Roles of synaptic activity in climbing fiber to Purkinje cell synapse elimination in the developing cerebellum

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論文の内容の要旨

論文題目 Roles of synaptic activity in climbing fiber to Purkinje cell synapse elimination in the developing cerebellum
(発達期小脳の登上線維―プルキンエ細胞シナプスの刈り込みにおけるシナプス活動の役割)

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In both central and peripheral nervous systems of the vertebrate, early formed immature circuits are redundant and require refinement to transform them into functionally mature circuits during development. An important process of refinement is synapse elimination in which some synapases are selectively strengthened/ maintained and the other synapses are eliminated. Studies at the developing neuromuscular junction (NMJ) have demonstrated that less active motor axons are eliminated through competition with more active axons. Similarly, the importance of neural activity has been shown in refinement processes of the central nervous system (CNS) including the hippocampus, retino-geniculate synapse, visual cortex and somatosensory cortex. It has been shown that, in those brain regions, axons conveying weaker inputs subsequently shrinke and axons with stronger inputs are maintained and/or expand their territories. These lines of evidence suggest that competitive processes among synaptic inputs regulate developmental synapse elimination in the CNS similar to those in the NMJ. However, it remains unknown to what extent competition among synaptic inputs contributes to the whole processes of developmental synapse elimination. This is presumably because of the difficulty to block synaptic transmission completely in only a part of presynaptic neurons during the entire course of postnatal neural circuit refinement. It remains also to be elucidated whether common mechanisms underlie developmental synapse elimination at different regions of the CNS. In this respect, elimination of redundant climbing fiber to Purkinje cell synapses during postnatal development of the cerebellum provides a good model of developmental synapse elimination in the CNS.

In the cerebellum, each Purkinje cell is innervated by multiple climbing fibers around birth. A single climbing fiber is selectively strengthened in each Purkinje cell from postnatal day 3 (P3) to P7. Then, from P9, only the strengthened climbing fiber (the "winner" climbing fiber) translocates along growing Purkinje cell dendrites and forms synapses there, whereas the other weaker climbing fibers ("loser" climbing fibers) stay on the somata and are subsequently eliminated from the somata from P7 to aroud P11 ("early phase" of climbing fiber elimination) and from around P12 to P17 ("late phase" of climbing fiber elimination). It has been shown that synaptic inputs and neuronal activities in Purkinje cells are required for elimination of redundant loser climbing fiber synapses from Purkinje cells. However, it remains unclear which synaptic inputs, winner or loser climbing fibers, are necessary for the elimination of loser climbing fibers. Moreover, roles of competition among synaptic inputs in the winner-loser discrimination processes are largely unknown.

In the present study, I established an experimental system in which synaptic transmission from a subset of climbing fibers to Purkinje cells is abolished during the course of climbing fiber synapse elimination. For this purpose, I introduced tetanus toxin light chain (TNLC) into a subset of inferior olivary neurons that project climbing fibers to the contralateral cerebellum. This experimental system enables me to investigate the fate of the "absolutely weaker" climbing fibers, which are incapable of releasing glutamate and therefore are inevitably weaker than the other control climbing fibers that do not express TNLC. Using this new experimental system combined with morohological and electrophysiological analyses, I investigated whether and how climbing fiber synaptic activity contributes to the selection of a single winner climbing fiber, dendritic translocation of the winner, and elimination of the loser climbing fibers.