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FOCUSED REVIEW

Betaine—The dark knight of the brain

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Abstract

The role of betaine in the liver and kidney has been well documented, even from the cellular and molecular point of view. Despite literature reporting positive effects of betaine supplementation in Alzheimer's, Parkinson's and schizophrenia, the role and function of betaine in the brain are little studied and reviewed. Beneficial effects of betaine in neurodegeneration, excitatory and inhibitory imbalance and against oxidative stress in the central nervous system (CNS) have been collected and analysed to understand the main role of betaine in the brain. There are many 'dark' aspects needed to complete the picture. The understanding of how this osmolyte is transported across neuron and glial cells is also controversial, as the expression levels and functioning of the known protein capable to transport betaine expressed in the brain, betaine-GABA transporter 1 (BGT-1), is itself not well clarified. The reported actions of betaine beyond BGT-1 related to neuronal degeneration and memory impairment are the focus of this work. With this review, we underline the scarcity of detailed molecular and cellular information about betaine action. Consequently, the requirement of detailed focus on and study of the interaction of this molecule with CNS components to sustain the therapeutic use of betaine.

KEYWORDS
Alzheimer's, betaine, dementia, epilepsy, GABA, neurodegenerative disease, neurodevelopmental disorders, oxidative stress, Parkinson's, PTSD, schizophrenia

1 | INTRODUCTION

The solute carrier (SLC) 6 family of secondary active transporters includes neurotransmitter sodium symporters responsible for transporting neurotransmitters such as dopamine transporters, serotonin transporter and γ-aminobutyric acid (GABA) transporters. One of the GABA transporters is betaine-GABA transporter 1, BGT-1 (SLC6A12), which is expressed in the liver, kidney and brain.[1] It has a unique ability to translocate both GABA and betaine (an osmolyte found in animals, plants and microorganisms) across the membrane.[2] While the roles of betaine and BGT-1 in liver and kidney have been studied well, they are very ambiguous and understudied in the brain. At the same time, there is a remarkable surge in the literature on betaine, demonstrating its

positive role and therapeutic potential in neurological and neurodegenerative diseases, which demands focused attention from the scientific community. A review discussing and presenting contemporary information on betaine and its transporter in the brain could help in pushing the frontiers. With this aim, we investigate literature evidence regarding possible mechanisms of action of betaine in the brain and review its beneficial role in the brain, and how this molecule can be accumulated and transported in this organ.

Betaine, also known as glycine betaine and as *N*,*N*,*N*-trimethyl glycine, is a zwitterionic amino acid derivative that can be endogenously produced by the oxidation of choline[3] and exogenously absorbed as a dietary nutrient. The name betaine comes from its discovery from *Beta vulgaris* (beets) in the 1860s, but later, it was found at high concentration in other dietary sources like wheat bran, spinach and seafood.[4–6] In mammals, from the physiological point of view, betaine serves primarily two roles: as one of the major osmolytes accumulated in the tissues for cell volume regulation, mainly in the kidney, and as a methyl donor for the toxic metabolite, homocysteine (Hcy), to convert it into methionine.[3,6] The daily betaine uptake in the human diet ranges from 1 to 2.5 g/day, based on individual consumption. The study on red blood cell physiology at high betaine doses showed mild perturbance and suggested that safe daily betaine intake was 9–15 g/day.[4] The active absorption of betaine in cells happens via different carriers and transporters (see Figure 1). Apart from BGT-1, the betaine could also be translocated via proton-coupled amino acid transport, PAT1 (SLC36A1), and also passive sodium independent in the epithelia.[3,4,7,8] Also, other transporters, such as proline transporter SIT1/XT3s1 (SLC6A20) that arises in the embryo post-fertilization, could act as the regulator of the oocytes-derived betaine levels.[9,10] Another SLC transporter in neurons, called SNAT2 (SLC38A2), is shown to interact with betaine, where it functions as a protective layer in the placenta against osmotic changes in maternal or foetal plasma.[11] Using these transport systems, betaine could be adsorbed and distributed across the human body. Rapid adsorption and distribution up to 1–3 mM within 1–2 h of intake have been reported in human studies about betaine supplementation.[4,12] However, it should be noted that the tissue concentration for an osmolyte would be higher than the plasma concentration.[13]

Apart from diet and supplementation, betaine can be synthesized via a two-step irreversible process using choline in mitochondria (see Figure 1). Firstly, the enzyme choline dehydrogenase oxidates choline into betaine aldehyde. And then, betaine aldehyde is converted to betaine by the same enzyme in the presence of

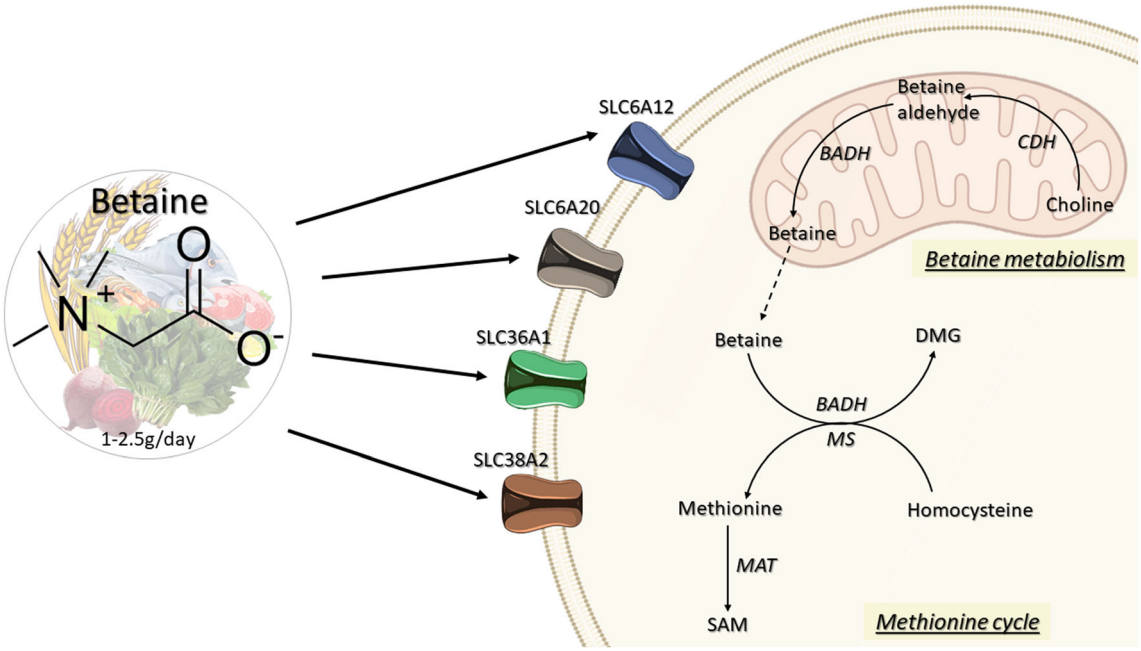

FIGURE 1 Cellular metabolism of betaine. Betaine is found in abundance in beets, wheat bran, seafood and spinach. Once it enters the cell through betaine/GABA transporter 1 (BGT-1 - SLC6A12), IMINO transporter (SIT-1/XT3s1 - SLC6A20), proton/amino acid transporters (PAT-1 - SLC36A1), or sodium-dependent neutral amino acid transporter-2 (SNAT-2 - SLC38A2) it is metabolized according to the methionine cycle to synthesize methionine from homocysteine. Also, in the mitochondria, betaine can be directly synthesized from choline in small quantities. All the pathway enzymes refer human metabolism: choline dehydrogenase (CDH); betaine-aldehyde dehydrogenase (BADH); betaine-homocysteine methyltransferase (BHMT); methionine synthase (MS); methionine adenosyltransferase (MAT).

nicotinamide adenine dinucleotide (NAD^+). This betaine is catabolized via transmethylation reactions involved in vital biological processes.[4] This transmethylation is catalysed by betaine-homocysteine methyltransferase (BHMT), which detoxifies Hcy by converting it into methionine and producing *S*-adenosylmethionine (SAM).

1.1 | The dual role and distribution

Betaine helps maintain the intracellular osmotic pressure, as it binds little to nothing with protein surfaces and enables cellular control of water surface tension. Thus, it stabilizes protein structure and function, while protecting cells, proteins and enzymes from osmotic stress. This role is relevant, especially in the kidney, where betaine can be present in extraordinary concentrations (>100 mM).[3] Other than the kidney, betaine is also found in the human liver and brain. However, the role of osmolyte and methyl donor has been studied in the liver and kidney, and much less in the nervous system. Moreover, recently, it was shown that BHMT, one of the enzymes involved in the detoxification of homocysteine, is present not only in the liver and kidneys but is also expressed in the intestine and white adipose tissue, suggesting a role of betaine also in these tissues.[6,14,15] Betaine is a potential therapeutic against alcohol-induced and metabolic-associated diseases and heavy-metal toxicity in the liver.[6,16] Betaine supplementation was also shown to have a role in muscle strength and power.[17] It helps to improve body composition in both males and females, but improvement of muscular performance only in males has been reported.[18] Betaine also helps against heat tolerance and increases resilience against thermal stressors.[19] Recently, an increasing number of studies show beneficial effects of betaine in cognition, early-stage neuronal development and in reducing neurodegeneration and memory impairment, suggesting an important role of betaine in human (neuro)physiology.[12]

1.2 | Betaine: A therapeutic nutrient

Traditional eastern medicines have effectively used herbs and food ingredients as therapeutics for several different diseases. The primary advantage of such substances over modern medicine would be the absence of any severe side effects. One approach by modern pharmacologists has been to integrate these herbs and nutrients with currently effective drug administration and develop new therapies. Betaine is one such stable, natural and non-toxic substance that has shown beneficial effects in several diseases.

Homocystinuria, a sulphur metabolism pathway disorder characterized by increased accumulation of Hcy in cells and plasma, can cause osteoporosis, arteriosclerosis, dislocated eye lenses, intellectual disability and neurodegenerative pathologies such as Alzheimer's, Parkinson's and dementia.[20] As a treatment, betaine therapy (6–9 g/day of oral administration) is used to decrease Hcy levels by converting it to methionine and thus increasing the flux through the re-methylation pathway. Since 2020, betaine is an FDA-approved drug marketed as Cystadane®. This treatment has not been reported to cause any severe side effects except mild body odour and a rare possibility of cerebral oedema due to hypermethioninemia.[20,21] Apart from homocystinuria, betaine supplementation also shows beneficial effects on diseases such as alcohol-induced liver diseases, hepatic steatosis, heart disease, dehydration and heat tolerance.[3,4,6,17,19,22] As said above, an increasing number of papers and studies demonstrate the beneficial role of betaine in the brain as well. However, the positive effects in the CNS are very little understood and investigated. In this work, we present an overview of papers that highlight the potential therapeutic role of betaine in neuronal disease and disorders. The cellular or molecular mechanism involved are also point out when they were known and clearly reported by the literature considered.

1.3 | The presence of betaine in the brain

The reported betaine concentration in the vertebrate brain is lower than in the liver and kidney.[1,13] The SLC6 transporter BGT-1 is thought to be the primary regulator of betaine in the brain. In literature, BGT-1 localization has been reported in the cerebral cortex, cerebellum, brainstem, hippocampus, microvessels (i.e., blood-brain barrier BBB) and leptomeninges.[23–25] The expression and localization of BGT-1 in the brain has been debatable, due to the lack of controls for specificities of the antibodies used and/or for the use of cell cultures instead of intact brains.[1] While some reports indicate isolated expression of BGT-1 on the surface of the neocortex and rule out the role of BGT-1 in regulation of GABA in rodent CNS,[1,24,26] other reports are suggesting astrocytic and neuronal expressions of BGT-1 in hippocampal slices of mice and support the clinical and behavioural studies showing beneficial neuroprotective effects of betaine against oxidative and osmotic stress.[12,27,28]

Since the relationship between blood plasma concentration and tissue accumulation of betaine is not very related, there are some anomalies in the reported betaine blood plasma concentration (1–3 mM).[13,29–31] Knight and

collaborators have shown time, dose and osmolarity-dependent betaine accumulation in the hippocampal tissues of mice.[12] They showed that the active betaine accumulation also affects the accumulation of other osmolytes in nervous tissues. Under isosmotic conditions, betaine significantly reduces the accumulation of creatine, taurine and myo-inositol but not glutamate. On contrary, under hyperosmotic conditions, betaine increases the accumulation of glycine and glutamate. Also, it is to be noted that the betaine intracellular accumulation reaches a peak (8 h after first exposure) around 12 mM, which is four times higher than the given extracellular concentration (3 mM). This work suggests that apart from being an osmolyte and serving as a methyl donor, betaine could also influence GABA production/recycling and GABAergic pathways, which resonates with the findings of Kunisawa et al. that showed mediation of GABAergic pathways by betaine.[32]

Interestingly, the suggested role of betaine in the brain has not been limited to its osmolyte characteristic only. The recent work on nematodes *Caenorhabditis elegans* involving the betaine transporter SNF-3 (a BGT-1 ortholog that can only transport betaine) and receptor ACR-23, expressed in neurons and body muscles, suggests a possible signalling role of betaine for locomotion.[33,34] Peden and collaborators show that SNF-3 clears the extracellular betaine, which could be toxic for betaine-gated ACR-23, using the signalling pathway.[33] When seen with the work of Senesi and collaborators where they observe muscle fibre promotion by betaine activating insulin gain factor IGF-1 using signal pathway, it could be hypothesized that betaine might play a signalling role in the brain.[1,35]

1.4 | Effects of betaine in neurological diseases and disorders

To have healthy physiological functioning and stable control of neuronal circuits, the excitatory/inhibitory (E/I) balance of the brain must be maintained. Since the E/I ratio is essential to maintain and regulate signalling transmission, the inhibitory system represents a key point to re-stabilize the neural network function when a predominance of excitation over inhibition rises, as in brain disorders.[36] GABA is the primary inhibitory neurotransmitter in the adult CNS, and the imbalance in its levels can be related to many neurodevelopmental and neurodegenerative diseases such as autism spectrum disorder (ADS), schizophrenia, epilepsy, depression, Parkinson's and Alzheimer's disease (AD) (Figure 2).[37]

1.4.1 | Role in epilepsy

The GABA transporters regulate GABA synaptic concentration; the majority of GABA uptake in the brain is done by GABA transporter 1 (GAT1). It is a pharmaceutical target to treat disorders related to neuronal E/I imbalance; consequently, it is often the target for antiepileptic and anticonvulsant drugs.[38] The FDA-approved antiepileptic drug, Tiagabine, is a selective inhibitor of GAT1.[39,40] The synergic anticonvulsant effect of tiagabine with the selective inhibitor EF1502 on both GAT1 and BGT-1 raised a functional role of BGT-1 in regulating diffused GABA from synaptic regions.[41,42] While the controversies around the localization of BGT-1 failed to justify if it could play any effective role in the clearance of

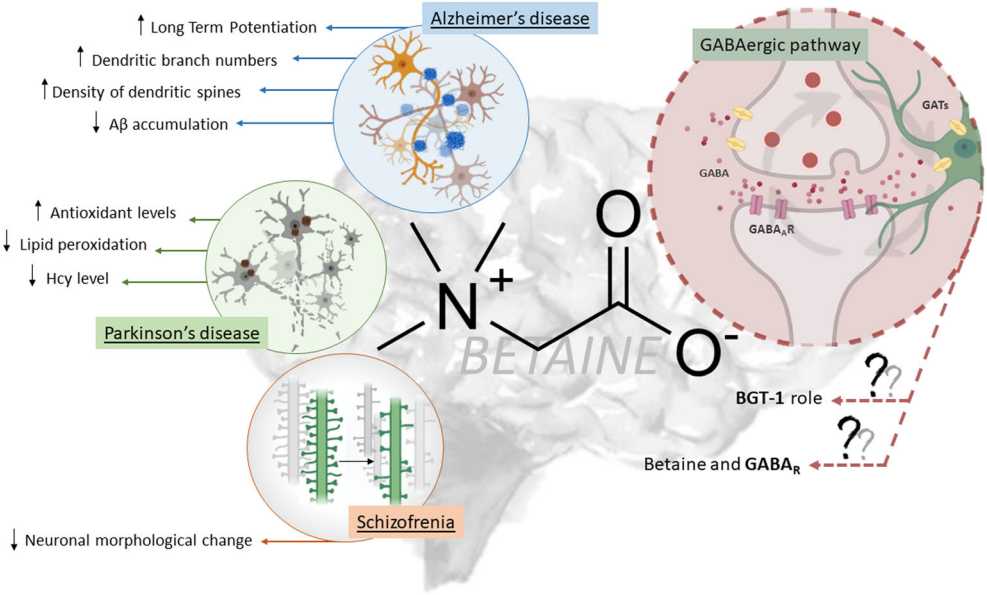

FIGURE 2 Schematic for the role of betaine in the brain. Betaine plays an active role in neuroprotection and against oxidative stress in cells. In neurodegenerative disease such as Alzheimer's, Parkinson's and schizophrenia, betaine can be a possible therapeutic. Although betaine is actively regulated by BGT-1 in GABAergic pathways, the complete mechanism behind is to be determined.

GABA, the development of BGT-1 knockout (KO) mice by Lehre and collaborators shed some light on this.[1] The seizure threshold experiments on BGT-1 KO mice showed no alteration and ruled out a role of BGT-1 in seizure susceptibility.[26] This work suggests that EF1502 is an anticonvulsant because it inhibits GAT1; the inhibition of BGT-1 is irrelevant in controlling the seizure threshold. However, this study fails to address the compensatory mechanism from other GATs, which could have masked the effects arising from the deletion of BGT-1. Although this work implies, based on BGT-1 KO mice, that the synergic anticonvulsant effect of tiagabine and EF1502 should be due to GAT1 and not BGT-1, it requires conclusive evidence where such synergic anticonvulsant effect would be recorded using GAT1 KO mice and/or GAT1-BGT-1 KO mice.[26] Also, in 2020, Lie et al.[43] studied healthy adult mice and not samples from epileptic patients, limiting the direct correlation of these results with seizure-controlling therapies. Hence, BGT-1 still might be playing a role in epileptic seizures and GABAergic imbalance in CNS, which demands the development of BGT-1-specific brain permeating inhibitors.

1.4.2 | Role in stress-related disorders

The stress-induced psychiatric disorders like depression, anxiety and post-traumatic stress disorder (PTSD) are associated with abnormalities in GABAergic neurotransmission functioning.[37,44,45] The study of water-immersion restraint strain (WIRS) induced stress (in mice) resulting in memory impairments showed amelioration by betaine.[32] This improvement could be inhibited by antagonists of BGT-1, $GABA_A$ and $GABA_B$ receptors. Also, the betaine treatment post-WIRS significantly decreased the expression of GABA transaminase (GABA-T), the enzyme responsible for breaking down GABA when not needed. GAT1, GAT3 and BGT-1 expressed in astrocytes regulate GABA levels,[46] and inhibition of GABA-T also increases GABA levels in the synaptic cleft.[47] As betaine is transported by BGT-1 and decreases GABA-T expression, betaine could be asserting its positive effects by changing GABA levels in the CNS. Thus, betaine does not work only as a substrate of BGT-1, but it could also interact largely with the entire GABAergic system.

In psychology, social defeat is seen as a form of stress that could cause depression, anxiety, PTSD and so forth.[48] The resilience against such stress can be mediated by adaptive changes in neural circuits of neurotransmitters (like GABA) and molecular pathways.[49] Anhedonia is one of the main symptoms of stress-related disorders. While studying the role of the brain-gut-microbiota axis in such disorders, Qu and collaborators found that the mice subjected to chronic social defeat stress (CSDS), when given betaine supplementation, showed resilience to anhedonia via anti-inflammation action.[50] This study reports amelioration of the abnormal diversity and composition of the microbiota in the host's gut after CSDS by betaine supplementation; however, the specificity of the microbiome or conclusive evidence of CSDS is the reason behind the abnormal composition of gut microbiota. But overall, the study implicates the gut-brain axis playing a role in susceptibility to stress-related disorders, and betaine supplementation could be a prophylactic nutrient to prevent or minimize the relapse by stress in patients of such psychiatric disorders.[50]

1.4.3 | Neuroprotective role against Alzheimer's and dementia

AD is the most prevalent neurodegenerative disease that is characterized by progressive impairment of cognition, memory and intellectual functions. So far, there have not been many approved agents that ameliorate cognition and the overall function of AD patients, and different therapeutical approaches have been developed.

The damage caused to cellular proteins, lipids and DNA, due to the excessive production of reactive oxygen species and reactive nitrogen species, is collectively called oxidative stress. The brain is more susceptible to oxidative damage, which has been correlated with the pathogenesis of diseases like AD and vascular dementia (VaD).[51] The amyloid-ß (Aß) aggregation is hypothesized to play a pivotal role in the onset and progression of AD; hence, it could be an important biomarker in AD-like pathologies.[52] Aß is generated by amyloid precursor protein (APP) via sequential cleavage from ß- and γ-secretases. The generation and deposition of Aß have been associated with altered oxidative stress, inflammation, tau phosphorylation and synaptic dysfunction, contributing to the progression of the disease and eventually leading to death. Also, the increased levels of Hcy have been associated with the onset of AD, along with hyper-homocysteinemia.[53]

As betaine is an effective methyl donor to convert Hcy to methionine, a therapeutic approach is being developed to use betaine supplementation to target increased Hcy and reduce AD progression. Chai and collaborators report that betaine supplementation ameliorates AD-like Hcy-induced memory deficits, enhances long-term potentiation and increases dendritic branch numbers and density of dendritic spines.[54] It also attenuated the tau phosphorylation and Aß accumulation by altering APP processing.[54,55] In a study, Sun and collaborators demonstrated that subjects treated with betaine supplementation showed amelioration in cognitive deficit resulting in

better recall of words, improved visual–spatial capacity and so forth.[56] Their results showed betaine supplementation (200 μg/kg for a month) reverses Aß accumulation and stimulates the regulation of memory-related protein (NR1, NR2A and NR2B); however, their small sample size and absence of molecular mechanism description need to be considered. Overall, betaine could be an effective therapeutic tool to treat AD but the mechanism of action of this molecule in AD needs to be investigated.

VaD is the other most common type of dementia in aged people after AD and lacks effective therapy. Chronic cerebral hypoperfusion (CCH) is thought to be the primary reason behind cognitive impairment in VaD patients. The rats underwent the surgery of applied permanent bilateral occlusion of common carotid arteries; to produce a condition of CCH in humans, Nie and collaborators report that betaine administration, in rats, could mitigate the memory deficits induced by CCH.[51] They studied the CCH-induced decline of synaptic proteins PSD93, PSD95 and MAP 2, which are critical for learning, memory and synaptic plasticity. This investigation on spatial learning memory retention was done using the Morris water maze examination that revealed that betaine treatment restores the expression of these synaptic proteins. They proposed that CCH induces loss of postsynaptic expression of PSD93, PSD95 and MAP 2 via increased oxidative damage, which betaine treatment prevents and ameliorates memory deficits. However, they do not suggest any possible mechanism that using betaine suppresses oxidative stress. Nevertheless, this evidence furthers the therapeutical role of betaine in neurodegenerative disease.[51]

1.4.4 | Protective role against Parkinson's

Parkinson's disease (PD) would be the second most prevalent neurodegenerative disease (only after AD) characterized by uncontrolled muscular activity, an increase in the metabolic concentrations of sulphate and nitrate compounds, a decline in dopamine levels due to neuronal degeneration and sleep disturbance. In PD patients, the oxidative stress in the brain has been suggested to give rise to the processes leading to dopaminergic neuronal degeneration[57,58] While the modelled motor aspects of PD in animals have highlighted the molecular pathways and mechanisms by which oxidative stress could yield progression of PD, the clinical studies have produced inconsistent results.[57,59] Interestingly, the inhibitory effects of betaine on the neurotoxic nitric oxide (NO), one of the free radicals causing oxidative damage in microglial cells, show that betaine could be used as an antioxidant in PD treatment.[60]

Unfortunately, this oxidative stress in PD patients does not arise only due to the imbalance between the production of free radicals (like NO and H_2O_2) and the antioxidant mechanism of the body for detoxification. The administration of the prominently prescribed dopaminergic drug for PD called laevo-3-4-dihydroxyphenylalanine (Levodopa, L-DOPA) increases plasma levels of Hcy.[61] The high concentration of L-DOPA could produce excessive Hcy, which in turn increases oxidative stress that would assert toxic effects on dopaminergic neurons. The L-DOPA toxicity could be prevented by the addition of antioxidants at physiological concentrations or by soluble factors generated by glial cells.[62] Moreover, to cross the BBB and avoid peripheral toxicity, L-DOPA is often administered with a dopa decarboxylase inhibitor such as benserazide, which by catechol-o-methyltransferase elevates Hcy levels further. The clinical and experimental trials in PD patients show that a high accumulation of Hcy could contribute to accelerated neurodegeneration and the onset of atherosclerotic and neuropsychiatric symptoms.[63,64] Hence, such treatment overall poses a risk of hyperhomocysteinemia in PD patients, leading them towards other neurodegenerative diseases such as AD and dementia.[65] Alirezaei and collaborators studied the effects of betaine administration (in rats) on oxidative stress and increased Hcy levels induced by L-DOPA/benserazide treatment.[66] They demonstrated the neuroprotective qualities of betaine against L-DOPA-induced oxidative stress in the brain tissues of rats. They propose that, by continuous generation of SAM, betaine could decrease excessive Hcy levels generated by L-DOPA/benserazide, elevate antioxidant levels and decrease lipid peroxidation. However, this study requires supportive evidence of physiological parameters like the behavioural test in PD animal model.

Rotenone is an inhibitor of mitochondrial complex I, breaks ATP production and enhances the production of mitochondrial ROS causing apoptosis and inducing neurotoxicity. It is widely used as a model of the pathogenesis of PD. Neuronal cell death is one of the major factors behind cognitive decline in AD and PD. It was demonstrated that betaine performs neuroprotective effects against rotenone-induced neurotoxicity in PC12 cells.[67] The increasing oxidative stress and inflammation in the brain can cause brain ischemia and ischemic stroke. The betaine treatment of PC12 cells (with oxidative stress induced by H_2O_2) resulted in decreased pro-inflammatory cytokine production and reduced oxidative stress.[68] Betaine also increased the expression of antioxidative enzymes and non-enzymatic genes. These results showcase how betaine can and should be considered as a protector against oxidative stress and neurodegeneration.

1.4.5 | A therapeutic agent for schizophrenia

Schizophrenia has always had sleep dysfunction as one of its primary descriptions.[69] The sleep pressure, the driving force of the homeostatic process, builds up during wakefulness and dissipates when asleep. Sleep pressure and sleep disturbance are associated with onsets for patients with psychosis. It is shown that with increasing high sleep pressure, specific metabolomic alterations occur like decreased levels of betaine in the whole brain.[70] Hence, betaine is proposed as one of the biomarkers for the diseases and treatments associated with sleep deprivation.

The neurons in schizophrenic brains tend to undergo gross morphological changes. The neuronal morphogenesis-related traits are significantly alleviated by a high-betaine diet, suggesting that betaine, through a neuroprotective mechanism, could be effective for refractory schizophrenia patients.[71] In CHDH- (a gene for betaine synthesis) deficient mice, schizophrenia-related molecular perturbations in the brain were recorded. It was shown that betaine supplementation induced improvements in cognitive performance dependent on genetic background.[72] These observations suggest that betaine could fit as treatment for patients with schizophrenia, as an atypical drug at initial low doses, under observation of the response to treatment and side effects;[73] even if also in these conditions, the cellular and molecular mechanism is not understood.

2 | DISCUSSION

Given its dual role, betaine has always been considered an important nutrient for human physiology. But the evident growing literature highlights a possible third role, which is the positive effects of betaine in CNS disorders. The betaine in the liver and kidney has been well studied, reviewed and understood. Despite the reported benefits of betaine supplementation in improving brain conditions, the mechanism of action at the cellular and molecular level is not yet clear.

In this review, we highlight the positive effects and therapeutic potential of betaine in brain-associated diseases like AD, PD, dementia, schizophrenia, depression, PTSD, epilepsy and anhedonia reported in recent literature. Although BGT-1 can actively uptake betaine, the little expression in the brain and lack of understanding around its role and the role of betaine in the CNS raise questions over the mechanism behind accumulation and its impact on the brain. The work of Zhou and collaborators localizes BGT-1 in leptomeninges, which is supported by the BGT-1 KO mice model of Lehre and collaborators, ruling out any significant role of BGT-1 in controlling levels of GABA (in mice) and suggesting it as a facilitator to the probable signalling role of betaine.[1,24,26,33–35] On the other hand, the work of Knight in mouse hippocampal slices (containing little meninges) show active uptake and accumulation of betaine and correlate this with reported astrocytic and neuronal expression of BGT-1.[12,28,74] Whereas this conclusion fails to address the issue of uncertainty around immunochemistry data (due to the absence of BGT-1 KO then as a negative control),[1] it is certainly supported by the reported beneficial effects of betaine supplementation in neurological and neurodegenerative diseases. Another problem with their conclusion is that they simply credit the reported rapid astrocytic and neuronal uptake of betaine by BGT-1 without considering or falsifying the involvement of any other transport mechanism in the brain. For example, Nishimura and collaborators showed that the osmo-sensitive system A transporter SNAT2, expressed in central neurons, can transport betaine and could be involved in its regulation.[11] Moreover, Kunisawa and collaborators also highlight this issue by showing that the interaction of betaine with the GABAergic pathway could not be limited to just BGT-1.[32] Their results indicate a possible betaine interaction with $GABA_A$ and $GABA_B$ receptors. The work from Ibi and collaborators supports this hypothesis by showing that the prevention of cognitive impairment by betaine is mediated by BGT-1 but not its antioxidant effects.[75] Thus, the mechanism behind the reported uptake and accumulation of betaine in hippocampal slices[12] could not be limited to just BGT-1. Hence, it is critically important to explore any possible involvement of other transport mechanisms for betaine in the brain, to satisfactorily demystify its beneficial effects.

With such ambiguities over BGT-1 localization, one could simply question the presence of betaine in the brain itself. The recent work of Wang and collaborators on cylindrical polymer brushes (CPB) in vivo answers this question by modification of CPB using betaine.[76] The macromolecule CPB cannot cross the BBB by itself, but its modification with betaine (poly-carboxyl) allows it to successfully cross BBB via BGT-1 expressed on capillaries.[76] Thus, BGT-1 can not only transport betaine across BBB, but it can also help in the development of nano-drugs modified with betaine.[76,77]

Knight and collaborators also showed that, under hyperosmotic conditions, betaine significantly influences the uptake of glycine and glutamine.[12] Since glycine is the precursor to GABA and glutamine to glutamate, a possible role for betaine in maintaining the balance between inhibitory and excitatory neurotransmission cannot be denied. Also, the effects of betaine against stress-induced diseases and memory loss indicate a connection with the GABAergic pathway in CNS.[32,50,51,54–56,66,71,72]

Betaine exhibits neuroprotective properties that could prevent the progression of neurodegenerative diseases like AD, PD and dementia.[51,54–56,60,66] Along with choline, folic acid, vitamin B6 and B12, betaine in the maternal diet is correlated with early neuronal development and attenuation of cognitive function at the later stage of life.[78] One way betaine helps is by reducing the Hcy levels in the neurons and promoting the expression of memory-related proteins.[54,55] Also, it can convert Hcy to methionine and increase SAM, which protects the brain against a variety of toxic agents causing oxidative stress.[79]

As a therapeutic, betaine is already in use as an FDA-approved drug to treat homocystinuria. The reported side effects (for 6–9 g/day) are relatively mild such as gastrointestinal illness, mild body odour, increased urination, feeling dry mouth and preference for salty food.[80] The excess of betaine has been associated with cardiovascular disease and pulmonary hypertension.[81,82] While there are very few side effects recorded for betaine,[83,84] there is still not enough information on the long-term effects of regular betaine supplementation.

3 | CONCLUSION

Although betaine is not considered an essential osmolyte, its beneficial and therapeutic roles in human physiology make it important in the diet. The role of betaine in diseases related to the liver and kidney is better understood but not so for the brain. The reported effects of betaine in the past two decades confirm its neuroprotective and antioxidative qualities with a positive correlation with the GABAergic pathway, but very little is known about the mechanisms that using betaine asserts these effects. With emerging results showing the involvement of betaine with neurological pathways, it is critically important to explore the contribution of all possible transport mechanisms for betaine in the brain, to satisfactorily demystify its beneficial effects. Despite having such a protective role against several neurological diseases, very little is known about its molecular targets, implying betaine simply as the dark knight of the human brain.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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