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BRIEFING
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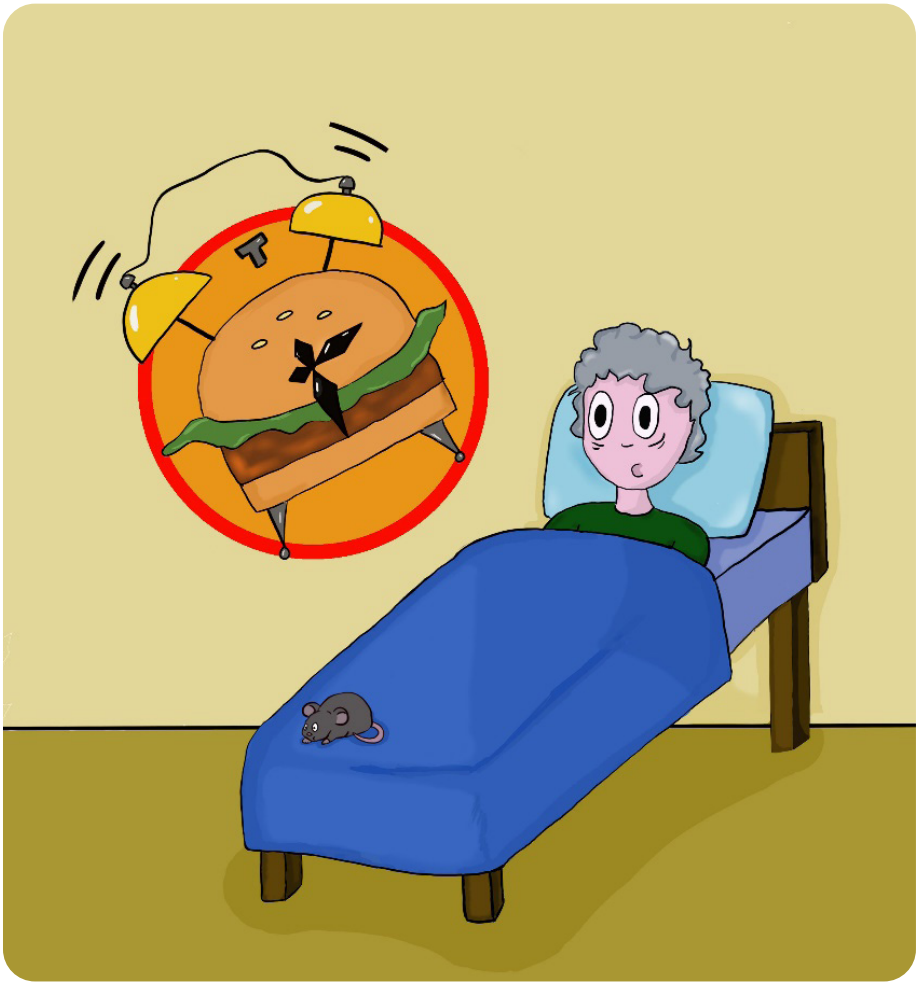
Could food fix a broken body clock?

SUMMARY

Many physiological processes and behaviours follow an approximate 24h pattern called a circadian rhythm, which are primarily entrained by the daily cycle of light and dark. Robust circadian rhythms are important for health, including our mood, metabolism and immune system. However, circadian rhythms become blunted with ageing. Time-restricted feeding could replace light as the main 'entrainer' and be used to restore circadian rhythms in old age.



You've got rhythm

We light-loving humans generally limit the majority of our daily activities to the daytime and sleep through the night, making us diurnal in contrast to nocturnal animals, who are active at night. This change in our activity over a 24 hour cycle is the clearest example of a biological rhythm. However, it is not only the change from light to dark that guides our behaviour; we have our own internal timekeeping system or 'body clock' that can run independent of light information. The mammalian body clock is a tiny brain region located in the anterior hypothalamus called the suprachiasmatic nucleus (SCN). Its position directly above the optic chiasm (where the optic nerves cross in the brain), puts it in the ideal place to receive light information from the eyes. Then, through a variety of hormonal and neural signals, the SCN communicates light information to the rest of the body, organising a multitude of physiological

processes into circadian (circa- approximately, dian- day) rhythms. The importance of the SCN was demonstrated in a seminal study where bilateral lesioning of the SCN resulted in the abolishment of behavioural and hormonal rhythms in rats.

Circadian rhythms are entrained or driven by zeitgebers ('time-givers'). Light is widely acknowledged to be the most potent zeitgeber, but other external cues like feeding time and temperature are also important.

The ideal circadian system is stable, strong in amplitude and keeps everything in phase or synchronised. Unfortunately, circadian rhythms can be disrupted in many ways, from a late-night party to a difficult work schedule. Mutations in key genes that control circadian rhythms underlie numerous sleep disorders and their deletion in animal models can cause complete fragmentation of sleep-wake behaviour. Beyond feeling a bit tired, this disruption can seriously affect health. Studies have shown that five nights of sleep restriction in healthy participants reduced insulin sensitivity by 24%, which could increase the risk of developing diabetes. Another study showed that sleep restriction resulted in inappropriate immune system activation, which has been linked to greater risk of cardiovascular disease. Disrupted circadian rhythms are also a risk factor for psychiatric disease and are associated with treatment resistance and symptom relapse. With wide-ranging effects on multiple systems, the link between circadian rhythms and health is hard to ignore.

To be blunt

With continually improving healthcare, the elderly population is growing. However, will good health accompany longer lifespans? The robustness of circadian rhythms can positively affect longevity, but with old age comes blunted circadian rhythms. Increased daytime napping and falling asleep earlier in the evening is highly characteristic of ageing. Reports also show age-related blunting in other important circadian rhythms including the secretion of hormones, such as melatonin and cortisol. Is this an inevitable part of ageing or a pathological problem to be solved? If late night parties are not to blame, then what is? The importance of the SCN in this disruption is evident from studies where transplanting a foetal SCN into the brains of aged rats improved circadian rhythmicity. Moreover, in ageing, there is a reduction in the synchronicity and rhythmic firing of the SCN neurones, resulting in reduced SCN output. These changes may lead to a desynchronization between the SCN and the peripheral clocks so that the rest of the body is not receiving the correct time of day information. Perhaps the answer to fixing a broken body clock lies with a circadian system where light is not the main input, and the SCN is not the main driver.

Eat to the beat

Enter the feeding zeitgeber. When a rodent is fed at the same time each day it develops feeding anticipatory activity (FAA), an increase in activity a couple of hours before food is delivered. Surprisingly, this behaviour occurs independent of the SCN. If the SCN is lesioned or key clock genes are disrupted, rodents can still develop normal FAA. However, despite a 30-year search, the location of the feeding entrainable oscillator (FEO) remains elusive. Given its powerful entrainment of the peripheral clocks, the FEO has the potential to replace the SCN as the central pacemaker and restore rhythmicity when it is weakened. This hypothesis is supported by studies that show FAA is well conserved in aged rodents and that feeding time has a more powerful effect in aged mice compared with younger mice. Two weeks of time-restricted food delivery strengthens blunted activity rhythms and reduces sleep fragmentation in aged rodents. In another example, when an arrhythmic mouse model was put on a time-restricted feeding schedule, normal activity-rhythms were restored with a new peak in activity before feeding time. This demonstrates that time-restricted feeding can strengthen and restore circadian rhythms that would otherwise be entrained by light. Similar regimes are yet to be tested in aged humans, but encouragingly time-restricted eating has been shown to improve sleep in healthy, overweight adults.

There is more work to be done, but the protective effects of time-restricted feeding represent an exciting therapeutic avenue to promote healthy ageing.

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