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NEUROTRANSMISSION

A new take on glutamate

In the brainstem and spinal cord, glutamate and glycine are the classic mediators of excitatory and inhibitory neurotransmission, respectively. However, previous studies have shown that glycine can also participate in excitatory transmission in the brain through allosteric modulation of the NMDAR (*N*-methyl-D-aspartate receptor), which is activated by glutamate. Now, Wang and colleagues highlight further neurotransmitter crosstalk by demonstrating that glutamate can potentiate inhibitory Cl^- currents mediated by glycine receptors (GlyRs) in the brainstem and spinal cord.

The authors performed whole-cell patch clamp recordings on cultured spinal neurons. Application of glutamate and a cocktail of glutamate receptor blockers potentiated GlyR-dependent inhibitory postsynaptic currents (identified by their sensitivity to the GlyR antagonist strychnine). The effect of glutamate was occluded by saturating doses of the competitive NMDAR inhibitor D(–)-2-amino-5-phosphonovaleric acid (AP5), suggesting that these ligands share a previously unknown binding site on the GlyR. Single-channel recordings indicated that potentiation of inhibitory transmission was mediated by increasing the frequency of GlyR channel opening.

To rule out a possible involvement of glutamate receptors in this effect on GlyR-mediated currents, the authors transfected recombinant human GlyRs into HEK293 cells, which lack glutamate receptors. Whole-cell recordings showed that glutamate alone had no effect on the membrane potential, confirming the absence of classic glutamatergic signalling. However, the amplitude of the inhibitory current produced by glycine administration was significantly increased by co-application of glutamate. These effects were mimicked by various glutamate-like ligands, including NMDA.

Do these non-classic actions of glutamate occur *in situ*? In acute spinal cord slices from rats treated with glutamate receptor blockers, increasing the concentration of endogenous glutamate by inhibiting glutamate transporter activity reproduced the potentiation of GlyR-mediated currents, suggesting that this could be a physiologically relevant mechanism. Therefore, analogously to the ability of glycine to facilitate excitatory neurotransmission in the brain, glutamate can have an inhibitory role in the spinal cord, suggesting that reciprocal modulation of these opposing systems might be a general means of regulation. The concentrations of glutamate that were required to enhance glycine-dependent transmission are consistent with a homeostatic mechanism to protect against excessive excitatory activity, which may be activated during seizures and spastic hypertonia.

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