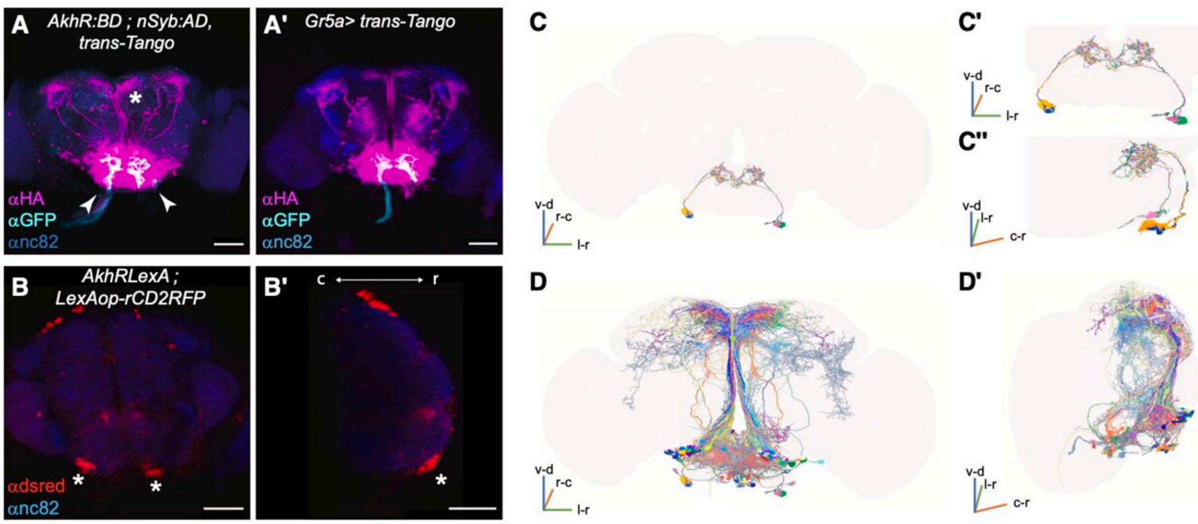
How hunger influences aversive learning in fruit flies

September 1 2024, by Ingrid Fadelli



AKHR neurons connect to DANs via ascending SEZ output neurons. Credit: *Neuron* (2024). DOI: 10.1016/j.neuron.2024.04.035

Internal states that animals experience while they are thirsty, hungry, sleepy or aggressive have been found to be linked with the combined activity of various neuromodulators and neurotransmitters. These chemical messengers can drastically change the excitability and functional connectivity of neurons, which in turn plays a role in shaping the animals' behavior.

Past studies on Drosophila (small fruit flies) showed that energy homeostasis in these insects is regulated by various neurohormones/modulators, which impact their physiology and behavior in different ways. These include insulin-like peptides (dILPs) and adipokinetic hormone (AKH), hormones with the same functions as insulin and glucagon in mammals, respectively.

Researchers at University of Oxford's Center for Neural Circuits and Behavior recently carried out a study investigating how these hunger-associated neurohormones influence the learning of associations between stimuli and unpleasant or negative outcomes (i.e., aversive learning) in fruit flies. Their paper, published in *Neuron*, shows that the hormone AKH plays a key role in modulating aversive reinforcement learning.

"Hungry animals need compensatory mechanisms to maintain flexible brain function, while modulation reconfigures circuits to prioritize resource seeking," Eleonora Meschi, Lucille Duquenoy and their colleagues wrote in their paper. "In Drosophila, hunger inhibits aversively reinforcing dopaminergic neurons (DANs) to permit the expression of food-seeking memories. Multitasking the reinforcement system for motivation potentially undermines aversive learning."

Aversive learning is an evolutionary process through which animals start to associate specific stimuli with unpleasant outcomes, after repeated negative experiences following the exposure to these stimuli. This often results in behaviors aimed at trying to avoid the stimulus and the experiences associated with it.

Fruit flies, for instance, can be trained to associate specific odors with electric shocks or alternatively with positive rewards (e.g., the intake of sugar or other nutrients). The researchers set out to investigate whether hunger modulated the establishment of connections between an odor and electric shocks in flies.

To do this, they deprived flies of food for a period of 24 hours and explored how this affected their aversive learning. The team then used various optogenetic techniques and in vivo imaging tools to better understand the role that neurohormones played in the effects they observed.

"We find that chronic hunger mildly enhances aversive learning and that satiated-baseline and hunger-enhanced learning require endocrine adipokinetic hormone (AKH) signaling," wrote Meschi, Duquenoy and their colleagues. "Circulating AKH influences aversive learning via its receptor in four neurons in the ventral brain, two of which are octopaminergic."

The researchers' experiments revealed that AKH, the fly equivalent of glucagon, sets baseline and hunger-enhanced levels of aversive learning, acting through specific neurons that release the neurotransmitter octopamine. This neurotransmitter modulates the inputs sent to dopaminergic neurons involved in reinforcement aversive learning.

"Connectomics revealed AKH receptor-expressing neurons to be upstream of several classes of ascending neurons, many of which are presynaptic to aversively reinforcing DANs," wrote Meschi, Duquenov and their colleagues.

"Octopaminergic modulation of and output from at least one of these ascending pathways is required for shock- and bitter-taste-reinforced aversive learning. We propose that coordinated enhancement of input compensates for hunger-directed inhibition of aversive DANs to preserve reinforcement when required."

The findings of this recent study contribute to the understanding of how hunger affects aversive learning in Drosophila, specifically highlighting the key role of the neurohormone AKH. In the future, it could inspire further research aimed at validating the patterns observed by the researchers across other animal models.

More information: Eleonora Meschi et al, Compensatory enhancement of input maintains aversive dopaminergic reinforcement in hungry Drosophila, *Neuron* (2024). DOI: 10.1016/j.neuron.2024.04.035