SYNAPTIC PHYSIOLOGY

Closing the gap

Signalling through electrical synapses that are formed by gap junctions between neurons is important in the development of the mammalian central nervous system. Neuronal gap junctions are abundant immediately after birth, but subsequently decrease in number and remain at a low level, being confined to specific subsets of neurons in adults. Writing in *Nature Neuroscience*, Harsha Arumugam and colleagues show that the maturation of glutamatergic transmission is responsible for gap junction uncoupling during development.

These researchers studied gap junction coupling in slices of the paraventricular nucleus and the supraoptic nucleus of the rat hypothalamus, as well as in dissociated hypothalamic cultures, by using the coupling tracer neurobiotin, which passes through gap junctions. They found that the incidence of dye coupling increased during the first 2 weeks of postnatal development or in culture, and then declined significantly. These changes in gap junction coupling correlated with changes in the expression of connexin 36 — a neuron-specific gap junction protein.

When the hypothalamic cultures were chronically treated with the NMDA (*N*-methyl-D-aspartate) receptor antagonist dizocilpin, developmental uncoupling of gap junctions and downregulation of connexin 36 were abolished — an effect that was mimicked in cultures by the voltage-gated sodium channel blocker tetrodotoxin, which attenuates action potentials.

Arumugam and co-workers next set out to determine the signal transduction pathways involved in downregulation of connexin 36 expression and uncoupling of neuronal gap junctions during development. They found that gap junction coupling and connexin 36 expression did not decrease in hypothalamic cultures treated with either an inhibitor of the calcium/calmodulin-dependent protein kinases II and IV (CaMKII/IV) or a blocker of protein kinase C (PKC).

In addition, overexpression of the calcium–cyclic AMP responsive element-binding protein (CREB), which is found downstream of the CaMKII/IV and PKC pathways, accelerated the decrease in connexin 36 expression and gap junction uncoupling in culture, whereas overexpression of a dominant-negative mutant form of CREB had the opposite effect. Consistent with a role for CREB in NMDA-mediated effects, application of NMDA to hypothalamic cultures increased the amount of phosphorylated and, therefore, activated CREB, and this effect could be blocked by inhibitors of CaMKII/IV and PKC.

The researchers conclude that NMDA receptor-mediated glutamatergic transmission and action potentials are important for regulating developmental gap junction uncoupling and decreases in connexin 36 expression. This makes sense, as neuronal gap junction uncoupling occurs during the first 3 weeks of postnatal development, which is also the main period of chemical synapse formation and increased synaptic activity.

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ORIGINAL RESEARCH PAPER Arumugam, H. *et al.* NMDA receptors regulate developmental gap junction uncoupling via CREB signaling. *Nature Neurosci.* **8**, 1720–1726 (2005)
FURTHER READING Söhl, G. *et al.* Expression and functions of neuronal gap junctions. *Nature Rev. Neurosci.* **6**, 191–200 (2005)
WEB SITE
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