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Is there a Place for Klotho in Alzheimer's disease?

Alzheimer's disease, a major healthcare concern, lacks an effective pharmacological therapy to change its irreversible progression. In this work, we present Klotho, a protein associated with aging that is involved in the regulation of numerous physiological processes and is a serious candidate to be a pharmacological target to act on. Klotho's mRNA has been found in neurons of a variety of brain regions (cortex, hippocampus). The best studied and prominent function of Klotho is as the co-receptor of fibroblast growth factor 23 (FGF23), through which Klotho controls renal phosphate excretion and vitamin D metabolism. Reduced serum levels of Klotho in mice have been associated with a shorter life expectancy and with numerous pathological conditions such as renal disease, vascular calcification, neurodegeneration, and others. Moreover, overexpression of Klotho leads to opposite effects resulting in increased survival rates. In this review we address different signaling pathways in which Klotho is involved in one way or another, focusing on those pathways that could serve as pharmacological targets to modify the evolution of Alzheimer's disease. We describe how Klotho inhibits signaling cascades involved in cellular senescence, fibrosis, inflammation, and apoptosis all of which are mediated by tumor growth factor ? (TGF- ?), nuclear factor kappa K (NF- ? B), insulin-like growth factor 1 (IGF-1) or Wnt. We also highlight how Klotho is able to activate anti-inflammatory and antioxidant signaling pathways. Although there are no drugs that act specifically on Klotho, compounds currently on the market such as hormone-based drugs, pravastatin, losartan, fosinopril, and rapamycin have been shown to increase the expression of this protein and are also discussed.