Abstract

Recent years have witnessed a revolution in our understanding of signaling in neuronal compartments and the manifold functions of a variety of stimulations that regulate protein translation locally. Glutamate is the principal excitatory neurotransmitter in mammalian CNS and also acts as a cue guiding axonal and neuronal migration during the early phase of development. In this study, we found that glutamate stimulates axonal translation by binding to AMPA receptors and metabotropic glutamate receptors and activating Ca^{2+} influx and the mTOR signaling. These data demonstrate that glutamate-induced stimulation of local translation may partake in regulating axonal functions during development.

The dependencies of axonal translation on neuronal types and stimulating reagents have also been studied here. Our results suggest that local translation can be activated by glutamate, BDNF, Netrin-1, and semaphorin 3A stimulation in cortical axons but not in hippocampal ones. Furthermore, Netrin-1- or semaphorin 3A-induced enhancements of translation are mediated by pathways different from those mediating the BDNF- or glutamate-induced enhancements of translation in cortical axons. Taken together, our finding from this thesis implies the mechanisms underlying axonal translation depend on they neuronal types as well as on the nature of stimulation reagents.

中文摘要

神經發育的過程中，遠端軸突受到外界刺激後立即產生的反應，會受到局部蛋白質新生所調控。麩氨酸 (glutamate) 為一種哺乳類中樞神經系統的主要神經傳導物質，在早期發育時期，麩氨酸也作為一種引導軸突因子。研究指出，胞外麩氨酸的濃度會間歇性的升高，進而誘導生長中的軸突找到正確的目標細胞。本篇研究中，我們發現培養中的大鼠大腦皮質神經細胞，經麩氨酸刺激後，能促使皮質神經的軸突有局部蛋白質新生。其中，促離子型麩氨酸受器，如: AMPA 受器，以及第一型和第二型代謝型麩氨酸受器，受到麩氨酸處理後會被活化，並引發 mTOR (mammalian target of rapamycin) 的訊號傳遞，並透過鈣離子通透的 AMPA 受器和 TRPC (transient receptor potential canonical) 的開啟，使胞內鈣離子濃度增加，進而促進軸突新生蛋白質的增加。另外，受到 BDNF (brain-derived neurotrophic factor) 刺激的神經軸突，也有局部蛋白質新生的現象。在第二部分的研究中，我們發現麩氨酸、BDNF 以及生長椎引導因子 Netrin-1 和 semaphorin 3A 的刺激下，大腦皮質神經軸突會有局部蛋白質新生現象，而海馬迴神經軸突則不會。另外，Netrin-1 和 semaphorin 3A 在大腦皮質神經軸突引發的局部蛋白質新生似乎受到非 mTOR 訊息傳導路徑所調控，與麩氨酸和 BDNF 的調控機制並不相同。因此，我們認為麩胺酸、BDNF、Netrin-1 和 semaphorin 3A 所引發的大腦皮質神經軸突之蛋白質新生，是透過不同的訊息傳遞路徑所調控。