

論文の内容の要旨

論文題目 神経回路形成における CaM キナーゼ I 機能の解明

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Following polarity formation, the neuritogenesis of cortical neurons is heavily influenced by complex extracellular gradients of neurotrophic and guidance factors as well as neurotransmitters released from neighboring cells. Ca²⁺ signaling is activated by many of these extracellular stimuli, and is believed to play a major role during both axonal and dendritic growth. Here I show that Ca²⁺/calmodulin-dependent protein kinase I α (CaMKI α) is a critical factor for axonal growth and refinement during early stages of cortical development. The axon-specific morphological phenotype required a diffuse cytoplasmic localization and a strikingly α -isoform-specific kinase activity of CaMKI. Unexpectedly, treatment with Muscimol, a GABA_A receptor agonist, selectively stimulated elongation of axons but not of dendrites, and a CaMKK-CaMKI α cascade critically mediated this axonogenic effect. Consistent with these findings, during early brain development, while the GABA effect was still largely excitatory, in vivo knockdown of CaMKI α resulted in an impaired growth of terminal axonal

branches of the interhemispheric callosal projections into the contralateral cortices.

Thus, the CaMKK-CaMKI α cascade may play a critical role in GABA-regulated axon elongation and path finding, and contribute to fine-tuning the formation of an accurate cortical network during early brain development.