大脳皮質ニューロンにおける脳由来神経栄養因子（BDNF）の輸送と、GABA作動性ニューロンに対する効果

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Brain-derived neurotrophic factor (BDNF) is assumed to be sorted into a regulated secretory pathway, transported in neurites and then released from neurons. Among these processes, less attention has been paid to trafficking mechanisms. To address questions of whether the trafficking of BDNF is different between axons and dendrites and regulated by neuronal activity, we analyzed movements of green fluorescence protein (GFP)-tagged BDNF in axons and dendrites of living cortical neurons by time-lapse imaging. To evaluate effects of neuronal activity on trafficking we applied glutamate, and analyzed changes in the movements of BDNF-GFP and the level of intracellular Ca\(^{2+}\) and membrane potentials. We found that 59\% of BDNF-GFP expressed as vesicular puncta in neurons moved rapidly in axons in the anterograde direction, while in dendrites BDNF-GFP puncta did not move in such a manner, and only 36\% of the puncta moved in either direction. The velocity of transport of these puncta in dendrites was slower than that in axons. An application of glutamate caused a sudden suspension of the trafficking of puncta and a marked decrease in the fluorescence intensity of the puncta in most cases. Glutamate also induced a massive increase in intracellular Ca\(^{2+}\) level and a strong depolarization. Analysis using antagonists of glutamate receptors and Ca\(^{2+}\)-free external solution indicated that the trafficking in neurites is suspended by a certain level of Ca\(^{2+}\) influxed mainly through N-methyl-D-aspartate receptors. Such a suspension of trafficking may be a prerequisite for BDNF to be released in an activity-dependent manner.
ラクトンを興奮させると停止し、その後放出され脳光が減弱すること、3）このグルタミン酸の作用は主に NMDA 受容体を介する Ca²⁺ のニューロン内への流入により生じること、4）軸索終末より放出された BDNF は GABA 作動性ニューロンの樹状突起発達を促進する因子として機能すること、などを示唆する結果を示した。これらの結果は BDNF のニューロン内での輸送機構とその役割について新たな知見を加えるものである。よって、本論文は博士（理学）の学位として十分価値あるものと認める。