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NEUROTRANSMISSION

Gas for global tuning

Nitric oxide (NO) is a recognized regulator of neurotransmission that contributes to learning and memory. Owing to the difficulty in obtaining direct *in vivo* measurements of this compound, its short half-life and low concentrations, the physiological roles of NO, and in particular the mechanism through which it regulates neuronal excitability, are poorly understood. Using the calyx of Held synapse in the auditory brainstem as a model, Forsythe and colleagues demonstrate that NO functions as a volume transmitter, mediating non-synaptic communication between neurons to tune their excitability to the incoming glutamatergic transmission.

IMAGE SOURCE/PHOTODISC

At the calyx of Held synapse, each of the principal neurons of the medial nucleus of the trapezoid body (MNTB) receives input from one calyciferous axon. Because of its large size, this synapse is used as a model for the study of transmitter release. Here the authors showed that MNTB neurons generate NO in response to synaptic stimulation. Perfusion of the glutamate receptor antagonist AP-5 blocked this effect, suggesting that neuronal NO synthase (nNOS) is activated by Ca^{2+} influx through NMDA (*N*-methyl-D-aspartate) receptors at this postsynaptic site.

To investigate the effects of NO diffusion on neighbouring cells, the authors combined Ca^{2+} imaging and the use of a fluorescent probe that is activated by NO. Synaptic stimulation triggered an increase in Ca^{2+} concentration in the MNTB neuron receiving the calyceal input, but not in neighbouring cells that had no active calyceal input. Despite this, the same stimulation led to a global increase in NO fluorescence, indicating that the NO that is generated by synaptic stimulation can diffuse widely and act as a volume transmitter, passing information between cells without the need for a synapse.

Whole-cell patch-clamp recordings revealed that NO suppressed the K^+ channel Kv3 and inhibited glutamate receptors in MNTB neurons, thus reducing postsynaptic excitability and neuronal firing rate. These changes were absent in nNOS-knockout mice. Presynaptic neurotransmitter release was not affected, suggesting that NO has primarily a postsynaptic modulatory action. Finally, the authors were able to corroborate these findings *in vivo,* showing that sound-induced changes in MNTB neurons in mice were blocked by nNOS antagonists or by ketamine anaesthesia (which blocks NMDA receptors and indirectly suppresses nNOS).

The ability of NO generated by active neurons to modulate Kv3 currents in neighbouring inactive ones suggests that it has a key role in regulating the excitability and, potentially, the homeostasis of a whole population of cells, and could help to explain links between aberrant NO signalling, Alzheimer's disease and vascular dementia.

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ORIGINAL RESEARCH PAPER Steinert, J. R. *et al.* Nitric oxide is a volume transmitter regulating postsynaptic excitability at a glutamatergic synapse. *Neuron* **60**, 642–656 (2008)