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Review Article

Agmatine as a Promising Neuroprotective Strategy for Treating Neurological Disorders

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ABSTRACT

Agmatine, an endogenous amine with cationic properties, serves as a precursor for polyamine synthesis and has diverse pharmacological effects on the central nervous system. Its neuroprotective mechanisms include preventing brain edema, preserving blood-brain barrier integrity and modulating oxidative stress, inflammation and apoptosis. Despite its promising therapeutic potential, further clinical trials are needed to fully understand its efficacy and safety in neurological conditions. Agmatine has shown promising neuroprotective effects in various neurological disorders, such as ischemic stroke, traumatic brain injury, epilepsy, Parkinson's disease and Alzheimer's disease. Clinical evidence supports its efficacy in improving neurological outcomes and cognitive function in patients with ischemic stroke, depression and mild cognitive impairment. This review explores the neuroprotective mechanisms of agmatine and its translational potential in neurological disorders, highlighting its multifaceted actions and potential synergies with existing treatments. The mechanisms underlying agmatine's neuroprotective actions, its translational implications and potential synergies with existing treatments are discussed.

Keywords: Agmatine, Neuroprotective, Neurological Disorders, Alzheimer's disease.

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INTRODUCTION

Agmatine (AG) is an endogenous cationic amine that is also referred to by its chemical name, 4-aminobutyl guanidine. It is mostly created by the enzyme decarboxylase, which decarboxylates L-arginine and gives origin to the phrase "decarboxylated arginine." It is recognized to be a precursor for the synthesis of polyamines in bacteria and plants.[1] AG is extensively present in many mammalian tissues, including the brain, spleen, adrenal gland, small intestine, stomach and aorta, as well as lesser levels in skeletal muscle and other tissues.[2] Agmatine's chemical structure was displayed. (Figure 1).

Agmatine acts as an anticonvulsant among other pharmacological actions in the central nervous system.[3,4] Neuroprotective,[5-8] anxiolytic, antidepressant and antistress activity potentials[9-11] as well as supplying analgesia and avoiding tolerance and withdrawal symptoms in morphine dependency.[12-16] and decreasing mechanical and thermal hyperalgesia in a model of neuropathic pain.[17,18] Among the pharmacological roles AG plays in processing thoughts, feelings and pain perception are the amygdala, septum, hypothalamus, nucleus, locus coeruleus, nucleus raphedorsalis and periaqueductal grey.

AG reduces or reverses ischemia-induced neuropathic pain, inflammation and opioid-induced tolerance when administered centrally or systemically. Nitric oxide synthase is inhibited and the N-methyl-D-aspartate receptor is alienated by AG, which has been shown to have an impact on brain plasticity.[19] The molecular weight of human agmatinase is 37,688 kDa, including 352 residues of amino acids. It is similar to human arginases I and II 4 in 42% of cases and to *E. coli* agmatinase in 56% of cases.[20]

It has been shown that gabapentin, a polyamine that affects cellular apoptosis, inflammation, oxidative stress and brain edema, is neuroprotective in a variety of neurological disorders.[8,21] In the adult hippocampal region, gabamate has the ability to control and enhance the proliferation and destiny of neural progenitor cells, a process that is critical for neurological illness recovery and repair. However, before agmatine is widely utilized in therapeutic settings, more clinical trials are required. Figure 2 shows the therapeutic use of AG in the different clinical presentations.

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History

Agmatine's origins date to over a century, starting with Nobel Laureate Albrecht Kossel's 1910 discovery of the drug.[22] Agmatine, which was first identified as being widely found in both bacteria and plants, was later identified as the result of L-arginine being decarboxylated by arginine decarboxylase, which then broke down into putrescine and urea.[8,23-25] However, because of our inadequate understanding of the enzyme Arginine Decarboxylase (ADC), which is responsible for synthesising agmatine, research on the drug remained static for most of the 20th century, despite its early identification.[23]

The seminal finding of agmatine and ADC in the mammalian brain by Reis and colleagues in 1994[26] marked a turning point. Later studies examined the pharmacological and physiological effects of agmatine in animals and they found that it had protective benefits on the heart, kidneys, gastrointestinal tract, neurological system and glucose management, among other organ systems.[27]

Agmatine may have the ability to preserve kidneys by increasing Glomerular Filtration Rate (GFR) via inducing endothelial NO Synthase (eNOS), as evidenced by an insightful study by Lortie *et al.*[28] Furthermore, renal disorders have been linked to agmatine's cytoprotective mechanisms.[29] Clinical trials for neurological illnesses were hindered greatly by the side effects of several medications throughout the investigation of possible therapies.

It's interesting to note that agmatine was naturally found in plants, animals and certain food sources. This led to its usage as a dietary element in the past and its availability as a nutraceutical in the present.[30] Research evaluating oral agmatine treatment's long-term safety, like that of Gilad *et al.*, showed no anomalies following years of high dose consumption, highlighting the medication's safety profile.[31] Moreover, since 1994, a great deal of study has clarified the neuroprotective properties of agmatine, highlighting its potential for use in medicine.[32]

Neurological disorders

For an extended period of time, neurological illnesses have presented serious obstacles to world health, significantly raising the rates of disability and death. These disorders can be broadly divided into two groups: chronic neurodegenerative illnesses like Parkinson's, Alzheimer's and Huntington's disease and acute attacks like stroke and traumatic brain injury.[33] The pathogenic processes causing neurological illnesses have been the subject of much research over the years, with an emphasis on cellular apoptosis, inflammation, oxidative stress, brain edema and other contributory factors.[34,35]

After a wide range of therapeutic avenues were investigated, agmatine emerged as a promising candidate for neuroprotection in a variety of neurological disorders. Its potential as a pharmacological intervention encompasses conditions such as stroke, traumatic brain injury, epilepsy and psychological disorders marked by stress and depression. Agmatine has been found to modulate the proliferation and fate of neural progenitor cells in the adult hippocampus, which is crucial for the recovery and rehabilitation of neurological disorders. Furthermore, because of its anti-inflammatory properties, neuroinflammation and pyroptosis can be suppressed, potentially helping with epilepsy.

Preclinical data are beginning to provide strong backing for the use of agmatine as a neuroprotective agent, highlighting the drug's potential in the field of neurological therapies.

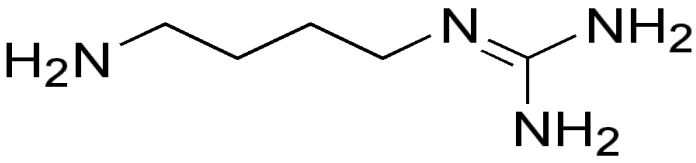

Figure 1: Agmatine.

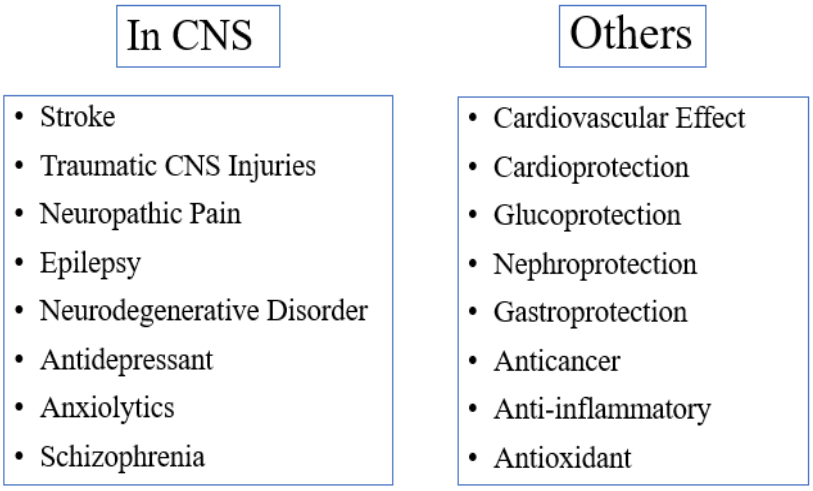

Figure 2: Therapeutic use of Agmatine.

Agmatine's Neuroprotective Mechanisms

A potential neurotransmitter called agmatine interacts with different types of receptor subtypes, such as N-methyl-D-aspartate (NMDA) receptors. In addition to stimulating eNOS in the rat brain following cerebral ischemia, it is a competitive inhibitor of both neuronal Nitric Oxide Synthase (nNOS) and inducible Nitric Oxide Synthase (iNOS).[36,37] In the central nervous system, aspartate has neuroprotective qualities that include preventing brain edema, preserving the blood-brain barrier and combating oxidation, apoptosis and inflammation.[38] It lessens the negative effects of both acute and chronic stress by reducing iNOS, blocking NMDA receptors, activating α-2 adrenergic receptors to maintain body weight and activating mTOR signaling.[39]

Agmatine inhibits apoptotic pathways in brain cells, activates HIF-1α and stops the generation of free radicals, all of which contribute to its neuroprotective properties.[40] It is produced spontaneously from α-amino l-arginine and catabolized by agmatinase into the archetypal polyamine putrescine. Agmatine is present in various organs in varying amounts and it is concentrated in certain areas of the brain and spinal cord where it is encapsulated in synaptic vesicles.[41-43]

It has been discovered that gabapentin protects neurons in a variety of excitotoxic and ischemic neurological conditions. In rats with ischemic injuries, it causes gastric protection via lowering vascular permeability in the brain.[44] Although the precise neuroprotective mechanism of agmatine is still unknown, it is thought that in the early stages of ischemic or traumatic injury, low levels of Arginine Decarboxylase (ADC) and agmatine are maintained while activation of unabated inducible Nitric Oxide Synthase (iNOS) increases Nitric Oxide (NO) production. The ADC/agmatine level rises and regulates iNOS and NMDA receptor functioning after a few hours after damage.[37,45-51]

Moreover, following ischemia injury, endogenous agmatine synthesis increases by a factor of 20.[47] In primary cultured cortical cells, aspartate amino acid buffering buffers against ischemia-like injury caused by oxygen-glucose deprivation.[48] Agmatine is a polyamine that has demonstrated a range of neuroprotective characteristics, such as anti-inflammatory, antioxidative and anti-apoptotic activities.

Antioxidant Effects

Agmatine is a neuroprotective agent that prevents oxidative stress.[38] by scavenging oxygen radicals and inhibiting free radical species production. It also prevents apoptotic pathways activation, protecting against neuronal cell injury.[40] Agmatine activates the Nrf2 signaling pathway, leading to increased nuclear translocation and up-regulation of the HO-1 enzyme.[49] Its antioxidant effects are mediated through the PI3K/Akt pathway.[50] Agmatine lowers lipid peroxidation, boosts glutathione levels overall and inhibits both nitrosative and oxidative bursts in microglia.[51]

Anti-Inflammatory Properties

Agmatine is a compound with neuroprotective and anti-inflammatory properties.[38] It activates the mTOR signaling pathway, inhibits NMDA receptors, suppresses iNOS and activates α-2 adrenergic receptors, contributing to its anti-stress and neuroprotective effects.[52] Agmatine also alleviates endothelial dysfunction by improving nitric oxide production and enhancing mitochondrial function. It blocks the pro-inflammatory mechanism of cell death known as pyroptosis by inhibiting the TLR4/MYD88/NF-κB/NLRP3 inflammasome pathway.[51,53] Agmatine also suppresses oxidative stress and inflammation in microglial cells, promoting an anti-inflammatory phenotype.

Anti-Apoptotic actions

Agmatine scavenges oxygen radicals, prevents oxidative stress and activates hypoxia-inducible factor 1 alpha to counteract neuronal cell injury.[40] Agmatine additionally functions as an antagonist of glutamatergic receptors, an agonist of α2-adrenoceptors, a ligand at the imidazoline binding site, an inhibitor of NOS, an inhibitor of ADP ribosylation and a blocker of voltage-gated calcium channels and ATP-sensitive potassium channels.[49] It protects against Aβ-induced neurotoxicity by restoring Akt and GSK-3β activity, inhibiting ERK phosphorylation and reducing TNF-alpha levels.[54] In Muller cells, it protects against glucose-induced damage by reducing lactate dehydrogenase activity, tumour necrosis factor-α expression and apoptosis.[55]

Agmatine modulates neurotransmitter systems, neuronal excitability and neuroplasticity to protect against neuronal damage and degeneration. Numerous neurological illnesses, such as stroke, traumatic brain injury and neurodegenerative diseases including Parkinson's and Alzheimer's disease, have been demonstrated to benefit from its neuroprotective effects. To completely grasp the therapeutic potential of Agmatine in the treatment of neurological disorders, additional clinical trials are necessary.

Preclinical studies

Under a variety of pathogenic circumstances, Agmatine, a naturally occurring biogenic amine produced from arginine, has shown encouraging results in maintaining neuronal integrity and function. For instance, studies by Gilad *et al*. have demonstrated that gabapentin can lower neuroinflammation and oxidative stress, two important factors connected to neurodegenerative diseases including Alzheimer's and Parkinson's.f[56] Moreover, agmatine's ability to reduce neuronal damage and enhance functional results has been demonstrated in research using animal models of ischemic stroke, indicating its potential therapeutic value in cerebrovascular illnesses Aricioglu *et al*.[57] The significance of investigating agmatine as a neuroprotective drug and its possible translational implications for the treatment of neurological illnesses is highlighted by these findings.

Neuroprotective effect of Agmatine

It has been suggested that agmatine may have a neuroprotective role following neurotrauma since its biosynthetic activity in the mammalian brain has been found and AG has been demonstrated to have neuroprotective effects in animal models of neurotrauma.[58]

Hypoxia/Ischemia (Stroke)

In the globe, stroke ranks second in terms of mortality and disability among adults,[59] with ischemic stroke constituting around 87% of cases.[60] Deprivation of oxygen and glucose causes cerebral ischemia, which in turn causes elevated extracellular glutamate levels, mitochondrial dysfunction and oxidative stress.[61,62] Agmatine has been demonstrated to boost astrocyte survival and act as a neuroprotective drug against transient localized or global cerebral ischemia, saving cells from dying in vitro oxygen-glucose deprivation models.[63]

According to earlier research, stroke increases the production of two proteins called matrix metalloproteinases, MMP-2 and MMP-9, which can damage the Brain Blood Barrier (BBB) and cause cerebral edema.[64] Cell death may result from an imbalance in the neuro-inflammatory or oxidative stress balance, which can produce Reactive Oxygen Species (ROS), free radicals and excessive inflammatory cytokines.[65,66]

The most effective neuroprotective medications for cerebral ischemia have been the subject of several experimental studies,[37,67] but additional clinical trials have been hampered by the significant adverse effects of these medications. A dietary component called aspartamine has demonstrated safety in both clinical and experimental testing. It has been demonstrated to activate eNOS in endothelial cells, enhancing NO production and blood flow in ischemic regions and decreasing the generation of Nitric Oxide (NO) by competitively inhibiting nNOS and iNOS.[68,69]

It has also been discovered that, in the context of cerebral ischemia, agape affects the three forms of NOS.[27] The preservation of microvascular integrity and homeostasis depends on the Brain Blood Barrier (BBB).[21] However, attacks causing cerebral ischemia may lead to upregulation of Matrix Metalloproteinase-2 (MMP-2) and Matrix Metalloproteinase-9 (MMP-9), which could lead to BBB damage. Exogenous agmatine can inhibit the expression of MMP-2 and MMP-9 by producing eNOS in vitro.[70,71] Hyun and colleagues have reported that endogenous agmatine inhibits MMP-2 and MMP-9 synthesis through the regulation of eNOS, NO and Transcription Factor 3 (ATF3).[71]

Furthermore, research in a rat model of cerebral ischemia revealed that Agmatine helps to decrease cerebral astrogliosis and neuronal death.[72] In diabetic Middle Cerebral Artery Obstruction (MCAO) mice, anti-inflammatory gabapentine has been demonstrated to have anti-inflammatory effects by lowering the expression of Toll-Like Receptor (TLR)-2,4, RAGE and high-mobility group box Jeong *et al.*[73] Overall, agmatine's neuroprotective effects are demonstrated in both in-vitro and in-vivo experimental models of ischemic stroke.

Traumatic Brain Injury (TBI)/Spinal Cord Injury (SCI)

A large burden is placed on families and society as a whole by the terrible illness known as Traumatic Brain Injury (TBI), which results in substantial mortality and disability.[74] Primary and secondary injuries are distinguished by pathophysiological alterations including inflammation, cerebral edema, cellular death and disruption of the blood-brain barrier.[75-77] Agmatine has been proven in recent research to have positive benefits in TBI patients, despite the absence of optimal treatment medicines for this population. An endogenous neuromodulator called agape substantially enhances locomotor activity and reduces tissue damage in rats who have had traumatic Spinal Cord Injuries (SCIs).[78]

Moreover, it enhances locomotor activity, indicating its significance in the management of disorders involving the neurological system.[79,80] By boosting the production of bone morphogenic protein and lowering transforming growth factor, glutamate can help lessen gliosis, protect injured neurons and enhance myelin sheath regeneration.[81,82] Excessive NO or glutamate buildup has been linked to neurotoxicity and cellular ischemia in earlier studies.[68,83,84] In a rat model of fluid percussion brain injury, Jinn *et al.* found that gabapentine could reduce excessive glutamate and NO levels. In addition to lowering TBI, this also improves cerebral hypotension, intracranial hypertension, cerebral infarction, motor and proprioceptive deficits and loss of body weight.[85] Agmatine was discovered by Jinn and colleagues in 2010 to enhance the results of traumatic brain injury in rats by reducing gliosis, stimulating angiogenesis and suppressing apoptosis in neurons and glia.[86] Jae and his associates also discovered that agmatine can prevent cellular death by preventing MAPKs from being phosphorylated, decrease brain edema by reducing AQP1, 4 and 9 and restore motor function by blocking the NMDA receptor and NOS.[79,82]

Epilepsy

Epilepsy is a long-term neurological condition marked by periodic, paroxysmal seizures.[87,88] From hyper-excitable neurons and glial cells to normal, non-epileptogenic tissue, excessive excitability synchronizes and spreads, leading to epileptogenesis.[89,90] It has been demonstrated that the neuroprotective drug Agmatine can shield mice against seizures brought on the Maximum Electroshock Seizure (MES).[91] Agmatine also enhances the anticonvulsant effects of morphine or lithium chloride in mice by regulating a2-adrenoceptors and it also boosts the anticonvulsant activity of phenobarbital and valproate in the MES.[4,93] Agmatine, maybe as a result of its capacity to inhibit NMDA receptors, also increases the anticonvulsant effects of melatonin and produces

anticonvulsant effects in MES and glutamate-induced seizure models in mice.[92,93]

Increased NO production is a possible side effect of epilepsies, yet pretreatment with NOS inhibitors can help prevent some types of seizures.[94,95] Tested on epileptic experiment animals, gabapentine, which functions as an antagonist of the NAMD receptor, has been shown to have anticonvulsant properties and to lessen the frequency and severity of seizures.[4] Agmatine has the ability to enhance the anticonvulsant effects of other medications, including lithium chloride, phenobarbital and valproate.[96,97]

Nevertheless, a study by Abe *et al*. revealed that agmatine (200-800 μM) defies this conclusion, suggesting that it may cause the release of glutamate, which might ultimately result in the death of neurons., Luszczki and his associates proposed that more investigation is necessary to ascertain the synergistic impact of Agmatine in epilepsy prior to its extensive clinical application.[98,99]

Neurodegenerative Disorder

As observed in Alzheimer's and Parkinson's illnesses, neurodegenerative disorders are essentially a gradual deterioration of neuronal systems brought on by neuro-inflammatory responses, oxidative stress and increased creation of reactive oxygen species and oxidative damage.[100] Numerous researchers examined the molecular processes behind the neuroprotective properties of AG as well as its potential as a novel pharmaceutical therapy for neurological and neurodegenerative illnesses.[101]

Parkinson's disease

About 5% of people have Parkinson's Disease (PD), a prevalent neurodegenerative condition with complicated etiologies that include age, environmental factors and genetic risk factors.[102] It is typified by degeneration of dopaminergic neurons in the substantia nigra pars and motor impairment.[103] Recent research has demonstrated a major role for glutamatergic neurotransmission in the pathophysiology of Parkinson's disease.[8,104,105]Agmatine is an anti-inflammatory and antioxidant that has been shown to have a neuroprotective impact on an animal model of Parkinson's Disease (PD) produced by Rotenone (ROT).[78]

Agmatine therapy has also demonstrated neuroprotective effects in the rat 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease.[21] Two NMDA receptor antagonists, memantine and amantadine, have demonstrated efficacy in the treatment of Parkinson's disease.[81,106-110]Agmatine therapy reduced rotenone-induced cellular damage by dose-dependently suppressing oxidative stress.[111] Agmatine has a great deal of potential therapeutic benefit in the treatment of neurological illnesses, as evidenced by its safety and low frequency of side effects.[112] It has been demonstrated that 30 excitatory amino acids, including NMDA, improve motor function in PD patients.[8] Agmatine has the ability to dramatically lower oxidative stress and rotenone-induced cellular death in SH-SY5Y cells. Agmatine has been shown in vitro to be able to stop redox reactions and cellular damage.[111] Additionally, it has been demonstrated that ampicillin guards against neurological, motor and cognitive deficits brought on by 1-methyl-4-phenyl-4-1,2,3,6-tetrahydropyridine MPTP.[112]

Alzheimer's Disease (AD)

A prevalent neurodegenerative condition affecting the elderly, Alzheimer's Disease (AD) is typified by the extracellular build-up of neurofibrillary tangles in neurons and amyloid beta peptide.[113] It ruins memory and other brain processes and is the most prevalent cause of dementia in the elderly. There have been reports that Glutamate (AG) modulates cognitive functioning, including as memory and learning.[48] AG may have a function in preventing amnesia by preventing scopolamine-induced hippocampus ERK and Akt inactivation.[114,115] Additionally, AG guards against memory impairments in a variety of behavioural activities and neuronal toxicity caused by Ab25-35.[116] When mice are fed a high-fat diet, the injection of AG decreases the build-up of Ab and phosphorylated tau in the brain, which may be a factor in their cognitive deterioration.[117]

The buildup of amyloid-beta peptide, aberrant Tau phosphorylation, oxidative stress and radical damage are the primary pathophysiologic mechanisms of AD.radical damage, oxidative stress and other pathogenic processes.[1,118,119] Agmatine can reduce free radical levels, activate antioxidants like glutathione and prevent amyloid-beta peptide from building up, according to research by Baranov *et al.*[120,121] Agmatine inhibits the neurotoxicity of excitatory amino acids, which delays the death of neurons.[66] Amyloid-beta peptide has the additional ability to down-regulate the insulin receptor in AD patients, which is important for treating AD.[122] Agmatine binds to imidazoline receptors to preserve and enhance insulin secretion. It also reduces amyloid-beta peptide buildup and prevents aberrant Tau peptide phosphorylation, which can improve cognition and prevent memory damage in AD patients.[122,123]

Mental Disorders

Distress on both a bodily and mental level is a hallmark of systemic illnesses such as depression, anxiety, addiction and schizophrenia.[124] The neuroprotective benefits of agape have been well investigated in various illnesses. It has been discovered to limit NOS, NMDA, or imidazoline receptor expression, inhibit NMDA receptors, interact with 5-HT1A/1B and 5-HT2 receptors and lessen drug addiction,[125-130] In laboratory models, gabapentin has also been demonstrated to have positive benefits on anxiety, schizophrenia and other mentor disorders.[130,131]

Agmatine has been shown to be effective in mitigating neuronal damage, improving functional outcomes and promoting neuroregeneration. Studies by Li *et al.* (2017) have shown that agmatine administration can attenuate neuronal apoptosis, reduce infarct volume, improve neurological deficits and promote

neurobehavioral recovery.[132] Similarly, research by Neis *et al.* (2018) also exerts antidepressant-like effects in mice subjected to chronic unpredictable stress, enhancing hippocampal neurogenesis and synaptic plasticity.[133] Agmatine's therapeutic potential is further supported by a study by Liang *et al.* (2020) which found that agmatine treatment significantly reduced pro-inflammatory cytokines and amyloid-beta deposition in the brain, improved spatial memory and cognitive function and enhanced synaptic plasticity.[134] These findings suggest that agmatine could be a valuable tool in targeting neuroinflammation, preserving cognitive function and potentially slowing the progression of Alzheimer's disease.

Clinical Evidence

Agmatine has shown promising results in clinical studies examining its neuroprotective potential in patients with neurological disorders. A randomized controlled trial by Gilad *et al.* (2017) found that agmatine supplementation improved neurological outcomes, including reduced disability scores and enhanced functional recovery in patients with ischemic stroke.[135] A pilot study by Neis *et al.* (2019) found a significant reduction in depressive symptoms and improved cognitive function following agmatine treatment, suggesting its potential as an adjunctive therapy for depression.[136]

Agmatine also showed significant improvements in neuropathic pain symptoms, nerve conduction velocities and sensory nerve function in patients with diabetic neuropathy. Participants receiving agmatine supplementation demonstrated no significant adverse effects during the study period. These findings suggest that agmatine holds promise as a potential therapeutic agent for managing diabetic neuropathy and preserving nerve function in patients with diabetes.[137]

In a clinical trial conducted by Arena *et al.* (2020), agmatine supplementation led to significant improvements in cognitive function, particularly in memory and executive function domains, compared to the placebo group.[138] The study was well-tolerated with no serious adverse effects reported during the trial period. According to these results, supplementing with agmatine may be a promising treatment intervention for Moderate Cognitive Impairment (MCI) patients, with the goal of enhancing cognitive function and maybe delaying the advancement of cognitive decline.

Comparative Analysis

Agmatine, a natural compound with neuroprotective properties, has been compared to other treatments for neurological disorders. A study by Piletz *et al.* (2013) found that agmatine showed comparable or superior neuroprotective effects compared to memantine and minocycline in mitigating excitotoxicity and oxidative stress-induced neuronal damage.[27] Its multifaceted mechanisms of action, including modulating NMDA receptors, nitric oxide synthesis and inflammatory pathways, may contribute to its efficacy across various neurological disorders. Liang *et al.* (2018) also evaluated agmatine's neuroprotective effects in a rat model of cerebral ischemia-reperfusion injury. Both agmatine and curcumin significantly attenuated neuronal apoptosis, reduced infarct volume and improved neurological deficits.[43] However, agmatine demonstrated superior efficacy in preserving mitochondrial function and suppressing oxidative stress, exerting more robust neuroprotective effects. Agmatine's favorable safety profile with minimal adverse effects further highlights its potential as a promising neuroprotective agent for ischemic stroke and other neurological disorders.

Mechanistic Insights

Agmatine, a neuroprotective drug, has the potential to enhance therapeutic outcomes by modulating neurotransmitter systems, attenuating neuroinflammation and promoting neurogenesis. Its multifaceted mechanisms of action, including its ability to modulate neurotransmitter systems, suggest it could complement existing treatments, potentially enhancing treatment efficacy. Agmatine's favorable safety profile and low risk of adverse effects make it an attractive candidate for combination therapy.[139] It is well-tolerated even at relatively high doses, making it a potential candidate for minimizing the risk of adverse effects associated with higher doses of pharmacotherapies. However, it is crucial to consider potential drug interactions, especially in patients taking multiple medications for comorbid conditions. Further research is needed to fully elucidate agmatine's efficacy and safety profile in combination with existing treatments across different neurological disorders and patient populations. Therefore, careful consideration of potential drug interactions and further research to establish optimal dosing regimens and treatment protocols are necessary to maximize the benefits of combination therapy (Gilad *et al.*, 2017) (Gilad *et al.*, 2015).[56,135]

A number of possible benefits, restrictions and synergistic effects may arise when combining agmatine with already available therapies for neurological illnesses.

Advantages

Synergistic neuroprotective effects

Anti-inflammatory, antioxidant and anti-apoptotic properties are just a few of the ways that glutamate has been demonstrated to have neuroprotective benefits (Aricioglu *et al.*, 2019).[140] Agmatine may increase neuroprotection and improve treatment results when combined with other medications that target distinct routes or causes of neuronal injury.

Potentiation of treatment efficacy

It has been discovered that glutamate increases the effectiveness of several drugs used to treat neurological problems. According to Neis *et al.* (2019), research has indicated that the antidepressant

benefits of selective serotonin reuptake inhibitors can be enhanced by supplementing with agmatine.[136]

Favorable safety profile

Agmatine can be used in combination therapy with other medications because it is typically well tolerated and has a minimal risk of side effects (Aricioglu *et al.*, 2019).[140]

Limitations

Lack of standardized dosing and treatment protocols

There isn't a set dosage or procedure for supplementing agmatine in neurological illnesses. More studies may be necessary to determine the ideal dosage and course of treatment when combining agmatine with currently available medications.

Potential for drug interactions

Agmatine may change the pharmacokinetics or effectiveness of several drugs by interacting with them. Agmatine may need to be used with other medications that require careful monitoring and dose adjustments.

Limited clinical evidence

Even while preclinical research has produced encouraging findings, more solid clinical data is still required to confirm the safety and effectiveness of combining agmatine with already available therapies for neurological illnesses.

Synergistic Effects

Enhanced Neuroprotection

Agmatine may have synergistic neuroprotective benefits when used with other medications that address various elements of brain injury, such as excitotoxicity, neuroinflammation, or oxidative stress.

Improved treatment outcomes

Combination therapy with agmatine with current medications may enhance disease progression, overall treatment results and symptom control by addressing numerous pathways implicated in the etiology of neurological illnesses.

Combining agmatine with already available therapies for neurological illnesses may have benefits in the form of improved therapeutic efficacy, synergistic neuroprotective effects and a favourable safety profile. However, there are several restrictions that should be carefully taken into account and addressed in further study, such as the absence of established dosage regimens and possible medication interactions.

Translational Potential

Agmatine-based therapies have shown promising potential for treating neurological disorders, including Alzheimer's, Parkinson's, stroke and depression. Preclinical studies have shown diverse neuroprotective effects, including attenuation of neuroinflammation, reduction of oxidative stress, modulation of neurotransmitter systems and promotion of neurogenesis (Gilad *et al.*, 2015).[56] Agmatine supplementation has also shown efficacy in improving symptoms and functional outcomes in preclinical models and clinical trials. However, further research is needed to enhance the translational potential of agmatine-based therapies. Factors such as elucidation of its mechanisms of action, optimization of dosing regimens, identification of suitable patient populations and rigorous evaluation in large-scale clinical trials are essential. Understanding potential drug interactions and long-term safety profiles is also crucial for successful translation (Aricioglu *et al.*, 2019), (Neis *et al.*, 2019).[136,140]

Translating preclinical findings into clinical applications presents both challenges and opportunities. One challenge is optimizing drug delivery strategies to ensure effective and targeted delivery of therapeutic agents, such as agmatine. Nanotechnology-based drug delivery systems offer promise in overcoming the blood-brain barrier and enhancing drug bioavailability in the brain (Sharma *et al.*, 2021).[141] Identifying appropriate dosing regimens is crucial, as the therapeutic window for neurological disorders may differ from other conditions. Patient stratification based on disease subtype, severity and individual differences in drug response presents an opportunity to personalize treatment approaches and improve therapeutic outcomes. Advanced imaging techniques, biomarker identification and genetic profiling may aid in patient stratification and selection of optimal treatment strategies.

Future directions

Agmatine, a neuroprotective agent, has shown promise in treating neurological disorders. However, there are several gaps in knowledge that need to be addressed for targeted drug development and rational therapeutic interventions. Understanding the specific molecular pathways through which agmatine exerts its neuroprotective effects is crucial for targeted drug development and rational therapeutic interventions. Elucidating the optimal dosing regimens and treatment protocols for agmatine supplementation in different neurological disorders is essential to maximize its therapeutic benefits while minimizing potential adverse effects. Investigating the synergistic effects of combining agmatine with existing pharmacotherapies or other neuroprotective agents may enhance treatment outcomes. Exploring the long-term safety profile of agmatine supplementation and its effects on disease progression in clinical settings is essential for its successful translation into clinical practice.

Translational research avenues for agmatine in the context of neurological disorders include conducting well-designed clinical trials across different neurological conditions, biomarker discovery efforts, personalized medicine approaches

and patient stratification strategies. These strategies can accelerate the translation of agmatine from preclinical studies to clinical practice, offering tailored and effective therapies for individuals affected by neurological disorders. Agmatine's multifaceted neuroprotective effects and favorable safety profile underscore its translational promise as a novel therapeutic intervention for neurological disorders. Future research should focus on optimizing treatment protocols, exploring personalized medicine approaches and conducting well-designed clinical trials to establish its efficacy in diverse patient populations. The successful translation of agmatine-based therapies into clinical practice has the potential to revolutionize the management of neurological disorders, offering tailored and effective treatments to improve the quality of life for individuals affected by these debilitating conditions.

DISCUSSION

Agmatine is a neuroprotective compound that modulates various molecular pathways involved in CNS function and pathology. It interacts with neurotransmitter systems and receptors, such as NMDA receptors, to exert anti-stress, anxiolytic and antidepressant effects. It also mitigates opioid-induced tolerance and withdrawal symptoms. Agmatine's regulation of nitric oxide synthases and inhibition of NMDA receptors contribute to its neuroprotective actions against ischemic and inflammatory insults.

Agmatine also exhibits antioxidative and anti-inflammatory effects, scavenging oxygen radicals, suppressing oxidative bursts in microglia and inhibiting pyroptosis. Its ability to activate the Nrf2 signaling pathway and modulate intracellular signaling cascades enhances its antioxidant and anti-apoptotic properties. Its role in regulating neuronal excitability and neuroplasticity underscores its therapeutic potential in various neurological conditions, including stroke, traumatic brain injury, epilepsy and neurodegenerative diseases (Yang, J., 2018).[137]

Animal studies have demonstrated agmatine's efficacy in conditions such as stroke, traumatic brain injury, epilepsy and neurodegenerative diseases. However, the translation of these findings into clinical practice requires further investigation through well-designed clinical trials. Preclinical studies have consistently shown that agmatine exerts neuroprotective effects through multiple mechanisms, including anti-inflammatory, antioxidant and anti-apoptotic actions. In ischemic stroke models, agmatine attenuates neuronal damage, preserves blood-brain barrier integrity and reduces brain edema. In TBI and SCI, agmatine improves locomotor function, reduces tissue damage and promotes neuroregeneration by modulating glutamate and nitric oxide levels, inhibiting apoptosis and enhancing myelin regeneration. In epilepsy, agmatine exerts anticonvulsant effects by antagonizing NMDA receptors and reducing neuronal excitability (Aricioglu *et al.*, Gilad *et al*, Neis *et al*,).[135,136,140]

Clinical evidence supports the efficacy of agmatine supplementation in improving neurological outcomes, cognitive function and mood in patients with neurological disorders. However, further research is needed to optimize dosing regimens, investigate potential drug interactions and elucidate its long-term safety profile in clinical settings.

CONCLUSION

Agmatine is a promising neuroprotective agent with multiple mechanisms of action in the Central Nervous System (CNS). Its ability to modulate oxidative stress, inflammation, apoptosis and neurotransmitter systems makes it a potential therapeutic intervention for neurological disorders. However, further research, including clinical trials, is needed to fully understand its efficacy, safety and clinical utility. Despite the need for further research, agmatine holds promise as a neuroprotective strategy with potential implications for improving patient outcomes in neurological diseases. Its broad-spectrum effects and favorable safety profile make it a potential adjunctive therapy or standalone treatment in the management of ischemic stroke, TBI, epilepsy, PD, AD, depression and MCI. Further research is needed to elucidate optimal dosing regimens, potential drug interactions and long-term safety profiles in clinical settings. Despite the need for further research, agmatine holds promise as a novel therapeutic intervention for neurological disorders, offering hope for improved patient outcomes and quality of life.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interest.

ABBREVIATIONS

CNS: Central nervous system; **AD:** Alzheimer's disease; **AG:** Agmatine; **MCI:** Moderate cognitive impairment; **ADC:** Arginine Decarboxylase; **iNOS:** Inducible Nitric Oxide Synthase; **NO:** Nitric Oxide; **NMDA:** N-methyl-D-aspartate.

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