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## Klotho protein deficiency leads to overactivation of μ-calpain

Hiroshi Manya, Tamao Endo

Glycobiology Research Group
Tokyo Metropolitan Institute of Gerontology,
Foundation for Research on Aging and Promotion of Human Welfare,
35-2 Sakaecho, Itabashi-ku, Tokyo 173-0015, Japan

The *Klotho* mouse is an animal model that prematurely shows phenotypes resembling human aging. Here we report that, in homozygotes for the *klotho* mutation (*kl*$^{-/-}$), $\alpha_{II}$-spectrin is highly cleaved, even before the occurrence of aging symptoms such as calcification and arteriosclerosis. Because $a_{II}$-spectrin is susceptible to proteolysis by calpain, we examined the activation of calpain in *kl*$^{-/-}$ mice. *m*-Calpain was not activated but μ-calpain was activated at an abnormally high level, and an endogenous inhibitor of calpain, calpastatin, was significantly decreased. Proteolysis of $a_{II}$-spectrin increased with decreasing level of Klotho protein. Similar phenomena were observed in normal aged mice. Our results indicate that the abnormal activation of calpain due to the decrease of Klotho protein leads to degradation of cytoskeletal elements such as $\alpha_{II}$-spectrin. Such deterioration may trigger renal abnormalities in *kl*$^{-/-}$ mice and aged mice, but Klotho protein may suppress these processes.

Keyword: klotho, calpain, calpastatin, spectrin, calcium homeostasis