Pausing to Regroup: Thalamic Gating of Cortico-Basal Ganglia Networks

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The idea that new neurons generated in the mature brain can facilitate their own migration through the complex brain parenchyma to their proper target areas by modifying their migratory highway to suit their directional movement has potentially significant implications. Although the existence of rostral migratory stream-like long distance migration in the adult human brain remains controversial (Curtis et al., 2007; Sanai et al., 2007), the ability to modify the migratory route to facilitate the targeted movement of endogenously generated or transplanted neuroblasts will have a significant impact on regenerative strategies. An important aspect of this process is the role of astroglial cells in the modification of the migratory route to facilitate new neurons’ ability to modify their migratory route with the help of astroglial cells in the mature brain will help optimize these strategies.

REFERENCES

Pausing to Regroup: Thalamic Gating of Cortico-Basal Ganglia Networks

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How the cholinergic and dopaminergic systems of the striatum interact and how these interface with the massive neocortical input to the striatum are classic questions of cardinal interest to neurology and psychiatry. In this issue of Neuron, Ding and colleagues show that a key to these puzzles lies in the thalamic inputs to the striatum targeting its cholinergic interneurons.

Imagine you are a runner and you had to stop at a busy intersection. From long experience you know that it will be a while before it is your turn to cross, so while you wait, you start thinking about your friend and direct your attention away from the intersection. Finally, the walk sign comes on, and you stop day-dreaming and start to cross the street. Now imagine that suddenly, a fast-moving truck honks at you as you begin to cross—your attention is strongly redirected now, and to avoid being run over, you freeze on the sidewalk and watch the truck barrel past.

What mechanisms are responsible for redirecting your attention and interrupting your ongoing activity—first in the subtler case of noticing the walk sign and interrupting your day-dreaming, and then in the more dramatic freezing in response to the horn, interrupting your run? The intralaminar nuclei of the thalamus are thought to be critical for this redirection of attention, and in this issue of Neuron, Ding et al. (2010) demonstrate cellular mechanisms by which thalamic circuitry may interact with cortico-basal ganglia networks to interrupt ongoing motor behavior and redirect attention toward salient stimuli.

Previews

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The key, they believe, lies in the projections of the intralaminar thalamic neurons to the striatum, especially to the cholinergic interneurons of the striatum, which release acetylcholine (ACh) on being stimulated. These interneurons fire tonically and are thought to correspond to the “tonically active neurons” (TANs) that, in behaving monkeys, exhibit a burst-and-pause firing pattern in response to salient stimuli (Aosaki et al., 1995; Apicella, 2007; Blazquez et al., 2002; Morris et al., 2004). These responses are then usually followed by a post-pause facilitation phase, and they are known to depend on intact dopaminergic and intralaminar thalamic inputs to the striatum (Aosaki et al., 1994; Matsumoto et al., 2001). Lesions of the intrastriatal dopamine system or of the intralaminar thalamic nuclei eliminate the acquired pause and post-pause facilitation but do not always affect the initial burst of the burst-pause sequence.

In this issue of Neuron, Ding et al. aim to clarify the mechanisms by which thalamic activity gives rise to the burst-and-pause firing of cholinergic striatal interneurons. Using whole-cell recordings from striatal neurons in mouse brain slices that preserve both cortical and thalamic axonal input, they show that a burst of thalamic stimulation (50 Hz) elicits a burst-and-pause firing pattern in cholinergic striatal interneurons that is similar to the classic response of these cells observed in vivo. Importantly, this thalamically driven burst-and-pause response depends on dopamine in in vitro conditions, as has been observed in vivo. Ding et al. show that blockade of D2 receptors with sulpiride reduces the pause phase of the response, whereas increasing dopamine drive by applying cocaine (a dopamine transporter antagonist) increases the duration of the pause. Consistent with the idea that the ACh released during the initial burst phase of the response activates nicotinic ACh receptors (nAChRs), which are known to stimulate the release of dopamine from terminals in the striatum (Exley and Cragg, 2008), Ding et al. find that application of nAChR antagonist to the slice prep also reduces the duration of the pause phase of the response.

At the heart of the Ding et al. results is the finding that the thalamically induced burst-and-pause response of the cholinergic interneurons has important consequences for cortico-striatal synaptic transmission. Ding et al. stimulated thalamic afferents to elicit the burst-and-pause response in striatal cholinergic interneurons and then stimulated cortical afferents after a delay and measured the resulting EPSCs from striatal medium spiny projection neurons (MSNs). They performed the experiments using slices from BAC transgenic mice in which GFP labeled either MSNs expressing D1 dopamine receptors or MSNs expressing D2 dopamine receptors. Thus, they could study the effects that the thalamic stimulation had on cortical inputs to the two main classes of striatal projection neurons.

At physiological temperatures, they found that cortical stimulation applied at a short delay after thalamic stimulation (25 ms) resulted in a reduction in the EPSC amplitudes recorded from either the D1 or D2 MSNs. However, when the cortical stimulation was applied after a longer delay following the thalamic stimulation (250 ms or 1 s), they found that the cortico-striatal EPSCs were facilitated in MSNs expressing D2 receptors, but not in those expressing D1 receptors. The facilitation was progressive, suggesting that the decay time of the EPSCs was being enhanced by the thalamic stimulation.

Paired-pulse experiments suggested that the short-latency reduction in cortico-striatal EPSC amplitude resulted from a presynaptic decrease in glutamate release. Scopolamine-induced muscarinic blockade blocked both the short-latency and long-latency effects, but the two effects appeared to depend on different types of muscarinic receptors. Ding et al. recorded from BAC D2 mice in which the M1 muscarinic receptors were knocked out and found that the early presynaptic effect was still present—suggesting that this early effect probably depends on M2/M4 receptors. However, the late facilitation of D2 MSNs was gone, implicating M1 receptors in this longer-lag facilitation of cortico-striatal transmission.

This dichotomy in responses among different classes of MSNs is intriguing. MSNs expressing D1 receptors have been shown to correspond to direct pathway striatonigral neurons, the activation of which is thought to release desired movements. By contrast, D2 receptors are found on MSNs in the indirect striato-pallidal pathway, and excitation of these neurons is thought to suppress unwanted or competing movements. The initial suppression of cortico-striatal transmission in both classes of MSN, followed by the facilitation of indirect pathway neurons, suggests that a burst of thalamic input to the striatum following the presentation of a salient stimulus may serve to interrupt ongoing cortico-striatal processing by exciting a burst of activity in cholinergic interneurons. The subsequent pause in cholinergic interneuron activity then would serve to enhance indirect pathway processing and suppress now-unwanted motor behavior (Figure 1). This may then be what enables you to avoid being hit by that oncoming truck!

The study by Ding et al. shows the power of multisite slice preparations and the combination of cell-specific targeting to approach circuit-level questions at the cellular level. This is especially impressive, because despite many elegant previous studies, the functions of acetylcholine in the striatum have been notably difficult to identify, and the interactions between acetylcholine and dopamine have been perversely recalcitrant to even the most extensive studies (Centonze et al., 2003; Cragg, 2006). Still further, the interactions of these systems with the massive glutamatergic inputs from the neocortex and thalamus are not well understood. Thus, it has been difficult to form a systems-level view of these interactions or to link in vitro studies to studies in behaving animals. These problems for the field are understandable given the new findings of Ding et al., which build on this earlier work. They suggest that at least three types of acetylcholine receptor, together with glutamate and dopamine receptors, work differentially at presynaptic and postsynaptic locations to underpin thalamic modulation of cortico-striatal processing dependent on striatal cholinergic interneurons!

Many questions remain regarding how the thalamo-striatal mechanism uncovered by Ding et al. for modulating cortico-striatal transmission may relate to and interact with other ongoing cortico-basal ganglia-thalamocortical loop processing. At the network level, for example, it is known that the fast-firing interneurons...
of the striatum are powerfully influenced by cholinergic interneurons and that these fast-firing interneurons can exert strong influences on the entire striatal network activity (Koos and Tepper, 2002). And of course, at the same time that the thalamic modulation occurs, other sources of modulation occur also, not addressed in this study. Yet again, there is intriguing evidence that the cortical inputs to the D1 and D2 MSNs themselves are different (Lei et al., 2004) and so could contribute to the effects found by Ding et al. Further, much evidence suggests that the cholinergic neurons themselves are heterogeneous (Aosaki et al., 1995; Yamada et al., 2004), as is the thalamic input to the cholinergic interneurons (Matsumoto et al., 2001). Finally, one of the most striking characteristics of the cholinergic system of the striatum is that it is concentrated in the striatal matrix, not in striosomes, and evidence suggests that the cross-border interactions could be important for motivational modulation of striatal circuitry (Aosaki et al., 1995, et seq.). Even so, the Ding et al. study points the way toward bridging the gap between single neuron and circuit function in basal ganglia-based networks.

Other questions remain as well. It is increasingly clear that precise timing and synchronous activity in these circuits is critical to their function (Aosaki et al., 1995; Cragg, 2006; Joshua et al., 2009). How does a stimulus-induced thalamic activation play into this precisely timed network? Ding et al. have shown that a burst of ACh release can modulate cortico-striatal synaptic transmission, but what is the function of the precisely timed pause response of the cholinergic interneurons? These are issues that could critically influence the eventual interpretation of the modulatory mechanism suggested by Ding et al.

Another issue still to be addressed is how these findings relate to cortico-striatal plasticity, essential for action planning and behavioral learning. The striatum is thought to be a key site for reinforcement-based learning, and indeed, the burst-and-pause responses of TANs have been shown to develop with training (Aosaki et al., 1995; Apicella, 2007; Blazquez et al., 2002). Dopamine-containing neurons are likewise known to develop phasic responses to conditioned stimuli predicting reward, and evidence suggests that the interactions between the dopaminergic neurons and TANs are carefully orchestrated (Cragg, 2006; Joshua et al., 2009; Morris et al., 2004).

Ding et al. have uncovered a potential mechanism for interrupting and redirecting attention and ongoing motor behavior, but it remains unclear how this redirection can result in the appropriate activation of a new motor response. The function of the post-pause facilitation of the cholinergic interneurons, so characteristic of TANs in many situations (Aosaki et al., 1995; Apicella, 2007; Morris et al., 2004), may relate to this issue. Perhaps after freezing to avoid the oncoming truck, the post-pause rebound/facilitation may help reactivate the “Go” pathway. Maybe this is what lets you finally cross that street?

Remarkably, Lee et al. (2006), recording in monkeys performing a Go/No-Go task,
found that the strongest responses of the TANs were for self-timed No-Go responses—recalling the differential effects suggested by Ding et al. on the D2 indirect pathway neurons. Moreover, the responses of TANs can be used with remarkable accuracy to predict whether a movement will occur in response to a conditioned stimulus (Blazquez et al., 2002). Yet, in other experimental situations, TANs respond without any movement (Lee et al., 2006); and TAN responses can be modulated by many contexts, rewarding or aversive (Apicella, 2007), can have a directional movement preference along with or instead of being reinforcement related (Shimo and Hikosaka, 2001), or can exhibit firing related to internally generated states (Lee et al., 2006). Thus, in some situations, it is likely that the burst-and-pause responses that develop signify less the interruption of an ongoing motor program and more the change in network state arising from the presentation of an external conditioned stimulus or an internal cue. They may also function in the direction of upcoming cue-evoked movements. Thought of in this way, the burst-and-pause responses of ACh interneurons may relate not only to the interruption of ongoing motor behavior and the redirection of attention but also to the more subtle shifts in cortico-basal ganglia network processing that occur following a predictive or instructive stimulus, whether external or internal (Apicella, 2007). If so, your learned reaction to the walk sign may engage the same cortico-basal ganglia circuitry as your unlearned freeze to avoid being run over!

REFERENCES

The Plurality of Our Senses Offers Behavioral Superiority, because We Often Perceive Our Environment More Accurately when Combining Evidence across the Modalities. Given the manifold impact of the brain’s multisensory nature on perception and behavior, there is considerable interest in the questions of where and how our brain merges the sensory information (Stein and Stanford, 2008). Recently, a number of studies highlighted the role of early sensory areas in this process, and demonstrated signs of multisensory processing even down to primary sensory cortices (Ghazanfar and Schroeder, 2006; Kayser and Logothetis, 2007). At times, these were taken to suggest that primary cortices have access to information captured by other modalities. In this issue of Neuron, Lemus et al. (2010) put this notion to a test by directly probing whether neurons in primary auditory and somatosensory cortices encode information about stimuli presented to the other modality.

In their study, the authors employed variants of the flutter discrimination task, which has been extensively used to study