Rejected flies turn to booze

Single neurotransmitter underlies rewards from sex and alcohol.

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A male fruitfly will try to court a female by nuzzling her genitals, tapping her abdomen and singing with his wings. If all that fails, he drowns his sorrows in booze.

Researchers from the University of California, San Francisco (UCSF), and the Howard Hughes Medical Institute's Janelia Farm Research Center near Ashburn, Virginia, have found that male fruitflies (*Drosophila melanogaster*) are more likely to choose to eat alcoholic food if they have been sexually rejected by females.

The team shows that a signalling chemical called neuropeptide F (NPF) in the fly's brain underpins this behaviour. Males have low levels of NPF if they are denied sex, and this apparently drives them to seek rewards in alcohol. Given extra NPF artificially, however, even a sex-starved male fly will turn away from the drink.

"The work provides a molecular link between natural rewards like sex, and drug rewards like alcohol," says Ulrike Heberlein, a neurologist at UCSF who led the study, which is published today in *Science*[1].

It is important to discover that the same chemical could underlie the rewarding nature of both sex and alcohol, says Todd Thiele, a neurobiologist who studies alcoholism at the University of North Carolina, Chapel Hill. The results fit in with the idea that alcohol co-opts or takes over the neural pathways that govern natural rewards, he explains: "an outcome that may lead to alcohol dependence".

A similar signalling chemical, called neuropeptide Y (NPY), acts in the human brain - and studies are already under way to see whether NPY levels are linked to preference for alcohol or addictive drugs.

Sex, drugs and NPF

In the fruitfly study, Janelia Farm neurologist Galit Shohat-Ophir subjected male flies to four days of repeated rejection by pairing them with females who had already mated. The spurned males preferred alcohol-spiked meals to their normal food, whereas mated males had no such preference. And if males got a last-minute chance to mate after rejection, their fondness for alcohol fell away.

By manipulating parts of the fly's brain that produced and received NPF, Shohat-Ophirshowed that reducing the amount of the neurotransmitter inclined flies towards alcoholic foods. But raising NPF removed that preference. NPF could also be rewarding without either sex or booze: when Shohat-Ophir conditioned the flies to associate a burst of NPF with a particular smell, they gravitated towards that smell.

In mammals, NPY might similarly act as a currency of reward. Stressful events can reduce levels of the neurotransmitter in mice and rats[2], which drink more alcohol if their NPY levels fall[3]. "There has been evidence in rodents for almost everything we have suggested, but I don't think anyone has tied it together," says Shohat-Ophir.

NPY could be the connection between negative experiences and humans seeking rewards in drug dependence. If so, Heberlein says, it might be possible to break this link by boosting levels of the neurotransmitter — like feeding NPF to flies to stop them turning to alcohol. Heberlein notes that people who have committed suicide[4] and those with post-traumatic stress disorder[5] (PTSD) tend to have

low brain levels of NPY, although the direction of cause and effect is unclear.

“NPY and drugs that affect the function of its receptors are already in clinical trials for anxiety, PTSD, mood disorders and obesity and have been suggested as treatment for alcoholism,” says Shohat-Ophir.

For now, Shohat-Ophir herself wants to stick with studying flies to understand what NPF does in the brain. Not all the connections are clear: for example, flies that consume alcohol don’t reduce their courtship behaviour. Shohat-Ophir suspects that NPF activates neurons that secrete dopamine, a chemical commonly associated with rewarding feelings. “We want more depth into the molecular mechanism,” she says.

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