Studies on transcriptional mechanisms of synaptic plasticity-related genes and its physiological roles in neurons

Akiko Tabuchi
(Graduated School of Medicine & Pharmaceutical Sciences, University of Toyama)

Synaptic transmission plays essential roles not only for transducing or proccessing several informations, but also for activating gene expression in neurons. The "neuronal activity"-dependent transcriptional activation is required for long-lasting, functional changes that involved in memory consolidation or drug addiction. Thus, an elucidation of the molecular mechanism underlying neuronal activity-dependent transcription of synaptic plasticity-related gene, has shed light on an understanding of neuronal function and disorders as well as an identification of new target molecules for drug design. Here we have introduced studies on synaptic plasticity-related brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and PACAP genes.

Transcriptional activation of BDNF and PACAP genes, which is commonly regulated by a key transcription factor, cAMP response element-binding protein (CREB), at least in part contributes to neuronal activity-dependent neuronal survival. Among at least four distinct promoters of BDNF gene, promoters I and III are differentially activated by Ca^{2+} signals via NMDA receptor and L-type voltage-dependent Ca^{2+} channels. Especially, BDNF gene promoter I activation requires the cooperative binding of upstream stimulatory factor (USF) and CREB to a CRE/USF binding site. With respect to PACAP gene, neuronal activity induces not only the CREB-mediated transcription but also stabilization of PACAP mRNA through post-transcriptional mechanism, both of which eventually result in an effective accumulation of PACAP. In contrast, unlike BDNF and PACAP genes, NT-3 gene transcription is regulated by Sp3/4. One of the most important future directions is to elucidate how long-lasting changes in neuronal plasticity is “epigenetically” and “structurally” controlled. Taken together, our ongoing studies aimed at understanding the relationship between the link of neuronal morphology, epigenetic regulation to gene expression and “long-lasting” neuronal responses would be warranted.