This Week in The Journal

Nigrothalamic Regulation of Motor Timing

Julien Catanese and Dieter Jaeger
(see pages 1878–1891)

The basal ganglia participate with cortex and thalamus in recurrent regulatory loops that promote particular movements and inhibit premature or inappropriate movements. The output nuclei of the basal ganglia, including the substantia nigra pars reticulata (SNr), provide inhibitory output to the thalamus, including the ventromedial, ventral anterior, and ventral lateral nuclei (VM/VAL). The VM/VAL, in turn, send glutamatergic projections to the anterolateral premotor cortex to activate motor plans. Thus, SNr inhibits movement initiation and the inhibition of SNr allows motor preparation to proceed. Catanese and Jaeger elucidate how this circuit works to promote action in a delayed choice task in mice.

Mice were trained to lick a left or right water spout in response to an air puff, but they had to wait until an auditory cue was presented before initiating the response. Recordings of single units in the VM/VAL revealed that the spike rate of most individual neurons increased at different points during trials. This was manifest at the population level by a ramping up of activity across the delay period, with activity peaking shortly before the onset of licking. Notably, the rate of ramping was faster on trials in which mice licked before the go cue was presented than on trials when licks were properly timed. Conversely, no ramping was apparent in trials in which mice failed to lick. Consequently, a linear classifier was able to decode performance from the population activity during the delay period. As predicted from previous work, activation of channelrhodopsin-expressing SNr terminals reduced firing of target neurons in the VM/VAL. Remarkably, this reduced the number of premature licks and increased the number of trials on which licking was omitted.

Based on these and previous results, the authors propose that the VM/VAL is under tonic inhibition from the SNr, which suppresses the production of unintentional movements. To initiate a specific action, the activity of subsets of SNr neurons must be inhibited. This allows VM/VAL activity to increase, and when the activity surpasses a threshold, it activates motor commands in prefrontal cortex. Such a design would not only prevent random or impulsive movements, but would also allow precise timing of sequential movements in complex behaviors.

Elevated Lamin B1 in Neurons Made from Human Dystonia Cells

Baojin Ding, Yu Tang, Shuaipeng Ma, Masuma Akter, Meng-Lu Liu, et al.
(see pages 2024–2038)

Dystonias are a heterogeneous group of movement disorders characterized by involuntary muscle contractions. The most common form of inherited isolated dystonia, called DYTI, results from a three-nucleotide deletion in TORIA and consequent loss of a glutamic acid (E) residue in Torsin A. TORIA is a ubiquitously expressed protein that localizes to the endoplasmic reticulum (ER) and the nuclear envelope, where it associates with both membranes and the cytoskeleton. The functions of TORIA are unclear, but it has been proposed to contribute to nuclear positioning, formation of nuclear pores, trafficking of ribonucleotide particles and proteins, and the ER stress response. Many of these processes are disrupted by knocking out TORIA or overexpressing the mutant protein TORIAE in animal models. Notably, however, animals heterozygous for TORIAE show minimal motor deficits (Gonzalez-Alegre, 2019, Neurobiol Dis 127:233). Therefore, these models might not faithfully reflect the pathology found in humans, where heterozygous TORIA mutations produce dystonia.

To investigate how heterozygous expression of TORIAE affects human neurons, Ding et al. generated motor neurons from fibroblasts or induced pluripotent stem cells (iPSCs) from DYTI patients and control subjects. Neurons derived from DYTI cells had shorter, less branched neurites than control neurons. In addition, DYTI neurons had misshapen nuclei, with fewer nuclear pore complexes and abnormal thickening of the nuclear lamina—the meshwork of intermediate filaments that underlies and supports the inner nuclear membrane. Nucleocytoplasmic transport was also impaired in DYTI motor neurons, and mRNAs accumulated in the nucleus.

Notably, expression of Lamin B1, one of the intermediate filaments that compose the nuclear lamina, was elevated in DYTI neurons, and, unlike in control neurons, the protein was present in the cytoplasm as well as the nucleus. Moreover, overexpressing TORIAE in neurons derived from control iPSCs disrupted nuclear mRNA export and led to upregulation and mislocalization of Lamin B1. Finally, knocking down Lamin B1 in DYTI neurons reduced the number of cells with abnormal nuclear morphology, decreased nuclear accumulation of mRNAs, and increased neurite outgrowth and branching. These results suggest that defects in nuclear morphology in neurons that express TORIAE result from overexpression and/or mislocalization of Lamin B1. Future work should determine whether reducing Lamin B1 expression can ameliorate dystonia.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.41.9.2021