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News

Eye-damaged mice lose sight of the time

Mice lacking some retinal cells have an altered body clock.

Lucas Laursen

Mice with specific light-sensing cells removed from their retinas can see perfectly well but can't tune their body clock, scientists have shown. The discovery provides more evidence that light detection by the retina is crucial for mammals to stay on a 24-hour circadian cycle.

Without these cells, called melanopsin-expressing retinal ganglion cells (mRGCs), the mice slip to a 23.5-hour cycle, which gradually throws their daily routine, report researchers led by Satchidananda Panda at the Salk Institute for Biological Studies in La Jolla, California, in the journal PLoS ONE[1].

In the absence of light, mammals naturally adopt a roughly 23.5-hour cycle of sleeping and waking. We therefore have to adjust to the world's 24-hour rhythm using light cues. Unlike other retinal cells that feed into the visual field in our brains, the mRGCs measure just the intensity of light. mRGCs release the photopigment melanopsin, which helps the brain to control pupil size, some hormone levels, and the daily sleep routine.

No time: mice with damaged retinas can lose the ability to fine-tune their body clock.

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Take the strain

Panda's team tested a strain of mice whose mRGCs were sensitive to a diphtheria toxin. The toxin crossed from the bloodstream to the mRGCs, disabling about 90% of the cells while leaving the rest of the retina intact.

“We were not sure that the diphtheria toxin would cross the blood-retina barrier,” says Panda of the technique. “We were kind of lucky that it did.”

The affected mice reverted to a 23.5-hour cycle, the same as mice left in complete darkness. They also lost most of their ability to regulate pupil size over the course of the two-week treatment. The mice were still able to navigate the so-called ‘cliff test’, in which they hopped from a platform to a safe landing area, indicating that the rest of their visual system remained intact.

Panda's results echo those of a recent study of mutant mice with mRGCs genetically programmed to degenerate[2], which also showed that these cells are an important component of the body clock.

"What the new approach does is allow you to decide what point in time you want to [disable] the cells,” says Mark Hankins of the University of Oxford, UK, an author on this second study.

Sleep on it

Panda says that the next step is to eliminate the cells earlier in the mouse life cycle to test whether they can compensate for the missing light information while they are developing. “If you could use it to test [the effect] at various stages and see what impact that has, that could be interesting,” says Hankins, who points out that neither group has done that yet.

“The big question is whether individuals with sleep disorders lack these cells,” adds Panda.

If so, he says, mRGCs are “a very exciting drug target”, particularly now that his team have shown that chemicals can enter these cells. It might one day be possible to create 'pharmaceutical darkness' or restore the eye’s ability to detect daylight in patients who have trouble sleeping, says Panda.

Hankins thinks more work in this area might point to sleep therapies: “By understanding the precise mechanisms of light transduction in those cells you might flag up targets for pharmaceuticals.”

References

1. Hatori, M. *et al. PLoS ONE* 3, e2451 (2008).
2. Güler, A. D. *et al. Nature* 453, 102–105 (2008).