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Genetic and Molecular Studies of Learning and Memory in *Drosophila*

Fruit flies can learn. They can identify a specific chemical odor that they have experienced with electric shock and avoid it. Moreover, they can remember to avoid it for several days. The Quinn lab is investigating the molecular mechanisms underlying learning acquisition and memory storage by inducing and selecting single-gene mutations that affect learning or memory, and by engineering transgenic fly strains that disrupt these processes.

Two of the first learning mutations-*rutabaga* and *dunce*- affect the enzymes adenylyl cyclase and cyclic-AMP phosphodiesterase respectively. This implicates the second-messenger molecule cyclic AMP as central in *Drosophila* learning. The lab has manipulated enzymes downstream from cyclic AMP (e.g.. CREB) by genetic engineering and has found defects on learning and memory. Nevertheless they believe that the straightest path to genuinely novel information about learning involves isolating new mutants that affect learning and cloning the altered genes. Of the mutants we have isolated *radish* has by far the most interesting behavior. Mutant radish flies flunk one long-term memory test established by vertebrate researchers, but they pass the second like normal flies. Thus studies with *radish* indicate that there are at least two separate types of long-term memory. Understanding one form of long-term memory - consolidated memory - depends on cloning the *radish* gene. The lab has localized the *radish* gene to a 180-kilobase interval of DNA on the fly's X-chromosome and is intensively involved in finding the relevant gene transcript within this interval.

Amnesiac was isolated years ago in the Quinn lab as a forgetful fly. The lab isolated another (rapidly clonable) mutant allele of *amnesiac* on the basis of its ability to suppress the female-sterility of another learning mutant,*dunce*.The *amnesiac* gene encodes the precursor of a peptide neurotransmitter.

Selecting mutant strains by breeding populations and testing them for learning is labor-intensive. The expedited cloning of *amnesiac* indicated a shortcut. Mutant, *dunce* flies lack a cyclic AMP (cAMP) metabolizing enzyme, and these flies have elevated cAMP levels in their tissues. Learning-mutant *amnesiac* (in cAMP-stimulatory neuropeptide) have compensatory defects; these restore female fertility. The lab has started a generalized screen for secondary mutations that suppress *dunce's* female sterility, and they have isolated several intriguing new genes -e.g., novel transcription factors and identified second-messenger molecules.

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