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Sleepless for science: Flies show link between sleep, immune system

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Go a few nights without enough sleep and you're more likely to get sick, but scientists have no real explanation for how sleep is related to the immune system. Now, researchers at the Stanford University School of Medicine are finding that fruit flies can point to the answers.

What they have learned thus far is that illness and sleep disruption may be a two-way street: sick flies can't sleep, and losing sleep makes them more susceptible to infection.

"When flies get sick, they stop sleeping," said David Schneider, PhD, assistant professor of microbiology and immunology. "Disrupting sleep in turn disrupts the immune system, which makes them even more infected and it's downhill from there in a 'spiral of death.'" Schneider is the senior author of a study on the sleep patterns of flies that will be published in the May 15 issue of *Current Biology*.

Schneider worked with postdoctoral scholar Mimi Shirasu-Hiza, PhD, who is the study's first author, to examine the connection between illness and sleep patterns by infecting fruit flies with one of two bacteria - Streptococcus pneumoniae or Listeria monocytogenes.

The infected flies lost their "day" and "night" patterns of activity, which are part of the regular changes that occur in the course of a day, called circadian rhythm. Uninfected flies alternate between 12 hours of high activity and 12 hours of low activity. The researchers found the sick flies had fewer sleep sessions and shorter periods of continuous sleep than did

healthy flies. They basically just didn't sleep well, concluded the researchers.

The researchers can't say for sure say whether a disruption of the brain's central clock, which is the area of the fly brain that exhibits circadian gene activity, was responsible for the changes seen in the sick flies. But the behavior of the ill flies looked a lot like that of flies known to have disruptions in their genes controlling circadian rhythm.

So the next step, after confirming that flies lost sleep when infected, was to ask the converse: when sleep is disrupted, does that affect immunity"

The challenge was how to disrupt the flies' sleep. Schneider tried building a machine that jostled the flies randomly. "All it was really good at doing was throwing the tubes around the room," said Schneider. "Also it was too regular, the flies got used to it so they could nap."

Another option was to keep the flies in continuous light. But Schneider and Shirasu-Hiza decided that an even better way would be to turn to established fly strains isolated decades ago that possess disruptions in their genes controlling circadian rhythm. In this case, these mutant flies could be kept under exactly the same light and temperature conditions as the normal flies.

They looked at flies that were defective in one of two genes, called "timeless" and "period". They found that the loss of either gene's function made the flies more sensitive to bacterial infections and these sick flies died significantly faster than control flies, which lived two to four times as long as the sick ones.

"We want to know how the internal clock knows the animal is infected, and how does the immune system know that you are not sleeping properly"" said Schneider. "How do those messages get sent back and

forth""

Their findings also raise the question of why the flies have a change in their sleep pattern when infected. The researchers speculate that from an evolutionary standpoint, there may be some microbes that are fought better when sleep is disrupted, although clearly not the two microbes they tested in the current study. "We think that is the reason flies do this," said Schneider, "but sometimes it's a good thing, sometimes it's a bad thing."

Building on their findings, they can begin to answer these questions. Shirasu-Hiza will be testing mutant flies with other circadian rhythm genes missing.

They hope their work inspires researchers who work on vertebrates to explore the molecular underpinnings of the interaction between sleep and immunity.

"The cool thing is that many of the clock genes are conserved between flies and vertebrates; we have 'period' and we have 'timeless'," said Schneider. "As usual, it doesn't work in exactly the same way, but what the fly does is let us find genes that are involved in the process, and then go figure out exactly how they are rewired to work in the human. The fly is really good for prospecting."

Source: Stanford University Medical Center