Pharmacological Insights and Therapeutic Potential of Homotaurine in Neurological Disorders: A Review of Preclinical and Clinical Studies

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Abstract. Homotaurine (Tramiprosate) is a naturally occurring amino sulfonate that exhibits structural similarities with GABA and Taurine. As a GABA-A receptor agonist, it regulates GABAergic activity and has strong neuroprotective properties. Homotaurine's mechanism of action involves reducing amyloid-beta (Aβ) aggregation, thereby mitigating Alzheimer's disease (AD) and mild cognitive impairment (MCI). It stabilizes Aβ monomers, inhibits oligomer formation, and reduces Aβ42 levels in the cerebrospinal fluid. Furthermore, homotaurine's antioxidant properties and its ability to penetrate blood-brain barrier enhance its therapeutic potential. Clinical and experimental research show that it improves cognitive function in Alzheimer's disease and mild cognitive impairment, improves cognitive performance in Parkinson's disease, and provides neuroprotection in diabetic and glaucomatous retinopathy. ALZ-801, an optimized prodrug, has higher absorption and tolerance than oral homotaurine. Further study is needed to support its efficacy across all neurological disorders. Overall, homotaurine is a versatile and promising candidate for treating several types of neurological disorders.

Keywords: Homotaurine, Pharmacology, Neurological disorders, Alzheimer's disease, Mild cognitive impairment, GABA-A-receptor agonist

1 Introduction

Homotaurine (Tramiprosate, Alzhemed) is a GABA-A receptor agonist produced by red sea algae that has shown promise in the treatment of Alzheimer's disease (AD) and mild cognitive impairment (MCI). It stabilizes amyloid-beta (Aβ) monomers and prevents oligomer formation, providing neuroprotective benefits. In addition to its anti-amyloid and antioxidant characteristics, homotaurine is being studied for glaucoma, diabetic retinopathy, Parkinson's disease, and epilepsy. Clinical investigations indicate that it can improve cognitive function, reduce Aβ42 levels, and pass the blood-brain barrier[1-3].

The review is focused on providing a full overview of homotaurine, including its chemical features, modes of action, therapeutic potential, clinical effectiveness, and limitations. This

FPCS 2024, November 13-14, Bengaluru, India

DOI 10.4108/eai.13-11-2024.2355680

study aims to emphasize homotaurine's neuroprotective properties and its potential for treating a variety of neurological disorders while highlighting the need for more research and clinical.

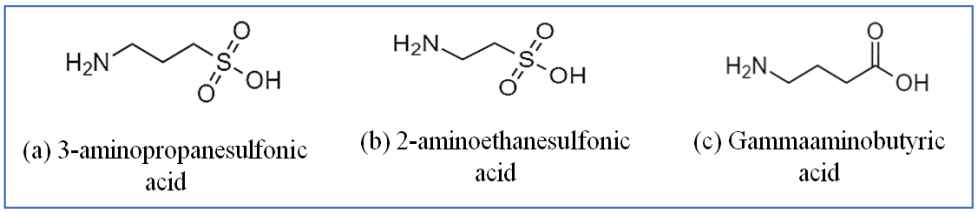

Fig. 1: Chemical structure of Homotaurine(a), Taurine(b) and GABA(c)

2 Overview of Homotaurine

Chemical properties:
Homotaurine (3-amino-1-propanesulfonic acid; 139.18 g/mol) is a white powder that dissolves in water at pH 7.4. It is a superior homolog of taurine and a structural analogue of GABA, distinguished by a sulfonic group rather than a carboxylic group **Fig. 1** [1], which allows it to pass the blood-brain barrier. This sulfonic group may also protect DNA from oxidative damage induced by free radicals[4-7].
Pharmacology of homotaurine:
Mechanism of action. The mechanism of homotaurine involves action on amyloid beta(Aβ) and also anti-inflammatory action in individuals suffering fromMild cognitive impairment (MCI) and Alzheimer's disease (AD). In addition, the other mechanism of homotaurine is related to GABA-A receptor(GABA-AR) agonistic activity, which is a GABA-dependent pathway.[8]
As a strong agonist of the GABA-AR, homotaurine works by binding itself to GABA receptors more strongly than other molecules with a comparable structure. Chlorine flows into neurons and causes hyperpolarization of the membranes and inhibits neuronal activity dose-dependently as a result of this binding. The **Fig. 2** [2] showsa pictorial representation of the GABA agonistic activity of homotaurine. It is noteworthy that administering GABA-AR antagonists to neurons beforehand can counteract the effects of homotaurine. The aforementioned underscores the function of homotaurine in regulating GABAergic activity and implies its possible therapeutic use in treating neurological disorders that include GABAergic malfunction[9-11].
When homotaurine penetrates the CNS (central nervous system), it binds to the soluble Aβ, a harmful protein that is known to accumulate and create deposition of amyloid plaque in the brain tissue. Subsequently, it stabilizes Aβ42 monomers by preferentially binding to Aβ40 and Aβ42 (Lys 16, Lys 28, Asp23) peptides rather than the fibrillar Aβ structure. As a result, the formation of oligomers and amyloid aggregation is inhibited. Inhibiting the formation and elongation of oligomers provides neuroprotection action against the deposition of Aβ in the neuronal cell and dose-dependently lowers Aβ42 levels in cerebrospinal fluid (CSF) [12],[13]. The pictorial representation of homotaurine's anti-amyloid action is shown in **Fig. 3**[3].

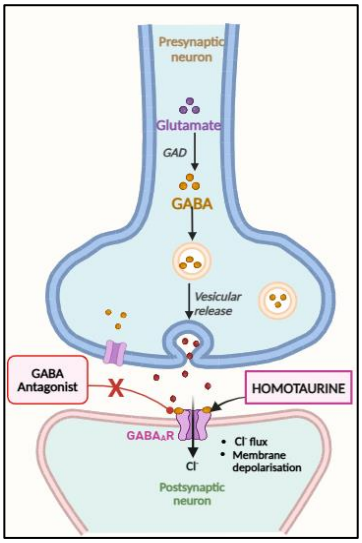

Fig. 2 Homotaurine's GABA agonist mechanism

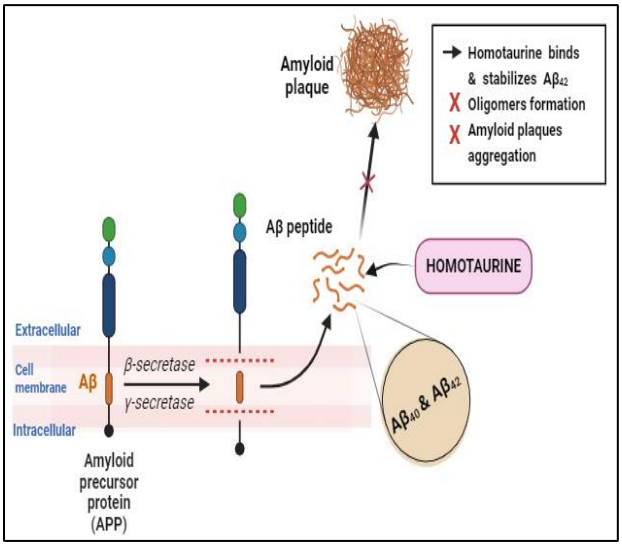

Fig. 3 Anti-amyloid mechanism of Homotaurine

Pharmacokinetics of Homotaurine. Orally administered homotaurine undergoes extensive gastrointestinal metabolism, resulting in nausea, vomiting, and considerable pharmacokinetic variability. To address these issues, ALZ-801, a prodrug of homotaurine, was developed. ALZ-801 improves gastrointestinal tolerability and lowers oral pharmacokinetic variability while preserving homotaurine efficacy. It achieves dose-dependent plasma concentrations and has a longer elimination half-life, with oral bioavailability ranging from 50 to 100%. ALZ-801 absorbs effectively in the upper gastrointestinal tract, transforms to homotaurine in the liver, and enters the brain (~40%). Both are largely removed by the kidneys[14],[15].

Therapeutic benefits. Homotaurine is effective in treating Alzheimer's disease (AD), epilepsy, Parkinson's disease, moderate cognitive impairment, and glaucomatous retinopathy. It has neuroprotective, anti-oligomer, anti-amnestic, and antioxidant qualities, as well as a reduction in inflammation in diseases such as multiple sclerosis and diabetic retinopathy. It is also safe, well-tolerated, and has been shown to improve sleepiness and memory[3],[16-19].

3 Therapeutic Potential of Homotaurine Against Neurological Disorders

3.1 Alzheimer's Disease (AD)

Alzheimer's disease is a degenerative brain disorder that has become a leading cause of dementia, especially in older people[20].

Pre-clinical studies. In Alzheimer's research, homotaurine has demonstrated strong neuroprotective and disease-modifying properties. In mouse neuronal models, it prevents Aβ neurotoxicity and reverses Aβ-induced LTP blockage[21],[22]. Crossing the blood-brain barrier decreases amyloid plaques and plasma Aβ levels. Homotaurine promotes non-toxic tau aggregation, which may prevent harmful tau-actin interactions[23]. Furthermore, it shows GABA-dependent and independent action by binding to GABAAR, decreasing Aβ42 aggregation, and suppressing ERK1/2 and caspase activation in primary rat neurons [24].

These findings emphasize its dual anti-amyloid and neuroprotective activities through GABAergic and non-GABAergic pathways, making it a promising choice for Alzheimer's disease therapy[25].

Clinical studies. Homotaurine is a promising treatment for Alzheimer's disease (AD) due to its ability to pass the blood-brain barrier and reduce CSF Aβ42 levels while remaining safe and tolerable[14]. Phase III trials showed cognitive benefits (ADAS-cog and CDR-SB) in APOE4/4 persons who received 150 mg daily[26]. Reanalysis found that targeting Aβ oligomers can improve cognitive and disease-modifying effects in mild Alzheimer's disease cases (MMSE 22–26)[27]. The Alphase trial found that homotaurine reduced hippocampus volume loss and slowed cognitive decline, especially in early-stage ApoE4 carriers, highlighting its ability to improve memory and delay progression of the disease[28].

3.2 Mild Cognitive Impairment (MCI)

It is believed thatMCI represents the stage between dementia and the typical cognitive loss associated with healthy aging.The MCI is a heterogeneous condition that is classified as amnestic MCI (aMCI) and non-amnestic (naMCI) depending on whether memory impairment occurs[29].

Clinical studies of Homotaurine in MCI. Homotaurine has showed promise in the treatment of amnestic mild cognitive impairment (aMCI), which is a common precursor to Alzheimer's disease (AD). Studies show that it improves short-term memory, lowers hippocampus and temporal lobe volume loss, and retains cognitive function, as demonstrated by higher Clinical Dementia Rating (CDR) [30]. and Mini-Mental State Examination (MMSE) scores. Homotaurine's effects, particularly in synaptic plasticity, were noticeable after 4-12 months of treatment, indicating that it has potential as a symptomatic treatment for early cognitive impairment, including multi-domain MCI (mMCI)[31]. .Homotaurine alters short latency afferent inhibition (SLAI), implying decreased cholinergic transmission via GABA activity [32].In aMCI patients with the APOEε4 allele, its anti-inflammatory actions may improve memory loss and modulate brain inflammation in early Alzheimer’s [11]. Furthermore, it improves cognitive performance in moderate MCI by boosting anti-inflammatory cytokines (IL-33, IL-10) while decreasing IL-18, indicating therapeutic promise in early AD [33].

3.3 Parkinsonism Disease (PD)

Parkinson's disease, the second-most prevalent neurological disorder, frequently leads to impairment of memory due to difficulties with long-term memory and learning. Cognitive decline is linked to hippocampus interactions with dopaminergic systems, which are important for behaviour, synaptic plasticity, and memory. Homotaurine may assist to reduce these symptoms[34],[35]. A single-blind, randomized, controlled study assessed the safety and efficacy of homotaurine in individuals with PD-related cognitive impairment. In the PD-homotaurine group, Homotaurine seemed safe and could help treat excessive sleepiness, therefore more research is necessary to determine whether it helps PD patients maintain a healthy sleep-wake cycle[18].

3.4 Gaba Agonistic Actvity

Homotaurine as GABA agonist in Multiple Sclerosis (MS). Recent research have highlighted homotaurine's therapeutic promise in MS, demonstrating that it lowers pro-inflammatory Th17 and Th1 responses, increases regulatory T-cell responses, and reduces CNS inflammation in experimental autoimmune encephalomyelitis models[16]. Homotaurine's ability to suppress antigen-presenting cells and limit epitope dispersion implies

that it could be a promising, BBB-permeable therapy for MS and other CNS inflammatory disorders[19].

Homotaurine as GABA agonist in Diabetes. Taurine and its analogues, particularly homotaurine, have been shown in diabetic rat models to increase antioxidant enzyme activity, reduce oxidative stress markers such as malondialdehyde, and prevent membrane damage. Homotaurine shown significant efficiency in reducing diabetes-related oxidative stress and protecting cellular membranes[36].By decreasing levels of malondialdehyde (MDA), nitric oxide (NO), and glutathione disulfide (GSSG), homotaurine, a taurine analogue, lowers oxidative stress in type 2 diabetes. It shows potential as a therapeutic agent for diabetes-related oxidative stress and in combination therapy for type 1 diabetes. [37], [38].

Homotaurine as GABA agonist in Convulsion: In a variety of epileptic models, homotaurine exhibits potent anticonvulsant properties. It is more effective than taurine at lowering electrographic spike activity in focal epilepsy without changing EEG rhythms. It causes widespread spikes at lesser dosages in Petit Mal-type epilepsy and protects against convulsions and CNS cytotoxicity in multifocal seizures brought on by kainic acid. These results demonstrate its potential as an epilepsy therapy[39]

Homotaurine in Autism Spectrum Disorder (ASD). Autism Spectrum Disorder (ASD) is a complicated neurodevelopmental disease characterized by brain abnormalities and GABAergic transmission imbalances. Homotaurine has showed potential in treating ASD symptoms, as evidenced by in-silico and in-vivo investigations employing a valproic acid (VPA) rat model. It reduced behavioral impairments, oxidative stress, and neuroinflammation while restoring Purkinje cell density and GAD67 expression in the cerebellum[40].

Homotaurine in Catatonia. In addition to the therapeutic advantages already discussed, homotaurine can counteract the catatonia induced by baclofen by blocking the activity of the GABA-B receptor. These results imply that homotaurine has GABA-B antagonistic action as well[41].

Homotaurine in pneumonitis and viral infection. Homotaurine, a GABAA receptor agonist, has significant potential for lowering inflammation and improving outcomes in respiratory disorders, including viral infections such as mouse hepatitis virus (MHV-1) and COVID-19. It improves disease severity, mortality, and viral load in the lungs while outperforming GABAB-specific agonists such as baclofen. These findings suggest homotaurine as a prospective therapeutic drug for viral-induced pneumonitis and severe respiratory infections, with clinical applications in COVID-19[42], [43].

3.5 Glaucoma

Preclinical studies. Homotaurine improves RGC survival in glaucoma by reducing GSK-3β activity and regulating the PI3K/Akt pathway. When paired with bioactive chemicals like forskolin and L-carnosine, it lowers retinal dysfunction, prevents RGC loss, and inhibits apoptosis, indicating that it could be used as a multitarget glaucoma care method in addition to IOP reduction[44], [45].

Clinical studies. Clinical studies indicate that homotaurine, when coupled with forskolin, citicoline, and vitamin E, has neuroprotective effects in glaucoma treatment. It enhances foveal sensitivity, retinal ganglion cell activity, and retinal fiber layer stability, indicating that it has the potential to slow the course of glaucoma. These findings show homotaurine's potential in neuroprotective therapy for glaucoma, while more clinical trials are required[46-48]

3.6 Anti-Inflammatory Activity

Homotaurine has been found to have anti-inflammatory characteristics in several studies, including its potential in Alzheimer's disease (AD) and diabetic retinopathy (PDR). In AD, it lowered pro-inflammatory cytokine IL-18, and in PDR, homotaurine coupled with curcumin and vitamin D3 reduced pro-inflammatory cytokine levels, implying a synergistic action. Furthermore, in optic nerve injury models, homotaurine reduced cytokine release and apoptosis while boosting retinal ganglion cell survival, indicating its promise in neurodegenerative illnesses.[16],[19],[49]

3.7 Homotauirne In Cholinergic Dysfunction (Symptomatic Treatment)

Homotaurine may provide therapeutic effects for cognitive impairments caused by traumatic brain injury (TBI) by increasing cholinergic function. Cholinergic dysfunction causes a variety of symptoms in Parkinson's disease (PD), and tramiprosate (ALZ-801) is used to improve cholinergic transmission. Vascular dementia (VaD), which is associated with cerebral lesions and cholinergic impairments, may benefit from cholinesterase inhibitors such as tramiprosate, which could improve treatment outcomes when combined with other medications[50-52].

4 Conclusion

In conclusion, as a GABA-AR agonist and anti-amyloid agent, it demonstrates neuroprotective effects by inhibiting Aβ aggregation and deposition, potentially offering benefits for Alzheimer's disease and mild cognitive impairment. Homotaurine exhibits promising pharmacological properties and therapeutic potential in various neurological disorders. Furthermore, it shows promise in epilepsy, Parkinson's disease, and glaucomatous retinopathy, suggesting its versatility in neurological therapeutics. With its safety profile and antioxidant activity, homotaurine emerges as a valuable candidate for treating inflammatory CNS conditions and diabetic retinopathy.

Acknowledgement

We are thankful to the chairman, management, principal, teaching, and non-teaching staff of Acharya & BM Reddy College of Pharmacy, Bengaluru for providing us with necessary support throughout our review submission.

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