Dispatches

Appetitive Learning: Memories Need Calories

Recent studies of the way animals learn challenge the idea that food learning relies mainly on how food tastes. Work on *Drosophila* has now shown that flies must ingest food with a metabolic benefit to form a lasting memory for a learned odour.

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Knowing how to identify rewarding food is one of the most important things we animals learn. On my desk is a picture of a three-tier sponge cake adorned with flowers. The picture of the creamy cake is enough to trigger memories of how I felt during and after consuming other cakes (my mouth is watering). In his classical studies with dogs, Pavlov discovered that visual or auditory stimuli could be conditioned by pairing them with a closely timed presentation of a sensory cue that reflexively produced an instinctual behaviour, for example salivation when sucrose is applied to the tongue [1]. Pavlov inferred that the brain can learn the temporal contingency that one sensory event can predict another; in his experiments, this was often an auditory cue that predicted the arrival of the taste of food.

Since Pavlov, the notion that appetitive learning results from temporally-structured sensory input has dominated the way we think about the way the brain learns about nutritious food. A recent series of papers, including two in this issue of *Current Biology* [2,3], has begun to challenge this idea. Independently, three labs have now shown that sweet taste is not enough to form a lasting preference for associated visual or olfactory cues. In addition, these groups found that an animal's preferences could be formed after the consumption of a metabolically rewarding but tasteless food.

A recent experiment with mice first hinted that a food's rewarding properties depend as much on its caloric value as its taste [4]. Mice with defective taste receptor genes preferred to feed from bottles containing sucrose solution in spite of the fact that they lacked the ability to taste it. Wild-type mice liked the taste of the 'artificial sweetener' sucralose — a substance that tastes sweet but provides no caloric benefit — but neither the taste-defective nor wild-type mice developed a lasting preference for bottles containing sucralose.

Two groups now report convincing evidence that fruit flies evaluate the reward quality of food independently of their sense of taste during learning (Figure 1) [2,3]. To test this idea, both groups trained flies using combinations of foods containing non-metabolisable, sweet-tasting sugars, such as arabinose, or tasteless but metabolisable sugar alcohols, such as sorbitol. They found that flies responded to arabinose as if it was as sweet as sucrose, but the flies could not survive by feeding on arabinose alone. Both groups also observed that even though the flies could not taste sorbitol, they survived when left no choice but to feed on it. Using an established assay for training flies to associate odours with sucrose [5], Burke and Waddell [2] found that flies rapidly learned to associate calorie-less arabinose with an odour; in fact, they learned it as quickly as if they had been trained with sucrose. Using another learning paradigm, Fujita and Tanimura [3] showed that flies could learn to pair an odour with tasteless sorbitol, though in this case it took the flies several hours to learn the association.

Learning how to identify a signal associated with food is only useful for survival if one can remember it. In a pivotal experiment, Burke and Waddell [2] provide a link between how much of learning is due to paired sensory input and how much is due to its metabolic value. They found that flies do not form a lasting memory for odours associated with metabolically false rewards. To establish that the 'sugar hit' was the necessary ingredient in the formation of a long-term memory, they added sorbitol to arabinose to provide the metabolic reward missing during olfactory conditioning. This time, the flies remembered the odour as well as if they had been trained with sucrose. Strikingly, they found that the post-ingestive evaluation of reward quality happens very rapidly: given an immediate choice between an odour signalling arabinose laced with sorbitol or an odour signalling arabinose alone, the flies ran towards the odour previously associated with the arabinose-sorbitol solution. When given a reward that was both sweet and calorific, the flies learned quickly and remembered well.

What is the mechanism that causes the nutrition gained from consuming food to influence the formation of long-term memories for visual, auditory, or olfactory cues? The answer may lie in the changes that occur in the blood that are detected throughout an animal's body, including the brain. de Araujo *et al.* [4] hypothesized that an increase in haematic glucose could be the signal

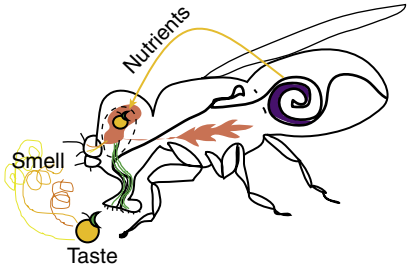

Figure 1. Sketch of a cross-section of a fruit fly.

When flies learn to identify odours associated with good food items, they use a presently unknown post-ingestive pathway (orange line) as well as their sense of taste to inform them about the food's nutritional value. This nutrient pathway activates the consolidation of long-term olfactory memories. Purple indicates the fly's midgut; green lines indicate taste projections; pink indicates the central ganglion and the fused thoracic/abdominal ganglia.

that affects neurons in the mouse brain. When this group fed mice sucrose, they found that blood glucose peaked about 20 minutes afterwards. The change in blood glucose accompanying sucrose consumption also increased activity in the 'reward' neurons in the nucleus accumbens (the so-called 'pleasure' centre of the brain) when the taste defective mice licked the bottle they associated with reward. If changes in blood sugar are involved in the brain's evaluation of reward, the experiments by Burke and Waddell [2] suggest that these changes happen rapidly in flies, as the flies in their assay were able to recognize an odour based on the metabolic quality of its associated reward within a few minutes.

Whether the brain detects the metabolic quality of a consumed reward using glucose as the signal or whether this signal also involves other molecules like insulin [6,7] are mysteries yet to be solved. Intriguingly, fruit flies express gustatory receptors throughout their bodies [8], including their central brain neuropil structures. One receptor class, Gr28, has been found highly expressed in the suboesophageal ganglion [8], a structure involved in the regulation of feeding behaviour [9]. Post-ingestive signals could target the suboesophageal ganglion or act more directly on the circuits involved in establishing olfactory memories. For example, a fruit fly's long-term appetitive olfactory memories are established and maintained in a subset of neurons in the mushroom body [5,10]. If sugar receptors were expressed in these neurons, their activation by glucose could affect the protein-synthesis-dependent processes underlying long-term memory formation [11]. Alternatively, neurons projecting to the mushroom bodies could provide information about nutrient status to impact long-term memory consolidation [12].

These experiments collectively show that while sweet taste can facilitate rapid learning, lasting memories depend on whether or not the food reward had real value to the animal. The fact that both mice and flies need a metabolic reward to remember an odour-taste association may reflect conserved mechanisms in animals for behaviours involved in the regulation of feeding. This might have medical ramifications if the artificial sweeteners that we use by the tonne to sweeten our foods and drinks are only fooling our brains in the short-term. Surely every cake I've eaten before contained the real thing.

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Cell Migration: Katanin Gives Microtubules a Trim

New evidence suggests that katanin — best known for severing microtubules in their more stable regions — localizes at the leading edge of migratory cells and trims microtubules at their dynamic plus ends.

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In recent years biological research has resulted in an expanding knowledge of the toolbox of proteins and mechanisms used by cells to get their work done. Cells of various types need to accomplish tasks such as division, migration, polarization, and extension of processes. Microtubules are instrumental to these various tasks, acting as architectural elements, force transduction elements, and also as railways for organelle transport. The ability of cells to rapidly reconfigure microtubules from one type of array into another, or to enable the microtubules to participate in complex processes, such as cell division or migration, requires proteins that very precisely take apart microtubules so that other proteins can then put them back together, as needed, and where needed. Studies have emerged from various laboratories on a category of enzymes called microtubule-severing proteins that hydrolyze ATP in order to break the lattice of the microtubule. In an exciting turn of events, a new paper now shows that katanin, the prototype microtubule-severing protein, can sever and/or depolymerize microtubules at their highly dynamic plus ends within