DEVELOPMENT

Timing the switch

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Establishing how neuronal activity contributes to synaptic development and plasticity is of key importance for understanding the formation of neuronal circuitry. In contrast to its usual function as an inhibitory neurotransmitter, γ-aminobutyric acid (GABA) mediates excitatory signalling, which is important for neuronal maturation and integration, during early development. The mechanisms underlying the timing of this excitatory period and the subsequent switch to inhibitory neurotransmission are poorly understood. In their recent *Science* paper Berg and colleagues show that nicotinic and GABA-mediated activity interact to control both this transition and later aspects of neuronal development.

The early excitatory effects of GABA-mediated neurotransmission are the result of a reversed chloride gradient, which is no longer present after neuronal maturation. However, the mechanisms by which the chloride gradient matures were unclear. The authors showed that, in chick ciliary ganglion neurons, the switch to inhibitory GABA-mediated neurotransmission occurs by embryonic day 14. The addition of nicotinic acetylcholine receptor antagonists delayed this transition, indicating that nicotinic receptor activity is required to 'switch off' the period of GABA-mediated excitation. Similar results were obtained in chick spinal cord neurons using antagonists and by comparing hippocampal neurons from wild-type and nicotinic receptor knockout mice.

The chloride gradient is governed by the activity of various chloride transporters. Blocking nicotinic receptors resulted in an extended 'immature' pattern of chloride transporter expression: there were higher levels of NKCC1 (also known as SLC12A2), which is responsible for accumulating chloride inside the neuron, and lower levels of KCC2 (also known as SLC12A5), which acts to extrude chloride from the cell. This provides a mechanism by which the chloride gradient is regulated by nicotinic receptor activity.

The authors next investigated the importance of the onset of inhibitory GABA-mediated neurotransmission for neuronal development. In cultured ciliary ganglion neurons, overexpression of KCC2 accelerated the switch to inhibitory neurotransmission and resulted in dramatic differences in neuronal morphology and synapse formation. In KCC2-expressing cells, exposure to GABA resulted in a unipolar morphology and a reduction in the number of developing synapses. Interestingly, both in culture and *in ovo* these effects were also shown to rely on nicotinic receptor activity, suggesting a combined synergistic effect of GABA and acetylcholine. The authors suggest that GABA-mediated inhibitory signalling might suppress the activity of voltage gated calcium channels, allowing nicotinic receptor activity to alter gene expression through the activation of transcription factors.

This study demonstrates how interactions between GABA-mediated neurotransmission and nicotinic activity can shape different stages of nervous system development. Extending these principles to other neurotransmitter systems could add to our understanding of the contribution of neuronal activity to synapse development.

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ORIGINAL RESEARCH PAPER Liu, Z., Neff, R. A. & Berg, D. K. Sequential interplay of nicotinic and GABAergic signalling guides neuronal development. *Science* **314**, 1610–1613 (2006)