TRAPing Seizures in the Striatum

Activation of the Basal Ganglia and Indirect Pathway Neurons During Frontal Lobe Seizures

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There are no detailed descriptions of neuronal circuit active during frontal lobe motor seizures. Using activity reporter mice, local field potential recordings, tissue clearing, viral tracing, and super-resolution microscopy, we found neuronal activation after focal motor to bilateral tonic-clonic seizures in the striatum, globus pallidus externus, subthalamic nucleus, substantia nigra pars reticulata and neurons of the indirect pathway. Seizures preferentially activated dopamine D2 receptor–expressing neurons over D1 in the striatum, which have different projections. Furthermore, the D2 receptor agonist infused into the striatum exerted an anticonvulsant effect. Seizures activate structures via short and long latency loops, and anatomical connections of the seizure focus determine the seizure circuit. These studies, for the first time, show activation of neurons in the striatum, globus pallidus, subthalamic nucleus, and substantia nigra during frontal lobe motor seizures on the cellular level, revealing a complex neuronal activation circuit subject to modulation by the basal ganglia.

Commentary

Stephen King opined, in *The Colorado Kid* that, “sooner or later, everything old is new again.” It is one of the delights of science that we can make “old” targets new again, with new approaches that provide greater resolution and heightened precision. In their recent manuscript, Brodovskaya and colleagues examined an “old” set of structures—the basal ganglia, using new approaches to map, with cell-type specific resolution, the pathways engaged by seizures originating in the frontal cortex.

The basal ganglia are an obligate component of the vertebrate brain, with a gross organization that is conserved across more than half a billion years of evolution. Long predating the elaboration of the neocortex, the basal ganglia consist of input nuclei (eg, the striatum, consisting of the caudate and putamen), output nuclei (eg, the substantia nigra pars reticulata [SNpr], the internal segment of the globus pallidus [GPi]), and nuclei that connect these structures (eg, the external segment of the globus pallidus [GPe] and the subthalamic nucleus [STN]). Basal ganglia output regions potently control activity within the thalamus, superior colliculus, and brainstem locomotor control regions. While the basal ganglia are most commonly thought of for their role in movement and movement disorders, they contribute to so much more—decision-making, arousal, eye movement, feeding behavior, and yes, epilepsy.

In the early 1950s, Stoll, Ajmone-Marsan and Jasper demonstrated the rapid recruitment of the caudate nucleus, globus pallidus, substantia nigra, and subthalamic nucleus after strychnine injection or electrical stimulation of the temporal pole in cats. Through the 50s and 60s, Walker and colleagues extended these findings to the primate brain and to a range of cortical and subcortical initiation sites. Thus, by the 1970s, it was unambiguous that the basal ganglia were engaged by seizure activity, but the role of these nuclei in seizure initiation, propagation, and termination remained opaque. In the early 1980s, Gale and colleagues demonstrated that GABAergic inhibition of the SNpr was potently anticonvulsant, and a likely site of action of GABAergic anti-seizure drugs. Shortly thereafter, Turski and colleagues demonstrated that focal pharmacological activation of the striatum disrupted seizures. In the 1990s, a series of studies from Shehab and colleagues suggested disinhibition of targets such as the superior colliculus was critical for these basal ganglia–mediated effects. Together, these studies laid the groundwork for the concept that the basal ganglia might represent an endogenous system to control seizure activity.

Coincident with this trajectory was the detailed elaboration of the functional architecture of the basal ganglia, and the emergence of the “direct” and “indirect” pathway model of basal ganglia function, which remains the prominent (if not prevailing) model of basal ganglia function. In this model, GABAergic, dopamine D1 receptor–expressing striatal neurons project directly to GABAergic striatal output nuclei (SNpr and GPi). Activation of these neurons inhibits output nuclei and disinhibits their thalamic and brainstem targets. By
contrast, D2 receptor–expressing striatal neurons project to the GPe, which inhibits the STN (an important source of excitatory drive to output nuclei). Thus, activation of the indirect pathway disinhibits the STN, *increases* excitatory drive to the SNPr, and decreases activity in thalamic and brainstem projection targets.

Brodovskaya and colleagues’ findings fit into this larger framework and, importantly, provide previously unattained levels of specificity with respect to the pathways activated. Using an immediate early gene (cFos)–driven Cre recombinase for targeted recombination in active populations (TRAP), the authors expressed a fluorescent reporter in cells activated during seizures. This approach is an elegant derivative of classic immediate early gene expression studies in epilepsy.10 Seizures were evoked by implantation of a cobalt wire into the frontal cortex, which produces repeated events in the hours after implantation. The authors found robust activation of the striatum, ipsilaterally to the cobalt focus, with a lesser degree of activation in the contralateral striatum. This profile was also observed in the GPe, STN, and SNR, as well as in motor thalamus. Within the striatum, there was a striking difference in TRAP-labeled neurons between direct (D1-expressing) and indirect (D2-expression) pathway striatal projection neurons: while 80% of indirect pathway neurons were activated by seizures, only 20% of direct pathway neurons were activated. Based on these findings, they found that intrastriatal injection of sumanire, a dopamine D2 agonist, which suppresses activity of D2-expressing neurons, transiently abolished seizure activity, consistent with prior reports in a model of limbic seizure activity.11

The engagement of the basal ganglia during seizures originating from diverse foci (including frontal cortex) and in a variety of species is well established. However, the detailed mapping they performed using TRAP mice, tissue clearing, and super-resolution microscopy revealed interesting and novel patterns and provided new circuit-level insight to the basal ganglia in epilepsy. No prior immediate early gene studies in epilepsy have provided this level of detail. First, there was a striking rostrocaudal gradient in activation of the striatum, with a greater percentage of cells activated in rostral as compared to caudal regions. Second, activated cells were generally confined to the striatal matrix compartment and absent from striosomes. Inputs to the caudate/putamen are heterogeneous across the rostrocaudal axis,12 with rostral zones receiving preferential input from prefrontal and motor cortices; mid-rostrocaudal zones, by contrast, receive relatively higher input from somatosensory cortex, and caudal zones have relatively higher input from amygdala, visual, and auditory cortices. Similarly, “limbic” associated prefrontal cortex preferentially innervates the striosomal compartment, as compared to the matrix. Whether the intrastriatal pattern of active populations would differ as a function of seizure focus is both unexplored, and a necessary step in translating this to brain stimulation approaches.

Perhaps the most striking finding of the study was the preferential activation of the indirect pathway. While the “TRAP” method provides a several hour time-averaged snapshot in time, real-time recording of activity within direct and indirect pathway neurons during seizure activity may reveal temporal patterns of interplay between the direct and indirect pathways that may be missed when analyzed over longer time scales. Given the long-established role for GABAergic tone in the SNPr in regulating seizure threshold, and given that the predominant source of GABAergic inhibition of the SNPr is the striatal direct pathway, the findings of Brodovskaya suggest that there is far more at play. In the canonical direct–indirect pathway model, these two pathways provide a “break” and an “accelerator” in nigral activity, respectively. In this case, seizures appear to tap the accelerator without touching the break. Again, whether this same pattern would persist with seizure foci other than frontal cortex remains to be seen, but these findings clearly point, at least at the level of the striatum, to the indirect pathway as a promising target to control seizure activity. While things have been somewhat quiet on the basal ganglia front in epilepsy, this work joins several other recent studies in re-examining these “old” targets in a new light.13,14 Given the excellent track record of basal ganglia targeted deep brain stimulation in Parkinson’s disease, new opportunities to extend our knowledge of these circuits in epilepsy have exciting translational potential.

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