Neuroscience

Cerebellar neurons that curb food consumption

Richard Simerly & Ralph DiLeone

Artificial activation of neurons identified in a brain region called the cerebellum reduces food intake in mice. The findings could have implications for people with appetite disorders. See p.269

The desire to consume food is one of the strongest drives in nature, and its opposition by inhibitory signals is required to maintain an optimal energy balance. In calorie-rich environments, how much we eat is jointly influenced by our internal state (for example, how hungry we feel) and the effect of environmental cues, such as the aroma or visual appeal of food. When we are hungry and see or smell a meal, we initiate a series of actions that will lead to us consuming the food. If we feel full or lack an appetite, we would probably push the plate away and end the meal. Low *et al.*[1] show on page 269 that neuronal cells in a brain region called the cerebellum have a key role in regulating satiety and meal termination.

When the delicate balance between the drive to eat and the signals that counteract this drive is disrupted, unhealthy patterns of eating behaviour can occur. For example, individuals with Prader–Willi syndrome (PWS), a genetic condition characterized by an insatiable appetite, are prone to developing obesity[2]. Low and colleagues used functional magnetic resonance imaging (fMRI) — a technique used to visualize localized metabolic changes in the brain as a proxy for neural activity — to track the brain's responses to seeing images of food in individuals with PWS and control participants. The authors observed a difference in fMRI responses to food images between the individuals with PWS and the control participants, in a small region at the base of the cerebellum called the deep cerebellar nuclei (DCN).

Next, the authors used cell-labelling approaches in mice to identify the neurons in the outer (lateral) part of the DCN that were activated by the consumption of food. Artificially activating lateral-DCN neurons in mice (using a technique called chemogenetics) led to a pronounced reduction in food intake. Notably, whereas the frequency of eating bouts and the rate of eating were not affected, both the meal size and the duration of bouts were reduced, suggesting that these lateral-DCN neurons are involved in meal termination. Moreover, the effects of artificial activation of lateral-DCN neurons on food intake occurred regardless of whether the mice were hungry or fed, and did not seem to depend on whether the food tasted particularly pleasant.

The authors then used high-resolution gene-expression profiling techniques to identify the molecular characteristics of the 'food-activated' lateral-DCN neurons, including the expression of marker genes that distinguishes them from other lateral-DCN neurons. Using a technique called calcium imaging, the authors visualized the activity of cells expressing one of these marker genes as the mice received food cues. The results suggest that a distinct class of excitatory neuron (that is, glutamatergic neurons) in the lateral DCN is activated when food is presented, and confirmed that the neurons' activation suppresses food intake.

The neural circuits that regulate feeding behaviour are often divided into those that regulate food intake on the basis of 'need' or hunger state, and those that affect food intake on the basis of 'wanting' or reward-based feeding[3,4]. Although the distinctions between these behaviours and circuits are not absolute, a brain region called the hypothalamus is thought to be central to mediating hunger-state responses, whereas signalling by the neurotransmitter molecule dopamine is associated with the rewarding properties of eating.

Most research on how the brain controls food intake focuses on the hypothalamus or on regions that are strongly connected to it[5–7]. The cerebellum has long been known to have bidirectional neuronal connections with the hypothalamus[8]. Low and co-workers report that, whereas the artificial activation of hypothalamic neurons expressing a protein called AgRP increases food intake, this response could be overridden by simultaneously activating neurons in the lateral DCN. Although this finding suggests that the activity of lateral-DCN neurons affects the activity of

From the archive

Official rules about who can be called a chemist, and changes in the number of topics a science lecturer might cover.

100 years ago

British chemists are placed in the anomalous position, not occupied by their brethren in other civilised countries, of sharing their denomination with practitioners of a different craft — namely, pharmacy. It is, in fact, only by courtesy of the Pharmaceutical Society that they call themselves chemists, because, unless they hold a qualification from that body, they are not legally entitled to do so. The Pharmacy Acts Amendment Bill, read ... in the House of Commons on November 3, aims at correcting this error in occupational nomenclature by conferring on the Institute of Chemistry alone the authority to designate any person a "chemist" ... Part of the ignorance which prevails in the public mind concerning chemistry may be traced to the nominal association of the subject with pharmacy, an association from which pharmacists themselves do not derive any benefit, and which has led them to adopt a variety of sub-titles, including "cash chemist," "stores chemist" and "Continental chemist."

From *Nature* 8 December 1921

150 years ago

The biographer of a Scottish Professor says (we fear boastfully) that his friend had lectured on anatomy, chemistry, physiology, pathology, medical jurisprudence, and medicine, and that he was well qualified also to lecture on botany, mineralogy, and geology. There were giants then surely, but their day is past; for the Professor of Natural History in Glasgow University is just now trying to procure the erection of a new Chair, on the ground that geology or comparative anatomy is, either of them, as much as he can effectively teach. Perhaps no better indication of the enormous progress of Science during the last half century could be found than the facts we have mentioned. The earlier professor found his multifarious duties possible because the subjects were very limited.

From *Nature* 7 December 1871

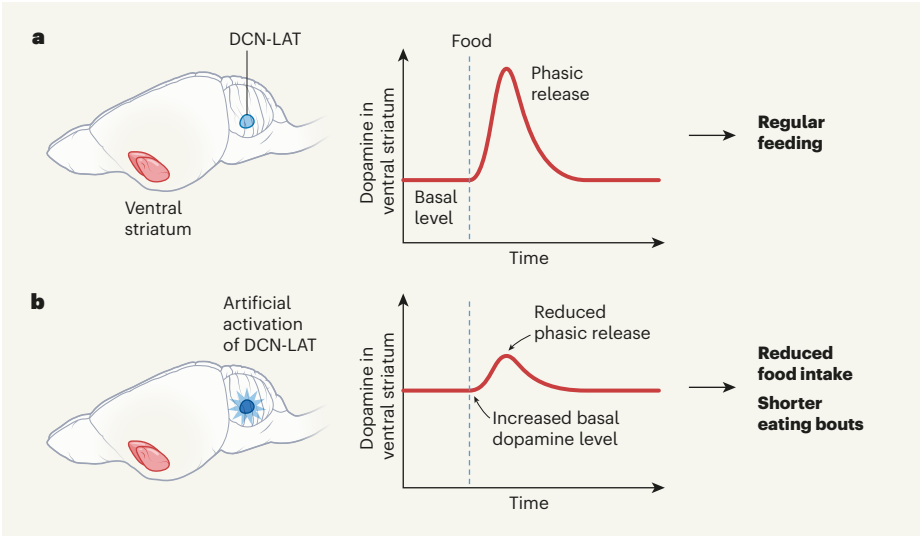

Figure 1 | A set of neurons in the cerebellum modifies the reward value of food. Low *et al.*[1] studied the effects of artificially activating a population of neuronal cells in a brain region called the cerebellum on the feeding behaviour of mice. **a**, Rapid, transient (that is, phasic) increases in the levels of the neurotransmitter molecule dopamine, released in another part of the brain called the ventral striatum, reflect the reward value associated with food. **b**, The basal levels of dopamine were increased in mice in which a set of neurons in a region of the cerebellum called the lateral deep cerebellar nuclei (DCN-LAT) were artificially activated using a method called chemogenetics. This increase led to a reduction in the phasic release of dopamine. Mice with activated lateral-DCN neurons ate less food than did control mice — mostly because their bouts of feeding were shorter than those of the controls.

AgRP-expressing cells, a direct neural connection remains to be demonstrated. It is also possible that projections from lateral-DCN neurons and AgRP-expressing neurons converge on common downstream targets to suppress food intake.

Dopamine is involved in the regulation of various motivated behaviours. The authors found that basal levels of dopamine increased in the ventral striatum — a part of the brain that is known to process rewards — after artificial activation of lateral-DCN neurons (Fig. 1), suggesting that these neurons might modulate food intake by influencing the activity of dopamine-releasing neurons. Activation of lateral-DCN neurons also attenuated the rapid, transient (that is, phasic) release of dopamine in the ventral striatum that is normally observed in response to food or food cues[9,10] and that is associated with the reward value of food. Using chemogenetics, the authors reduced the activity of dopamine-releasing neurons in mice with activated lateral-DCN neurons, to lower the basal dopamine levels in the ventral striatum to those of control mice. This manipulation restored the phasic increases in dopamine levels in response to food in these mice, leading the authors to suggest that lateral-DCN activation might reduce the rewarding value of food by increasing basal dopamine levels in the ventral striatum.

The relationship between dopamine signalling and food intake is complex, because both high and low levels of dopamine have been associated with increased feeding behaviour[11,12]. Moreover, dopamine neurons encode various types of information related to sensory input, motivation and learning[13]. The present work can be viewed through the lens of broader models of dopamine function that emphasize its role in balancing the conservation and expenditure of energy by regulating decisions about whether to stay and 'exploit' the rewards present in an environment, or use energy to 'explore' and seek a more rewarding environment[14]. Specifically, Low and co-workers' findings are consistent with observations of decreased feeding (representing reduced exploitation) seen in mice with higher basal levels of dopamine than usual[11].

"The cerebellum might function as a 'brake' on neural networks that promote food intake."

The authors suggest that the cerebellum might function as a 'brake' on neural networks that promote food intake. Although the work by Low *et al.* does not specify possible pharmacological approaches for treating individuals with PWS, the authors' findings indicate that it might be useful to determine whether lateral-DCN neurons can be targeted by such approaches or by gene therapies that take advantage of our understanding of the genetic underpinnings of PWS[15].

The cerebellum is generally known for its role in coordinating and calibrating movements, functioning as an effective predictor of the 'error' between intended and actual movements, and of the effects of behaviour on subsequent sensory inputs[16,17]. The cerebellum has also been proposed to filter what is known as interosensory information — sensory information encoding an internal state[18]. Although the specific sensory pathways that affect the activity of lateral-DCN neurons remain undefined, and it is unclear which cell types in the reward pathways are influenced by lateral-DCN neurons, the results reported by Low and colleagues expand our knowledge of the cerebellum as an integrator of sensory and motor signals that is required for maintaining motor balance. The observation that lateral-DCN neurons modulate the activity of both hypothalamic and dopamine pathways suggests that the cerebellum might accomplish a similar balancing act for meal termination — with clear consequences for how much we eat.

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