Insomniac flies resemble sleep-deprived humans

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Researchers at Washington University School of Medicine in St. Louis have created a line of fruit flies that may someday help shed light on the mechanisms that cause insomnia in humans. The flies, which only get a small fraction of the sleep of normal flies, resemble insomniac humans in several ways.

"Insomnia is a common and debilitating disorder that results in substantial impairments in a person's quality of life, reduces productivity and increases the risk for psychiatric illness," says senior author Paul Shaw, Ph.D. "We think this model has clear potential to help us learn more about the causes of insomnia and someday develop ways to test for or treat them in the clinic."

The findings are published June 3 in The Journal of Neuroscience.

One of Shaw's co-authors, Stephen Duntley, M.D., directs the Washington University Sleep Medicine Center.

"Insomnia is frustrating for clinicians for several reasons, including its high prevalence, uncertainties about how to define and categorize it, and how little we know about the pathophysiological mechanisms that can contribute to it," Duntley says. "The wonderful thing about this new model is that it lets us begin to sort out some of the many potential mechanisms, genetic and otherwise, that may underlie insomnia, hopefully leading to new interventions."

Shaw's lab was the first to show that fruit flies enter a state of inactivity comparable to sleep. The researchers demonstrated that the flies have periods of inactivity where greater stimulation is required to rouse them. Like humans, flies deprived of sleep one day will try to make up for it by sleeping more the next day, a phenomenon referred to as increased sleep drive or sleep debt.

As he studied the healthy flies, Shaw noticed that a few flies naturally slept less than others. He decided to take flies with insomnia-like characteristics and breed them to amplify those qualities. The flies he bred had difficulty falling asleep in normal circumstances, and their sleep was often interrupted or fragmented. He also used hyper-responsiveness to stimuli as a breeding guide. For example, if researchers turned on a light at night, insomniac flies woke and stayed up the rest of the night, while the healthy flies went back to sleep. The flies that stayed up were added to the breeding pool.

After generations of selective breeding, Shaw's group had produced a line of flies that naturally spent only an hour a day asleep—less than 10 percent of the 12 hours of sleep normal flies get. They quickly noticed an obvious and surprising behavioral change: even though flies have six legs, the insomniac flies fell over more often.

"We sent them to experts in neurodegeneration in flies to see if their lack of sleep or the breeding had somehow damaged their brains," Shaw says. "But the experts said there weren't any physical brain abnormalities."

Shaw briefly entertained the possibility that the flies might be sleepwalking but realized that declines in balance have also been reported in sleep-deprived humans. In addition, other indicators suggested the flies weren't getting enough sleep. His lab previously isolated a biomarker for sleepiness that is present in flies and human

saliva, and the insomniac flies had high levels of it. The flies also were slower learners and gained more fat, two indicators for fly sleep deprivation that Shaw identified earlier. Similar symptoms also occur in sleep-deprived humans.

Lead author Laurent Seugnet, Ph.D., says that while the insomniac flies "clearly suffer consequences" from their lack of sleep, they also show some resistance to the adverse effects of sleep deprivation. For example, while 70 hours of sleep deprivation will kill a normal fly, the insomniac flies can spontaneously go up to 240 hours without sleep and still survive.

"Overall, the flies are able to perform better than they should, given how much sleep they miss," says Seugnet. "That makes it tempting to speculate that insomnia is like drug addiction. As it increases the body's overall vulnerability and risk of collapse, it also seems to boost certain factors that help resist collapse."

When researchers screened the genome of the insomniac flies for changes in gene activity levels, they found altered activity levels for genes involved in metabolism, nerve cell activity and sensory perception. Shaw's lab had previously demonstrated that the activity levels of at least two of these genes are changed in sleep-deprived humans.

Researchers speculate that some genes altered by insomnia and sleep deprivation may simultaneously contribute to both detrimental and temporarily advantageous effects. Shaw has conducted follow-up studies of the altered genes and how restoring normal genetic activity levels affects insomnia and its symptoms. He will publish the results in a forthcoming paper.

More information: Seugnet L, Suzuki Y, Thimgan M, Donlea J, Gimbel SI, Gottschalk L, Duntley SP, Shaw PJ. Identifying sleep regulatory

genes using a Drosophila model of insomnia. *The Journal of Neuroscience*, June 3, 2009.

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