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## **PRESS RELEASE (2025/3/24)**

## Chronic jet lag disrupts metabolism differently in male and female mice

Sex hormones, like estrogen and testosterone, could play a critical role in how metabolism is impacted by an out-of-sync body clock.

Fukuoka, Japan – Jet lag is one of the worst parts of long-distance traveling or shift work—it makes us tired and cranky, and also plays havoc with our metabolism (and therefore our weight). Now, new research on mice suggests that the way jet lag impacts our metabolism may depend on our sex.

Frequent shifts in light-dark cycles—inducing a state of chronic jet lag—cause drastically different effects on male and female metabolism in mice, say researchers from Kyushu University. The study, published in the journal, *Biology of Sex Differences,* found that the body clocks of female mice are more easily disrupted than the clocks of male mice, and revealed opposing metabolic effects; jet-lagged male mice gained weight and developed glucose intolerance, while jet-lagged females lost weight compared to female mice without jet lag. The findings imply that metabolism is not only influenced by jet lag, but also by a complex interplay of insulin and sex hormones, leading to different effects in each sex.

"Chronic jet lag, where a person's body clock is consistently out of sync with natural day-night cycles, is a condition that affects many people, such as shift workers," says senior author Professor <u>Shinobu Yasuo</u> from Kyushu University's <u>Faculty of Agriculture</u>. "Chronic jet lag increases the risk of metabolic disorders, like obesity and diabetes, so understanding the biological effects of jet lag is very important."

However, studies on humans can be limited as other confounding factors affect metabolism, such as diet, stress, exercise, and genetics. By studying animals like mice under controlled conditions, it is easier to identify the direct effects of jet lag itself.

"The biggest issue so far is that animal studies have typically focused only on males, yet over half of all shift workers, such as nurses, are women," says Yasuo. "So for me, it was important to look at female mice too."

The body clock, or circadian clock, runs on a roughly 24-hour cycle that is kept in sync, or regulated, by light. In these experiments, the researchers manipulated the mice's body clocks by changing the timing of the overhead room lights. For the mice under control conditions, the lights were switched on and off every 12 hours, while for the mice under chronic jet lag conditions, the timing of the lights shifted forward by six hours every two days.

Over a period of eight weeks, researchers measured the body weight of the mice under control and chronic jet lag conditions and found that jet-lagged male mice gained weight and developed glucose intolerance, a condition which increases the risk of developing diabetes. However, the jet-lagged female mice lost weight, compared to controls.

"The outcome was very surprising. We expected both male and female mice to gain weight

under chronic jet lag, just to varying degrees," says Yasuo.

To determine what impact chronic jet lag was having on the mice's body clock, Yasuo and her colleagues measured the activity of clock genes in the liver and adrenal glands. They also monitored changes in the mice's deep body temperature, which acts as a marker of body clock activity, peaking during the day and dropping at night.

They found that under chronic jet lag conditions, female mice showed greater disturbance in clock gene activity and a weakened rhythm for deep body temperature, while male mice showed very little change.

In a later experiment, when male mice that had been castrated were put under chronic jet lag conditions, they responded similarly to female mice, showing perturbed body temperature and clock gene activity, and also losing weight. These changes were then able to be reversed when castrated mice received testosterone injections.

"Testosterone is therefore key to a resilient body clock in male mice. It also significantly impacts metabolism and how the body responds to glucose," says Yasuo. "This finding underscores the importance of taking sex into account when looking at jet lag's impact on metabolism."

In future studies, the researchers hope to unpick exactly why the male mice gain weight and develop glucose intolerance, despite little obvious change in clock gene activity. They also plan to examine the effect of the female sex hormone, estrogen, on the resilience of the body clock.

The weight loss seen in female mice also raises questions on the common perception that jet lag promotes weight gain.

"It could be that jet-lagged female mice are more sensitive to stress and anxiety," suggests Yasuo. "We also plan to research further into the effect of sex on appetite and food preference under chronic jet lag.

"Of course, human lifestyles are much more complicated. Different people respond to stress in different ways, or have different dietary or exercise habits," continues Yasuo. "But overall, this study highlights the need to take gender differences into account when recommending appropriate health strategies to people living irregular hours, like shift workers."

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For more information about this research, see "Sex-dependent effects of chronic jet lag on circadian rhythm and metabolism in mice" Tiantian Ma, Ryohei Matsuo, Kaito Kurogi, Shunsuke Miyamoto, Tatsumi Morita, Marina Shinozuka, Fuka Taniguchi, Keisuke Ikegami & Shinobu Yasuo, *Biology of Sex Differences*, <u>https://doi.org/10.1186/s13293-024-00679-z</u>

## About Kyushu University

Founded in 1911, <u>Kyushu University</u> is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia.

Through its <u>VISION 2030</u>, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

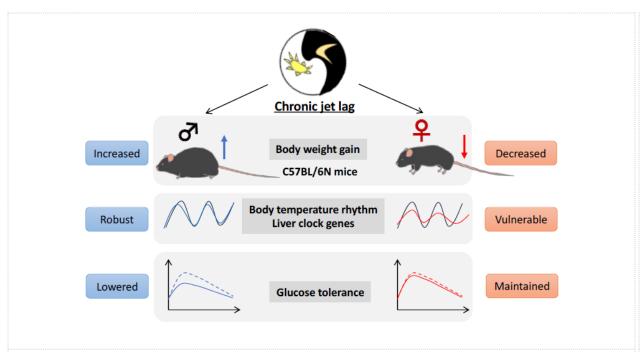


Fig. 1. Chronic jet lag affects male and female mice in different ways. Jet-lagged male mice gain weight and have a lower glucose tolerance, while female mice lose weight compared to controls, and their glucose tolerance remains unchanged. In males, the body clock is more resilient to jet lag, showing little change in clock gene activity in the liver and adrenal glands, or in the rhythm of deep body temperature. Female mice are more vulnerable to jet lag, with significant changes in clock genes and their body temperature rhythm.

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