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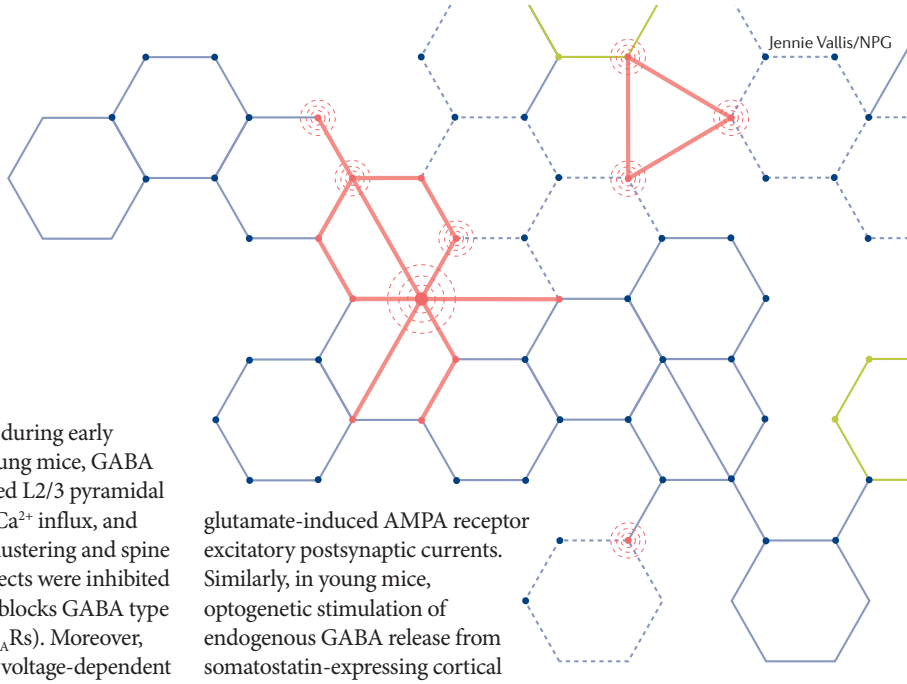

NEURONAL DEVELOPMENT

Signalling synaptogenesis

The spatial and temporal regulation of the formation of excitatory and inhibitory synapses is crucial for early postnatal development, but the mechanisms are not well understood. Here, Oh *et al.* describe how, in young mice, GABA released from cortical interneurons can drive the formation of both inhibitory and excitatory synapses on layer 2/3 (L2/3) pyramidal neurons.

The authors used two-photon GABA photolysis to determine the effect of locally released GABA on synaptogenesis during cortical development. Increases in the number of gephyrin (a postsynaptic protein that regulates GABA receptor clustering) puncta were measured to assess putative inhibitory synapse formation, and the formation of putative excitatory synapses was indicated by increases in the number of dendritic spines.

In young mice (postnatal days 6–8), uncaging of GABA on L2/3 cortical pyramidal neurons increased the number of both gephyrin puncta and dendritic spines. Owing to differences in chloride electrochemical gradients, GABA is excitatory during early development. In young mice, GABA uncaging depolarized L2/3 pyramidal neurons, triggered Ca^{2+} influx, and induced gephyrin clustering and spine formation; these effects were inhibited by gabazine, which blocks GABA type A receptors ($GABA_A$Rs). Moreover, inhibition of L-type voltage-dependent calcium channels (VDCCs) and T-type VDCCs caused dispersal, and reduced clustering, of gephyrin puncta, respectively; spine formation was also inhibited by blockade of these channels. Thus, at early postnatal stages, GABA activates $GABA_A$Rs, resulting in Ca^{2+} entry via VDCCs and the formation of putative inhibitory and excitatory synaptic structures.

Are these synaptic structures functional? Inhibitory postsynaptic currents following GABA uncaging were increased at the locations of new gephyrin puncta, but not at adjacent control locations, indicating recruitment of $GABA_A$Rs and formation of functional synapses. Newly formed spines were also functional, as revealed by increased glutamate-induced AMPA receptor excitatory postsynaptic currents. Similarly, in young mice, optogenetic stimulation of endogenous GABA release from somatostatin-expressing cortical interneurons increased the number of both gephyrin puncta and new dendritic spines in cortical pyramidal cells near the axon terminals of the interneurons. Conversely, selective blockade of GABA release from somatostatin-expressing interneurons reduced both the number of gephyrin puncta and spine densities, particularly in distal apical dendrites. Overall, these results suggest that, at early postnatal time points, cortical GABA release regulates the shaping of both inhibitory and excitatory circuitries.

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ORIGINAL ARTICLE Oh, W. C. *et al.* De novo synaptogenesis induced by GABA in the developing mouse cortex. *Science* **353**, 1037–1040 (2016)

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