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Linking immunity and sickness-induced sleep

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We are all familiar with the sleepiness experienced during sickness. What is less often appreciated is that this increased need for sleep is caused by the release of signaling molecules by our own immune and nervous systems, and not by the infectious agents themselves (1). Indeed, for the spread of a virus or a bacterium, it would be much better if we were out and about when sick, instead of sleeping. On page 509 of this issue, Toda *et al.* (2) reveal another facet of the interplay between sleep and immunity by identifying NEMURI (NUR), an antimicrobial peptide (AMP) produced by the fruit fly *Drosophila melanogaster*, that also has sleep-promoting properties. Because humans synthesize more than 100 different AMPs (3), this work could have implications for interactions between sleep and immunity during human disease.

To identify novel regulators of sleep, Toda *et al.* overexpressed 8,000 different genes within the nervous system of adult fruit flies and assessed whether any of them caused a change in sleep. Only one gene, which they named *nemuri* after the Japanese word for sleep, consistently increased total amounts of sleep. Sleep is regulated by both the circadian clock (a biochemical oscillator that regulates a wide range of biological functions according to the daily cycle of light and darkness) and by an independent but closely intertwined homeostatic process (4). Overexpression of *nur* had minimal effects on the circadian clock but made it more difficult for flies to wake up in response to stimulation. Conversely, flies in which *nur* was inactivated were easier to wake and had trouble falling asleep afterward. These experiments suggest that *nur* is involved in the homeostatic need for sleep—the sleepiness we experience after prolonged wakefulness. Although our understanding of the molecular workings of the circadian clock is quite advanced, identifying a regulator of sleep pressure is exciting because this process is poorly understood. However, the story became more complicated when the authors looked for peptides similar to NUR in other organisms.

The NUR peptide was found to be most similar to fish cathelicidins, a family of AMPS that are also conserved in mammals. The authors showed that NUR is secreted and has direct antimicrobial properties, and thus is a bona fide AMP. In addition to increasing sleep, over-expression of *nur* in the nervous system increased the ability of flies to survive a bacterial infection. Expression of endogenous *nur* in the brain was induced after either sleep deprivation or bacterial infection, in accordance with a dual role in the homeostatic regulation of sleep under normal conditions and in the increased sleep that follows infection. Indeed, upon bacterial infection, fruit flies in which *nur* is inactivated showed a smaller

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increase in sleep relative to flies expressing wild-type *nur*. Strikingly, *nur* expression was induced in only a single neuron per brain hemisphere, which suggests that it is part of a small and highly specialized neuronal circuit. Induced NUR accumulates in the dorsal fan shaped body (dFSB), a brain region in fruit flies that plays a critical role in sleep regulation (5), implying a direct mechanism of action (see the figure). Do the protective effects of NUR during infection stem from its antimicrobial effects or from its role as a sleep-inducing peptide? Because NUR induction during infection takes place in only a pair of neurons in the brain, and thus likely increases overall NUR levels only slightly, the latter explanation seems more likely. This could be tested if the antimicrobial and signaling domains of NUR are distinct enough to allow the construction of mutants with only antimicrobial or only sleep-promoting properties.

The idea that increased sleep during infection is somehow protective is appealing. It agrees with the common experience of the recuperative properties of a good night's sleep and would provide a teleological justification for the well documented ability of the immune system to modulate sleep during an infection. One meta-analysis (6) showed that among rabbits exposed to the same dose of pathogens, those that slept more were more likely to survive. However, correlation does not prove causation, and neither a replication in other systems nor an investigation of the underlying mechanisms has been reported. Fruit flies (7) and mice (8) that sleep more after infection show higher survival, but this observation is complicated by the fact that increased sleep was induced by sleep deprivation prior to infection. The identification of NUR—a molecule that regulates normal sleep homeostasis, is induced during infection, is required for the sleep increase that occurs during infection, and has direct antimicrobial properties—provides a clear mechanistic link between increased sleep and increased survivability during an infection. NUR is constitutively produced outside the brain, whereas its expression in the brain is low until induced by infection or sleep deprivation. The broad constitutive expression could be part of a baseline contribution to immune defense through the antimicrobial properties of NUR, whereas increased brain expression could serve to put the animals to sleep in response to sleep deprivation or sickness.

Interestingly, *nur* expression is induced not only by sleep deprivation and infection, as shown by Toda *et al.*, but also by a variety of chemicals and stressors (9). This suggests that *nur* could be involved in the response to organismal or cellular stress in general, with sleep deprivation and infection being just a subset of potential insults. The importance of stress-induced sleep (SIS) has only recently been appreciated, mostly because of work using invertebrate model systems in which signaling through epidermal growth factor receptor (EGFR) has been shown to induce sleep in response to a variety of stressors (10). SIS appears to be protective, as blocking the signaling pathway that mediates SIS reduces the survival of worms exposed to heat (11) and of fruit flies exposed to heat or infection (12). It will therefore be interesting to determine whether NUR-induced sleep after infection is mediated by the EGFR sleep-modulating system. Increased sleepiness, fatigue, and malaise in humans are hallmarks of many disorders, including generalized anxiety and depression, and can extend long after recovery from infections, physical injuries or surgery. It is tempting to speculate that these symptoms could stem from the dysregulation of a normally adaptive mechanism that induces sleep in response to stressors.

The identification of *nemuri* by Toda *et al*. reveals a mechanism through which stressors can be translated by the nervous and immune systems into increased sleep. This work suggests that human AMPs could have similar sleep-inducing properties with potential clinical implications.

References

1. Imeri L, Opp MR, Nat. Rev. Neurol 10, 199(2009).
2. Toda H et al., Science 363, 509(2019). [PubMed: 30705188]
3. Wang G, Pharmaceuticals 7, 545(2014). [PubMed: 24828484]
4. Bobérly AA, Hum. Neurobiol 1, 195(1982). [PubMed: 7185792]
5. Donlea JM et al., Science 332, 1571(2011). [PubMed: 21700877]
6. Toth LA et al., Proc. Soc. Exp. Biol. Med 203, 179(1993). [PubMed: 8502660]
7. Kuo TH, Williams JA, Sleep 37, 859(2014). [PubMed: 24790264]
8. Renegar KB et al., Sleep 23, 1(2000).
9. Brown JB et al., Nature 512, 393(2014). [PubMed: 24670639]
10. Davis KC, Raizen DM, J. Physiol. 595, 5415(2017). [PubMed: 28028818]
11. Hill AJ et al., Curr. Biol 24, 2399(2014). [PubMed: 25264259]
12. Lenz O et al., Brain Behav. Immun 47, 141(2015). [PubMed: 25668617]

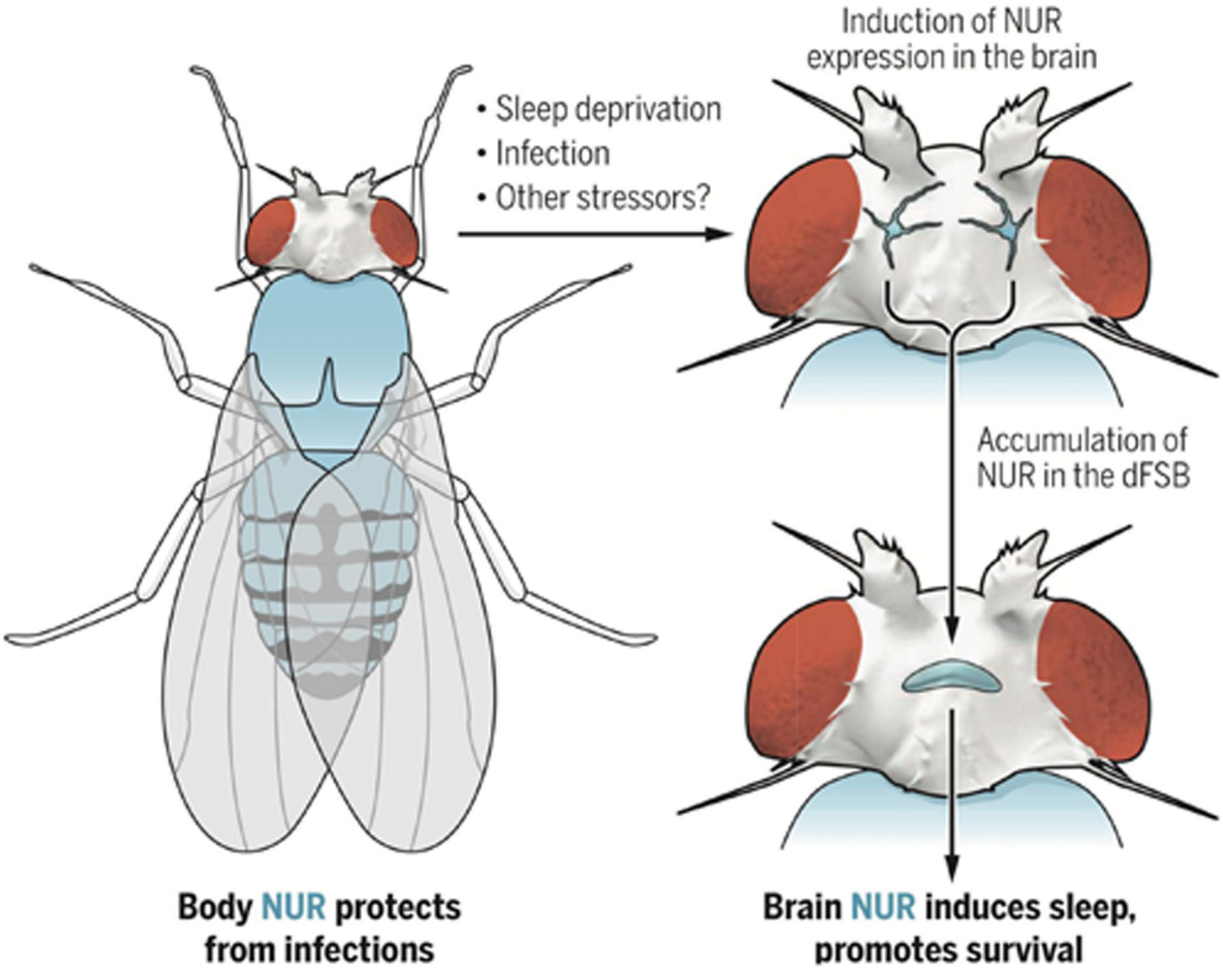

Figure. Promoting sickness-induced sleep

In fruit flies, NUR has direct antimicrobial properties and is synthesized outside the brain where it presumably contributes to innate immunity. During infection, sleep deprivation, and potentially other stressors, NUR is produced by a pair of neurons in the brain and accumulates at the dorsal fan-shaped body (dFSB), a brain region known to promote sleep.