recent findings have shown altered intestinal microbial communities and dysbiosis of the gut micro biota in circadian disrupted mice and jet lagged humans. The sleep and circadian disruption in humans alters the gut microbiota, contributing to an inflammatory state and metabolic disease associated with shift work. There is a close relationship between insufficient sleep, circadian misalignment and the gut micro biota (Fig. 1).

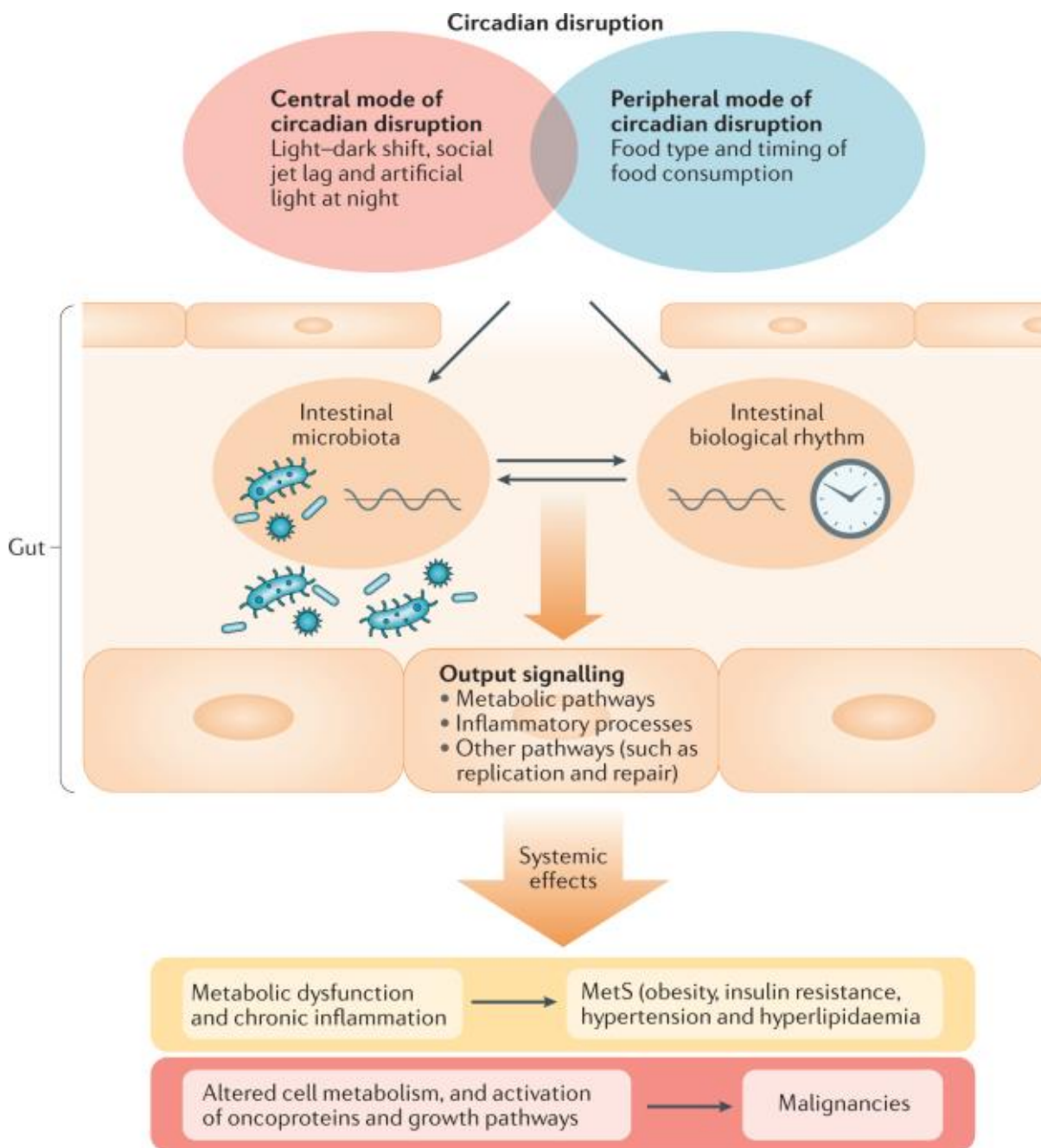


Figure 1: Showing Effect of disruption of circadian rhythm on intestinal microbiota and biological clock which can lead even malignancy (for more details see ref. No. 5).

Shift workers should maximize their exposure to bright light (sunlight or, for night workers, specially constructed bright artificial light boxes) at times when they should be awake and ensure that the bedroom is as dark and quiet as possible during sleep [22-26]. Wearing sunglasses during the morning commute home in anticipation of sleep is also useful. Sleep masks and white-noise devices are helpful.

Conclusion

Clinicians and scientists even lately considered intestinal microbiota as diabolic and with heavy doses of antibiotic they created imbalance in the population of the intestinal microbiota and people suffered with various disorders. Now it is established that intestinal microbiota also regulates

many body systems and essential part of the body. The cross-talk between circadian and microbiota is a comparatively new area for more research.

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