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REVIEW

Klotho: molecular mechanisms and emerging therapeutics in central nervous system diseases

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Abstract

Klotho is recognized as an aging-suppressor protein that is implicated in a variety of processes and signaling pathways. The anti-inflammatory, anti-apoptotic, anti-oxidant, and anti-tumor bioactivities of klotho have extended its application in neurosciences and made the protein popular for its lifespan-extending capacity. Furthermore, it has been demonstrated that klotho levels would reduce with aging and numerous pathologies, particularly those related to the central nervous system (CNS). Evidence supports the idea that klotho can be a key therapeutic target in CNS diseases such as amyotrophic lateral sclerosis, Parkinson's disease, stroke, and Alzheimer's disease. Reviewing the literature suggests that the upregulation of klotho expression regulates various signaling pathways related to autophagy, oxidative stress, inflammation, cognition, and ferroptosis in neurological disorders. Therefore, it has been of great interest to develop drugs or agents that boost or restore klotho levels. In this regard, the present review was designed and aimed to gather the delegated documents regarding the therapeutic potential of Klotho in CNS diseases focusing on the molecular and cellular mechanisms.

Keywords Klotho · Inflammation · Oxidative stress · Neuroprotection · Neurological disorders

Abbreviations

CSF	Cerebrospinal fluid
FGF	Fibroblast growth factor
NMDARs	N-methyl-d-aspartate receptors
AD	Alzheimer's disease
PD	Parkinson's disease
LTP	Long-term potentiation
ALS	Amyotrophic lateral sclerosis
CNS	Central nervous system
TGF-β	Transforming growth factor β
IGF-1	Insulin-like growth factor 1
NF-KB	Nuclear factor κB
CYT	Cytoplasmic
TM	Transmembrane
FOXO	Forkhead box protein O
MnSOD	Manganese superoxide dismutase
SOD2	Superoxide dismutase
CAT	Catalase
ROS	Reactive oxygen species
IRS	Insulin receptor substrate
Tet1	Ten-eleven translocation methylcytosine dioxygenase
LPS	Lipopolysaccharides
PKA	CAMP-dependent protein kinase
CREB	CAMP response element binding protein
6-OHDA	6-Hydroxydopamin
ACE	Adenosine-1-converting enzyme
HUVECs	Human umbilical vascular endothelial cells
AngII	Angiotensin II
BBB	Blood-brain barrier

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MCAO	Middle cerebral artery occlusion
SNC	Substantia Nigra Pars Compacta
CamKII	Ca^{2+}/calmodulin-dependent protein kinase II
TLE	Temporal lobe epilepsy
Nrf2	Nuclear factor erythroid 2-related factor 2
GBM	Glioblastoma multiforme
VEGF	Vascular endothelial growth factor
MBP	Myelin basic protein
MAG	Myelin-associated glycoprotein
GFAP	Glial fibrillary acidic protein

Introduction

Klotho level, a longevity factor, declines with aging, renal failure, diabetes, and neurodegenerative disorders. Elevating klotho through acute peripheral administration and transgenic overexpression attenuates aging-related disorders and increases lifespan [1, 2]. Klotho is highly expressed in the kidneys and is also found in other tissues such as the brain (choroid plexus, cerebrospinal fluid (CSF), Purkinje EC cells, cerebral white matter, and neurons) and lungs [3]. The most apparent data about klotho activity described the enzyme as a regulator for vitamin D, phosphate, and calcium, while other physiological roles seem to be involved [4]. Klotho is also known to be a membrane-bound coreceptor for fibroblast growth factor (FGF) 23 or a soluble endocrine mediator that causes various bodily functions [5]. Following cleaving from its transmembrane form, α-klotho is released into the bloodstream as a hormone and exerts effects on insulin, FGF, and Wnt signaling in addition to a regulatory role in the correct functioning of N-methyl-d-aspartate receptors (NMDARs) [6, 7]. The experimental studies have claimed that systemic elevation of klotho would result in synaptic plasticity, cognition, and neural resilience to aging, Alzheimer's disease (AD), and Parkinson's disease (PD) [8]. Klotho has been known to act against inflammation and oxidative stress, and be involved in the regulation of autophagy [9]. On the other hand, klotho inadequacy seems to significantly impact the process of human aging and age-related disorders. The anti-aging protein can augment synaptic GluN2B levels in the hippocampus and cortex [10] so that an elevation in klotho levels would result in an upsurge of NMDAR-dependent genes responsible for memory consolidation, namely Fos. Through the activation of NMDAR, klotho increases long-term potentiation (LTP), which is crucial for acquiring knowledge and memory [1]. A large body of studies has proved that klotho plays a vital role in the treatment of a wide range of diseases including stroke [11], neurodegenerative diseases [12], brain tumor [13], and amyotrophic lateral sclerosis (ALS) [14]. This review summarizes the applications and possible mechanisms and functions of klotho in diseases related to the central nervous system (CNS) and reveals the latest research progress in this regard.

Structure and functions of Klotho

The klotho gene family includes α-klotho, β-klotho, and γ-klotho. The α-Klotho form is located on chromosome 13q12 and comprises four introns and five exons with a molecular weight of 130 kDa [15]. The klotho contains a short intracellular domain composed of 10 amino acids and an extracellular domain consisting of KL1 and KL2 catalytic domains. Both of the domains possess a length of nearly 450 amino acids and exhibit sequence similarity to 1 β-glycosidase family [15]. There are three distinct types of α-klotho protein including transmembrane klotho, secretory klotho, and soluble klotho (Fig. 1). ADAM10/17 metalloproteinases (α-secretases) digest the extracellular klotho domain so that the soluble α-klotho (s-klotho) would be released into CSF, urine, or blood and acts as an endocrine, autocrine, and paracrine hormone on the target cells [16]. Secretory klotho, having a molecular weight of 70 kDa, is formed by alternate splicing of klotho exons and can be detected in the blood, urine, and CSF [17].

Both β-klotho and γ-klotho belong to the category of type 1 single-pass transmembrane proteins [18]. β-Klotho is made of a β-glycosidase-like domain and has 42 percent amino acid sequence similarity to klotho. β-Klotho is primarily expressed in the liver, followed by the gastrointestinal tract, spleen, and kidneys. γ-Klotho comprises a family 1 glycosidase-like extracellular and a short intracellular domain. It exhibits a high expression level in the kidneys [19], eyes, and brown adipose tissue [20]. β-klotho acts as an obligatory co-receptor for FGF19 and FGF21 regulating bile acid synthesis and energy metabolism [21]. γ-Klotho forms complexes with numerous types of FGFR (1b, 1c, 2c, and 4) that increase the activity of FGF19. However, the biological functions of γ-Klotho remain predominantly elusive [22].

As mentioned, both the membrane-bound and soluble forms of klotho act as coreceptors for FGF23. In mice, a deficiency in either klotho or FGF23 leads to a rise in 1α-hydroxylase activity and a higher production of active vitamin D, resulting in hyperphosphatemia and hypercalcemia. Accordingly, it has been suggested that hypervitaminosis D and hyperphosphatemia are involved in the accelerated aging phenotype [23]. Klotho can inhibit several aging-related pathways in various ways such as transforming growth factor β (TGF-β), insulin-like growth factor 1 (IGF-1), nuclear factor κB (NF-κB), and Wnt/β-catenin, so that apoptosis, immune dysfunction, cellular senescence, inflammation, and neoplasia can be caused by these pathways [24, 25].

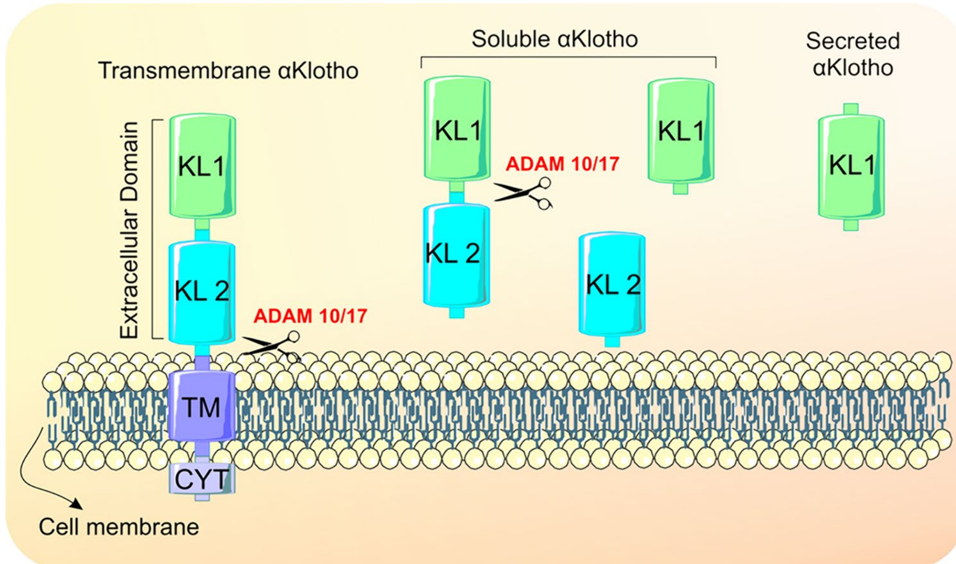

Fig. 1 Schematic structure of αKlotho protein and the different forms of secreted klotho. The full-length transmembrane α-Klotho consists of 3 domains: cytoplasmic (CYT), transmembrane (TM), and extracellular which has 2 internal repeats, KL1 and KL2. The extracellular domain of it is cleaved by membrane proteases such as ADAM10 and ADAM17 from 2 different points to release 3 types of shed αKlotho

Intracellular signaling pathways and klotho

Insulin/IGF-1/PI3K/Akt/FoxO signaling pathway

The insulin/IGF-1 pathway impacts on aging and lifespan. Insulin sensitivity is a marker of healthy longevity in humans [26]. Furthermore, soluble klotho has a negative regulatory effect on IGF-1, leading to a reduction in the activity of downstream signaling cascades, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB or AKT) pathways [27]. Mammalian members of the forkhead box protein O (FOXO) class of transcription factors are involved in regulating many processes such as oxidative stress, cellular differentiation, growth, survival, cell cycle, and lipid metabolism [28]. FOXO proteins are negatively regulated by the IGF-1/PI3K/AKT signaling pathway. Activation of insulin/IGF-1 signaling raises the activity of serine-threonine kinase Akt. FOXOs are phosphorylated and thus inhibited by activated Akt. Phosphorylated FOXOs are excluded from the nucleus and cannot act as transcription factors [29]. Furthermore, klotho carries anti-oxidative activities through the inhibition IGF-1/PI3K/AKT signaling pathway and stimulation of the FOXOs in neurons. Blockade of the insulin/IGF-1 pathway releases the inhibition of the FOXOs, which leads to their nuclear migration into the nucleus and the expression of multiple genes encoding antioxidant enzymes. These enzymes include manganese superoxide dismutase (MnSOD), superoxide dismutase (SOD2), and catalase (CAT). As a result, the reactive oxygen species (ROS) are eliminated, and resistance to oxidative stress is increased in mammals at both the organismal and cellular levels (Fig. 2). Accordingly, it has been found that klotho potentially enhanced FOXO-3a activity and CAT expression in astrocytes [29]. Klotho's ability to suppress insulin/IGF-1 signaling may be related to klotho's anti-aging properties, as extensive genetic evidence indicates that moderate inhibition of the insulin-like signaling pathway is an evolutionarily conserved mechanism to prevent aging. In mammals, increased lifespan has been reported in mice with lacking insulin receptors in adipose tissue, heterozygous for the null allele of the IGF-1 receptor gene, lacking insulin receptor substrate (IRS)-1, and lacking IRS-2 in the brain [30, 31].

P53/p21 signaling pathway

Cellular aging is triggered by oxidative stress and dysfunction of the mitochondria through the stimulation of the p53/p21 pathways. The p53 protein serves as a tumor growth suppressor and can be activated by the kinase known as ataxia telangiectasia-mutated, which in turn activates p21. The activation of p21 effectively hinders the proliferation of cells [32]. A deficiency in klotho leads to p53/p21 overexpression via inhibiting the new cell formation and increasing the population of senescent cells [33]. Consequently, the supplementation of klotho mitigates cellular senescence by inhibiting the signaling pathway of p53/p21 [34]. In an investigation that focused on the impact of epigenetics on neuronal cell death, an exploration was conducted to examine the involvement of DNA methylation and demethylation. As mentioned above, the study demonstrated that the prevention of apoptosis was noted in cerebellar granule cells and cortical neurons due to oxidative stress after the inhibition of DNA methyltransferase. It was discovered that the suppression of ten-eleven translocation methylcytosine dioxygenase (Tet1), an essential catalyst for DNA demethylation, prominently enhances the occurrence of apoptosis in

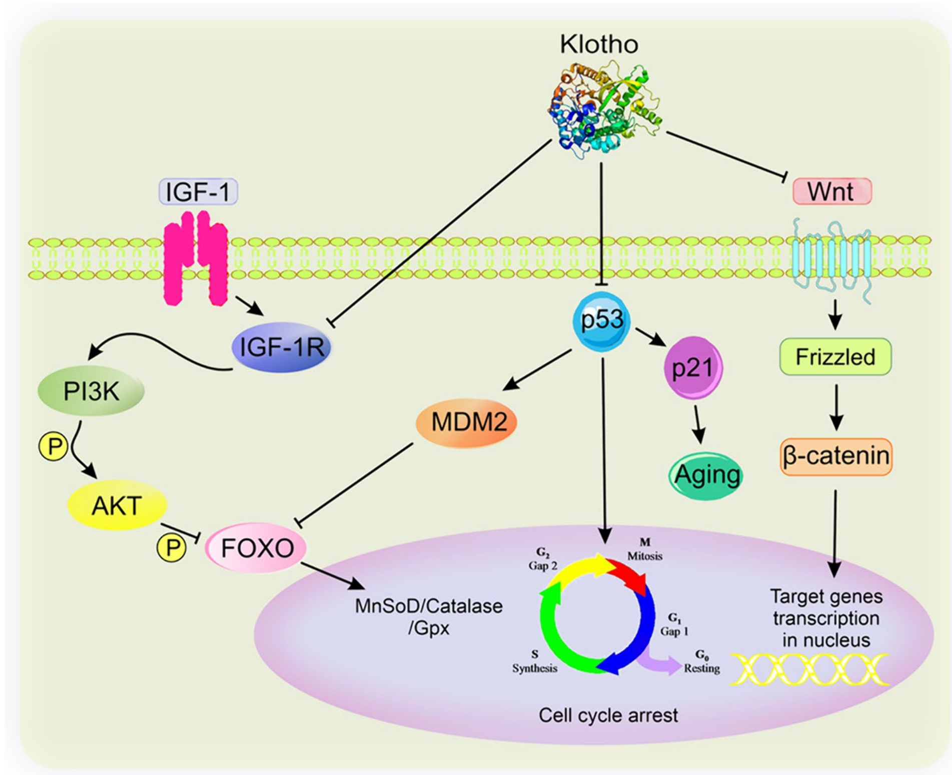

Fig. 2 Schematic representation of klotho interactions with IGF-1/PI3K/Akt/FoxO, P53/p21, and Wnt/β-catenin signaling pathways. The IGF-1/PI3K/Akt inhibition by klotho increases FOXO activity and promotes antioxidant defense by inducing the expression of GPx, catalase, and MnSOD. Klotho suppresses aging and cell cycle arrest by inhibiting P53/p21 signaling. Moreover, klotho inhibits the Wnt/β-catenin pathway. *GPx:* glutathione peroxidase, *MnSOD:* Manganese-superoxide dismutase, *FOXO:* forkhead box protein O

cerebellar granule cells provoked by hydrogen peroxide [35]. Although the direct or indirect regulation of klotho by Tet1 has yet to be determined, there exists a correlation inversely between klotho expression and CpG hypermethylation of its promoter region [36]. The up-regulation of the p53/p21 pathway and the induction of premature senescence of human cells were observed upon inhibiting klotho expression using klotho shRNA. Therefore, the mediation of neuronal protection through DNA methylation and demethylation may be facilitated by the klotho and p53 pathway. This implies that the klotho and p53 pathway may be a potential molecular therapy for neurodegenerative disorders and aging [37]. The klotho participates in controlling cellular lifespan and chronic age-related disorders through the suppression of p53 and the decrease in p21 protein levels (Fig. 2) [37]. In the HT-22 cells lacking klotho, lipopolysaccharides (LPS) induces a state of oxi-nitrosative stress and genomic instability accompanied by telomere dysfunctions. This leads to the activation of p53/p21 and subsequent cell cycle arrest. Therefore, endoplasmic reticulum stress, inflammation, and apoptotic cell death occur. Hence, these results propose that klotho plays a role as part of the cellular defense mechanism that protects neuronal cells against LPS-induced neuroinflammation and the associated emerging issues related to neurodegenerative disorders [38].

cAMP/PKA signaling pathway

The cAMP signaling can be described as a complex system consisting of various components. This system involves the activation of Gs protein-coupled receptors as well as adenylyl cyclase in the membrane. Moreover, it includes the generation of cAMP and subsequent activation of cAMP-dependent protein kinase (PKA) in the cytoplasm. Another crucial step is the phosphorylation of the cAMP response element binding protein (CREB), which occurs in the cytoplasm. In conclusion, this signaling pathway leads to the induction of cAMP-dependent gene expression in the nucleus [39]. The cAMP signaling pathway modulates a wide array of intracellular processes related to the control of cellular differentiation, proliferation, and apoptosis via the activation of cAMP-dependent PKA [40]. The cascade dependent on PKA holds significant importance in maintaining brain homeostasis and regulating inflammation. Moreover, its malfunctioning leads to the advancement of some neurodegenerative disorders such as PD [41]. Consistent with previous research findings, it has been demonstrated that the activity of cAMP-dependent PKA plays a crucial role in providing neuroprotection to dopaminergic neurons against oxidative stress induced by 6-Hydroxydopamine (6-OHDA). Furthermore, the inhibition of cAMP-dependent PKA by H-89 resulted in cellular toxicity [42]. Exogenous klotho was administered in the 6-OHDA rat model of PD for the first time. This was done to observe its potential in reducing astrogliosis, apoptosis, and oxidative stress. Additionally, it was found that a portion of its protective effect is reliant on the PKA/CaMKII/CREB cascade. This observation demonstrates that the advantageous impact of klotho is more effectively countered when a PKA inhibitor is present as compared to a CaMKII inhibitor [42]. Another study also described the ability of the circulating klotho to upregulate cAMP, specifically within endothelial cells. The findings indicated that the klotho protein functions as a humoral factor, thereby enhancing the activity of adenosine-1-converting enzyme (ACE) in human umbilical vascular endothelial cells (HUVECs) through a cAMP–PKA-dependent pathway. They found that the klotho protein potentially improves endothelial dysfunction by regulating antioxidant and reactive oxygen agents [43]. Wang et al. have demonstrated that the transfer of the klotho gene would result in a reduction of intracellular superoxide production and subsequently oxidative stress in the smooth muscle cells of rat aortas (RASM) [44]. The expression of the klotho gene also meaningfully mitigated oxidative damage, production of superoxide, and apoptosis induced by angiotensin II (AngII). Interestingly, the delivery of the klotho gene increased the intracellular cAMP levels and PKA activity in RASM cells in a dose-dependent manner. Therefore, the findings of this study propose a novel mechanism that could potentially facilitate the suppression of Nox2 expression by klotho. Specifically, this mechanism involves the upregulation of klotho, which causes an increase in cAMP levels, activation of PKA, and ultimately a reduction in the expression of Nox2 protein [44]. It was noted that the deficiency of Nox2 reduces cellular proliferation, vascular inflammation, and neointimal thickening after experimental angioplasty [45].

Wnt signaling pathway

The Wnt signaling pathway in different organisms has been related to numerous biological processes, including proliferation, differentiation, inflammation, mitosis, migration, neurogenesis, and regeneration [46, 47]. Several diseases, such as cancer, AD, PD, schizophrenia, and diabetes, have been associated with deregulation of this signaling pathway. Therefore, Wnt signaling has been investigated as a potential treatment strategy for various disorders [48–51]. Moreover, in recent years, the Wnt pathway has received more attention in neurophysiological animal studies [52]. Three Wnt signaling cascades have been identified, including a canonical pathway known as Wnt/β-catenin-dependent, as well as the non-canonical pathways such as Wnt/calcium and planar cell polarity (PCP) [53]. Although the Wnt signaling pathway was identified about 30 years ago, the scientists interested in investigating this pathway continue to develop rapidly [54]. Changes in Wnt signaling are associated with alterations in klotho expression or function in several tissues, including the kidneys, blood vessels, heart, bones, and brain, particularly the choroid plexus [55]. These connections highlight the complex interactions between klotho and Wnt signaling pathways in diverse physiological and pathological contexts [55]. Klotho has been shown to act as an antagonist of Wnt/β-catenin signaling, and the absence of klotho can lead to aberrant Wnt signaling activity, which can exacerbate cognitive deficits and neurodegeneration in mouse models [55, 56]. TGF, IGF-1, Wnt, and NF-κB are four pathways that are differentially involved in aging and are inhibited by klotho [57]. Recent studies indicate that klotho can bind to soluble Wnt ligands and inhibit the Wnt pathway [58]. Accordingly, soluble forms of several Wnt ligands, including Wnt3a and Wnt5a, have been shown to interact with klotho [59]. Also, α-Klotho binds to Wnt5A and prevents it from binding to its receptors, such as Frizzled receptors (Fig. 2). It has been demonstrated that klotho deficiency leads to the activation of Wnt signaling which accelerates aging and exhaustion of neural stem cells [60].

NF-κB

NF-κB plays a multifaceted role in the brain and the precise effects in the brain depend on the intensity of activation and the interplay with other signaling pathways [61]. Klotho has a role in the modulation of NF-κB signaling, exhibition of anti-inflammatory effects, and contributes to neuroprotection [58]. Studies on primary cortical neurons have shown that pretreatment with α-klotho modulated the secretion of pro-inflammatory cytokines induced by LPS [62]. Klotho may exert neuroprotective effects against cerebral ischemic injury by inhibiting retinoic-acid-inducible gene-I (RIG-I)/NF-κB inflammatory signaling following upregulation of cerebral klotho expression through gene delivery [63]. Also, klotho has a protective effect against neurological and psychiatric disorders and may have anti-seizure effects via several mechanisms, like RIG-I/NF-kB [64]. Furthermore, it was observed that inflammation has a critical role in the inhibition of klotho gene expression in colorectal cancer cells by activating the Toll-like receptor 4 /NF-κB signal pathway [65].

The effects of klotho on neurological disorders

Stroke

Ischemic stroke is one of the leading causes of morbidity and mortality in both developed and developing countries [66]. It is induced by transient or permanent blockage of the cerebral vessels, resulting in neuronal damage and neurological deficits, such as learning or memory impairment and locomotor dysfunction [67]. The pathophysiology of stroke is complex and implicates several processes, including energy failure, enhanced intracellular calcium levels, acidosis, disruption of the blood–brain barrier (BBB), excitotoxicity, activation of glial cells, and infiltration of leukocytes [66]. Apoptosis, mitochondrial dysfunction, inflammation, overproduction of ROS, endothelial dysfunction, and oxidative damage are thought to be among the underlying mechanisms of ischemia–reperfusion injury [68].

A large body of research showed that klotho plays a critical role in brain ischemia. Several studies reported that the levels of klotho mRNA and protein were reduced in stroke patients and animal models following cerebral ischemia [69, 70]. Moreover, a reduced concentration of irisin, as a myokine that is cleaved from fibronectin type III domain-containing protein five by proteolytic enzyme, and klotho in CSF were reported in stroke patients with impaired cognition [11]. Upregulation of klotho by systemic administration of exogenous irisin decreases oxidative stress and improves cognitive impairment in mice with middle cerebral artery occlusion (MCAO). Treatment with irisin or swimming for 4 weeks before MCAO improved spatial learning and memory as well as visual recognition memory. Furthermore, irisin could increase the expression of FOXO3a and MnSOD and decrease the expression of phosphorylated FOXO3a as well as reduce ROS formation in the MCAO group [11]. Besides, the upregulation of klotho expression by preconditioning exercise (3 weeks) can decrease infarct size and increase MnSOD expression in ischemic rats [71].

STAT4-mediated klotho upregulation contributes to cerebral ischemic preconditioning-induced cerebral ischemic tolerance via inhibition of neuronal pyroptosis. A day before induction of ischemia, injection of klotho into the lateral ventricle decreased neuronal necrosis. Moreover, inhibition of klotho expression enhanced the expression of the pyroptosis-associated proteins (Gasdermin D, pro-caspase-1, NLRP3, and cleaved caspase-1) [72]. Klotho upregulation via peroxisome proliferator-activated receptor gamma (PPARγ) contributes to the induction of cerebral ischemia tolerance by brain ischemic preconditioning [73]. In this regard, Jin and colleagues demonstrated that klotho knockdown worsens cerebral ischemic damage by increasing ROS levels [11].

Amelioration of neurological outcomes and neurobehavioral scores, recovery of body weight, and increase in the number of surviving neurons was observed with lentivirus-mediated overexpression of klotho in the area CA1 of hippocampus and caudate putamen (CP) three days after cerebral ischemia in mice [74]. Klotho overexpression considerably suppressed the post-ischemia inflammatory response, reflected by the attenuation of microglia and reactive astrocytes activation, inhibition of RIG-I/NF-kB signaling, and pro-inflammatory cytokines generation (TNF-α and IL-6) in mice following bilateral common carotid occlusion model of cerebral ischemia [74]. A study conducted by Long et al. showed that Ligustilide, an enhancer of klotho, inhibited the RIG-I/NF-κB p65 and Akt/FoxO1 pathways and prevented neuroinflammation (IL-6 and TNF-α levels) and oxidative stress following bilateral common carotid occlusion model of cerebral ischemia [69]. Besides, the ligustilide could prevent the development of neurological deficits and protect neurons in the CA1 and CP regions against cerebral ischemia [69].

The intracerebral overexpression of Klotho in rats was accomplished by the administration of lentivirus carrying full-length rat Klotho cDNA into the lateral ventricle of the brain, followed by MCAO surgery after a three-day interval. This approach led to a decrease in infarction volume and amelioration of neurological deficits by suppressing P38-MAPK activation, thereby downregulating AQP4 expression [75]. Overall, these studies illustrate that restoration of klotho levels can be an excellent therapeutic target for improving stroke.

Parkinson's diseases

Nearly 1% of people over 60 and 4% of people over 80 suffer from PD, a common neurological disorder, and is associated with a loss of midbrain dopaminergic neurons and the appearance of Lewy bodies which are mainly composed of α-synuclein [76]. Besides debilitating features of PD such as motor (bradykinesia, gait disturbances, stooping posture, resting tremor, and rigidity) and non-motor dysfunctions (anxiety, depression, sleep disorders, and cognitive impairment), Parkinsonian patients experience comorbidities, including high rate of infections, cardiac and gastrointestinal disorders, and fall-related damages [77, 78]. It has been known that inflammation [79], oxidative stress [80], mitochondrial dysfunction [81], and apoptosis [82] are implicated in the pathophysiological progress of neuronal degeneration in PD [83]. The relevant preclinical and clinical models [42] have supported the involvement of klotho in PD and highlighted a clinical potential for the klotho pathway in PD pathogenesis [82]. Kosakai et al. [84] showed that klotho-deficient mice had lower levels of striatal dopamine as well as a significant reduction in mesencephalic dopaminergic neurons from the substantia nigra pars compacta (SNC) and ventral tegmental area. In contrast, treatment with acute injection of klotho fragment reduced motor and cognitive deficits, and increased synaptic plasticity in the hippocampus in a PD mouse model expressing transgenic α-synuclein [85]. Additionally, the intracerebroventricular injection of klotho in the toxin rat model of PD alleviated striatal levels of oxidative stress, GFAP, α synuclein, and DNA fragmentation (apoptosis marker). In addition, klotho reduced contralateral rotations and improved the performance of rats in narrow beam task [42]. Tyrosine hydroxylase (TH) is the rate-limiting enzyme for the biosynthesis of catecholamines like dopamine, noradrenaline, and adrenaline [86]. Exposure of cells to neurotoxins such as 6-OHDA causes loss of TH-positive neurons in midbrain SNC. Klotho could hinder the deterioration of neurons that express tyrosine hydroxylase (TH) in the SNC [42]. Besides, administering a PKA inhibitor and Ca^{2+}/calmodulin-dependent protein kinase II (CamKII) inhibitor diminished the positive impact of klotho. This suggests that the ability of klotho to protect neurons is mediated by the PKA/CaMKII/CREB signaling pathway [42].

PD patients irrespective of gender had reduced CSF protein levels of klotho and FGF23 compared to controls. Furthermore, low CSF levels of klotho were related to higher scores in the Unified PD Rating Scale part III and the Hoehn and Yahr Scale [87]. A study found that compared to age-matched control, serum klotho levels were reduced in PD patients, but CSF klotho levels increased in the same patients versus controls [88]. Additional research is needed to clarify the function of klotho in PD as indicated by these inconsistent results.

Alzheimer's diseases

AD is a polygenetic neurodegenerative disorder that occurs more frequently with age and primarily exhibits neuroinflammation, mitochondrial dysfunction, extracellular amyloid-beta (Aβ) plaque, and neurofibrillary tangle deposition deposits within the cells [89–91]. These factors are related to a gradual decline in cognitive function and damage to nerve cells [92, 93]. Klotho alleviates cellular inflammation by inhibiting the release of cytokines (IL-1β, IL-6, and TNF-α) and enhancing the expression of miR-29a. IL-10 has been proven to suppress most of the pro-inflammatory cytokines by the inhibition of NF-κB. Klotho triggers the release of IL-10, likely by activating the JAK2/STAT3 signaling pathway, which results in the suppression of NF-κB, a critical transcription factor of pro-inflammatory cytokines [94]. Furthermore, klotho modulates the Wnt1/pCREB signaling cascade in AD patients' peripheral blood mononuclear cells [95].

Recent investigation has suggested that klotho inhibits the progression of AD related to aging, by suppressing insulin/IGF-1 signaling and oxidative stress in the murine model of AD [96].

In amyloid precursor protein/presenilin 1(APP/PS1) mice, the increase in klotho levels resulted in suppressing NLRP3 inflammasome activation and promoting Aβ clearance. This was achieved through the regulation of Aβ transporters and an increase in M2-type microglia [97]. The overexpression of klotho through injecting lentivirus that carried full-length mouse klotho cDNA improved cognitive deficits and reduced neuronal injury in aged APP/PS1 mice. Conversely, the knockdown of klotho led to a decrease in the transporter-mediated efflux rate of soluble Aβ1-42 across the human blood–CSF barrier in an in vitro monolayer model [97]. In this study, a battery of behavioral tests was used to assess cognitive function. In passive avoidance (hippocampus- and amygdala-dependent fear memory), overexpression of klotho significantly decreased step-down error times and increased the step-down latency. Moreover, klotho alleviated spatial memory impairment in APP/PS1 mice as evaluated by the Morris water maze test [97].

In the CNS, neuroinflammation can be initiated by inflammasomes, and the NLRP3 inflammasome is associated with AD. The inflammasome plays a crucial role in the innate immune system, and it mediates inflammatory responses and pyroptosis, leading to neurodegeneration [98]. In AD, the NLRP3 inflammasome is the most well-documented among the various types of inflammasomes. The activation of the NLRP3 inflammasome results in the production of caspase-1-mediated IL-1β and IL-18 in microglia cells. Klotho overexpression downregulated the IL-1β expression and suppressed activation of the NLRP3/caspase-1 signaling pathway in AD mice [97].

Autophagy is an important pathway to maintain homeostasis in the CNS by removing senescence-related proteins and damaged organelles. Studies have shown that autophagy is diminished in the brains of animal models of AD and AD patients, leading to the accumulation of Aβ [99, 100]. The enhancement of intracerebral klotho expression was associated with a marked decrease in p62 levels and an increase in the LC3B II/I ratio and both autophagosomes and autolysosomes in AD mice [101]. A study showed that upregulation of klotho by intracerebroventricular injection of a lentiviral vector that encoded klotho in APP/PS1 mice improved cognitive function, tau hyperphosphorylation, and brain capillary function at least partially associated with activation of the autophagy-mediated clearance of Aβ and inhibition of AKT/mTOR signaling [101]. Overexpression of klotho improved short-term, and long-term working memory, spatial learning and memory abilities as evaluated by Y-maze, passive avoidance, and Morris water maze tests [101]. They found that klotho mRNA and protein markedly reduced in the choroid plexus in 10-month-old APP/PS1 mice, while this decrease was meaningfully reversed by intracerebral administration of Lentiviral vector-mediated overexpression of klotho [101].

A similar study reported that a klotho enhancer, Ligustilide, decreased cerebral Aβ burden and ameliorated memory deficits via inducing alpha-processing of APP and klotho and also inhibition of IGF-1/Akt/mTOR [102].

Lipofuscins consist of oxidized lipid and protein complexes that accumulate during cellular and tissue senescence and are considered a marker of cellular oxidative damage, tissue senescence, and several aging-related diseases [103]. The lipofuscin accumulation in the CNS is related to neuronal loss, proliferation, and activation of glial cells. Overexpression of klotho can alleviate abnormal accumulation of lipofuscin in the brain of APP/PS1 mice [101]. Another study revealed that elevating klotho in human amyloid precursor protein (hAPP) mice increased the abundance of the GluN2B subunit of NMDA receptor in postsynaptic densities and NMDAR-dependent LTP and survival [2]. Klotho elevation in AD mice could prevent spatial and nonspatial learning and memory impairments, as demonstrated through behavioral tests including the water maze, novel object recognition, and passive avoidance tests [2].

Kuang and colleagues observed that ligustilide therapy (10 and 40 mg/kg, for 2 months) attenuated $A\beta_{1-42}$ accumulation, p-Tau level, neuronal loss, and memory deficits in aged SAMP8 mice. They found that the neuroprotective effects of ligustilide were mediated through klotho upregulation, thus inhibiting the IGF-1 pathway, induction of FOXO1 activity, and activation of antioxidant enzymes in the brain of 10-month-old SAMP8 mice [104]. It has been reported that simvastatin administration (5 mg/kg, for 21 days) was able to increase the hippocampal expression of klotho and MnSOD and improve the cognitive decline in streptozotocin model of sporadic AD [105]. In addition, part of klotho's beneficial effect in decreasing Aβ (1–42)-induced neurotoxicity in SH-SY5Y cells has been via inhibition of inflammation, apoptosis, oxidative stress, and modulation of Wnt1/pCREB/Nrf2/HO-1 signaling pathway [24]. Exogenous klotho could diminish levels of inflammatory biomarkers such as NF-kB, IL-1β, and TNF-α in Aβ-exposed cells [24]. Collectively, these data show that klotho reduces neuropathological alterations in AD animals. Further studies will identify the other mechanisms mediating the therapeutic effects of klotho in AD.

Amyotrophic lateral sclerosis (ALS)

ALS, known as Lou Gehrig's disease, begins when motor neurons in the spinal cord and brain become dysfunctional within weeks or months, leading to muscle atrophy, paralysis, and ultimately death [106]. No cure has been discovered for this devastating illness. Respiratory failure is responsible for most of the deaths in ALS patients within 3–5 years after various symptoms and signs appear [107]. ALS neuropathy is linked to elevated levels of excitotoxicity, inflammation, and oxidative stress. In the SOD1 mouse model of ALS, klotho overexpression led to delayed onset and progression of the disease, while females had longer survival rates. The results were not immediately apparent but were observed after 2 months [14]. The impact of klotho was found to be more significant in the spinal cord compared to the motor cortex. The klotho reduced the expression of proinflammatory cytokines (TNF-α, 1L-1β, and IL-6)and increased anti-oxidative and promyelinating factors in both the motor cortex and spinal cord, compared to SOD1 mice [14]. In the CSF of ALS patients, reduced levels of vascular endothelial growth factor (VEGF) are reported during the early stages of the disease [108]. Deficiency in VEGF is related to the motor neuron death [109]. Zeldich et al. [14] have demonstrated that klotho increased the VEGF expression in the spinal cord of SOD1 mice. The upregulation of myelin-associated glycoprotein (MAG) and myelin basic protein (MBP) mRNA in the spinal cord of SOD1 mice with klotho overexpression confirms the beneficial influence of klotho on myelin maintenance. Besides, klotho overexpression could normalize the number of Ionized calcium-binding adaptor molecule 1(Iba1)-positive cells and increase the number of neuronal nuclei (NeuN)-positive cells in the lumbar spinal cord of SOD1 mice [14]. These findings indicate that klotho enhances motor neuronal survival by reducing neuroinflammation in the lumbar spinal cord in SOD1 mice.

Epilepsy

Epilepsy is the most common serious brain disorder and is characterized by a long-term risk of recurrent unprovoked seizures, affecting more than 50 million people worldwide [110]. An emerging body of evidence supports the relevance of neuroinflammation in the pathophysiology of epilepsy, leading to neuronal damage [111]. Clinical studies have reported elevated levels of proinflammatory cytokines in serum or CSF [63, 112]. In patients or animal models with epilepsy, neuroinflammation is a crucial player in the pathogenesis of cognitive impairment [113, 114]. Inflammatory factors typically enhance the excitability of brain neurons and lead to recurrent seizures, which subsequently aggravate neuron injury and exacerbate impairment of cognition function in temporal lobe epilepsy (TLE). Ferroptosis is associated with the accumulation of iron overload-dependent lipid peroxidation. Iron overload is a starting factor for ferroptosis in neurons. Iron can be stored in or transported by ferroportin (FPN) and be released from endosomes into the cytoplasm by divalent metal transporter 1 (DMT1), thereby avoiding iron overload and iron-related toxicity [115]. Also, during ferroptosis glutathione depletion causes glutathione peroxidase 4 (GPX4) inactivation and oxidative stress. Ferroptosis results in cognitive impairments in individuals with TLE [116]. Klotho ameliorated cognitive impairments and exhibited neuroprotective properties via inhibiting ferroptosis and oxidative stress in lithium-chloride and pilocarpin-induced TLE rat models [116]. Overexpression of klotho inhibited iron accumulation by upregulation of FPN expression and suppression of DMT1 expression in the hippocampus of TLE rats. Moreover, klotho overexpression enhanced the expression of GPX-4 and GSH and also reduced ROS in the hippocampus of TLE rats [116].

Klotho could alleviate NLRP3 inflammasome-mediated inflammation by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway in the TLE rat model [117]. TNF-α has been found to reduce the klotho level in TLE patients by affecting the NFκB transcription pathway [118]. Notably, in a rodent model of chronic epilepsy produced by pentylenetetrazol, curcumin-loaded nanoparticles are shown to exert a neuroprotective effect through downregulation of TNF-α and upregulation of klotho and erythropoietin [119].

Glioblastoma multiforme

Glioblastoma multiforme (GBM) is the predominant and highly malignant primary tumor of CNS in adults, with a median survival rate of less than one year from diagnosis [120]. Despite patients undergoing intensive standard treatment, such as surgical intervention combined with chemotherapy and/or radiotherapy, this rare astrocytoma has a very poor prognosis. Between the heterogenous cell populations comprising the GBM tumor mass, cancer stem cells play a pivotal role in promoting therapy resistance, tumor expansion, and recurrence [121]. Klotho gene expression was found to be decreased in glioblastoma, oligodendroglioma, and astrocytoma in comparison to controls [122]. Cell viability is reduced by exogenous klotho (1.25-5 ng/mL) in the GBM cell line [123]. Melekhin et al. reported that overexpression of the isolated secreted klotho could reduce A-172 human glioblastoma cell growth and increase the number of caspase-active cells [124] (Table 1).

Table 1 Effects of klotho in neurological disorders

Disease	Species	Outcomes	References
Cerebral ischemia	Mouse	MnSOD and FOXO3a ↑, ROS↓, improved cognition	[11]
	Rat	Improved the neurological scores, brain infarction area↓, MnSOD ↑	[71]
	Mouse	Inhibited proinflammatory cytokines generation and overactivation of glia, suppressed oxidative stress, RIG-I/ NF-κB p65, and Akt/FoxO1 pathways	[69]
	Rat	Improved neurobehavioral deficits, infarct volume↓, AQP4, and P38 MAPK expression ↓	[75]
Parkinson's diseases	Rat	Striatal levels of MDA, ROS, GFAP, α synuclein, pCREB, and DNA fragmentation↓	[42]
	Mouse	Motor and cognitive deficits ↓, induced neural resilience	[85]
Alzheimer's diseases	PBMCs of AD patients	IL-6↓, IL-1β↓, TNF-α↓, Wnt1 expresstion↓, miR-29a expression ↑	[95]
	Mouse	Cognitive impairment↓, Aβ burden↓, ameliorated neuronal damage, inhibited activation of the NLRP3/caspase-1 signaling pathway	[97]
	Mouse	Cognitive deficits ↓, prevented GluN1 and GluN2A depletions, GluN2B level↑,	[2]
	Mouse	Memory impairments ↓, Aβ1-42 accumulation, p-Tau level, and neuronal loss ↓, oxidative stress ↓, FoxO1 activation ↑, inhibited IGF-1 signaling	[104]
	Mouse	Improved cognitive, Aβ1-42 accumulation ↓, LC3II/I↑, p62↓, SYP↑, p-AKT/AKT protein↓ level, p-mTOR/mTOR↓	[101]
	Human SH-SY5Y neuroblastoma cells	NF-kB↓, IL-1β ↓, TNF-α ↓, ROS↓, caspase 3 activity and DNA fragmentation↓, SOD ↑, modulation of Wnt1/pCREB/Nrf2/HO-1 signaling	[24]
Amyotrophic lateral sclerosis	Mouse	Iba1↓, TNF-α, and IL-6↓, delayed weight loss, rescued motor neuron, myelin-related genes such as MBP and MAG expression↑	[14]
Epilepsy	Rat	GPX-4 and glutathione expression↑, ROS ↓, cognitive deficits ↓	[116]
	Rat	NLRP3, IL-1β, and caspase-1 expression proteins ↓, Nrf2↑	[117]
	Mouse	TNF-α ↓ and neuronal loss ↓	[119]
Glioblastoma multiforme	Cell line	Cell viability↓	[123]
	Cell line	Cell growth↓, caspase-active cells↑	[124]

pCREB: phospho-cAMP-response element binding protein, *MDA* :malondialdehyde, *PBMCs:* peripheral blood mononuclear cells, *GPX-4:* Glutathione peroxidase-4, *TNF-α:* Tumor necrosis factor-alpha, *IL-12a:* Lnterleukin-12 subunit alpha, *IL-1β:* Interleukin-1 beta, *Nrf2:* Nuclear factor erythroid 2-related factor 2, *Iba-1:* Ionized calcium-binding adaptor molecule 1, *GFAP:* Glial fibrillary acid protein, *MAG:* Myelin-associated glycoprotein, *MBP:* Myelin basic protein

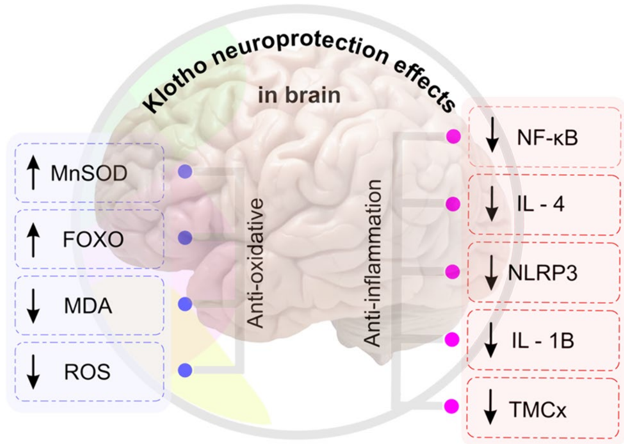

Fig. 3 Anti-oxidative and anti-inflammation effects of klotho in neurological disorders. *ROS*: reactive oxygen species, *MDA:* malondialdehyde, *MnSOD:* Manganese-superoxide dismutase, *FOXO:* forkhead box protein O, *IL:* Interleukin, *TNF-α:* tumor necrosis factor-alpha

Conclusion and future directions

Findings indicate that overexpression of klotho in the CNS could be a potential strategy for the treatment of neurological dysfunctions (Fig. 3). Several lines of evidence have shown the neuroprotective role of klotho in CNS disorders. Its potential therapeutic value derives from its ability to improve CNS pathogenesis to reduce cognitive deficits, oxidative stress, inflammation, apoptosis, and stimulate autophagy. So far, most of the reported research on klotho has been conducted using animal disease models, and a significant amount of work must be done to introduce klotho therapy into the clinic. In addition, further studies are still required to establish the exact potential biological roles of klotho levels in neurological diseases.

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Declarations

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