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NEUROTRANSMISSION

GABA calls stop in the striatum

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Dopaminergic neurons in the substantia nigra pars compacta and the ventral tegmental area project to the striatum, in which they have important modulatory effects on striatal output. There is increasing evidence that these neurons use transmitters other than dopamine to influence striatal function, and a new study shows that they can inhibit striatal output by releasing GABA from dopaminergic terminals.

Tritsch *et al.* investigated the effects of optogenetic stimulation of midbrain dopaminergic neurons on striatal projection neurons (SPNs). SPNs come in two flavours — direct pathway SPNs express D1 dopamine receptors, and their activation is promoted by dopamine release, whereas indirect pathway SPNs express D2 receptors and are inhibited by dopamine. However, recordings from both types of SPN showed that they were inhibited by optogenetic activation of midbrain dopaminergic projections, and this effect was not prevented by dopamine receptor antagonists.

So, if dopamine is not responsible for the inhibition, what is? When the authors used a GABA receptor antagonist instead, the inhibitory effect was blocked; so the dopaminergic projections were mediating their inhibitory effect through GABA receptors. One possible explanation is that the inhibition is caused by GABA released from interneurons, rather than directly from dopaminergic terminals. The authors ruled this out by providing evidence that the dopaminergic neurons release GABA directly. Part of this evidence relates to the timing of GABA-mediated conductances and inhibitory postsynaptic currents, which were faster than would be expected if interneurons were involved.

In addition, a subset of dopaminergic midbrain neurons expresses glutamic acid decarboxylase, which is required to synthesize GABA. Normally, neuronal GABA is packaged into synaptic vesicles by the vesicular GABA transporter (VGAT), but light-evoked inhibitory postsynaptic currents persisted even when VGAT or the glutamate transporter VGLUT2 were genetically deleted from dopaminergic neurons. Surprisingly, pharmacological blockade of the vesicular monoamine transporter VMAT2 — which normally transports dopamine in these neurons — did prevent the inhibitory effect, suggesting that VMAT2 is responsible for packaging GABA into vesicles for synaptic release. Consistent with this, expression of VGAT in mice treated with reserpine (which inhibits VMAT2) restored the inhibitory effect.

To test the idea that VMAT2 could function as a vesicular GABA transporter, the authors expressed VMAT2 in GABAergic neurons in which VGAT had been genetically deleted (and which therefore could not release GABA) and found that VMAT2 restored GABA release.

One caveat that the authors point out is that, theoretically, the dopaminergic neurons could be releasing another molecule that activates GABA receptors and is transported by VGAT and VMAT2. However, it is most likely that GABA itself is responsible. These results add another layer of complexity to the functions of midbrain projections in the striatum and are likely to generate many further studies.

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PHOTODISC

ORIGINAL RESEARCH PAPER Tritsch, N. X., Ding, J. B. & Sabatini, B. L. Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature* **490**, 262–266 (2012)