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Alcohol Addiction: Chronic Ethanol Leads to Cognitive Dependence in *Drosophila*

Recent studies have found that *Drosophila* show detrimental effects of withdrawal from ethanol on learning, a preference for stimuli associated with intoxication, and a tendency to consume ethanol after frustrating social situations.

Conny H. Lin[2] and Catharine H. Rankin[1,2]

In their natural environment *Drosophila* breed on decaying plants and fungi. Rotting fruit often ferments and produces ethanol. Can flies become alcoholics as a result of this exposure to ethanol? This is not as foolish a question as it may at first seem. Recently, several studies have shown interesting effects of ethanol on *Drosophila* behavior that are strikingly similar to the kind of experiences humans have with alcohol, and that suggest *Drosophila* are an excellent model for understanding the biological foundations of these behavioral effects.

Alcoholics often report that they function better when they are drinking than when they stop. As they report in this issue of *Current Biology*, Robinson *et al.* [1] exposed *Drosophila* larvae to ethanol for five or six days and then tested their ability to learn in the presence or absence of ethanol. When *Drosophila* larvae are presented with an attractive smell paired with life-threatening heat shock, they learn to avoid the attractive smell. Larvae that were exposed to ethanol and then are without it for a day moved away from heat shock just as quickly as non-exposed larvae, but they did not learn to recognize the attractive smell that predicted the life-threatening heat shocks. Supplying the exposed larvae with ethanol restored this learning ability. Interestingly, flies exposed to ethanol for six days and tested with ethanol were also able to learn. The disruption of learning only occurred when exposed flies were removed from ethanol.

In mammals, alcohol is a nervous system depressant, turning down neuronal excitability [2]. In response the nervous system raises baseline neuronal excitability through a number of cellular and molecular changes to counteract this depressing effect of alcohol. These changes can include enhancing the excitatory N-methyl-D-aspartate (NMDA) signals and dampening the inhibitory γ-amino-butyric acid (GABA) signals. Together, the neuroadaptation to alcohol produces a hyper-excitable nervous system. This hyperactive nervous system is dependent on the presence of alcohol; otherwise, the hyperactive state can lead to over-excitatory consequences such as seizures. Interestingly, Robinson *et al.* [1] observed that the alcohol exposed *Drosophila* larvae tended to have seizures during withdrawal as well. Reinstating alcohol to exposed larva reduced the seizure tendency. This suggests that the larvae created a hyper-excitable nervous system through neuroadaptation to alcohol. The authors conclude that the flies exhibited chronic ethanol adaptation and that abstinence precipitated a withdrawal syndrome.

How does ethanol withdrawal affect learning and memory? Much is known about the learning and memory mechanisms and neuronal circuitry in *Drosophila*. Adult and larva *Drosophila* share the same olfactory associative learning center, the mushroom bodies, and the same genes are necessary for learning in both adult and larval flies [3,4]. Khurana *et al.* [3] showed that associative learning of smell and electric shock by fly larvae requires *dunce*, *rutabaga*, *radish*, and

amnesiac, the same genes required in adult fly learning. Recently Khurana *et al.* [4] found that *dunce* is involved in short-term memory in the same odor-heat shock paradigm Robinson *et al.* [1] used to study alcohol dependency.

The *dunce*, *rutabaga*, *radish*, and *amnesiac* genes encode components of the cAMP cascade that are also well-known ethanol targets [3,4]. *Dunce* encodes a cAMP-specific phosphodiesterase; *rutabaga* encodes an adenylyl cyclase; and *amnesiac* encodes an adenylyl cyclase-activating neuropeptide that has been shown to be hypersensitive to ethanol. The identity of *radish* was unknown until Guan *et al.* [5] recently discovered that the radish protein is a PKA phosphorylation target that travels between the nucleus and cytoplasm. These authors also showed that *dunce*, *rutabaga*, *radish*, and *amnesiac* mutation each disrupts specific aspects of synaptic connectivity. This finding increased our understanding for the role of the members in the cAMP cascade in synaptic reorganization. Connecting the cAMP cascade back to alcohol, a recent study demonstrated a key role for *rutabaga* in ethanol self-administration: Xu *et al.* [6] showed that flies preferred food with ethanol to food without ethanol and this preference was dependent on expression of *rutabaga* in the mushroom bodies. This shows an interesting convergence of ethanol self-administration and olfactory associative memory behavior onto *rutabaga* in the mushroom bodies. Future studies using Robinson *et al.*'s [1] model might reveal more about the relationship of the two.

Humans often drink too much because they find being drunk rewarding in some way. Do *Drosophila* find being drunk rewarding? Will they turn to drink to drown their sorrows? Two recent studies [7,8] have shown remarkable parallels between ethanol consumption in flies and humans. Kaun *et al.* [7] developed a conditioned place preference paradigm for flies and showed that flies perceive intoxicating levels of ethanol as rewarding. Flies were exposed to two odors, one in the presence of intoxicating levels of ethanol vapors, the other without. After training, flies preferred the odor that had been paired with the high level of ethanol! As in mammals this preference was dependent on dopamine. In this paradigm flies were exposed to ethanol vapor by the experimenters, but the question remained as to what might make flies voluntarily consume ethanol.

A clever study by Shohat-Ophir *et al.* [8] indicated that, like humans, flies try to drink their troubles away! One group of male flies was exposed to one-hour sessions of rejection by already mated females three times a day for four days, and another group to six-hour sessions of mating with multiple receptive virgin females for four days. Flies were then exposed to a two-choice task where they could consume food with or without ethanol. As you might guess, flies that had experienced repeated rejection consumed significantly more ethanol than successful flies! Shohat-Ophir *et al.* [8] showed that this increase in ethanol consumption was directly linked to an increase in expression of a neuropeptide, NPF, as failure at mating led to a decrease in NPF expression, while decreases in NPF expression led to increased ethanol consumption. The mammalian homolog of NPF is neuropeptide Y (NPY). In the nematode *Caenorhabditis elegans*, the NPY receptor homolog NPR-1 regulates ethanol behaviors [9]; in mammals stressful experiences regulate NPY levels, and NPY-deficient rats drink more ethanol than controls [10]. Thus, across phylogeny, the relationship between social stress, NPY and ethanol consumption seems to be remarkably conserved.

Will the rejected male flies become addicted to ethanol? Will they show cognitive dependence such that their ability to learn and remember will become dependent on the presence of ethanol? Will they lose their jobs and beat their larvae? Stay tuned — drunk flies can teach us a lot about the mechanisms underlying the debilitating aspects that ethanol has on human behavior!

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Speciation: Clash of the Genomes

Complete genomes of hybridizing bird species demonstrate the importance of the sex chromosomes, telomeres and centromeres to the initial stages of speciation.

Bettina Harr[1,*] and Trevor Price[2]

Living in central Sweden in the 18th century, Carl Linnaeus apparently did not see the Pied flycatcher (*Ficedula hypoleuca*), now one of Sweden's most common breeding birds (Figure 1) [1]. Nor would he have seen the Collared