Down with jet lag

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Journeys across several time zones make our internal body clocks go haywire. We feel exhausted and tense, and our sleep pattern is out of synch. As scientists at the Max Planck Institute for Biophysical Chemistry have now succeeded in demonstrating for mice, the clocks associated with individual organs in the body adapt to the new time at different speeds. As a result, the body's physiological processes are no longer coordinated. The adrenal gland plays a key role in this process. When the researchers switched off the adrenal clock or manipulated the synthesis of corticosterone by the adrenal gland with the help of metyrapone, the rodents adapted more quickly to the altered circadian rhythm. These insights could pave the way for a new approach to the hormonal treatment of the effects of jet lag and shift work. (*Journal of Clinical Investigation*, June 23, 2010).

Be they professional footballers on their way to the World Cup in South Africa or ordinary holidaymakers: people who cross several time zones by jet are prone to certain symptoms for a few days after the flight. During the day, they are crippled with exhaustion; at night they lie awake tossing and turning, unable to sleep, and many of the body's functions are activated at the wrong time. What we have here is a clear case of jet lag. Our "internal body clock", which still beats to our old rhythm of day and night, must adapt to the new external time. The process works, however: after a few days, we feel in synch with the outside world again.

The problems that arise with jet lag are a clear example of how external influences can disrupt our internal body clock. An entire network of molecular clocks found in the different organs coordinate the body's various physiological processes ranging from the heart beat, temperature, sleep requirement and hormone balance to behaviour. All of these clocks are controlled by the master pacemaker of the hypothalamic suprachiasmatic nuclei (SCN), which synchronises all of the body's "peripheral" clocks with the outside world. At molecular level, all of the clocks are based on a handful of "clock" genes and proteins that regulate each other interactively and thus generate a molecular time signal in the form of a circadian rhythm - a term which originates from the Latin for approximately (circa) and day (dies).

Scientists at the Max Planck Institute for Biophysical Chemistry have for the first time systematically studied how individual "clock" genes and the internal clocks of the different organs synchronise with the new external time in the case of jet lag. The researchers were surprised by their findings. "The internal clocks and the 'clock' genes adapt to the altered external influences at varying speeds," says Gregor Eichele, Director of the Institute's Genes and Behaviour Department. "When an organism suffers from jet lag, it would appear that the entire clock mechanism fails to tick at the right rhythm. As a result, numerous physiological processes are no longer coordinated."

Adrenal clock stabilises the status quo

As the GÃ¶ttingen-based researchers discovered, the adrenal clock plays a key role in the body's adaptation to a new circadian rhythm. When the scientists switched off the adrenal clock in mice, the rodents adapted their behaviour more quickly to the new time and made a more rapid return to their laps on the wheel in synch with the new external time. Therefore, a functioning adrenal clock keeps the organism in a temporally stable state and halts the excessively rapid adaptation of the central clock in the SCN. Physiologically, this makes complete sense. Sporadic light changes - a dark stormy sky or dark cinema - do not disrupt the entire clock mechanism. In the case of jet lag, however, this is precisely what causes the problem.

It is not necessary, however, to switch off the entire adrenal clock to enable the mice to better recover from jet lag. The experiments carried out by the researchers give reason to hope that a less drastic solution may be possible. The adrenal gland produces a series of important hormones, including adrenaline, noradrenaline and corticosterone (cortisol in humans). Completely switching off the adrenal clock would not, therefore, be advisable. "The time-dependent release of corticosterone was crucial in enabling our rodents to adapt more quickly to the new time," explains Eichele. When the scientists administered the active agent metyrapone to the mice, their corticosterone rhythm changed as did their sleeping/waking rhythm. "If the mice were given metyrapone at the right time, they adapted faster to the disturbed circadian rhythm. While the 'sleep hormone' melatonin, which is commonly used to treat jet lag, mainly acts by generating tiredness and is therefore more suitable for use when flying east than west, with metyrapone, the mice's internal clock can be turned both forwards and back," explains junior scientist Silke KieÃŸling.

New treatment approaches

The insights of the GÃ¶ttingen scientists could produce an entirely new approach to the treatment of jet lag in the future. Metyrapone is already approved as a medication for the treatment of the overproduction of glucocorticoids and mineralcorticoids. However, it remains to be demonstrated in "field trials" and tests in the sleep laboratory whether the administration of metyrapone is suitable for the treatment of jet lag, and whether it has any side effects in humans. "Our results from the mouse model are not necessarily transferable to humans," stresses Henrik Oster, who heads the research group "Circadian Rhythms". "With our mouse mutants, we have an excellent system on which we can base our search for chronobiologically effective substances. However, it remains to be confirmed by clinical studies whether these are as effective in humans as they are in nocturnal animals like mice."

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