

Neurobiology

Why extreme lack of sleep can kill you

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Limited sleep causes many health problems, and it can eventually lead to death in some extreme cases. Why is sleep essential for life? We found that sleep deprivation can kill animals through accumulation of toxic molecules in their intestines. Importantly, keeping the intestines healthy by clearing these molecules can prevent the fatal consequences of insufficient sleep.



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Most of us are familiar with the unpleasant changes to our mood, and our ability to think, even after a single sleepless night. An alarming fact is that up to 50% of adults worldwide are estimated to regularly skimp on sleep.

Sleep ensures proper brain function, but it also regulates metabolism, blood pressure and immune system. Therefore, it is not surprising that chronic lack of sleep can cause or aggravate many diseases, including Alzheimer's, diabetes or certain cancers. The most striking example emphasizing the importance of sleep comes from the observation that extreme sleep deprivation can kill some laboratory animals. Why these animals eventually die remained unknown for many years. In our study, we tackled this question, and identified a major

change that occurs in the body with insufficient sleep.

Fruit flies and mice are often used as model organisms, because they sleep similarly to humans. We started by studying flies as there are relatively simple but powerful tools to manipulate their sleep. Flies have different groups of neurons in the brain whose activation can prevent sleep. We engineered flies to produce in these neurons a protein that functions as a temperature-controllable switch. Turning the switch on (simply by changing the temperature in the environment) allowed us to activate sleep-preventing neurons. At low temperature (21°C), the neurons were inactive, and the flies slept normally. At higher temperature (29°C), the neurons were active, and the flies could

barely sleep. After ~10 days at 29°C, flies began to die, and were all dead by approximately day 20. For comparison, flies could live up to 40 days when we did not intervene with their sleep. These experiments reinforced the idea that sleep serves a vital function.

We then asked what killed sleep-deprived flies. Usually, sleep is associated with the brain, but we assumed that sleep loss could damage any part of the body. Therefore, we systematically examined different organs and discovered that the gut specifically contained high levels of molecules called Reactive Oxygen Species (ROS).

ROS are oxygen-derived molecules produced by living cells either intentionally or as byproducts of metabolism. They have important functions in the cell, but when their levels become too high, they can damage other molecules; this is called oxidation and is similar to metal rusting or a cut apple turning brown if left exposed to air. Indeed, the guts of sleep-deprived flies were full of damaged and dying cells.

Does lack of sleep impact human's gut the same way as in flies? We could not assess this directly in humans, but we could use mice, which are closer to humans than flies. We sleep-deprived them using a

gently rotating bar at the bottom of the cage. Like in flies, ROS accumulation and tissue damage occurred specifically in the intestines. Observing an identical outcome in two distantly-related animal species - insects and mammals - suggests that this may be a universal outcome of severe sleep deprivation.

To test whether ROS accumulation in the gut is the main cause of death, we cleared ROS from sleep-deprived flies by feeding them an antioxidant diet or by over-producing ROS-counteracting enzymes in the gut. Strikingly, if we maintained intestinal ROS levels low, flies survived even if they were almost completely sleepless, suggesting that ROS accumulation in the gut is a major cause of death during sleep loss.

Our work helps answering the long-standing enigma of why sleep is essential for life, but it also opens new questions. Why and how does sleep deprivation have such an impact on the gut? Does daily sleep actively detoxify the gut or is ROS accumulation a consequence of abnormal situation that the body cannot deal with? Assuming that similar processes occur in humans, keeping our guts healthy may then ameliorate certain negative health consequences of insufficient sleep.

