Hoyer C, Sartorius A, Aksay SS, Bumb JM, Janke C, Thiel M, Haffner D, Leifheit-Nestler M, Kranaster L. Electroconvulsive therapy enhances the anti-ageing hormone Klotho in the cerebrospinal fluid of geriatric patients with major depression. Eur Neuropsychopharmacol. 2018 Mar;28(3):428-435. doi: 10.1016/j.euroneuro.2017.12.012. Epub 2017 Dec 20. PMID: 29274997.

**Research on the role of Klotho in affective disorder is scarce, which is surprising in light of the fact that depression is associated with accelerated cellular aging as well as aging-related phenotypes and comorbidity observed in Klotho deficiency. On these grounds we investigated Klotho levels in the cerebrospinal fluid (CSF) and serum of eight geriatric patients undergoing electroconvulsive therapy (ECT) for severe depression. We hypothesize that ECT as a highly effective antidepressant treatment leads enhances Klotho levels. We found a significant difference between pre- and post-ECT CSF Klotho (792.5pg/ml vs. 991.3pg/ml, p=0.0020), but no difference in serum Klotho (602.5 vs. 594.3, p=0.32). Moreover, CSF Klotho increase positively correlated with the number of single ECT sessions that were performed in each patient (F1, 6)=7.84, p=0.031). Conjointly, the results of our exploratory study with a small sample size suggest a central nervous system-specific impact of ECT on Klotho, which may in turn partake in mediating the antidepressant effect of ECT. We suggest the modulation of neuroinflammatory processes, which have been ascribed pathophysiological relevance within the conceptual framework of the neuroinflammation hypothesis of depression, through ECT as a potential mechanism by which Klotho is enhanced in response to treatment. Further preclinical and clinical investigation should aim for a precise identification of the role of Klotho in depressive disorder.**

Brunoni AR, Supasitthumrong T, Teixeira AL, Vieira EL, Gattaz WF, Benseñor IM, Lotufo PA, Lafer B, Berk M, Carvalho AF, Maes M. Differences in the immune-inflammatory profiles of unipolar and bipolar depression. J Affect Disord. 2020 Feb 1;262:8-15. doi: 10.1016/j.jad.2019.10.037. Epub 2019 Oct 30. PMID: 31693974.

**Differences in immune profiles between BD and MDD patients exist, especially for the compensatory immune-regulatory system (CIRS): increased IL-10 is the primary immune-regulatory mechanism in MDD, while increased sTNFR2 and KLOTHO are the primary regulatory mechanisms in BD.**

Wu Y, Chen Z, Duan J, Huang K, Zhu B, Yang L, Zheng L. Serum Levels of FGF21, β-Klotho, and BDNF in Stable Coronary Artery Disease Patients With Depressive Symptoms: A Cross-Sectional Single-Center Study. Front Psychiatry. 2021 Jan 21;11:587492. doi: 10.3389/fpsyt.2020.587492. PMID: 33584362; PMCID: PMC7873935.

**The depression score was positively correlated with the severity of coronary artery stenosis, and serum FGF21, β-klotho, mBDNF, and proBDNF were closely related to the development of DS in patients with SCAD. These observations suggest FGF21, β-klotho, mBDNF, and proBDNF as potential diagnostic and/or therapeutic targets for SCAD with co-morbid depression.**

Prather AA, Epel ES, Arenander J, Broestl L, Garay BI, Wang D, Dubal DB. Longevity factor klotho and chronic psychological stress. Transl Psychiatry. 2015 Jun 16;5(6):e585. doi: 10.1038/tp.2015.81. PMID: 26080320; PMCID: PMC4490291.

**Chronic psychological stress is associated with accelerated aging and premature morbidity and mortality; however, the biology linking chronic psychological stress and its maladaptive effects remains largely unknown. Klotho is a pleiotropic hormone that regulates the aging process and promotes better brain and body health. Whether klotho is linked to psychosocial stress or its negative impact in humans has not been investigated. To address this gap, we recruited 178 healthy women who were either chronically high-stress maternal caregivers for a child with autism spectrum disorder (n = 90) or low-stress control mothers of a typically developing child (n = 88). We found that women under high chronic stress displayed significantly lower levels of the longevity hormone klotho compared with low-stress controls (t(176) = 2.92, P = 0.004; d = 0.44), and the decrease among those under high stress was age-dependent. In addition, high-stress caregivers who reported more depressive symptoms displayed even lower klotho levels compared with low-stress participants. These findings provide the first evidence that klotho levels are sensitive to psychosocial stressors and raise the possibility that klotho may serve as a novel biological link connecting stress, depression and risk for accelerated disease development. Furthermore, these findings have important implications for understanding the plasticity of the aging process and may represent a therapeutic target for mitigating the deleterious effects of chronic psychological stress on health and well-being.**

Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems. Mol Psychiatry. 2013 Feb;18(2):154-65. doi: 10.1038/mp.2012.167. Epub 2012 Nov 27. PMID: 23183489.

**Major depression and bipolar disorder are heterogeneous conditions in which there can be dysregulation of (1) the stress system response, (2) its capacity for counterregulation after danger has passed and (3) the phase in which damaging molecules generated by the stress response are effectively neutralized. The response to stress and depressed mood share common circuitries and mediators, and each sets into motion not only similar affective and cognitive changes, but also similar systemic manifestations. We focus here on two highly interrelated processes, parainflammation and endoplasmic reticulum (ER) stress, each of which can potentially interfere with all phases of a normal stress response in affective illness, including adaptive neuroplastic changes and the ability to generate neural stem cells. Parainflammation is an adaptive response of the innate immune system that occurs in the context of stressors to which we were not exposed during our early evolution, including overfeeding, underactivity, aging, artificial lighting and novel foodstuffs and drugs. We postulate that humans were not exposed through evolution to the current level of acute or chronic social stressors, and hence, that major depressive illness is associated with a parainflammatory state. ER stress refers to a complex program set into motion when the ER is challenged by the production or persistence of more proteins than it can effectively fold. If the ER response is overwhelmed, substantial amounts of calcium are released into the cytoplasm, leading to apoptosis. Parainflammation and ER stress generally occur simultaneously. We discuss three highly interrelated mediators that can effectively decrease parainflammation and ER stress, namely the central insulin, klotho and peroxisome proliferator-activated receptor-γ (PPAR-γ) systems and propose that these systems may represent conceptually novel therapeutic targets for the amelioration of the affective, cognitive and systemic manifestations of major depressive disorder.**

Pavlatou MG, Remaley AT, Gold PW. Klotho: a humeral mediator in CSF and plasma that influences longevity and susceptibility to multiple complex disorders, including depression. Transl Psychiatry. 2016 Aug 30;6(8):e876. doi: 10.1038/tp.2016.135. PMID: 27576165; PMCID: PMC5022081.

**To our knowledge, the role of Klotho in the human central nervous system and ts association with disease has notion studied directly. A single study of 804 subjects over 65 designed simply to compare lower and upper tertiles of Klotho levels reported that those in the lowest tertile had a significant increase in all-cause mortality and significantly greater cognitive impairment, as assessed by a MiniMental State examination score of less than 24. The Klotho-deficient mouse also shows an increase in mediators of oxidative stress in hippocampus at 5 weeks of age followed by a significant impairment of cognitive function at 7 weeks of age. Disturbed calcium homeostasis in neurons is associated with neuronal degeneration and death, a process that can proceed either rapidly (stroke) or slowly (Alzheimer's diseaseRecently, Klotho and transtherytin were shown to be activated by soluble amyloid precursor protein (APP)-β products possibly facilitating APPbeta sequestration. In addition to classic diseases of neurodegeneration, many of the consequences of Klotho deficiency occur in depressive illness.**

Gao X, Li Y, Sun Z, Xu H, Ma G, Deng Q, Zhang CX, Li R. Could α-Klotho Unlock the Key Between Depression and Dementia in the Elderly: from Animal to Human Studies. Mol Neurobiol. 2021 Jun;58(6):2874-2885. doi: 10.1007/s12035-021-02313-0. Epub 2021 Feb 1. PMID: 33527303.

**α-Klotho is known for its aging-related functions and is associated with neurodegenerative diseases, accelerated aging, premature morbidity, and mortality. Recent literature suggests that α-Klotho is also involved in the regulation of mental functions, such as cognition and psychosis. While most of studies of α-Klotho are focusing on its anti-aging functions and protective role in dementia, increasing evidence showed many shared symptoms between depression and dementia, while depression has been proposed as the preclinical stage of dementia such as Alzheimer's disease (AD). To see whether and how α-Klotho can be a key biological link between depression and dementia, in this review, we first gathered the evidence on biological distribution and function of α-Klotho in psychiatric functions from animal studies to human clinical investigations with a focus on the regulation of cognition and mood. Then, we discussed and highlighted the potential common underlying mechanisms of α-Klotho between psychiatric diseases and cognitive impairment. Finally, we hypothesized that α-Klotho might serve as a neurobiological link between depression and dementia through the regulation of oxidative stress and inflammation.**