Physiological role of Addicsin-Arl6ip1 complex in oxidative stress control

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Addicsin is a neuronal glutamate transporter EAAC1 negative regulator and forms Addicsin-Arl6ip1 complex (AA) with an anti-apoptotic factor Ar16ip1. EAAC1 extracellular glutamate uptake activity is regulated by the AA complex dynamics. However, physiological role of AA formation and its kinetic regulatory mechanism are largely unknown. Here, I investigated the relationship between dynamics of AA formation and oxidative stress sensitivity. First, C6BU -1 cells overexpressing Ar16ip1 or Addicsin Y110AL112A (Ar16ip1-binding ability deficient mutant) had significantly increased sensitivity to H_2O_2 oxidative stress. The mRNA expression ratio of Ar16ip1/Addicsin showed a very high correlation with H2O2-induced cytotoxicity (ED50). Moreover, Addicsin translocation from endoplasmic reticulum (ER) to plasma membrane(PM) was observed after 100 μM H_2O_2 exposure. Next, we investigated the physiological role of 112th Leu residue of Addicsin, which is completely conserved in evolution and present in the Arl6ip1-binding region. Addicsin L112A was localized at ER as well as the wild type, but Addicsin L112I, which had increased steric bulk, was localized at PM and somata, but not ER. Several reports showed that Arl6ip1 mutation causes hereditary spastic paralysis and Addicsin L112F was one of Addicsin coding SNPs. These results raise a possibility that the dissociation of AA induced by oxidative stress may play an important role in the homeostatic control of neuronal oxidative stress sensitivity.