BASAL GANGLIA CIRCUITRY

'Feedback' for consumption

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A new study discovered that ventral pallidal neurons projecting back to the nucleus accumbens promote consumption. The findings question the accepted direction of information flow through the ventral basal ganglia and open new avenues for studying how consumption is regulated in proportion to subjective value.

A mouse encountering a piece of cheese in the kitchen faces a deceptively simple decision – how much cheese should it eat? While this critical decision may primarily be driven by the homeostatic need for food, it must also take into account environmental factors, such as the prevalence of food, availability of tastier alternatives, and possible risk due to the resident cat. The relative weight of these experience-dependent variables is thought to be adjusted at the nucleus accumbens (NAc, also referred to as the ventral striatum), the input structure of the ventral basal ganglia. Outputs from the NAc then drive the animal to seek out and consume rewards, or to avoid threats[1,2]. In this issue of *Nature Neuroscience*, Vachez, Tooley et al.[3] report exciting new data that go against this broadly accepted flow of information: they show that ventral arkypallidal cells (vArkys) in the ventral pallidum (VP) — which is considered to be the primary output nucleus of the ventral basal ganglia — project back to and broadly inhibit cells in the NAc, causing the animal to prolong consumption of a liquid caloric reward. Their work raises interesting questions about the breadth of behaviors influenced by these cells, what circuits control their activity, and more broadly about the logic of information flow through the ventral basal ganglia.

A subdivision of the NAc, its medial shell (NAcSh), has long been known to play an important role in consummatory behavior. Inactivation of the NAcSh specifically increases food intake through a direct inhibitory projection to cells in the lateral hypothalamus (LH)[1]. Driven by inputs carrying state information about behavioral goals, salient stimuli and spatial context (from frontal cortex, basolateral amygdala and hippocampus, respectively), the NAcSh could thus act to decrease food intake, for instance in favor of exploration or escape. Consistent with this view, during consumption NAcSh activity is *inhibited* in proportion to the subjective value of the food[4], which in turn permits feeding by dis-inhibiting the LH[5]. However, the source of this inhibition has remained elusive, as the major inputs to NAcSh are glutamatergic. This puzzling state of affairs is resolved by the work of Vachez and colleagues. Using both *in vitro* and *in vivo* recordings in NAcSh while optogenetically stimulating vArkys, the authors found that these cells broadly inhibit both spiny projection neurons (SPNs) and interneurons.

If indeed vArkys can account for the inhibition of NAcSh during feeding, we would expect their activity to increase during feeding, and correlate positively with reward value. To test this, the authors used a free-access feeding paradigm in an arena where mice could drink from a spout dispensing chocolate milk and measured vArky axonal calcium signals in the NAcSh using photometry. Indeed, the signal peaked at feeding onset and correlated positively with feeding duration. Furthermore, infusing sucrose, water or quinine solution directly into the mouth showed that vArky activity correlated positively with the palatability of these solutions. Strikingly, on trials where mice actively rejected the bitter quinine solution, vArkys were markedly less active than on trials where it was consumed. This shows that vArky activity reflects the subjective value of the reward at a given moment, akin to what has been shown for the dip in NAcSh activity[4]. Whether vArky activity also reflects learned preferences, such as after conditioned taste aversion, remains to be tested.

Next, Vachez and colleagues tested whether optogenetically activating vArky axons in NAcSh could cause mice to increase consumption in the free-access paradigm. As predicted, mice had longer feeding bouts during closed-loop stimulation (triggered by feeding onset) compared to open-loop control sessions. In keeping with the proposed function of vArkys and the associated NAcSh in promoting consumption[2] (as

opposed to approach / seeking), stimulation did not induce mice to *initiate* feeding more often, nor did it reinforce self-stimulation.

But to what extent do vArkys normally contribute to the regulation of reward consumption? To answer this tricky question, the authors optogenetically silenced vArky cell bodies in the VP. This attenuated the feeding-related inhibition of NAcSh activity by around 30%, with a corresponding 25% decrease in the length of feeding bouts (again there was no effect on the number of bouts). The relatively modest effect could indicate that not all vArkys were silenced, perhaps because the elongated structure of the VP makes it difficult to reach all vArkys.

Taken together, this series of experiments by Vachez, Tooley et al. firmly implicates vArkys in the control of consummatory behavior. They convincingly show that vArkys can account for the hitherto unexplained inhibition of NAcSh activity at consumption onset. Thus, consumption of a reward appears to be controlled in part by a circuit that goes against the grain of classical basal ganglia circuitry: vArkys in the VP, the primary output nucleus of the ventral basal ganglia, project back to and inhibit the NAc, which in turn disinhibits cells in the LH, causing prolonged feeding. But where does the excitatory drive to vArkys come from?

To speculate on possible answers to this central question, we can turn to recent findings in the dorsal basal ganglia, where arkypallidal cells (Arkys) were first described. Like their ventral counterparts, Arkys in the globus pallidus external segment (GPe) inhibit the striatum, in contrast with prototypical GPe cells that project downstream to basal ganglia output nuclei[6,7]. Two recent studies have provided evidence for pathways leading to the excitation of Arkys. First, direct input from motor cortex to GPe was shown to preferentially excite Arkys rather than prototypical GPe cells[8]. As a possible parallel, prefrontal cortex provides direct input to GABAergic VP cells, which includes vArkys[9]. Second, stimulation of the striatal indirect pathway results in net excitation of Arkys, likely via a dis-inhibitory route where the stimulated SPNs inhibit prototypical cells that keep Arkys under constant inhibition[10,11]. Intriguingly, the photometry recordings in the present work[3] are also consistent with a possible dis-inhibition process: Before dropping at consumption onset, NAcSh bulk activity ramped up, and did so earlier than vArky activity[3]. Thus, this increase in NAcSh activity could cause inhibtion of "prototypical" VP neurons leading to a dis-inhibition of vArkys. How much of the findings in the dorsal basal ganglia apply to the NAcSh–VP circuit remains to be seen, as the NAcSh typically diverges from classic dorsal circuit principles[1].

More generally, we lack clear understanding of what controls activity in the VP, the primary output nucleus of the ventral basal ganglia. Excitation of canonical VP projection neurons drives motivated behavior[9], yet their primary input from striatal cells is inhibitory. Future experiments will need to determine where this excitatory drive originates, and how much of it is due to local dis-inhibitory circuits versus direct excitatory inputs from outside the basal ganglia. Conceptually, these two options are fundamentally different: direct input to VP circumvents dopamine-dependent learning at striatal synapses, whereas dis-inhibition resulting from striatal activity may still reflect such learning.

The significance of the authors' results reaches beyond the control of consummatory behavior. Considered together with recent discoveries delineating the dorsal arkypallidal circuit[6–8,10–12], the study highlights that this 'contrarian' circuit element is a general feature of basal ganglia architecture. Indeed, initial anatomical investigations of pallido-striatal projections, both in the ventral and dorsal basal ganglia, found that they maintain striato-pallidal topology[13,14]. In other words, for a given striatal area, there exists an arkypallidal population that can inhibit it. Thus, the arkypallidal pathway seems poised to dynamically suppress the expression of learned associations in *functional striatal domains* across the basal ganglia [fig 1].

There is some evidence for arkypallidal suppression of learned associations in the dorsal basal ganglia. In a task where rats had to withhold their response on a subset of trials with a stop cue, arkypallidal cells were selectively engaged by this cue and cancelled the prepared action by shutting down the striatum[12]. However, whether this stop cue activity resulted from striatal-dependent learning or was caused by inputs external to the basal ganglia remains to be determined. Furthermore, it is not known how regionally specific this shutdown of the dorsal striatum is. In motor tasks more generally, it is tempting to speculate that the arkypallidal circuit could serve to prioritise particular striatal domains, such as the dorsomedial, 'goal-directed' striatum in favor of the dorsolateral, 'habitual' area[15] (or vice versa).

The present study[3] investigated a projection from VP specifically to the medial NAcSh. This particular striatal region is well placed to suppress consummatory behavior based on experience, for instance curtailing feeding in a historically perilous spot. In the scheme we propose here [fig 1], vArkys could temporarily veto such experience-dependent adjustment of feeding. Similarly, other populations of vArkys could suppress experience-dependent approach or avoidance governed by the NAc core, as well as the expression of defensive behaviors governed by the rostral NAcSh[1,2].

With the field just beginning to investigate arkypallidal function, the exciting work by Vachez, Tooley et al.[3] raises important questions about similarities and differences between ventral and dorsal circuits, and under what conditions Arkys across the basal ganglia are engaged. This study contributes to a growing understanding that pallidal circuits, including the arkypallidal motif, constitute a critical missing piece in our understanding of when and how the basal ganglia influence what an animal does next.

Figure 1: Arkypallidal populations for the suppression of learned associations. Vachez and colleagues report that arkypallidal cells (Arkys) projecting from the ventral pallidum (VP) to the medial nucleus accumbens shell (NAcsh) are active during consummatory behaviour, and maintain consummatory licking by inhibiting NAcsh (which usually suppresses feeding). This can be seen as a 'veto' against the suppression of feeding. Analogously, neighboring Arky populations projecting to NAc core (NAcc) or lateral shell could veto approach / avoidance behaviors. Arkys in the globus pallidus external segment (GPe) target the dorsal striatum and have been shown to veto prepared actions. The type of action that is suppressed could depend on selective engagement of Arkys targeting the dorsolateral (DLS) or dorsomedial (DMS) striatum.

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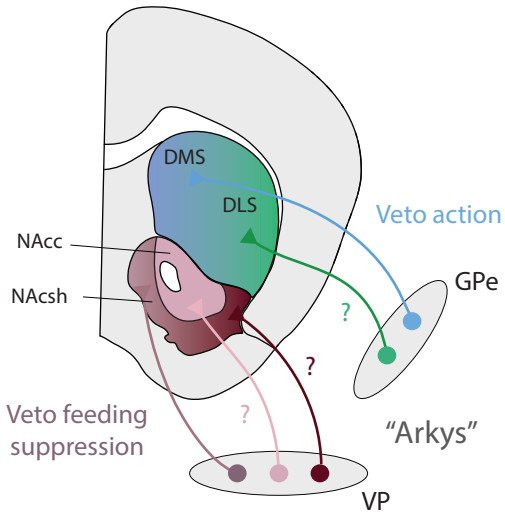
DMS
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