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CORTICAL DEVELOPMENT

Activity makes interneurons shape up

Electrical activity regulates the development of excitatory pyramidal neurons in the cerebral cortex; however, the role of such activity in the maturation of cortical interneurons is poorly understood. New research from Fishell and colleagues reveals that neuronal activity is essential not only for the correct migration of specific subtypes of interneurons but also for the morphological development of such cells.

To examine the effect of electrical activity on interneuron development in mice, the authors selectively overexpressed inward rectifier potassium channel 2 (IRK1; also known as Kir2.1) in embryonic caudal ganglionic eminence-derived interneurons; the upregulation of such channels leads to a decrease in resting membrane potential and suppression of neuronal excitability. Subsequently, they assessed the morphological development and cortical laminar migratory patterns of these neurons.

By postnatal day 8 (P8), certain subtypes of interneurons (calretin-positive and reelin-positive interneurons) expressing Kir2.1 exhibited alterations in morphology and aberrant cortical laminar migration. These phenomena seemed to be independently regulated by temporally distinct phases of neuronal activity, as shutting off Kir2.1 expression at P3 resulted in normal morphological maturation but altered migration.

Subsequently, the authors showed that application of kynurenic acid — a glutamate receptor blocker — to calretin- or reelin-positive interneurons at P3, but not earlier, caused morphological defects reminiscent of those observed with Kir2.1 overexpression. Taken together, these findings indicated that in these interneuron subtypes, correct migration required neuronal activity before P3, whereas proper morphological maturation required ionotrophic glutamate receptor-mediated activity from this time point onwards.

Migration and morphological development of GABAergic interneurons requires expression of the transcription factor DLX1. The authors showed that the levels of this protein and engulfment and cell motility protein 1 (ELMO1) — the expression of which is controlled by DLX1 — were downregulated in calretin- or reelin-positive, Kir2.1-expressing interneurons. Interestingly, calretin- or reelin-positive interneurons expressing a dominant-negative form of ELMO1 showed incorrect laminar migration but normal morphology. Moreover, overexpression of ELMO1 in calretin- or reelin-positive, Kir2.1-expressing interneurons rescued the migratory but not the morphological defects otherwise seen in these cells.

These results indicate that neuronal activity has an important role in controlling the migration and morphological maturation of certain subtypes of mouse cortical interneurons during development, and that the mechanistic basis underlying the migratory effects of such activity involves the expression of DLX1 and ELMO1.

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ORIGINAL RESEARCH PAPER De Marco Garcia, N. V., Karayannis, T. & Fishell, G. Neuronal activity is required for the development of specific cortical interneuron subtypes. *Nature* **472**, 351–355 (2011)