論文内容の要旨

論文題目

Timing-dependent actions of NGF required for cell differentiation

細胞分化における、神経成長因子のタイミング依存的働き

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Continuous NGF stimulation induces PC12 cell differentiation. However, why continuous NGF stimulation is required for differentiation is unclear. In this study, we investigated the underlying mechanisms of the timing-dependent requirement of NGF action for cell differentiation. To address the timing-dependency of the NGF action, we performed a discontinuous stimulation assay consisting of a first transient stimulation followed by an interval and then a second sustained stimulation and quantified the neurite extension level. Consequently, we observed a timing-dependent action of NGF on cell differentiation, and discontinuous NGF stimulation similarly induced differentiation. The first stimulation did not induce neurite extension, whereas the second stimulation induced fast neurite extension; therefore, the first stimulation is likely required as a prerequisite condition. These observations indicate that the action of NGF can be divided into two processes: an initial

stimulation-driven latent process and a second stimulation-driven extension process. The latent process appears to require the activities of ERK and transcription, but not PI3K, whereas the extension-process requires the activities of ERK and PI3K, but not transcription. We also found that during the first stimulation, the activity of NGF can be replaced by PACAP, but not by insulin, EGF, bFGF or forskolin; during the second stimulation, however, the activity of NGF cannot be replaced by any of these stimulants. These findings allowed us to identify potential genes specifically involved in the latent process, rather than in other processes, using a microarray and siRNA experiment. These results demonstrate that NGF induces the differentiation of PC12 cells via mechanically distinct processes: an ERK-driven and transcription-dependent latent process, and an ERK- and PI3K-driven and transcription-independent extension process.

< Summary diagram of the actions of NGF >