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# 論　文　内　容　の　要　旨

〔　題　　名　〕 Involvement of BDNF-TrkB and proBDNF-p75$^{NTR}$ signaling pathways in two contrasting forms of long-lasting synaptic plasticity (鏡像的な長期シナプス可塑性における BDNF-TrkB経路とproBDNF-p75$^{NTR}$経路の関与)

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The repetition of experience is often necessary to establish long-lasting memory. However, the cellular mechanisms underlying this repetition-dependent consolidation of memory remain unclear. The laboratory to which I belong previously found in organotypic slice cultures of the rodent hippocampus that repeated inductions of long-term potentiation (LTP) and long-term depression (LTD) led to a slowly developing long-lasting synaptic enhancement and suppression coupled with synapse formation and elimination, respectively. These phenomena should serve as useful in vitro models for analyzing the cellular mechanisms underlying the repetition-dependent consolidation.

In the part 1 of this thesis, I hypothesized that the enhancement and suppression are mediated by brain-derived neurotrophic factor (BDNF)-TrkB and proBDNF-p75$^{NTR}$ signaling pathways, respectively. proBDNF is a precursor form of BDNF and is recently emerging as a novel neurotrophic factor having various effects opposite to mature BDNF (mBDNF). When I masked either of the respective pathways, reversals of the enhancement and suppression were resulted. These results are readily explained by the alternative activations of the p75$^{NTR}$ pathway by mBDNF under TrkB-masking conditions and of the TrkB pathway by proBDNF under p75$^{NTR}$-masking conditions. The laboratory also previously reported that the expression of mRNA$^{BDNF}$ increased significantly during the period of 24 h after the third induction of LTP. Assuming that BDNF may play a role around this period, I invalidated mBDNF by the application of a BDNF-scavenger for limited periods of time. I found two separate time periods, in which the BDNF-scavenging was effective to suppress the long-lasting synaptic enhancement, the early (3-6 h after third LTP) period and the late (9-48 h after third LTP) one. This result suggests that there are multiple BDNF-dependent phases after the repeated inductions of LTP to lead to the long-lasting synaptic enhancement coupled with synapse formation.

In the Part 2 of this thesis, I conducted experiments to support my hypothesis further, taking advantage of transgenic mouse that cannot convert proBDNF to BDNF.

The obtained results were all in line with my hypothesis and I believe that the understanding of the mechanisms underlying long-lasting memory proceeded further.

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# 論文審査の結果の要旨及び担当者

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## 論文審査の結果の要旨

哺乳類脳における記憶の固定の機構は、未解明の部分が多い。その中で、安定培養下にある海馬切片に、長期増強現象（LTP）を繰り返し誘発した後に生じるシナプス新生現象（RISE）と、長期抑圧現象（LTD）を繰り返し誘発した後に生じるシナプス廃止現象（LOSS）は、有力な解析モデル現象として注目される。

櫻木君は「RISEは脳由来神経栄養因子（BDNF）を介し、LOSSはその前駆体分子（proBDNF）を介して起こる」との仮説を立て、これを実証した。同君は、BDNFはTrkB分子を主受容体とし、proBDNFはp75NTR分子を主受容体とするが、互いに他にも結合できることに着目して、「TrkBを抗体で遮蔽してRISE刺激を行えば、p75NTRが活性化してLOSSが生じ、p75NTRを抗体で遮蔽してLOSS刺激を行えば、TrkBが活性化してRISEが生じる」と予想して実行したところ、予想通りの結果をえた。また、proBDNFをBDNFに変換できない遺伝子改変マウスでは、RISEが起きないこと、シナプス数が下限まで減少しているためにLOSSも起きないことを示し、仮説をさらに強固なものにした。

これらの成果は、記憶の固定過程の細胞基盤と想定されるシナプスの新生・廃止の機構の理解を大きく進めるもので、本論文は同君に博士学位を授与するに値すると判断される。