論文の内容の要旨

論文題目 Motor protein KIF1A is essential for hippocampal synaptogenesis and learning enhancement in an enriched environment
(モータータンパク質 KIF1A は豊かな環境下で見られる、海馬シナプス形成、及び学習能力の増強に必須である)

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Environmental enrichment refers to housing conditions, where animals experience higher levels of sensory, motor, social and cognitive stimuli compared to a normal cage environment. Enrichment has a variety of effects on the brains of wild-type mice and rats at many levels, ranging from molecular and cellular to behavioral. At the cellular level, enrichment increases dendritic branching and length, the number of dendritic spines and the size of synapses on some neuronal populations. Furthermore, enrichment enhances hippocampal neurogenesis and synaptogenesis. Many of these morphological changes are consistent with enrichment-induced alterations in the expression of genes involved in synaptic function and neuroplasticity, such as neurotrophins and synaptic proteins. At the behavioral level, enrichment induces learning enhancement in various behavioral tests, reduces memory decline in aged animals, decreases anxiety and increases exploratory activity. Furthermore, enrichment has beneficial effects on brain disorders. It is reported that brain-derived neurotrophic factor (BDNF) plays an important role in these enrichment-induced neuronal changes; however, the precise mechanism underlying these effects remains uncertain.

The kinesin superfamily proteins (KIFs) are microtubule-based molecular motors that transport membrane organelles, protein complexes and mRNAs. KIFs have fundamental roles in neuronal function, plasticity, morphogenesis and survival by

transporting such cargos. Intriguingly, recent reports have shown that some KIFs (KIF5 and KIF17) are implicated in learning and memory. I therefore sought to examine possible alterations in levels of KIFs after enrichment, and then to investigate the possible relationship of KIFs to enrichment-induced structural and behavioral changes, such as hippocampal synaptogenesis and learning enhancement.

In this study, I found that enrichment causes a specific upregulation of kinesin superfamily motor protein 1A (KIF1A) in the mouse hippocampus and, in hippocampal neurons *in vitro*, BDNF increases the levels of KIF1A and of KIF1A-mediated cargo transport. Analysis of $Bdnf^{+/-}$ and $Kif1a^{+/-}$ mice revealed that a lack of KIF1A upregulation resulted in a loss of enrichment-induced hippocampal synaptogenesis and learning enhancement. Meanwhile, KIF1A over-expression promoted synaptogenesis via the formation of presynaptic boutons. These findings demonstrate that KIF1A is indispensable for BDNF-mediated hippocampal synaptogenesis and learning enhancement induced by enrichment.

This is the first report of a motor protein that plays a key role in enrichment-induced structural and behavioral changes. My findings suggest a new molecular motor-mediated presynaptic mechanism underlying experience-dependent neuroplasticity.