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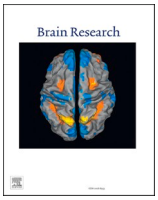

Review

The possible anti-seizure properties of Klotho

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ABSTRACT

Recurrent seizures in epilepsy may lead to progressive neuronal damage, which can diminish health-related quality of life. Evaluation and control of pathological processes in the brain is valuable. It seems imperative that new markers and approaches for seizure alleviation be discovered. Klotho (Kl), an antiaging protein, has protective effects in the brain against neurological disorders. It may also have antiseizure effects by improving creatine transfer to the brain, upregulating excitatory amino acid transporters, and inhibiting insulin/insulin-like growth factor-1 (IGF-1), Wingless (Wnt), transforming growth factor-beta (TGF-β), and retinoic-acid-inducible gene-I (RIG-I)/nuclear translocation of nuclear factor-κB (NF-κB) pathways. Stimulation and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) and apoptosis signal-regulating kinase 1 (ASK1)/p38 mitogen-activated protein kinase (MAPK) signaling pathways could also be considered other possible antiseizure mechanisms of Kl. In the present review, the roles of Kl in the central nervous system as well as its possible antiseizure properties are discussed for the first time.

1. Introduction

Epilepsy is one of the most common neurological diseases and affects approximately one percent of the world's population (Engel, 2014). It includes recurrent spontaneous seizures caused by an imbalance between stimulation and inhibition of the brain (Mehdizadeh et al., 2019). Recurrent seizures may lead to progressive neuronal damage that can affect health-related quality of life, especially in children (Barzegar et al., 2021; Mehdizadeh et al., 2019). Due to the importance of assessing and controlling pathological processes in the brain, discovering new markers and approaches for seizure alleviation seems to be necessary. Klotho (Kl) is well explained as an antiaging protein. It is mainly expressed in the kidneys and brain. It has protective roles not only in kidney diseases but also in neurological and psychological disorders (Abraham et al., 2012; Kale et al., 2023; Vo et al., 2018). According to recent studies, it may also have antiseizure effects. In the present review, the roles of Kl in the central nervous system (CNS) and its possible antiseizure mechanisms are discussed.

2. Klotho

Kl was discovered in 1997 by Kuro-o et al. (Kuro-o et al., 1997) in a group of mice that exhibited aging-like phenotypes and had a short lifespan, and eventually, it was identified as a gene with antiaging properties (Anamizu et al., 2005; Kamemori et al., 2002; Nagai et al., 2003). The *Kl* (α-Klotho) gene consists of five exons at chromosome 13q13.1 and is expressed mainly in the kidneys and brain and to a lesser extent in the heart and parathyroid glands (Hu et al., 2010a; Kuro-o, 2009; Xu and Sun, 2015). The gene product is a type 1 transmembrane protein with a molecular weight of approximately 130 kDa

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composed of 1044 amino acids. The extracellular portion of Kl consists of two domains, KL1 and KL2 (Xu and Sun, 2015). This membrane protein (m-Kl) acts as a coreceptor for fibroblast growth factor-23 (FGF23). The binding of FGF23 to its receptor requires the presence of Kl. The FGF23/Kl axis acts as the main regulator of calcium, phosphate, and vitamin D metabolism (Kurosu et al., 2006). Kl also has soluble forms. The extracellular portion of Kl can be cleaved by disintegrin and metalloproteinase 10 and 17 (ADAM10 and ADAM17) activity (Kuro-o, 2012). There are two cleavage points: one is adjacent to the plasma membrane, and the other is between the KL1 and KL2 domains. Cleavage in the vicinity of the membrane leads to the release of a protein possessing both KL1 and KL2 domains (p-Kl), while cleavage at the second point releases a protein containing only domain KL1 (p-KL1). Cleavage at both points results in the release of p-Kl1 and p-Kl2 separately. A secretary form (s-Kl) can also be expressed by alternative splicing of the *Kl* gene. Thus, Kl is found in five different isoforms, including a membrane protein (m-Kl) and four soluble forms (p-Kl1, p-Kl2, p-Kl, s-Kl) (Fig. 1). The soluble forms can mainly be found in blood, urine, and cerebrospinal fluid (CSF) (Cararo-Lopes et al., 2017; Chen et al., 2007). It has been revealed that the soluble forms have endocrine, paracrine, or autocrine roles. They can influence several target cells by affecting various metabolic pathways essential for maintaining health, such as the regulation of oxidative stress, growth factor signaling, ion homeostasis, and organ protection, which are all independent of FGFRs (Kim et al., 2015; Torbus-Paluszczak et al., 2018; Torres et al., 2007). Hu et al. (Hu et al., 2010b) demonstrated that Kl not only acts as a coreceptor for FGF23 but also functions by itself as a phosphaturic substance. They showed that intravenous injection of Kl could cause phosphaturia, which revealed its endocrine function. Kl in the renal distal and proximal tubules are juxtapositioned, suggesting that this protein possibly has paracrine roles by diffusing through the renal interstitium. Kl also exerts autocrine function. Kl can enzymatically modify glycans of the phosphate transporter by its autocrine activity in the proximal renal tubule, causing proteolytic degradation and internalization of the transporters and leading to phosphaturia (Hu et al., 2010b).

The importance of Kl roles has been determined not only in health but also in various diseases (Kuro-o, 2012, 2019). Kl has been identified to play important roles in the pathophysiology of aging-related disorders, such as chronic kidney disease (Zou et al., 2018), cardiovascular diseases (Martín-Núñez et al., 2020), diabetes (Nie et al., 2017), and cancer (Qiao et al., 2023). The possible neuroprotective and cognition-enhancing effects of Kl have recently gained attention due to its remarkable roles in neurological and psychiatric disorders (Abraham et al., 2016; Birdi et al., 2023). Multiple studies have revealed the protective roles of Kl against schizophrenia (Turkmen et al., 2021), Alzheimer's disease (Erickson et al., 2019), neuropsychiatric systemic lupus erythematosus (NPSLE) (Ushigusa et al., 2016), Parkinsońs disease (PD) (Zimmermann et al., 2021), and multiple sclerosis (MS) (Aleagha et al., 2015). However, there are a few studies revealing the association of Kl and epilepsy. Teocchi et al. (Teocchi et al., 2013) demonstrated that

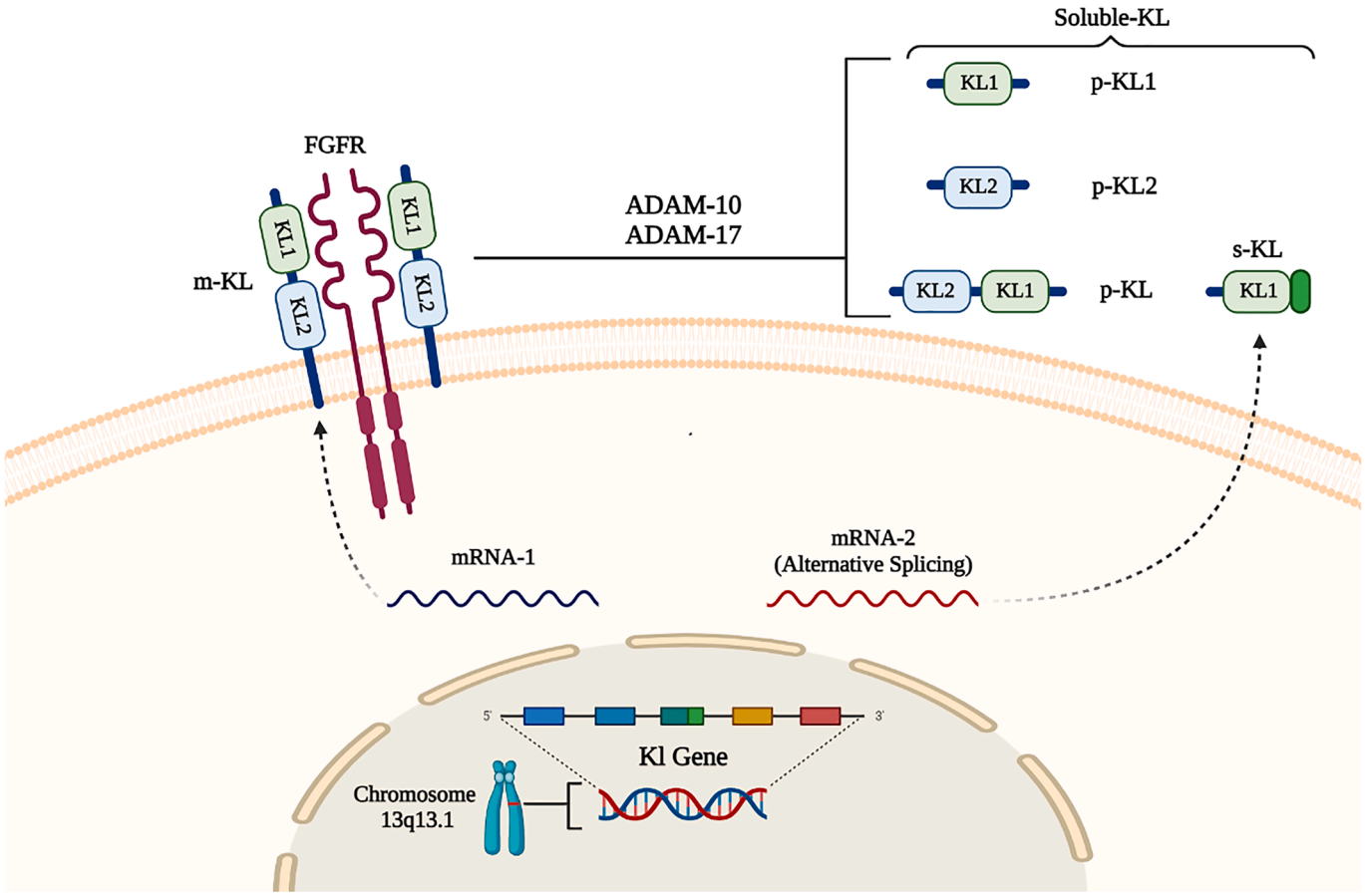

Fig. 1. The types of Klotho. The Klotho (*Kl*) gene consists of five exons at chromosome 13q13.1. The gene product is a type 1 transmembrane protein composed of two domains, KL1 and KL2, in its extracellular portion. This membrane protein (m-Kl) acts as a coreceptor for fibroblast growth factor-23 (FGF23). Kl also has soluble forms. The extracellular part of Kl can be cleaved by disintegrin and metalloproteinases 10 and 17 (ADAM10 and ADAM17). Cleavage in the vicinity of the membrane releases a protein containing both KL1 and KL2 domains (p-KL), while cleavage in the second point releases a protein containing only domain KL1 (p-KL1). Cleavage at both sites results in the release of p-KL1 and p-KL2 separately. A secretary form (s-KL) can also be produced by alternative splicing of the Kl gene. In alternative splicing, a protein is expressed similarly to p-KL1 but with a different C-terminus. It contains a short and unique sequence (tail) after KL1. Thus, Kl is found in five different isoforms, including a membrane protein (m-KL) and four soluble forms (p-KL1, p-KL2, p-KL, s-KL). Figure created with BioRender.com.

neuroinflammation and elevated tumor necrosis factor (TNF) in patients with temporal lobe epilepsy (TLE) could lead to hippocampal Kl downregulation. They suggested that Kl reduction may have broad implications not only for TLE but also for other neurodegenerative disorders associated with inflammation. Mansoor et al. (Mansoor et al., 2018) also showed that the administration of curcumin-loaded nanoparticles exerted neuroprotection by upregulating Kl and erythropoietin in an experimental model of chronic epilepsy. Although these studies have revealed the association of Kl and epilepsy, no study has demonstrated the possible anti-seizure properties of this protein, which is therefore discussed in the present review.

3. Klotho in the CNS

Most of the studies and information thus far have been on renal Kl; however, its cerebral roles are considerably less known. Therefore, elucidating the distribution and basic function(s) of Kl in the CNS and its possible roles in the pathophysiology of brain disorders can be very valuable.

3.1. *Klotho distribution in the brain*

The CNS is the second most abundantly Kl-expressing organ after the kidneys (Nakao et al., 2022). In a study by Clinton et al., the mRNA and protein of Kl were detected throughout the brain parenchyma, colocalizing in neurons and oligodendrocytes. The highest brain Kl amount was detected in the choroid plexus expressed by ependymal cells. Kl mRNA was also detectable in both gray matter (cortex) and white matter (fimbriae) (Clinton et al., 2013). The choroid plexus has three prominent roles: providing a barrier between blood and CSF, as a significant source of CSF production, and secreting CSF-soluble substances. Given the traceability of soluble Kl in CSF, it is logical that this protein is produced and secreted by the choroid plexus. Thus, just as the kidney is the primary source of plasma Kl, the main source of CSF Kl is the choroid plexus. The two tissues have similar gene expression patterns, such that the choroid plexus has also been introduced as "the kidney of the brain". (Cararo-Lopes et al., 2017). Kl can also be found in other brain regions, such as the cortex, cerebellum, hippocampus, striatum, substantia nigra, medulla, olfactory bulb, and different limbic areas, such as the thalamus, hypothalamus, and amygdala nuclei (Zeldich et al., 2014). Since there is no evidence that Kl can cross the blood–brain barrier and given the minimal exchange of fluids between the CSF and the brain parenchyma interstitial fluid, it is plausible that the detected Kl in the brain (brain Kl) is expressed locally (Cararo-Lopes et al., 2017).

Regarding intracellular distribution, Kl has been detected in the soma and dendrites of hippocampal neurons. M−Kl has also been found in pre- and postsynaptic membranes. In choroid plexus cells, Kl is present in cell membranes, rough endoplasmic reticulum, and near the nuclear membrane. In Purkinje cells, it has been identified in all cellular structures, including dendrites, axons, somas, and near the nuclear membrane. Kl has also been detected not only in the cell membranes but also in nuclear membranes. In neuronal nuclei, the highest amount of Kl is located in the peripheral region of chromatin, suggesting that Kl may also play some essential roles in the nucleus, possibly associated with ribosomes and rRNA synthesis. It may also participate in signal cascades associated with the cell's response to external stimuli (Boksha et al., 2017; German et al., 2012).

3.2. *Functions of brain Kl*

Although all roles of Kl in the nervous system are not yet fully understood, it may play an important role in neuroprotection (Abraham et al., 2012; Torbus-Paluszczak et al., 2018). It has been shown that the ratio of soluble Kl to its membrane form in the brain is higher than that in other organs, indicating the greater importance of soluble Kl roles in the brain (Cararo-Lopes et al., 2017). The sialidase activity of renal Kl affects the functions of ion channels on the cell surface (Roig-Soriano et al., 2023). With similar activity, Kl might alter synaptic activity in the synaptic cleft. It possibly influences numerous cell signaling pathways by preventing ligand–receptor interactions (Clinton et al., 2013).

Overall, Kl is necessary for healthy and normal brain function throughout life. Reduction of this protein is associated with nerve damage and brain dysfunction (Abraham et al., 2012; Cararo-Lopes et al., 2017; Torbus-Paluszczak et al., 2018; Vo et al., 2018). Preliminary animal studies have revealed that mutations (hypomorph) leading to *Kl* downregulation cause the depletion of Purkinje cells in the cerebellum. Decreased brain Kl can also lead to synaptic destruction, impaired axonal transportation, nerve fiber alteration, and nerve degeneration (Kuro-o et al., 1997; Shiozaki et al., 2008). It was shown in a study by Yokoyama et al. (Yokoyama et al., 2015) that heterozygotes expressing higher Kl (KL-VS) were associated with higher gray matter volume in the right dorsolateral prefrontal cortex (rDLPFC). It was important for executive brain function. Therefore, the higher the Kl level, the greater the brain volume and the better the performance across the life span. Kl is also essential in the maturation of oligodendrocyte precursors and the maintenance of myelin structure (Abraham et al., 2012). In a study by Emami Aleagha et al. (Aleagha et al., 2015), it was shown that the values of soluble Kl and total antioxidant capacity (TAC) in the CSF of patients with relapsing-remitting multiple sclerosis (RRMS) were significantly lower than those in healthy controls. Kl was positively correlated with TAC. There was a negative correlation between CSF Kl levels and the patients' expanded disability status scale (EDSS). Kl can also bind to soluble amyloid precursor protein (APPsβ) and prevent the formation of β-amyloid structures, protecting the CNS against amyloid toxicity and Alzheimer's disease (Erickson et al., 2019; Li et al., 2010). Semba et al. (Semba et al., 2014) measured Kl concentration in CSF samples taken from 20 old individuals with Alzheimer's disease, as well as 20 adults and 20 young people with normal cognition. The comparison results showed that the CSF Kl levels were higher in males than in females, lower in Alzheimer's patients than in healthy individuals, and higher in younger people than in elderly individuals. It was mentioned in a study by Ushigusa et al. (Ushigusa et al., 2016) that lower CSF soluble Kl might be associated with neuronal damage in patients with NPSLE. Therefore, CSF Kl could be considered a biomarker contributing to the diagnosis of NPSLE. In a study by Kosakai et al. (Kosakai et al., 2011), a decreased number of dopaminergic neurons was observed in Kl deficient mice. The animals presented degeneration symptoms in the mesencephalon that were associated with reduced dopamine levels in the striatum. Kl may also play an indispensable role in memory and learning ability. Mice lacking the *Kl* gene (Kl-KO) have been shown to have problems in learning and remembering, possibly due to reduced hippocampal synapses, axonal transport disorders, and hippocampal nerve damage (Shiozaki et al., 2008). Kl has also been shown to improve long-term potentiation (LTP) by inducing synaptic NMDA receptors and related genes such as FOS in the hippocampus and cortex, leading to learning and memory improvement (Dubal et al., 2015).

Therefore, Kl may have the potential to be considered not only as a diagnostic biomarker but also as a therapeutic approach for various neurological diseases. Although there are limited data revealing the role of Kl in the pathophysiology of epilepsy, this protein might also exert anti-seizure effects through the mechanisms mentioned below, making it a potential therapeutic target for epilepsy management.

4. Possible anti-seizure mechanisms

Epilepsy is characterized by recurrent seizures caused by excessive electrical activity in the brain (Barzegar et al., 2021; Mehdizadeh et al., 2019). The underlying mechanisms of seizures and epilepsy have traditionally been based on the theory of excitation/inhibition (E/I) imbalance. According to this theory, increased stimulation (increased glutamatergic synaptic activity or membrane depolarizing ionic currents such as Na and Ca), decreased inhibition (decreased gamma-

aminobutyric acid (GABA)-ergic synaptic activity or membrane hyperpolarizing ionic currents such as outward K^+ or inward Cl^- flux), or both leads to increased excitability and consequently an increased susceptibility to seizures and epilepsy (Shao et al., 2019). Therefore, the excitation threshold, or the neuronal membrane depolarization level, decreases, facilitating repeated discharge by a neuron. Hyperexcitable neurons form interconnected networks, and when discharged simultaneously, hypersynchronous firing occurs (Shao et al., 2019). Likewise, most of the currently available therapeutic approaches and antiseizure drugs (ASDs) have been designed with the aim of restoring the E/I balance by exerting opposite actions, i.e., decreasing excitation or increasing inhibition (Shao et al., 2019). For example, phenobarbital enhances GABA-A receptor function by increasing chloride channel open time to increase inhibition. Phenytoin, carbamazepine, and oxcarbazepine block Na channels, decreasing excitation. Vigabatrin inhibits GABA transaminase, increasing inhibition (Shao et al., 2019). Ooi et al. (Ooi et al., 2023) explored the disruption of the E/I balance in children with drug-resistant epilepsy by applying stereo-electroencephalography (SEEG) data. They observed that under an optimal stimulation intensity, vagus nerve stimulation (VNS) exerted anti-seizure effects, possibly by regulating the E/I imbalance.

Based on recent findings, the mechanism of seizures and epilepsy seems to not be explained solely by E/I imbalance theory, and this concept needs to be revised or expanded for the following reasons. New epilepsy-related mutations in genes such as *STXBP1*, *ARX*, *CDKL5*, *PCDH19*, *UBE3A*, and *PTEN* have been identified that do not have a simple or direct link to E/I imbalance as a mechanism of action (Shao et al., 2019). Some neurotransmitters, such as GABA, have paradoxical effects during growth and are not merely inhibitory or stimulatory. In addition, some anticonvulsant drugs, such as levetiracetam, brivaracetam (the analog of levetiracetam), and fenfluramine (a serotonin agonist), have been introduced that do not alter the function of any known inhibitory or excitatory neurotransmitter receptor or ion channel, and their mechanisms of action are not yet completely understood. The anti-seizure mechanisms of the ketogenic diet, a high-fat/low-carbohydrate/adequate-protein diet, are not yet completely clear. However, it is obvious that a simple E/I imbalance does not explain the mechanism of action of this diet therapy (Barzegar et al., 2021; Shao et al., 2019). Therefore, many known and unknown mechanisms and factors beyond the theory of E/I imbalance may have critical roles in seizure susceptibility and epilepsy, and recognizing them not only leads to an explosion of new therapeutic targets but also opens a new era in epilepsy management. Kl could be one of the agents that may exert antiseizure properties. The possible anticonvulsant mechanisms of Kl are mentioned as follows, most of which do not directly affect the E/I balance.

4.1. Creatine

Kl is involved in the transport of creatine to the brain (Almilaji et al., 2014). Creatine is a nitrogen-containing compound (N-amino-iminomethyl-N-methyl glycine) that is synthesized endogenously from glycine, methionine, and arginine predominantly in the liver and kidneys. Endogenous synthesis is sufficient for approximately half of the daily creatine requirement, and the remaining amount should be obtained by diet or dietary supplements (Kreider and Stout, 2021). Creatine plays an essential role in energy metabolism and is therefore vital for high energy-consuming organs, such as the muscle, heart, and brain (Wang et al., 2018). The N-phosphoryl group from phosphoryl creatine (PCr) is transferred to adenosine diphosphate (ADP). Through resynthesis of adenosine triphosphate (ATP), energy is transferred from the mitochondria to the cytosol. This mechanism is responsible for facilitating ATP homeostasis by creatine in high-energy-dependent organs (Roschel et al., 2021).

Recently, creatine has been revealed to have neuroprotective and anti-seizure properties (Kreider and Stout, 2021; Okwuofu et al., 2021). Creatine exerts antioxidant effects (Okwuofu et al., 2021), and a significant reduction in creatine levels leads to intracellular calcium accumulation, increased reactive oxygen species (ROS), and oxidative tissue damage (Sestili et al., 2011). Okwuofu et al. (Okwuofu et al., 2021) showed that creatine could ameliorate seizure severity and improve depressive and anxiety-like behaviors in an animal model of chronic epilepsy, possibly by enhancing antioxidant capacity.

Creatine may also act as a neurotransmitter. It can be synthesized in neurons and released depending on the action potential and eventually act as a postsynaptic agonist of GABA receptors. In a study by Gerbatin et al., chronic creatine supplementation protected the brain against seizure susceptibility by controlling GABAergic function (Gerbatin et al., 2019). Creatine has also been revealed to be one of the main CNS osmolytes (creatine influx in hyperosmotic conditions and efflux in hypoosmotic conditions) (Hanna-El-Daher and Braissant, 2016). These described effects and mechanisms suggest that creatine is beneficial to brain health.

The brain (astrocytes) can produce small amounts of creatine, most of which is taken from the blood through solute carrier family 6, member 8 (SLC6A8) (Roschel et al., 2021; Wang et al., 2018). The function of SLC6A8 in the brain is essential. Any deficiency or dysfunction of this creatine transporter leads to cerebral creatine deficiency, which can eventually cause mental retardation and seizures (Wang et al., 2018). Almilaji et al. (Almilaji et al., 2014) showed that Kl, with its β-glycosidase activity, could upregulate SLC6A8 activity by stabilizing the carrier protein in the cell membrane and increasing the maximal carrier transport. Therefore, Kl deficiency may impair creatine transfer to the brain. On the other hand, its sufficient amount may be associated with better creatine transfer to the brain and, consequently, maintaining brain health and protecting it against seizure-related diseases. However, more studies are needed in this area.

4.2. Excitatory amino acid transporters

Excitatory amino acid transporters (EAATs) belong to a family of transmembrane amino acid transporters that consist of five subtypes, including EAAT1 to EAAT5. In neurons and glia of the CNS, they are mainly identified for their role in the uptake of excitatory neurotransmitters, especially the amino acid glutamate. Clearance of excitatory neurotransmitters is necessary not only to maintain proper brain excitatory signaling but also to prevent excitotoxicity in the CNS. In addition, some EAATs have also been shown to be involved in the brain's antioxidant defense. They can mediate the cysteine uptake needed to produce glutathione as an important ROS scavenger (Malik and Willnow, 2019).

EAAT dysfunction is involved in various acute or chronic CNS disorders. It has been shown that the dysfunction of EAAT3 and EAAT4 may have roles in the pathophysiology of epilepsy and schizophrenia. EAAT3 is required to take up excitatory amino acids from the blood–brain barrier to neurons, retinal ganglion cells, and glial cells. This transfer occurs in Purkinje cerebellar cells by EAAT4. Decreased cerebral uptake of excitatory amino acids causes excitotoxicity (Almilaji et al., 2013). The function of these transporters is regulated by phosphatidylinositide (PI)-3-kinase signaling. This signaling pathway is sensitive to Kl, and it has been revealed that soluble Kl can enhance EAAT3 and EAAT4 levels in the brain (Almilaji et al., 2013). Almilaji et al. revealed that the abundance of EAAT3 and EAAT4 in the cell membrane was increased by Kl, leading to an elevated maximal transport rate of the carriers. This effect seemed to be dependent on the β-glucuronidase activity of Kl. Kl could also upregulate Na^+/K^+ATPase, maintaining the chemical gradient for Na^+ coupled transport. Therefore, Kl modifies the transportation of excitatory amino acids not only by upregulating EAATs but also possibly by maintaining the electrochemical gradient for Na^+. Thus, Kl may elevate the brain excitability threshold by upregulating EAATs, which eventually reduces the risk of excitotoxicity and seizure attacks. However, further studies are

necessary to confirm this hypothesis.

4.3. Insulin/IGF-1 pathway

The role of oxidative stress in the pathogenesis of epilepsy has been proven (Pauletti et al., 2017; Shin et al., 2011). Some factors, such as higher oxygen consumption, higher concentrations of unsaturated fatty acids, higher iron (catalyzes the formation of hydroxyl radicals), and lower antioxidant capacity, make the brain more prone to lipid peroxidation and oxidative damage than other tissues. Frequent seizures increase the brain's ROS content. On the other hand, increased brain oxidative stress can lead to seizure attacks, resulting in a vicious cycle (Mehdizadeh et al., 2019). Thus, oxidative stress may play a role in the onset and progression of epilepsy (Shin et al., 2011). One of the most important functions of soluble Kl is to increase resistance to oxidative stress (Kuro-o, 2008; Raeisi et al., 2016; Yamamoto et al., 2005). Soluble Kl can inhibit the insulin/insulin-like growth factor-1 (IGF-1) signaling pathway. Kuang et al. (Kuang et al., 2014) revealed that ligustilide-induced Kl upregulation could diminish memory deficits, amyloid accumulation, tau phosphorylation, and neuron loss, increase antioxidant defense, and decrease oxidative stress in the brains of aged senescence-accelerated mouse prone-8 (SAMP8) mice, possibly by inhibiting the insulin/IGF-1 pathway.

The binding of insulin/IGF-1 to their receptors via PI3K leads to Akt activation, which phosphorylates Forkhead Box subfamily O transcription factors (FOXOs). Phosphorylated FOXOs are removed from the nucleus and inactivated. Inhibition of insulin/IGF-1 signaling by factors such as soluble Kl reduces phosphorylation of FOXOs. Unphosphorylated (active) FOXOs translocate into the nucleus and stimulate the transcription of genes encoding antioxidant proteins such as catalase, manganese superoxide dismutase (SOD2), peroxiredoxin (Prdx) 2, Prdx3, and thioredoxin reductase 1 (Kuro-o, 2008; Yamamoto et al., 2005; Zeldich et al., 2014). Therefore, Kl may reduce seizure susceptibility by increasing antioxidant agents and diminishing oxidative stress in the brain.

4.4. Wnt pathway

It has recently been reported that soluble Kl can inhibit Wingless (Wnt) signaling by binding to several related ligands. Wnt proteins are secretory factors that are essential for the proliferation and maintenance of stem cells (Mazucanti et al., 2019). However, prolonged (chronic) activation of Wnt signaling may cause rapid depletion and destruction of nerve stem cells that can reduce the potential for nerve cell repair (Kuro-o, 2008; Muñoz-Castañeda et al., 2020). On the other hand, binding of Wnt proteins to their respective dimeric cell surface receptors (composed of the frizzled proteins and LRP5/6) activates the cytoplasmic disheveled (Dvl) proteins, which inhibit glycogen synthase kinase-3β (GSK-3β) by separating them from Axins. Inactivation of GSK-3, as a cytoplasmic serine/threonine-protein kinase, prevents the degradation of β-catenins by the cytoplasmic proteasomes, which leads to their accumulation and eventual translocation from the cytoplasm into the nucleus. In the nucleus, β-catenins affect the expression of related genes by stimulating certain transcription factors, including the T-cell factor (TCF) family of transcription factors (canonical Wnt pathway). Under oxidative stress conditions (caused by seizures) and antagonism of the canonical Wnt pathway by Kl, the translocation of β-catenin into the nucleus is reduced, shifting its binding preferences from TCFs to FOXOs, which activates FOXO transcriptional activity and ultimately improves the brain's antioxidant defense and reduces seizure susceptibility (Gu et al., 2019; Kuro-o, 2008; Manolopoulos et al., 2010).

4.5. Nrf2 pathway

Soluble Kl can also increase antioxidant defense in the brain by stimulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Nrf2 is a redox-sensitive transcription factor. It retains redox homeostasis by controlling antioxidant-response element (ARE)-dependent transcription and expression of antioxidant and detoxifying enzymes (Maltese et al., 2017). Under physiological conditions, the binding of Kelch-like ECH-associated protein 1 (Keap1) to Nrf2 inhibits its translocation from the cytoplasm into the nucleus. This binding also causes proteasomal degradation of Nrf2 in the cytoplasm. GSK3β also inhibits the transfer of Nrf2 into the nucleus through Nrf2 phosphorylation. In the presence of soluble Kl, Keap1-associated Nrf2 degradation and GSK3β-associated Nrf2 phosphorylation are inhibited, leading to the translocation of Nrf2 into the nucleus. In the nucleus, Nrf2 forms a heterodimer with small Maf proteins. These heterodimers bind to ARE in the promoter region of the target genes, leading to upregulation of antioxidant enzyme genes such as glutathione S-transferases (GSTs), NAD(P)H-Quinone oxidoreductase 1 (NQO1), thioredoxin, thioredoxin reductase, ROS scavengers, and glutathione (GSH) synthetic enzymes. Nrf2 can also regulate the expression of SOD2, Prdx1, Prdx3, Prdx5, GPx1, thioredoxin reductase 2 (TrxR2), and heme-oxygenase (HO-1) and increase glutathione levels (Kang, 2020; Maltese et al., 2017). In a study by Xiang et al., adeno-associated viral (AAV)-mediated overexpression of Kl (AAV-KL) in the bilateral hippocampus of rats attenuated neuroinflammation-induced neuronal injury and cognitive impairment by activating the Nrf2 signaling pathway in a rat model of TLE (Xiang et al., 2022). Therefore, Nrf2-mediated antioxidative and anti-inflammatory effects can be considered another possible anti-seizure mechanism of Kl.

4.6. Transforming growth factor-beta (TGF-β) pathway

TGF-β family proteins are a group of cytokines implicated in intercellular communication and intracellular processes, such as cell growth, migration, differentiation, apoptosis, inflammation, and expression of extracellular matrix proteins. The neurological functions of these multifunctional cytokines are increasingly being recognized (Dobolyi et al., 2012). Two TGF-β membrane receptors have been identified in the brain: activin-like kinase (ALK)-1 and ALK5. Some recent studies have suggested that they may have neuroprotective effects following cerebral ischemia, trauma, multiple sclerosis, neurodegenerative diseases, infections, and brain tumors (Dobolyi et al., 2012). However, the binding of TGF-β to the receptor has been shown to phosphorylate Smad proteins as intracellular mediators of the TGF-β signaling pathway. The interaction of Smad proteins leads to the formation of specific complexes that accumulate in the nucleus and ultimately alter the transcriptional activity of related genes. For example, in the brain, activation of TGF-β signaling causes astrocytic transformation, increased expression of inflammation-related genes, and reduced expression of GABA-related genes, inward-rectifier potassium channel (Kir 4.1), and glutamate transporters. Therefore, it leads to the accumulation of extracellular potassium and glutamate during the activation of neurons. As a result, activation of TGF-β signaling can eventually increase neural network excitability (Bar-Klein et al., 2014; Kim et al., 2017). Bar-Klein et al. (Bar-Klein et al., 2014) examined albumin-mediated stimulation of TGF-β signaling. The effects of blocking this pathway in preventing epilepsy were also evaluated. They showed that serum-derived albumin through ALK5 could stimulate TGF-β signaling in astrocytes, which might have a role in developing epileptogenesis. They also showed that losartan inhibited albumin-induced TGF-β activation in the brain and could prevent recurrent spontaneous seizures, an effect that lasted for weeks after stopping the drug. Doi et al. (Doi et al., 2011) revealed that Kl could inhibit the TGF-β1 signaling pathway by directly binding to the type-II TGF-β receptor and inhibiting TGF-β1 binding. Therefore, increasing TGF-β signaling activity in the brain may predispose a person to seizure and epilepsy. On the other hand, inhibition of this signaling pathway by factors such as soluble Kl can be considered a plausible treatment option for epilepsy. However, further studies are needed for confirmation.

4.7. Other possible mechanisms

Inhibition of retinoic-acid-inducible gene-I (RIG-I)/nuclear translocation of nuclear factor-κB (NF-κB) (Zhou et al., 2018) and activation of apoptosis signal-regulating kinase 1 (ASK1)/p38 mitogen-activated protein kinase (MAPK) signaling pathways (Brobey et al., 2015) may also be considered as other mechanisms of antioxidative, anti-inflammatory, and possibly anti-seizure effects of Kl in the brain.

5. Conclusion

Kl, an antiaging protein, has been shown to have protective roles against neurological and psychological disorders. It may have anti-seizure effects by mediating different factors and pathways, such as creatin, EAATs, insulin/IGF-1, Wnt, Nrf2, TGF-β, RIG-I/NF-κB, and ASK1/p38 MAPK (Fig. 2).

The present review indicates the probable antiseizure effects of Kl, which can be considered a potential therapeutic target for seizure-related diseases. However, further preclinical (animal) models of seizure and epilepsy studies evaluating the probable anti-seizure properties of Kl while considering the possible mechanisms are necessary to confirm this view unambiguously. There are still some challenges to be addressed, such as developing Kl-enhancing approaches in the brain and evaluating their safety and usefulness before clinical applications become commonplace.

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CRediT authorship contribution statement

All authors contributed to the study conception and design. **Nasrin Ranjbar:** Writing – original draft, Investigation, Literature search. **Mohammadreza Raeisi:** Writing – original draft, Investigation,

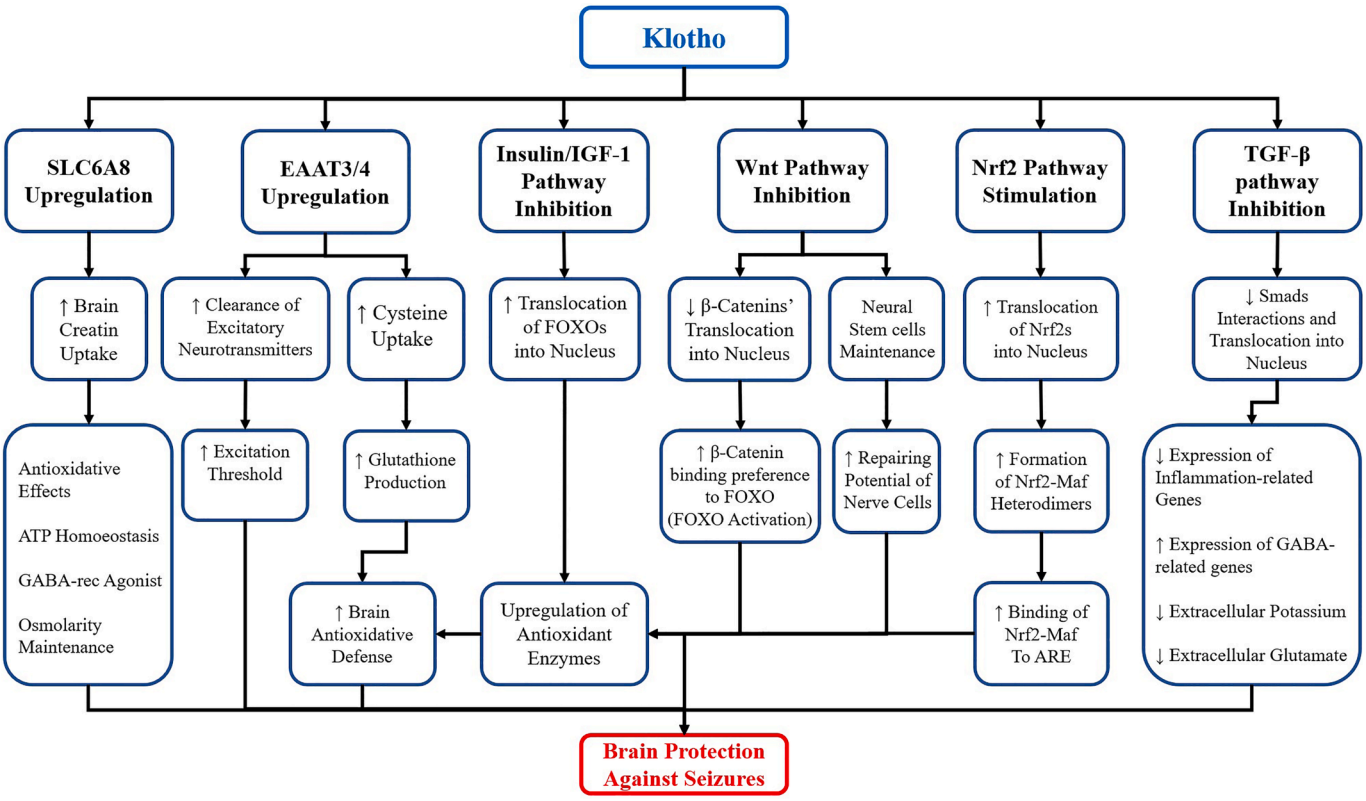

Fig. 2. The possible antiseizure mechanisms of Klotho in brain protection. Klotho (Kl) is involved in the transportation of creatine to the brain by upregulating solute carrier family 6, member 8 (SLC6A8) as the brain creatin carrier. Creatine has essential roles in brain energy metabolism and ATP homeostasis. It also acts as an antioxidant, osmolyte, and postsynaptic gamma-aminobutyric acid (GABA)-receptor agonist in the central nervous system (CNS). Kl can enhance excitatory amino acid transporter 3 and 4 (EAAT3/4) levels in the brain and is involved in excitatory neurotransmitter clearance and the prevention of excitotoxicity in the CNS. They can also mediate the cysteine uptake needed to produce glutathione as an important brain antioxidant. Kl can inhibit the insulin/insulin-like growth factor-1 (IGF-1) signaling pathway that reduces phosphorylation of the Forkhead Box subfamily O transcription factors (FOXOs). Unphosphorylated FOXOs translocate into the nucleus and stimulate the transcription of genes encoding antioxidant enzymes. Wingless proteins (Wnt) are secretory factors that are essential for the proliferation and maintenance of stem cells. However, prolonged activation of Wnt signaling may cause rapid depletion and destruction of nerve stem cells that can reduce the potential for nerve cell repair. Kl can inhibit Wnt signaling and maintain brain repair potential. On the other hand, the binding of Wnt proteins to their receptors prevents the cytoplasmic degradation of β-catenins, which leads to their translocation into the nucleus and affects certain transcription factors, including the T-cell factor (TCF) family of transcription factors. Under oxidative stress conditions and antagonism of the Wnt pathway by Kl, the translocation of β-catenin into the nucleus is reduced, which shifts its binding preferences from TCFs to FOXOs, activating FOXO transcriptional activity and ultimately improving the brain's antioxidant defense. Kl can also increase antioxidant protection in the brain by stimulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Kl inhibits the degradation and phosphorylation of Nrf2, leading to its translocation into the nucleus. In the nucleus, Nrf2 forms a heterodimer with small Maf proteins. These heterodimers bind to antioxidant response elements (AREs) in the promoter region of the target genes, leading to upregulation of the antioxidant enzyme genes. Activation of transforming growth factor-beta (TGF-β) signaling increases neural network excitability. The binding of TGF-βs to their receptors activates Smad proteins. The interaction of Smad proteins and their translocation into the nucleus can downregulate GABA-related genes and glutamate transporters. Therefore, increasing TGF-β signaling activity in the brain may increase neural excitability and predispose a person to seizures; however, Kl can reverse this effect.

Literature search. **Mohammad Barzegar:** Conceptualization, Validation. **Amir Ghorbanihaghjo:** Literature search, Investigation. **Siamak Shiva:** Literature search, Investigation. **Shahram Sadeghvand:** Literature search, Investigation. **Sohrab Negargar:** Literature search, Investigation. **Haniyeh Poursistany:** Literature search, Investigation. **Sina Raeisi:** Project administration, Conceptualization, Supervision, Investigation, Writing – review & editing. All authors commented on previous versions of the manuscript. All the authors have read and approved the final manuscript.

Declaration of Competing Interest

Nasrin Ranjbar and Mohammadreza Raeisi are equally contributed as first authors. The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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