論文の内容の要旨

論文題目

The mechanism of regulation of intracellular transport via KIF3 motor protein in neurons
（キネシンスーパーファミリーモーター分子 KIF3 による神経細胞内物質輸送の制御機構の研究）

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In neurons, N-cadherin plays an important role in synaptogenesis and synaptic plasticity. Recent studies have demonstrated that N-cadherin is transported along microtubule by KIF3, which is a member of kinesin superfamily proteins (KIFs) composed of KIF3A, KIF3B, and KAP3. However, the regulation of this transport is still unknown. Here I show that the phosphorylation of Ser 689 of KIF3A by Protein Kinase A (PKA) regulates the binding of KIF3 to N-cadherin. N-cadherin was observed as globular particles in dendrites of cultured hippocampal neurons. Transfection studies using N-cadherin–GFP revealed that N-cadherin–GFP containing particles were transported mainly distally in dendrites. To clarify the mechanism how KIF3–N-cadherin binding is regulated, I focused on the phosphorylation of KIF3. I identified the phosphorylation of Ser 689 of KIF3A *in vivo*, and identified PKA as a kinase responsible for Ser 689 phosphorylation *in vitro*. The phosphomimic KIF3A mutant (S689E) showed strong binding activity to N-cadherin and caused the enlargement of spine head in the transfected neurons. On the other hand, when the unphosohorylated KIF3A mutant (S689A) was transfected to the neurons, KIF3–N-cadherin binding was weakened and the size of the spine heads was decreased. These findings indicate the molecular mechanisms that N-cadherin transport is regulated via KIF3 phosphorylation by PKA, which underlies synapse development.