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Review Article

Agmatine: A potential Neurotherapeutic Agent

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Abstract

Agmatine, a natural polyamine disregarded almost for over 100 years, was discovered in year 1910. Almost after a decade, several researches on Agmatine indicated its modulatory action at multiple molecular targets such as, nitric oxide synthesis, neurotransmitter systems, and polyamine metabolism unbolt the new avenues for extensive therapeutic applications which includes neurotrauma and neurodegenerative diseases, antidepressant, cognitive disorders. Agmatine exerts its varied biological characteristics and therapeutic potential in diverse arena. Agmatine has been extensively researched for its neuroprotective effect in various types of neurological diseases, including stroke and trauma brain injury along with Parkinson's disease, Alzheimer's disease, Hypoxia /Ischemia. In the present review we have summarized the therapeutic potential of agmatine as protective and regenerative properties in the CNS.

Keywords: Agmatine, Neuroprotective, Alzheimer's disease, Parkinson's disease, CNS disorders.

1.0 Introduction

Agmatine (AG), chemically know as 4-aminobutyl guanidine an endogenous amine, cationic in nature and has been known to be precursor for the synthesis of polyamines in plants and bacteria and mostly synthesized by decarboxylation of L- arginine by enzyme decarboxylase hence called decarboxylated arginine.[1] AG is widely distributed into mammalian tissues, particularly in stomach, small intestine, aorta and in lower level in spleen, adrenal gland, skeletal muscle, and brain.[2]. AG plays various pharmacological roles like processing cognitions, emotions, pain perception, including amygdala, septum, hypothalamus, nucleus, locus coeruleus, nucleusraphedorsalis, and periaqueductal gray. AG when administers systemically or centrally, it prevents or reverses opioid-induced tolerance, inflammatory and neuropathic pain associated with ischemia. AG alienates the N-methyl-D-aspartate receptor and inhibits nitric-oxide synthase which demonstrated its effect in neural plasticity.[3] Human agmatinase contains 352 amino acid residues and has a molecular weight of 37,688 kDa. It has 56% similarity to E. coli agmatinase and 42% similarity to human arginases I and II [4] This review deals with the various therapeutic potential of Agmatine and its action on various systems.

The therapeutic potential of AG in the various clinical manifestations has been depicted in figure 1 and table 1.

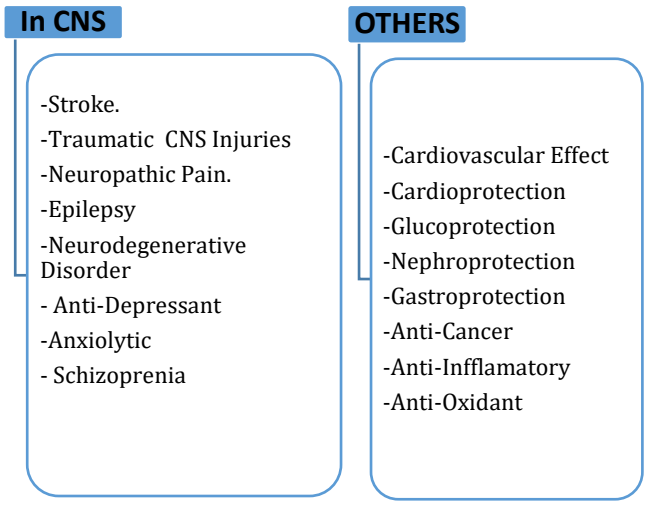

Figure 1: Therapeutic effect of agmatine

Table 1: **Therapeutic potential of agmatine in the various clinical manifestations**

Clinical manifestation	Comments
Stroke.	Ameliorate BBB disruption.
Traumatic CNS injuries.	Reduce astrocytic scar formation.
Neuropathic pain.	Given orally and is available as a nutraceutical.
Epilepsy	Several molecular targets related to neuroprotection.
Neurodegenerative disorder.	In-vivo studies in Parkinson's disease model.
Antidepressant properties.	Human biomarker studies
Anxiolytic properties.	Involvement of increased endogenous agmatine metabolism.

2.0 Neuroprotective effect of Agmatine

AG has been found to exert neuroprotective effects in experimental models of neurotrauma and the identification of agmatine and its biosynthetic activity in mammalian brain, it was hypothesized that agmatine might serve a neuroprotective role following neurotrauma.[5]

2.1 Hypoxia /Ischemia (Stroke).

Cerebral ischemia is a condition resulting from deprivation of oxygen and glucose that occurs mainly due impairing blood supply to specific brain regions.[6]. It leads to increased extracellular levels of glutamate causing, mitochondrial dysfunction, and oxidative stress. [7]. Literature suggests that agmatine is neuroprotective effect against transient focal or global cerebral ischemia and also increases astrocytes viability, rescuing these cells from death induced by in vitro oxygen-glucose deprivation model.[8]

2.2 Traumatic brain injury (TBI) / Spinal cord injury (SCI).

AG is an endogenous neuromodulator, significantly improves locomotor function and decreases tissue damage following traumatic SCI in rats. It also improve the locomotor activity in rats which, suggests that its importance to treatment of diseases related with nervous system [9,10] It is well recognized that the conjunction of acute and delayed events of TBI can lead to the development of psychiatric disorders, cognitive changes, seizures and epilepsy [11]. AG found to improve regeneration of myelin sheath, protect the damaged neurons and gliosis, after SCI by increasing the expression of bone morphogenic protein and decreasing the expression transforming growth factor. [11-12].

2.3 Implications for epilepsy.

Epilepsy is a neurologic disorder in which nervous system is disturbed by some activity causing seizures with severity increasing in accordance with age [13]. It has proven that AG used to treat epilepsy, orally and intraperitoneally administered agmatine protected against maximal electroshock seizure (MES)-induced seizure [14]. AG also potentiates the anticonvulsant effect of morphine or lithium chloride in mice through modulation on a2-adrenoceptors and enhances the anticonvulsant action of phenobarbital and valproate in the MES [15,16]. AG showed to potentiate the anticonvulsant effects of melatonin and elicited anticonvulsant effect in MES and glutamate-induced seizure models in mice, the probable mechanism related to its ability to antagonize NMDA receptors [17,18].

2.4 Neurodegenerative Disorder.

The neurodegenerative diseases are basically a progressive degeneration of neuronal systems due to neuro-inflammation, and oxidative stress that occurs due to increased production of reactive oxygen species and oxidative damage [19] as observed in Alzheimer and Parkinson's diseases. Many researcher reviewed about potential of AG as new pharmacological treatment for neurological and neurodegenerative diseases along with the molecular mechanisms underlying the neuroprotective effects.[20]

2.4.1 Parkinson disorder (PD)

PD is the second most common neurodegenerative disease which affects around 5% of the population. It is a disease with complex etiology such as genetic risk factors, environmental factors and aging. [21]. El-Sayed EK et al, investigated the neuroprotective effect of agmatine on a rotenone (ROT)-induced experimental model of PD and results showed that AG possesses a neuroprotective effect through its antioxidant and anti-inflammatory activities. [22] AG treatment also showed neuroprotective in the mouse 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease.[23] Reinforcing the involvement of the glutaminergic system in PD, clinical and pre-clinical findings demonstrated the efficacy of memantine and amantadine, two NMDA receptor antagonists, in the treatment of PD [11,24-28]. Treatment with AG decreased cellular damage caused by rotenone through suppression of oxidative stress in a dose-dependent manner. [29]. The safety and low incidence of adverse effects indicate the vast potential therapeutic value of agmatine in the treatment of neurological diseases. [30]

2.4.2-Alzheimer's disease (AD)

Alzheimer's is a progressive disease that destroys memory and other mental functions and is the most common cause of dementia among older people. It has been reported in many literature that AG modulate cognitive functions, including learning and memory. [31] AG prevents hippocampal ERK and Akt inactivation induced by scopolamine, suggesting the role of AG against amnesia. [32,33]. AG was also capable of protecting against Ab25-35-induced neuronal toxicity and memory deficits in a battery of behavioral tasks, including elevated plus maze, open field, memory version of the water maze task and object recognition memory task [34]. Additionally, AG administration reduced the accumulation of Ab and phosphorylated-tau in the brain, which may contribute to reduce cognitive decline in mice subjected to high-fat diet [35].

3.0 Effect of agmatine in Psychiatric disorder

3.1 Anxiety disorder.

Anxiety is a mental health disorder relates with feeling of worry, fear, stress, obsessive compulsive disorder and post-traumatic stress disorder. AG showed marked effect on

depression and anxiety like behaviour in mice through nitrergic pathway, which relates with modulation of oxidative–nitrergic stress and serum corticosterone levels. [36] AG reported as a potential therapeutic target in overcoming alcohol withdrawal symptoms such as anxiety and also causes a mild anxiolytic-like behavior in the elevated plus maze in rats [37, 38].

3.2 Depression.

Depression is a common and serious mood disorder with a high prevalence in the major population around the world [39]. Kale M et. al, in their research work, project agmatine as a potential therapeutic target for type-II diabetes mellitus associated depression, anxiety, and co morbidities[40]. The antidepressant-like effect of AG seems to be also dependent on the modulation of other signaling pathways such as, increase in phosphorylation of protein kinase A, protein kinase B/Akt, glycogen synthase kinase-3b and BDNF mediated signaling in the hippocampus [41]

3.3 Schizophrenia

Schizophrenia is commonly considered to be among the most intractable of mental illnesses and among the least comprehensible in terms of neurobiological mechanisms. [42] Agmatine has been proposed to be a neuromodulator and the polyamines, have been suggested to be responsible for sensory gating deficits seen in schizophrenia. Several studies indicates the role of AG in the pathophysiology of schizophrenia band high levels of agmatine metabolites (spermine and spermidine) are found in the plasma, cerebrospinal fluid, and brain tissues of patients compared with healthy controls [43, 44].

3.4 Cognitive enhancement: age-related changes and relevance to dementia

Cognitive decline in biological aging is a known and cognitive enhancement therapy designed to help people with schizophrenia and related cognitive disorder improve brain and cognitive development, social cognition, and increase vocational capabilities. [45]. AG treatment reported to prevent endothelial dysfunction associated with vascular dementia through endothelial nitric oxide synthase and amygdaloid brain-derived neurotrophic factor expression in aged rats. [46].

4.0 Effects of agmatine in learning and memory

Learning and memory considered to be basic features of human activity that is our ability to think new ideas and to retain it in memory [47]. Results of the work carried out by Utkan T et al, indicates that AG has an important role in modulation of learning and memory functions.[48] McKay BE et al, examined AG for its role in water maze place learning, fear learning. The results indicate that systemically administered AG selectively impairs behavioral inferences of specific types of learning and memory. [49,50]. A recent work investigated the levels of AG before, during and after the performance of the Morris water maze task. During the learning phase, the levels of AG found to increase by six times compared with the control group, suggesting that the endogenous AG system can be modulated during the learning process [51].

5.0 Anti-inflammatory effects

Inflammation is a complex immune response of organisms to the injury. Under normal conditions, inflammation could help to scavenge the necrotic cells or tissues, and initiate the tissue repair process [52]. Inflammatory neurodegeneration contributes to a wide variety of brain pathologies. AG also reported to exert its anti-inflammatory effect by reducing the level of inflammatory cytokines, like tumor necrosis factor (TNF)-α and interleukins (IL)-6 [53]. Kim JM et al investigated the anti-inflammatory effect of AG to reduce cerebral ischemic damage in diabetic rats. [54].

6.0 Antiapoptotic

Apoptosis is one type of cell death characterized by energy dependence and programmed cell death [55]. Zhu MY et al, demonstrated that AG can protect cultured hippocampal neurons from glucocorticoid induced neurotoxicity, via blocking of the N-methyl-D-aspartate receptor channels or a potential anti-apoptotic property. [56]. AG administration also prevent streptozotocin-induced memory deficit associated with hippocampal apoptosis [57]. Ag reported to prevent apoptosis induced by TNF-a in retinal ganglion cells in vitro and LPS-induced hippocampal caspase-3 activation [58,59]. The arginine metabolite agmatine protects mitochondrial function and confers resistance to cellular apoptosis. [60]. Some research findings indicates that AG could overcome the nicotine evoked hepatic oxidative stress and tissue injury and apoptosis. [61,62].

7.0 Antioxidant

AG has neuroprotective effects on retinal ganglion cells (RGCs) as well as cortical and spinal neurons. It protects RGCs from oxidative stress even when it is not present at the time of injury. [63]. Several studies have demonstrated the anti oxidative effect of AG in the setting of neurological diseases and it could ameliorate depressive like behavior by reducing the oxidative/nitrosative stress [64] Ivanna Bila et al, in their research found that treatment with AG in diabetic animals repair redox homeostasis and a balances antioxidant defence system enzymes in leukocytes.[65]

Conclusion

Agmatine, an endogenous polyamine is derived from arginine by decarboxylation process, is a neuromodulator that regulates multiple neurotransmitters and signaling pathways. A vast experimentation on agmatine demonstrates its neuroprotective activity and the treatment with agmatine could be new therapy for neurodegenerative diseases. The beneficial effect of agmatine reported in epilepsy and other neurodegenerative disorders including Alzheimer and Parkinson's disease. Agmatine also protects against inflammation, apoptosis and oxidative stress.

Consent for Publication

Not applicable.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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