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## **Sleep affects both our body and mind in different ways**

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Sleep affects both our body and mind in different ways. Recently, many researchers published study data about sleeping disorders including insomnia. These disorders were proved to be a risk of developing lifestyle-related diseases such as diabetes, high-blood pressure and obesity.

It has long been known that the state of our sleep affects the functions of the bowel. When you work in shifts or travel for a long time during overseas trips, gastrointestinal symptoms including diarrhea and constipation occur frequently. There are also research reports that many people with a sleep problem have irritable bowel syndrome (IBS) and reflux esophagitis.

The cause of these disorders is perhaps related to the body and mind becoming stressed by the sleep problem which might activate the sympathetic nerve and increase the secretion of cortisol which is a type of stress hormone. Recent studies have suggested that the balance of intestinal bacteria changes within a day due to sleep changes and may affect the functions of the digestive tract.

### **The relationship between sleep and circadian rhythm**

We repeat a cycle of sleep and wakefulness every day. The sleep is regulated by “homeostasis” and “circadian rhythm”. While we waking up during the day, we accumulate “sleeping debt”. Once the body reaches the threshold where we cannot continue to be awake, we fall asleep, and that decreases our sleeping debt. On the other hand, when we reach the arousal threshold after falling sleep, we will wake up.

These thresholds are adjusted by the circadian rhythm. If the sleeping time would be only adjusted by the thresholds responsible for sleep or arousal, the time for sleep or arousal

would stray with each passing day which will make us fall asleep or get up regardless of the day or night. This straying is adjusted to a cycle of about 24 hours by a circadian rhythm which is controlled by clock genes.

Mammals including humans change the body's internal environment in a 24-hour cycle just like the rotation of the earth. This cycle is called circadian rhythm and it is also known as the biological clock. Blood pressure and the body temperature are also controlled in a 24-hour cycle. The circadian rhythm is adjusted in the hypothalamus of the brain and controls the daily rhythm of various organs of the body. The circadian rhythm controls the rhythm of drowsiness. The daytime awakening and the night time sleep are determined along with the drowsiness caused by the sleeping debt.

### **A disturbance of the circadian rhythm deteriorates the conditions of intestinal & intestinal bacteria**

The circadian rhythms also exist in organs such as the liver and the gastrointestinal tract. Previous studies have shown that approximately 30% of the genes present in the intestinal tract follow circadian rhythms. Such a diurnal rhythm is inscribed in the proliferation of intestinal epithelial cells and intestinal permeability (to adjust the entry of food and foreign matters from the intestine). Since the diurnal variation is observed in genes which are involved in the absorption of nutrients such as sugar and amino acids, we can predict that the nutrient absorption is properly carried out when the circadian rhythm works without disruptions. Furthermore, the secretion of hormones that regulate our appetite also does not work properly when the clock gene does not function. Since the circadian rhythm is observed in immune cells which are involved in the intestinal immunity, we can also say that the rhythm of the body is deeply involved in the defense against intestinal infections.

Recently, several research groups have published their research results about the diurnal variation of intestinal bacteria. Based on these findings, the balance of intestinal bacteria changes within a day and this change is influenced by the circadian rhythm of the body.

When the diurnal variation affects the balance of intestinal bacteria, the synthesis of vitamins, the metabolism of nucleic acids, DNA repair, and cell proliferation by intestinal bacteria are also affected by the diurnal variation. However, no diurnal variation was observed among the intestinal bacteria of the mice from which their clock genes were destroyed. Furthermore, when the tested mice were forcibly disturbed from their sleep, their intestinal bacteria balance changed to that of the obese mice possess, the permeability of

their intestinal tract increased by this sleep disruption that made the barrier function impaired, and harmful substances derived from bad bacteria increased in the blood. In addition, when the intestinal bacteria of the sleep deprived mice was transplanted into germ-free mice, inflammation of the intestine occurred and resistance to insulin become exacerbated.

Based on this study results, we can understand that once the clock genes work properly in accordance with the circadian rhythm, the changes in intestinal bacteria will manifest themselves in a day which will provide proper synthesis of nutrients, as well as appropriate proliferation and repair of intestinal cells. On the other hand, if the circadian rhythm is disturbed, the proper balance of intestinal bacteria will not be maintained, and the risk of infection will increase due to malnutrition and a decreased intestinal barrier function.

Although the test described above was done with mice, there are studies with humans about the relationship between intestinal bacteria and the circadian rhythm. A study has found that test subjects who underwent jet lag during 8 hours of their flight showed a change in their intestinal bacteria becoming similar to the microbiota of obese people which commonly contains glucose tolerance was deteriorated. As a result of an intervention trial in which the subjects underwent 8 hours of sleeping for 2 days and 4 hours of sleeping for 2 days, a deterioration of insulin resistance and glucose tolerance was observed even though the shortening of the sleeping period was only for 2 days. Other study has reported that when 10 hours of sleep time were limited to 4 hours, the level of compounds derived from bad bacteria increased in the blood. Based on these results, we can think that the circadian rhythm of intestinal bacteria of humans will also be disturbed if we do not have a proper sleeping time.

### **Can the circadian rhythm and sleeping condition recover if the intestinal bacteria change?**

We have described so far about the fact that the condition of intestines and intestinal bacteria is deteriorated once the circadian rhythm is disrupted. However, what do you think will happen if we change the intestinal bacteria? Can we restore the circadian rhythm and sleeping condition?

The possibility of restoring the circadian rhythm by changing the intestinal bacteria has been already verified by the research with germ-free mice. A proper circadian rhythm is recognized in the mice with intestinal bacteria. However, germ-free mice showed a reduction

of the rhythm of the clock gene in the hypothalamus of the brain and the liver. The researchers also found that butyrate, which was produced by intestinal bacteria showed diurnal variation. When they administered butyrate to the germ-free mice every 12 hours, the circadian rhythm in the hypothalamus and the liver recovered. In addition, when they administered antibacterial agents to the mice with intestinal bacteria, the circadian rhythm at various organs changed.

From this research result, we can understand that there is a dual-directional impact to the circadian rhythm and the intestinal bacteria. When the circadian rhythm is destroyed, the balance of intestinal bacteria deteriorates and vice versa. We infer that the influence of intestinal bacteria may occur because the substance that is produced by intestinal bacteria like butyrate encourages the brain to adjust the circadian rhythm.

To accomplish the normalization of circadian rhythm in the intestinal tract, the meal ingestion rhythm is important as well as the balance of intestinal bacteria. Time restricted feeding is a method, as its name suggests, that restricts eating time and it is known as a way to restore the circadian rhythm of the intestinal tract. Here we take a look of an examination with mice as an example. Two groups of mice were fed with the same energy amount. Compared with the mice that were fed freely for 24 hours, the mice that were limited in their feeding time to less than 9 hours a day showed a suppression to accumulate in their body fat and prevention against the deterioration of glucose tolerance. Also, mice with restricted feeding time showed recovery of diversity and diurnal variation of their intestinal bacteria compared with mice fed freely with high fat diet. So, regular eating patterns can make intestinal bacteria possible to maintain their diversity and diurnal variation, and synchronize the clock genes which in turn lead the prevention of sleep disorders.

Other studies have also been published about cellular components of microorganism directly stimulating sleep. It discovered that muramil peptide derived from the microbial cell wall is a sleep-promoting component. Subsequently, it has also been reported that the components of microorganisms prolong the duration of non-REM sleep among animals which will deepen sleep and reduce the time of REM sleep. Patients with sleep disorders often complain of gastrointestinal symptoms, so improving gastrointestinal symptoms may also benefit sleep with the administration of probiotics or prebiotic. We believe that the components from microorganisms that are in fermented foods are good nutritional sources to improve our sleep. Also, we can expect that dietary fiber, oligosaccharides and

indigestible ingredients to become foods for good bacteria in intestines and produce short-chain fatty acids which will influence the brain and eventually affect to the adjustment of the circadian rhythm.

In summary, when the condition of sleeping worsens, the intestinal condition is disturbed. Maintaining the circadian rhythm of the body by regulating the rhythm of daily life is important in order to have a better intestinal environment. Conversely, keeping the intestinal bacteria in a good balance brings the correct sleeping pattern back. To accomplish a correct intestinal rhythm, not only the contents of the meal but also the timing and time to eat a meal are related. It is possible to get a good sleep if we pay attention to the rhythm of daily life, keep eating properly in order to balance the intestinal bacteria, and be aware of the timing of taking meals. Furthermore, proper body rhythm will lead to better health for us.