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EARLY AND LATE PHASES OF CLIMBING FIBER SYNAPSE ELIMINATION DURING CEREBELLAR DEVELOPMENT

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Purkinje cell (PCs) in the cerebellum are innervated by multiple climbing fibers (CFs) at birth. In mice, redundant CFs are eliminated and most PCs become innervated by single CFs by the postnatal day 21 (P21). Previous studies suggest that this refinement process can be divided into two distinct phases. During the first postnatal week, one CF is intensified relative to others and massive elimination of surplus CFs occurs (early-phase of CF synapse elimination). During the second postnatal week, the weaker CFs appear to be eliminated and the adult-type mono innervation pattern is attained. This process is dependent on synaptogenesis onto PCs from parallel fibers (PFs), the other excitatory inputs to PCs. We have shown that the late phase is critically dependent on PF synapse formation and activation of type 1 metabotropic glutamate receptor (mGluR1)-mediated signaling in PCs. Blockade of NMDA receptors within the cerebellum during the 2nd postnatal week causes persistent multiple CF innervation of PCs in adulthood, which is similar to that observed in mice lacking the mGluR1-mediated signaling. Functional NMDA receptors are absent in PCs but they are rich in mossy fiber (MF)-granule cell (GC) synapses. Therefore, these results indicate that the late phase is dependent on the activity along MF-GC-PF pathway that drives mGluR1-mediated signaling in PCs. Furthermore, we have recently found that the selective strengthening of single CF and the early phase of CF synapse elimination were severely impaired in mice lacking P/Q type voltage-dependent calcium channel (VDCC). Because the late phase of CF synapse elimination is normal in this mutant mouse, we conclude that calcium influx through P/Q type VDCC are crucial for the refinement of CF synapse during the first postnatal week. These results suggest that both the early and the late phases are dependent on neuronal activity but involve distinct signaling cascades in PCs.

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DENDRITIC SPINE PLASTICITY OF CEREBELLAR PURKINJE CELLS IN PHYSIOLOGIC AND PATHOLOGIC CONDITIONS

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Purkinje cell, a main efferent neuron of the cerebellum, bears many spines on its dendrites, which has been described by Ramon y Cajal. It has been believed that it might be the sites for communication between neurons. Subsequently, electron microscopic study established that the dendritic spines are certainly postsynaptic targets of excitatory presynaptic inputs. The shape and number of dendritic spines are dramatically changed under various physiological or pathological conditions such as development, environmental enrichment, learning, calcium concentration, hormonal state, mental retardation, and epilepsy. We have investigated Purkinje cell dendritic spine plasticity in acrobat (AC) learning model as a physiologic condition and rolling mouse Nagoya (RMN), an ataxic mutant as a pathologic model. With an advantage of high voltage electron microscopy, we could analyze the dendritic spine of Golgi impregnated Purkinje cells efficiently. The 3 dimensional organization of the synapse was evaluated in the AC animal cerebellum to understand local neuronal circuits in a status of learning. The length and density of Purkinje cell dendritic spine were increased in AC. The ratio of branched type spine was also increased in AC. In RMN the length of Purkinje cell dendritic spines has been decreased in tertiary dendritic branchlet. But we could observe numerous dendritic spines from proximal dendrite of the Purkinje cell. These results suggest that the morphology of the dendritic spine is engaged in physiological and pathological conditions.