SnapShot: Olfactory Classical Conditioning of *Drosophila*

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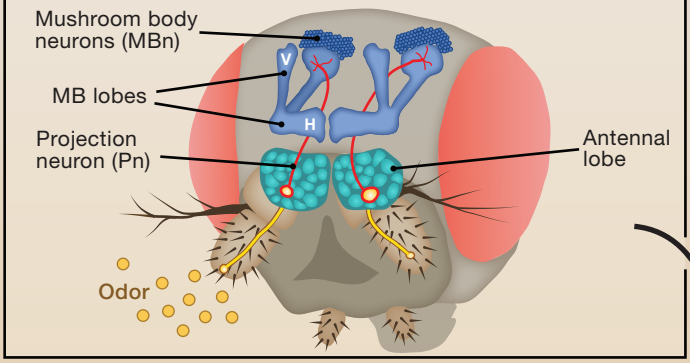
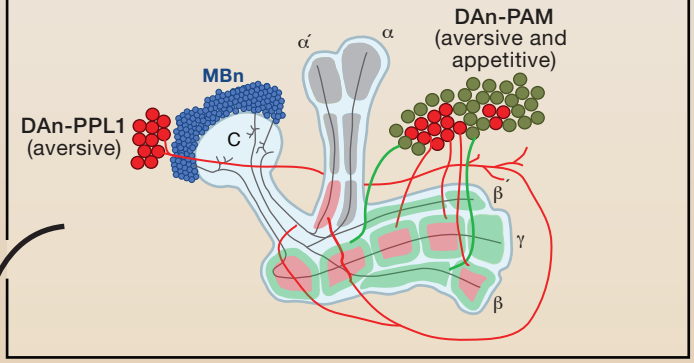
Cell

1 Conditioned stimulus (CS) pathway



2 Unconditioned stimulus (US) pathway



3 Acquisition

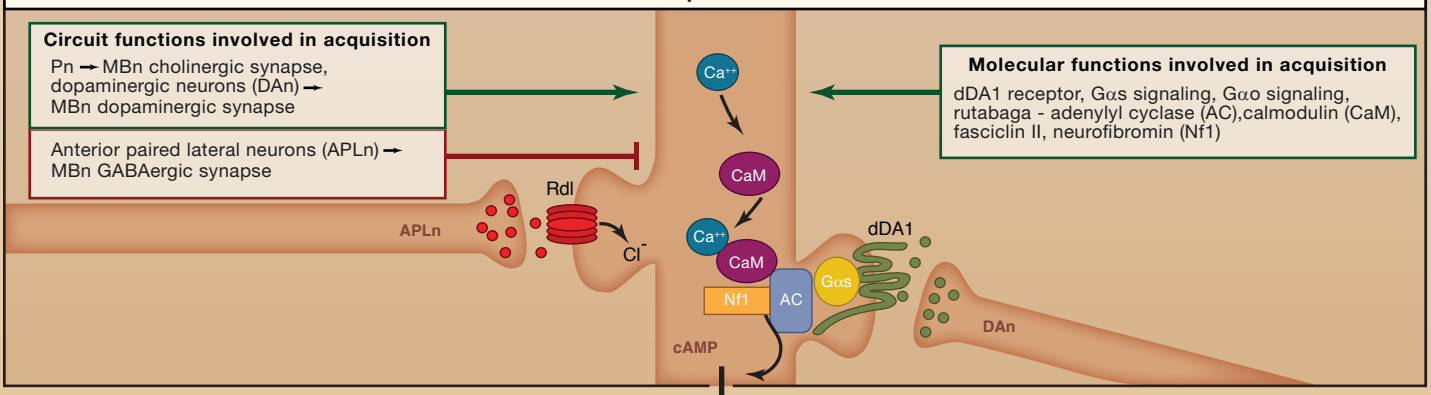
Circuit functions involved in acquisition

Pn → MBn cholinergic synapse, dopaminergic neurons (DAn) → MBn dopaminergic synapse

Anterior paired lateral neurons (APLn) → MBn GABAergic synapse

Molecular functions involved in acquisition

dDA1 receptor, Gαs signaling, Gαo signaling, rutabaga - adenylyl cyclase (AC),calmodulin (CaM), fasciclin II, neurofibromin (Nf1)



4 Short-term memory (STM)

Molecular functions involved in STM

Synaptic proteins (bruchpilot, glutamate receptor subunits, integrins, synapsin), voltage-gated potassium channels, signal transduction molecules (cAMP, PDE, PKA,14-3-3, casein kinase 1γ), and others

5 Intermediate-term memory (ITM)/consolidation

Circuit functions involved in ITM/consolidation

Dorsal paired medial neurons (DPMn)

Molecular functions involved in ITM/consolidation

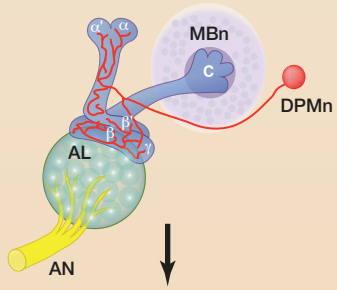
Amnesiac gene product

Circuit functions involved in LTM

Dorsal anterior lateral neurons (DALn)

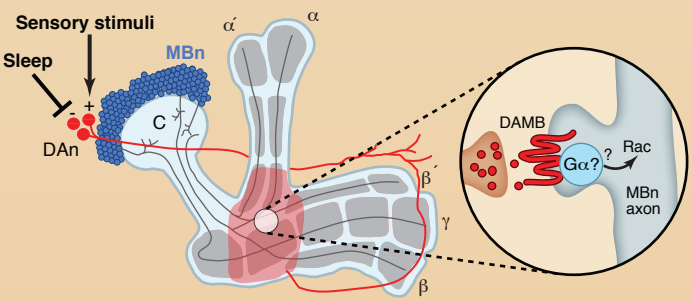
Molecular functions involved in LTM

Creb, staufen, pumilio, oskar, Cpeb, and others

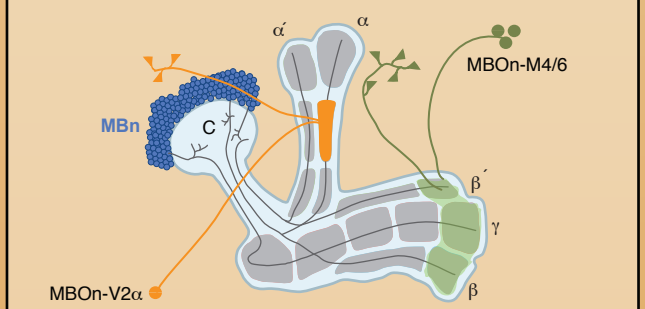


6 Long-term memory (LTM)

7 Active forgetting



8 Memory expression



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Classical conditioning with odor cues occurs when a specific odor conditioned stimulus (CS) is paired with an aversive unconditioned stimulus (US) such as electric shock or an appetitive US such as a food reward (Tomchik and Davis, 2013). This conditioning produces avoidance behavior to odors associated with an aversive US and approach behavior to those associated with an appetitive US. The memory components from such conditioning include acquisition; short-, intermediate- (consolidation), and long-term memory; active forgetting; and memory expression. Many different types of neurons within the olfactory nervous system—brain structures primarily involved in the processing of odorant cues—contribute to olfactory memory formation.

1. Conditioned Stimulus Pathway: The sensation and perception of specific odors (yellow circles) occurs from the activation of olfactory receptor neurons (ORn) in the antenna. Odor identity is established by the activation of odor-specific sets of projection neurons (Pn, red) located in the antennal lobe (AL, turquoise), the equivalent of the olfactory bulb in vertebrates (Masse et al., 2009). The Pn transmit odor identity to synapses (red branches) with the mushroom body neurons (MBn, blue circles) in the dorsal posterior brain. The MBn fall into three major classes, the α/β, α′/β′, and γ MBn (see 2). Their axons project through neuropil known as the horizontal (H) and vertical (V) MB lobes (blue), named according to the class of axons they contain. MBn are thus third order in the olfactory pathway (Tomchik and Davis, 2013).

2. Unconditioned Stimulus Pathway: Accumulated evidence indicates that dopaminergic neurons (DAn) are necessary and sufficient to serve as the US signal (Waddell, 2013). Two clusters of DAn (PPL1 and PAM) serve this purpose and innervate segments of the horizontal and vertical lobes. Those DAn providing aversive and appetitive US are colored red and green, respectively, along with the MB lobe regions that they innervate.

3. Acquisition: Acquisition occurs, in part, through the temporal coincidence of the odor CS and the aversive or appetitive US. MBn are intimately involved in acquisition. Information about the odor CS conveyed by Pn is transmitted to the MBn by the activation of MBn-expressed ACh receptors. This leads to an increase in intracellular calcium concentration. The US information is transmitted from DAn to MBn using the dopamine receptor, dDA1. Increased calcium, along with the activation of the dDA1 receptor on the MBn, produces a synergistic increase in cAMP concentration. The mobilization of the cAMP signaling system is essential for acquisition. Many different molecules are required for acquisition, including the relevant receptors, calmodulin-activated adenylyl cyclase, neurofibromin, and others. GABAergic input to receptors expressed by MBn from the APLn constrains acquisition (Tomchik and Davis, 2013).

4. Short-Term Memory (STM): Short-term memory is brought about, in part, through plastic changes in the MBn and other cell types due to the transient increase in cAMP level. Genetics and molecular biology have identified many different molecules required for STM, including various synaptic proteins, ion channels, cAMP signaling molecules, and others. A memory trace corresponding to STM, observed as an increased calcium response to the CS+ odor after aversive conditioning, is observed in the axons of the α′/β′ MBn (Tomchik and Davis, 2013; Davis, 2011).

5. Intermediate-Term Memory (ITM)/Consolidation: Consolidation into protein-synthesis-dependent LTM occurs across the first few hours after conditioning, making it difficult to distinguish effects of mutations on a specific temporal form of memory—ITM—or the process of consolidation. ITM/consolidation requires the reciprocal interactions between dorsal paired medial neurons (DPMn) and the MBn. The *amnesiac* gene product, expressed by the DPMn, is required for the expression of protein-synthesis-dependent LTM. A memory trace corresponding to ITM is observed in the processes of the DPMn innervating the vertical MB lobes (Tomchik and Davis, 2013; Davis, 2011).

6. Long-Term Memory (LTM): Protein-synthesis-dependent LTM requires the actions of the transcription factor, Creb, in the MBn along with genetic functions for local translation (staufen, pumilio, oskar, Cpeb) and a host of other genetic functions specifically involved in LTM. In addition to the MBn, the dorsal anterior lateral neurons (DALn, not shown) are required for LTM. A memory trace corresponding to LTM is observed in the vertical axons of the α/β MBn (Dubnau et al., 2003; Davis, 2011).

7. Active Forgetting: One mechanism for active forgetting involves release of dopamine (DA) from a small group of DAn (red) clustered near the MB calyx (C). These DAn innervate the MBn axons in an area joining the vertical and horizontal lobes. DA activates a receptor named DAMB that initiates the forgetting of memory traces stored in the MBn. This DA signal is suppressed by the state of sleep and is activated by sensory stimuli (Berry et al., 2015). The intracellular signaling for this receptor is at present unclear but may involve the downstream activation of the small G protein, Rac (Shuai et al., 2010).

8. Memory Expression: Synaptic output from a small group of glutamatergic neurons (MBOn-M4/6, green) that project dendrites into the distal tips of the horizontal lobes is required for the expression of both aversive and appetitive ITM and appetitive LTM. These neurons project their axons to a terminal field residing between the vertical and horizontal lobes. A memory trace, observed as an increased calcium response to the CS+ odor after aversive conditioning and a decreased response to the CS+ odor after appetitive conditioning, is observed in the dendrites of these neurons (Owald et al., 2015). Synaptic output from a small group of cholinergic neurons (MBOn-V2α, orange) that project dendrites into a defined segment of the vertical lobe is also required for the expression of aversive ITM and LTM (Séjourné et al., 2011). These neurons project their axons to lateral regions of the brain. A memory trace, observed as a decreased calcium response to the CS+ odor after aversive conditioning, is observed in the dendrites of these neurons. The relative activity of these and other MBOn with dendritic arbors in other segments of the MB lobes is thought to capture and integrate the activity of MBn to help drive avoidance or approach behavior (Aso et al., 2014).

ABBREVIATIONS

CS, conditioned stimulus; US, unconditioned stimulus; ORn, olfactory receptor neuron; Pn, projection neuron; MBn, mushroom body neuron; DA, dopamine; DAn, dopamine neuron; ACh, acetylcholine; APLn, anterior paired lateral neuron; STM, short-term memory; ITM, intermediate-term memory; AN, antennal nerve; LTM, long-term memory; DPMn, dorsal paired medial neuron; DALn, dorsal anterior lateral neuron; C, mushroom body calyx; MBOn, mushroom body output neuron.

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Dr. J. Berry produced some of the original artwork for a prior publication. The artwork has been modified and reproduced with permission from Berry and Davis (Progress in Brain Research 208, 293–304) and Davis (Neuron *70*, 8–19). I thank S. Tomchik and J. Berry for comments. Research was supported by R37NS19904-32 and 5R01NS052351-09.

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