This Week in The Journal

Extending an Olfactory Critical Period in *Drosophila*

Ankita Chodankar, Madhumala K. Sadanandappa, Krishnaswamy VijayRaghavan, and Mani Ramaswami

(see pages 5549–5560)

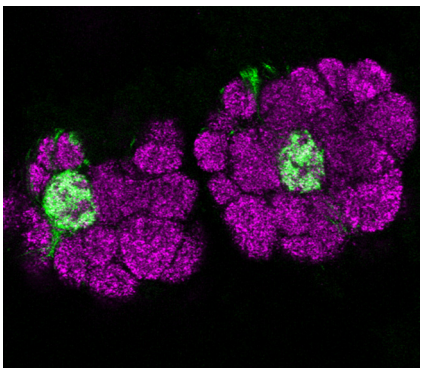
Sensory systems are designed to extract information from the environment; because constant stimuli provide little information, the nervous system reduces its responses to such stimuli. These adaptations can be mediated by short-term changes, like receptor desensitization, or much longer lasting changes involving circuit remodeling. Circuit remodeling is often restricted to critical periods early in life, however.

In *Drosophila* flies, continuous exposure to an odor for 4 d induces long-term habituation that lasts ~6 d. This habituation is mediated by increased inhibitory input to antennal lobe projection neurons (PNs) from local interneurons (LNs), and it is accompanied by volume changes selectively in glomeruli activated by the habituating odor. Notably, long-term habituation for several aversive odors, including CO_2 and ethyl butyrate, can only be induced in young flies. In contrast, no critical period exists for long-term habituation to the attractive odor geranyl acetate.

To better understand critical periods for olfactory habituation, Chodankar et al. exposed flies of different ages to CO_2 or ethyl butyrate. Four-day odor exposure beginning <36 h after eclosion induced long-term behavioral habituation accompanied by enlargement of odor-specific glomeruli. No behavioral habituation or volume changes occurred if odor exposure began >48 h after eclosion, however, unless olfactory sensory neurons were silenced for the first 48 h after eclosion. Importantly, selectively silencing sensory neurons that respond to a particular odor extended the critical period only for that odor.

Glomerular enlargement during habituation was accompanied by increases in dendritic arborization and postsynaptic sites only in PNs in glomeruli that responded to the habituating odor. Like behavioral habituation and glomerular growth, the increase in PN dendritic arborization required the expression of *rutabaga*, a Ca^{2+}/calmodulin-responsive adenylyl cyclase, in LNs. *Rutabaga* expression was also required in LNs for habitation-associated glomerular growth induced by geranyl acetate exposure.

These results show that closure of the critical period for long-term habituation in flies, like closure of the critical period for ocular dominance plasticity in mammals, requires sensory experience. Importantly, this regulation can be restricted to specific glomeruli by selectively silencing input to those glomeruli. How sensory experience closes the critical period and why the critical period does not close for geranyl acetate despite similar mechanisms of habituation must be investigated in future work.



Presynaptic terminals (purple) delineate olfactory glomeruli in *Drosophila* antennal lobes. VA6 glomeruli are innervated by sensory neurons that respond to geranyl acetate (green). See Chodankar et al. for details.

Links between Inflammation, Glucose, and Brain Function

John Kealy, Carol Murray, Eadaoin W. Griffin, Ana Belen Lopez-Rodriguez, Dáire Healy, et al.

(see pages 5681–5696)

Cytokines released during peripheral infections alter brain function, suppressing the desire to engage in physical activity and social interactions. These effects help conserve energy, promote recovery, and limit the spread of infection. But peripheral infections can also have detrimental effects on brain function, particularly by causing delirium, characterized by sudden, fluctuating attention deficits, confusion, and other cognitive symptoms. Although these symptoms typically resolve within a day, they can persist for months, prolong recovery, and increase the risk of dementia. Delirium is rare in otherwise healthy adults, but it is common in elderly people and those with underlying neurological conditions, in whom it occurs after >50% of hip fracture surgeries and sometimes during minor infections (Cunningham and MacLullich, 2013, Brain Behav Immun 28:1–13).

How cytokines alter behavior and why pre-existing neurological conditions increase the risk of delirium are incompletely understood. Kealy, Murray, et al. hypothesized that deficient glucose metabolism plays a role. To test this, they examined the relationship between blood glucose levels and sickness behaviors induced in mice by peripheral injection of the inflammatory agent lipopolysaccharide (LPS). As expected, LPS reduced spontaneous locomotion and increased plasma levels of the cytokine interleukin-1β. It also reduced blood and CSF glucose levels. Notably, activity levels were correlated with blood glucose levels in LPS-injected mice, but not in control mice. Moreover, glucose administration increased locomotion in LPS-treated mice without affecting interleukin-1β levels, and interfering with interleukin-1β signaling had no effect on LPS-induced decreases in blood glucose levels or spontaneous locomotion.

Like delirium, working memory is impaired after LPS injection only in mice with pre-existing conditions, such as prion-induced neurodegeneration. Kealy, Murray, et al. showed that insulin, which lowers blood glucose levels, also caused working-memory deficits selectively in mice with prion-induced neurodegeneration, and that glucose administration reduced LPS-induced working-memory deficits in such mice. Finally, markers of impaired glucose metabolism were higher in CSF of elderly patients who experienced delirium after hip fracture surgery than in patients who did not experience delirium.

These results suggest that systemic inflammation reduces blood glucose levels and that this hypoglycemia, rather than interleukin-1β, underlies reductions in activity. Impaired glucose metabolism associated with age or neurodegenerative disease may exacerbate the effects of infection-associated hypoglycemia, and thus increase the risk of delirium.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.40.29.2020