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Bitter gustatory perception protects Drosophila from escalating cocaine consumption preference.

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Cocaine is a psychostimulant with high addictive potential and high estimated heritability for abuse. Despite this strong genetic component, little is known about the specific genes and mechanisms that lead to the development of cocaine use disorder and currently there are no FDA-approved pharmacotherapies to treat it. Drosophila is a proven model organism to understand mechanisms of alcohol use disorder. Flies exposed to cocaine become hyperactive and reduce their sleep, features of intoxication similar to those observed in mammals. However, as of now, there is no evidence of cocaine preference in flies. We show that this is due to flies sensing cocaine as bitter and therefore avoiding its consumption. Bitter gustatory sensory neurons in the flies' forelegs are directly activated by cocaine exposure, reducing the likelihood for proboscis extension and consumption when encountering cocaine-containing solution.

Mutants for the bitter sensing GPCR Gr66a as well as flies with inhibited bitter sensing neurons show a significant reduction in cocaine avoidance in naïve animals assayed for a short period of time (up to 3 hours). In a longitudinal assay, flies with reduced bitter perception consume cocaine and develop experience-dependent preference towards the drug within 12-18 hours.

This is the first demonstration that this highly amenable model organism can display preference for cocaine. Because of the rapid behavioral change, as well as the general economy of scale, this will allow for high-throughput testing of genes associated with cocaine use in human GWAS, thereby establishing functional relevance of associated candidate genes for cocaine consumption.