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Researchers Find Genes Involved in Nicotine Resistance in Fruit Flies

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North Carolina State University researchers have gleaned insight into the genes involved in resistance to nicotine in the lab rat of many gene studies – Drosophila melanogaster, the fruit fly.

The research team led by Dr. Greg Gibson, William Neal Reynolds Professor of Genetics, and his graduate student, Gisele Passador-Gurgel, found that regulation of levels of a certain enzyme – ornithine amino transferase – plays an important role in establishing how long flies can tolerate nicotine. Gibson says that the amount of enzyme seems to do two things – it influences flies' ability to strip away toxins, and it helps establish how much the drug stimulates them.

Working with Dr. Nigel Deighton, director of NC State's new Metabolomics and Proteomics Laboratory on Centennial Campus, the group found evidence that the enzyme may act by affecting the levels of the neurotransmitters glutamate and GABA in the brain. One possibility, Gibson says, is that the inhibitory neurotransmitter GABA may negate the stimulatory effects of nicotine and help flies survive longer.

The paper describing the research is published in the February 2007 edition of *Nature Genetics*.

When exposed to nicotine, fruit flies get the quick, stimulatory buzz every cigarette smoker craves, but it's all downhill after that. Nicotine is essentially lethal to flies; the flies in the study only lived from 10 to 60 hours after exposure to the drug. Unpublished work in the lab suggests

that the flies actually become addicted to the very drug that will end up killing them. The researchers ruled out one possible explanation for this – that surviving flies are the ones that can digest the drug. Instead, they found a way to look at the targets of nicotine activity.

To do this, they introduced a concept they call quantitative trait transcript (QTT) mapping. NC State over the years has made major contributions to finding genes, or quantitative trait loci, that contribute to complex traits. This work suggests that similar strategies can be pursued by looking at the RNA instead of the DNA. RNA is a readout of the DNA code. “We propose that you can use gene expression profiling across a diverse set of individuals to find genes that are important for quantitative traits, or genetically complex traits which are regulated by a large number of genes,” Gibson says.

An interesting sidelight in the study was the observation that flies from North Carolina are more resistant to nicotine than flies from California. The researchers found that 30 percent of the North Carolina flies lived longer after exposure to nicotine – thus were more resistant to nicotine – than all but one California fly.

Gibson isn’t sure why, although he has a few theories. North Carolina flies may garner resistance from living near tobacco fields. California flies may have genetically lost their ability to resist nicotine. Many pesticides are nicotine-based, too, so the flies could have evolved some response to insecticides.

Gibson cautions against taking the information learned from flies and applying it to humans and nicotine because “Drosophila and people are a bit different, although there are intriguing similarities,” he said. One intriguing set of genes they found also seems to be activated in the lungs of human smokers, for example.

More importantly, he says, the QTT approach can be viewed as a way forward in the quest to provide “personalized” medicine; that is, providing drugs to people based on specific knowledge of their particular genomic identity.

Citation: “Quantitative Trait Transcripts for Nicotine Resistance in Drosophila Melanogaster”, Gisele Passador-Gurgel, Priscilla Hunt, Nigel Deighton and Greg Gibson, North Carolina State University; Wen-Ping Hsieh, National Tsing Hua University, Taiwan
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