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Tacrolimus decreases cognitive function via the regulation of Klotho in the hippocampal synaptic plasticity

Yoo-Jin Shin, Sun-Woo Lim, Cui Sheng, Dohyun Na, Eun-Jeong Ko, Byung-Ha Chung, Chul-Woo Yang
Department of Internal Medicine-Nephrology, School of Medicine, The Catholic University of Korea, Korea, Republic of

Objectives: The neurotoxicity of immunosuppressive agents is one of the major causes of neurological complications in kidney transplant patients. Klotho, an anti-aging gene, is known to play a major role in the brain related with a cognitive function. The aim of the present study was to investigate the influence of tacrolimus on cognitive function and the role of Klotho in the hippocampus.

Methods: Mice received tacrolimus (3mg/kg per day) injection for 6 weeks. The locomotor activity and hippocampal-dependent spatial memory were examined using open field test (OFT) and the Barnes maze, respectively. Klotho expression in the hippocampus was examined in the CA1 region using immunohistochemistry. The expression of neurotransmitter receptors in the hippocampus was evaluated using RT-qPCR, and we performed western blots for Forkhead box O transcription factors [FoxOs; phosphorylated FoxO3a (p-FoxO3a)] and manganese superoxide dismutase (MnSOD).

Results: There was a significant decrease of Klotho expression in the hippocampus in tacrolimus treated mice compared with the vehicle group. In this regard, it was confirmed that the decrease of hippocampal-dependent spatial memory function in the mice receiving tacrolimus. Klotho is expressed in the pyramidal neurons of the hippocampus and is located in adjacent synapses as well as in euchromatin of the nucleus, cytoplasm, and processes in the neurons. Tacrolimus treatment increased the Klotho-expressing inhibitory synapses and decreased the Klotho-expressing excitatory synapses in the CA1 region of the hippocampus. The inhibitory neurotransmitter receptor also increased in tacrolimus-treated mice, indicating a correlation with previous data. Moreover, we identified that Klotho regulation may be affected by oxidative stress in the hippocampus of tacrolimus-treated mice.

Conclusions: These data shows that tacrolimus treatment affects cognitive decline via the regulation of Klotho in the hippocampal synaptic plasticity. This finding suggest that tacrolimus treatment may cause psychiatric and neurological complications for patients, and should thus be used with caution.