This Week in The Journal

Acetylcholine Receptors Distinguish STN Neurons

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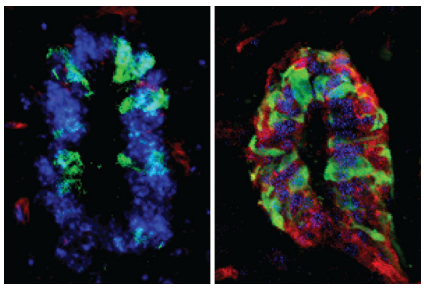
(see pages 3734–3746)

Abnormal synchronous oscillations in the subthalamic nucleus (STN) are closely linked to motor symptoms in Parkinson's disease. Disruption of these oscillations is associated with motor improvement during L-DOPA treatment and deep brain stimulation (DBS). As a component of the basal ganglia's "indirect pathway," the STN excites GABAergic neurons in the substantia nigra pars reticulata (SNr) and globus pallidus interna. Additionally, the STN has reciprocal connections with cholinergic neurons in the pedunculopontine tegmental nucleus (PPT) and with dopaminergic neurons in the SN pars compacta (SNc). These modulatory inputs influence synchronous oscillations in the STN: loss of dopamine induces the oscillations, whereas activation of cholinergic pathways via chronic nicotine use or PPT stimulation enhances the ability of L-DOPA and DBS to disrupt the oscillations.

Xiao et al. discovered that exogenous acetylcholine (ACh) increases spike rates in two distinct populations of mouse STN neurons in slices. One population expressed nicotinic ACh receptors (nAChRs) containing $\alpha4\beta2$ subunits, while the other population expressed $\alpha7$-containing nAChRs. Compared to $\alpha7$-expressing neurons, those expressing $\alpha4\beta2$ were more sensitive to ACh, and their activity remained elevated for a longer period after ACh application. Furthermore, $\alpha4\beta2$-expressing neurons received twice as many excitatory inputs and one-third as many inhibitory inputs as $\alpha7$-expressing neurons, so $\alpha4\beta2$-expressing neurons tended to be excited by local electrical stimulation, while $\alpha7$-expressing neurons were more often inhibited. Chronic nicotine exposure only affected $\alpha4\beta2$-expressing neurons: by increasing expression of $\alpha4\beta2$ receptors, it increased nicotine-induced currents and spontaneous firing rate in these neurons. Finally, although both populations activated neurons in SNr and SNc, $\alpha4\beta2$-expressing neurons had a greater effect on SNr GABAergic neurons, while $\alpha7$-expressing neurons had a greater effect on SNc dopaminergic neurons.

Together, these and previous results suggest that DBS disrupts synchronous oscillations in the STN partly by increasing the activity of $\alpha4\beta2$-expressing neurons relative to that of $\alpha7$-expressing neurons. This effect is probably enhanced by nicotine and by activation of cholinergic inputs. By primarily exciting GABAergic neurons in SNr, increased activation of $\alpha4\beta2$-expressing neurons likely increases inhibition of downstream dopaminergic neurons in SNc. Genetically targeting $\alpha4\beta2$-expressing neurons will help to elucidate their contribution to normal and abnormal circuit activity.



$\beta1$-integrin expression (red) is low in EZCs (green) of uninjured mice (left). Expression increases within 2 d of SCI (right). DAPI (blue) labels nuclei. See North et al. for details.

$\beta1$-Integrin Influences BMP Signaling in Astrocytes

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(see pages 3725–3733)

After spinal cord injury (SCI), some ependymal zone stem cells (EZCs) that surround the central canal of the spinal cord differentiate into astrocytes. Initially, these and previously generated astrocytes limit infiltration of inflammatory cells, assist in wound healing, and help restore homeostasis; but they later form a dense glial scar that hinders axon regeneration. Bone morphogenetic protein (BMP), which helps specify astrocytic fate in stem cells, contributes to both the positive and negative effects of "reactive" astrocytes, but interestingly, it does so through activation of distinct receptors (BMPRs). Specifically, BMPR1a is essential for limiting inflammation and promoting healing, whereas BMPR1b is thought to promote glial scar formation.

North et al. present evidence that $\beta1$-integrins regulate reactive astrocytes by limiting astrocyte generation and BMP signaling. After SCI, as EZCs proliferated and migrated to the injury site, $\beta1$-integrin expression increased. Selectively knocking out $\beta1$-integrin in ependymal cells caused more EZCs to migrate away from the central canal, differentiate, and express markers of reactive astrocytes after SCI. $\beta1$-integrin knockout also greatly reduced functional recovery from SCI.

Interestingly, although knocking out $\beta1$-integrin reduced expression of BMPR1a and BMPR1b, it increased activation of SMAD1/5/8 and p38, two downstream mediators of BMPR signaling. This effect may have resulted from a redistribution of BMPR1b into lipid rafts, which are thought to facilitate receptor-mediated activation of downstream signaling complexes. Indeed, the amount of BMPR1b present in lipid raft fractions increased after $\beta1$-integrin was knocked out, and disrupting lipid rafts reduced activation of SMAD1/5/8 and p38. Additional experiments indicated that $\beta1$-integrin interacts directly with BMPRs and that activation of BMPR increases expression of $\beta1$-integrin.

Together, these data suggest a model in which BMP signaling, activated in EZCs after SCI, is limited by BMPR-induced upregulation of $\beta1$-integrin. Through direct interaction with BMPR1b, $\beta1$-integrin prevents BMPR1b accumulation in lipid rafts, thus limiting its ability to activate downstream signaling. In this way, as well as by reducing the generation of new astrocytes, $\beta1$-integrin may limit glial scar formation, thus facilitating axon regeneration and functional recovery after SCI.

This Week in The Journal is written by Teresa Esch, Ph.D.