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FLIES ON CRACK: NEW STUDY ISOLATES GENE MUTATION RESPONSIVE TO COCAINE

Researchers at the University of California, San Francisco (UCSF) and New York University have discovered a gene mutation in fruit flies that alters sensitivity to crack cocaine and also regulates their internal body clock. The findings, reported in the December issue of Public Library of Science (PLoS) Biology, may have implications for understanding innate differences in sensitivity to cocaine in humans, potentially providing targets for development of drugs to treat or prevent addiction.

Headed by UCSF's Ulrike Heberlein, the research team discovered a mutation of the *Drosophila LIM-only* (*Lmo*) gene. Normal fruit flies increase their activity when exposed to low doses of crack cocaine over a one-minute period. At medium levels, fruit flies exhibit frenzied, jerky motions. At high doses, the flies become immobile. However, flies with the *Lmo* gene mutated were much more sensitive to crack cocaine and became immobile at much lower levels than normal fruit flies.

Heberlein's group also showed that *Lmo* is normally produced in the pacemaker neurons that control 24-hour—or circadian—rhythms of sleep/wake cycles in flies. Comprising about 10 cells per hemisphere, these neurons provide the fly with an internal clock, driving circadian rhythms of behavior even in the absence of light. While *Lmo* is found throughout the body, it is enriched in the brain. By expressing normal *Lmo* in over-sensitive mutants, the researchers discovered that *Lmo*'s cocaine-related effects were localized to the circadian pacemaker neurons.

The researchers then asked if the *Lmo* mutations also affect the normal rhythms in circadian behavior. Subsequently, NYU's Justin Blau, an assistant professor of biology, found that many *Lmo* mutant flies no longer had clear rhythms of sleep/wake cycles. Together, the two sets of findings showed that the new gene modulates sensitivity to cocaine within the cells of the fruit fly's internal clock.

Previous researchers had only been able to demonstrate that cocaine enhances the mammalian brain's ability to block re-uptake of dopamine by cells in a brain region called the nucleus acumbens. But numerous experiments show this is not the whole story. The latest study by Heberlein, Blau, and their colleagues reveal a more complex neurological process.

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From 400 different mutants, they identified seven with an increased response to cocaine, and for two of these, the disrupted gene was the same—*Lmo*. The *Lmo* protein, whose levels were reduced by the mutations, is known to regulate certain transcription factors during development. However, no developmental defects were detected in the loss-of-function mutants that might explain the cocaine effect. They also found that a third mutation in the same gene, previously associated with disruption in wing formation in fruit flies, *increased* levels of the *Lmo* protein and *decreased* response to cocaine. Thus, they concluded that *Lmo* appears to play a central role in regulating cocaine sensitivity.

The researchers suggested that because *Lmo*-related proteins are found in mammalian brains, the results may have implications for understanding innate differences in sensitivity to cocaine in humans, potentially providing targets for development of drugs to treat or prevent addiction.

“It’s been established the some individuals may be predisposed to addiction,” Blau added. “These findings suggest that a specific genetic make-up in humans could further explain why some individuals are more susceptible than others.”

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