Novel defense strategy against progressive neurodegeneration by controlling intracellular Zn^{2+} dysregulation

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The causes of progressive neurodegeneration, i.e., Alzheimer's disease (AD) and Parkinson's disease (PD) are unknown. The basal (static) concentration of intracellular Zn^{2+} is estimated to be approximately 100 pM and is extremely lower than that of intracellular Ca^{2+} (～100 nM), suggesting that intracellular Zn^{2+} homeostasis is crucial for neural function. Moreover, the basal concentration of extracellular Zn^{2+} is estimated to be approximately 10 nM and is age-relatedly increased based on age-related increase in brain extracellular Zn. We postulated that progressive neurodegeneration is due to age-related intracellular Zn^{2+} dysregulation, which is induced by rapid influx of extracellular Zn^{2+}. Neuronal amyloid $\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) accumulation is considered an upstream event in the AD pathogenesis. Here we report that Zn-$A\beta_{1\text{-}42}$ oligomers formed in the extracellular compartment are synaptic activity-independently taken up into neurons, followed by rapid intracellular Zn^{2+} dysregulation. PD is characterized by a selective loss of dopaminergic neurons in the substantia nigra pars compacta of the brain. Here, we report a unique mechanism of nigral dopaminergic degeneration, in which rapid intracellular Zn^{2+} dysregulation via the production of reactive oxygen species, especially hydrogen peroxide causes PD in rats, which is induced by paraquart and 6-hydroxydopamine. I will talk about novel defense strategy against progressive neurodegeneration by controlling intracellular Zn^{2+} dysregulation.