

Kinetic simulation study of cerebellar long-term depression

Shinya Kuroda
Kawato Dynamic Brain Project
ERATO
Japan Science and Technology
619-0288
kshinya@erato.atr.co.jp

Nicolas Schweighofer
Kawato Dynamic Brain Project
ERATO
Japan Science and Technology
619-0288
nicolas@erato.atr.co.jp

Mitsuo Kawato
Kawato Dynamic Brain Project
ERATO
Japan Science and Technology
ATR
619-0288
kawato@isd.atr.co.jp

ABSTRACT

Cerebellar long-term depression (LTD) is a process of decrease of synaptic strength between the parallel fibers (PF) and Purkinje cells (PC) induced by the conjunctive activation of PF and the climbing fiber (CF) [3,8]. Cerebellar LTD is thought to be a molecular and cellular basis for cerebellar learning [3,4,9]. Recent progress revealed that many signal transduction pathways are involved in the induction of cerebellar LTD [1,2,7]. Because multiple molecular signal transduction pathways are involved, the systematic relationship between cerebellar LTD and the currently known signal transduction pathways remains obscure. To address this issue, we built a new diagram of the signal transduction pathways and developed a simulation of a computational model of kinetics for the phosphorylation of AMPA receptors, known as a key step for expressing cerebellar LTD [6]. The phosphorylation of AMPA receptors in this model consists of an initial phase and an intermediate phase. We show that the initial phase is mediated by the activation of linear cascades of protein kinase C (PKC) whereas the intermediate phase is mediated by a mitogen-activated protein (MAP) kinase-dependent positive feedback loop pathway that is responsible for the transition from the transient phosphorylation of the AMPA receptors to the stable phosphorylation of the AMPA receptors. These phases are dually regulated by the PKC pathway and protein phosphatase pathway. Both phases also require nitric oxide (NO), although NO *per se* does not show any ability to induce LTD; this is consistent with a permissive role as experimentally reported. In addition, there are some discrepancies between the simulated and experimental results in the induction of the initial phase of LTD, suggesting that other mechanisms in addition to the phosphorylation of AMPA receptors are responsible for the initial phase of cerebellar LTD. Therefore, the kinetics simulation is a powerful tool for understanding and exploring the behaviors of complex signal transduction pathways involved in cerebellar LTD.

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