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AGMATINE A NOVEL NEUROTRANSMITTER: A GENERAL REVIEW

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Abstract:The aim of this study was to assess the role of agmatine as a novel neurotransmitter in the CNS and its other important actions in the body. The CNS, being the most injury-susceptible part of the mammalian body, has been observed to protect neurons from damage. Agmatine plays a vital role in neurological diseases. Previous studies have found that agmatine is related to the regulation of nitric oxide synthesis, relief from chronic pain, cerebral edema, and glucose regulation. It binds with imidazoline-binding sites and α2-adrenoreceptors and blocks N-methyl-D-aspartate receptors via voltage and concentration-dependent mechanisms, as well as other ligand-gated cationic channels including nicotinic and 5-HT3 receptors. In this review, we will focus on the pharmacological role of agmatine, establishing it as a novel neurotransmitter.

***Keywords*1**. Agmatine, Neurotransmitter, CNS (Central Nervous System), Pharmacological role,Imidazoline-binding, Neurological disorders, Neuroprotective effects, Pain modulation, Antidepressant effects, Neuroinflammation, Cognitive enhancement, Cardiovascular health, Metabolic hormone regulation, Safety and efficacy, Combination therapies

I. INTRODUCTION

Agmatine was discovered in 1910 by the German scientist Albrecht Kossel (WeilinXu et al., 2017). Agmatine is synthesized from the metabolic pathway of L-arginine decarboxylase. It is mainly located in the brain and other organs. It acts on various receptors and is a novel neurotransmitter of the brain. It is a polyamine and an endogenous ligand of imidazoline receptors formed by the decarboxylation of L-arginine by arginine decarboxylase (ADC) (Bousquet et al., 1984). In the mid-1980s, the concept of imidazoline binding sites, demonstrated in the central nervous system, was introduced and shown to be involved in central blood pressure regulation (Ernsberger et al., 1987). Mammalian agmatine was identified and characterized as a candidate for CDS (Li et al., 1994). It has also been found that agmatine inhibits nitric oxide synthase in rodents (Auguet et al., 1995). It has several biological effects in the CNS by acting on certain receptors and neuronal pathways. Due to its various biological effects, agmatine matches the criteria of a novel neurotransmitter in agmatinergic synapses (Reis and Raghunathan, 1998, 2000; Raasch et al., 2001). Agmatine is the key compound for the synthesis of polyamines. This pathway is also related to the synthesis of some important neurotransmitters, such as glutamate and GABA (Petroff et al., 2002). The CNS is the most sensitive part of the brain, and any acute or chronic, central or peripheral disorder is related to abnormal brain cell activity. Therefore, receptors are abundant in the brain. Agmatine is a beneficial neuroprotective agent that can protect or prevent neuronal damage in the CNS (Gilad et al., 1996). Agmatine is predominantly found in the brain associated with memory and plays a vital role in learning and memory (Reis and Regunathan et al., 2000). Agmatine inhibits the antioxidant pathway in streptozocin-induced Alzheimer's disease (AD) and AD-like interactions caused by brain insulin resistance (Iyer et al., 2002). Agmatine, an endogenous cationic amine, has been observed to exert various neurotherapeutic effects. It has

a high affinity for α2 adrenergic receptors, imidazoline binding sites, inhibits N-methyl-D-aspartate receptor (NMDA), and nitric oxide synthase (NO) (Tanver et al., 2017).

II. CHEMISTRY

Agmatine is chemically 4-aminobutyl guanidine. It is an endogenous novel neurotransmitter mainly located in the CNS. It is stored in synaptic vesicles in a large number of neurons with selective distribution in the central nervous system. It is terminated by selective reuptake, released by depolarization, and its action is terminated by selective reuptake or enzymatic degradation by agmatinase (Reis and Regunathan et al., 2000). Agmatine is a polar molecule due to the presence of amino and guanidine groups, which can participate in hydrogen bonding and electrostatic interactions with other molecules. It has a molecular weight of approximately 130.19 grams per mole. In physiological conditions, agmatine exists predominantly in its positively charged form, making it a polyamine and allowing it to interact with various receptors, enzymes, and ion channels in the central nervous system. Agmatine's chemical structure and properties contribute to its diverse biological functions, including neurotransmitter modulation, neuroprotection, and neuromodulation.

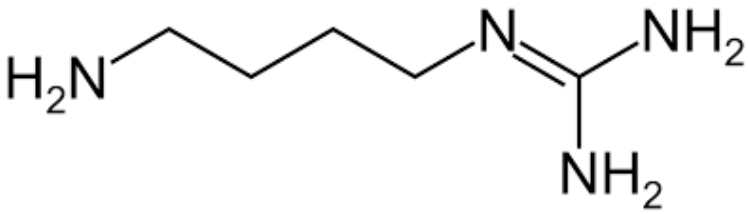

fig1: Structure of agmatine

III. METABOLIC PATHWAY

Agmatine biosynthesis by arginine decarboxylation is well-positioned to compete with the principal dependent pathway urea cycle and polyamine. Its degradation mainly occurs by hydrolysis, catalyzed by agmatinase, into urea and putrescine. For many years, it was believed that ADC did not exist in higher organisms and, therefore, ornithine decarboxylase (ODC) provided the only enzyme for mammals to synthesize polyamines. In 1994, enzymatic decarboxylation of arginine was demonstrated to also occur in the bovine brain to form agmatine; a human form of ADC has now been cloned and characterized (Lyo et al., 2006; Zhu et al., 2004; Li et al., 1993). In the central nervous system, agmatine is catabolized to form putrescine by an enzyme agmatinase (Iyer et al., 2002). In peripheral tissues, agmatine is alternatively oxidized by diamine oxidase to form guanido-butanoic acid, which is readily excreted from the body. Two brain-enriched enzymes, ADC, and agmatinase are the molecular engines that drive the newly named 'agmatine pathway' of polyamine biosynthesis agmatine pathway and the ODC pathway.

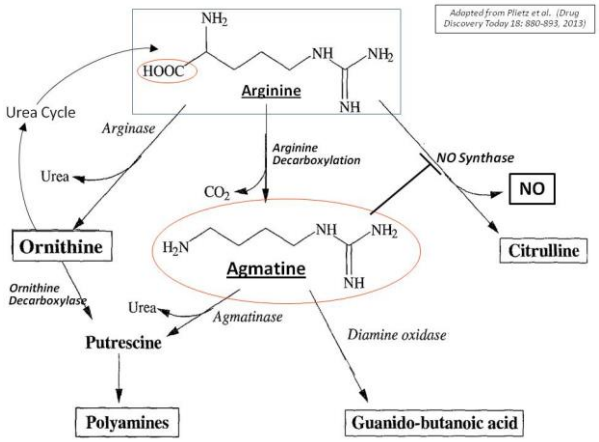

fig2: Metabolic pathway of agmatine synthesis

IV. PHARMACOLOGICAL ROLE

Agmatine is an endogenous ligand of imidazoline receptors, also binds with α2 adrenoreceptors, and blocks ligand-gated cation channels, particularly the NMDA class (Reis and Regunathan, 1998; Halaris and Pleitz, 2007). It has also been found that agmatine inhibits NOS in rodents (Auguet et al., 1995; Galea et al., 1996). Agmatine is not specific at adrenergic receptors, for it does not bind to all or β-adrenergic receptors. However, agmatine may have unique features, due to the organic cation, which may enter the cell via cation channels, including voltage-gated and ligand-gated Ca2+ channels. The latter include cholinergic, nicotinic, NMDA receptors. Thus, agmatine may be able to enter cells without metabolic conversion and not only interact with the channels but also reach receptors that are appended to mitochondria (Regunathan and Reis, 1996). Although agmatine binds to α-2 adrenergic receptors, it is not clear whether agmatine is an agonist or antagonist at the site, although most endogenous ligands are agonists. Agmatine appears to act as an agonist at presynaptic α-2 adrenergic sites in the rat tail artery and in the rabbit pulmonary artery to inhibit norepinephrine release (Gonzalez et al., 1996). While agmatine has been shown to bind to 11 and 12 subclasses of I-receptors, the functional response is not clear, partly because the signal transduction and cellular responses to the activation of I-receptors are not clearly established (WeilinXu et al., 2017).

V. PHARMACOLOGY

Agmatine, a derivative of the amino acid arginine, has shown promising potential in various areas including neuroscience, pain management, and athletic performance. Its future aspects could include:

Neurological Disorders: Continued research into agmatine's neuroprotective properties may lead to potential treatments for neurological disorders such as Alzheimer's disease, Parkinson's disease, depression, and Huntington's disease (Filipe et al., 2012).

Pain Management: Agmatine's role as a neuromodulator and its ability to inhibit certain neurotransmitters involved in pain perception could lead to the development of novel analgesic drugs with fewer side effects compared to traditional opioids.

Neurotransmitter Regulation: Further investigation into agmatine's interactions with neurotransmitter systems may provide insights into its potential for treating addiction, anxiety disorders, and other psychiatric conditions (Tayfun et al., 2012).

Athletic Performance: Agmatine ability to enhance nitric oxide production and improve blood flow may continue to be explored in the context of sports performance and muscle-building supplements.

Cardiovascular Health: Research into agmatine effects on blood pressure regulation and cardiovascular function could lead to the development of new therapies for hypertension and other cardiovascular conditions (Lichtenstein et al., 2006).

Combination Therapies: Investigating agmatine synergistic effects with existing drugs or compounds may uncover new therapeutic combinations for various medical conditions.

Safety and Efficacy: Continued studies on the safety profile and long-term effects of agmatine supplementation are necessary to ensure its efficacy and safety for clinical use.

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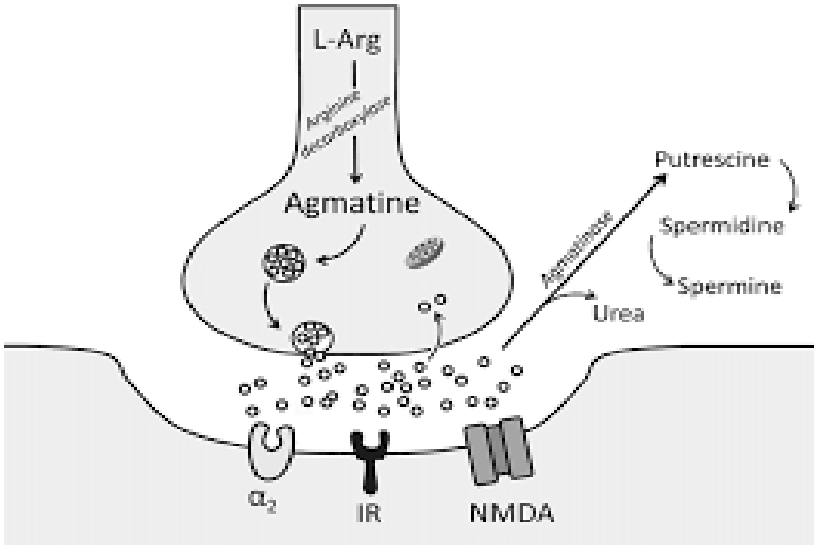

Figure 3: storage and release of the agmatine

VI. FUTURE ASPECTS

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VII. DISCUSSION

In this study we have observed that, the physiological function of agmatine in normal brain are still unknown, still agmatine has several molecules target and acts as antagonist in most target, so it has difficult to evaluate its function in whole body (Regunathan et al.,2006). Many reports have been published indicating that getting may be a key neurotrasnsmitter in several biological events and it play important role in etiopathogenisis of several CNS disease (Tayfun et al.,2011). It is a beneficial neuroprotective element use to protect and prevent the neuronal damage in the CNS. Many studies have reported that exogenous agmatine is nontoxic and exhibits neuroprotective action in both in-vivo and in-vitro animal models of neurotoxic and ischemic brain injuries (Gilad et al.,1996). Agmatine were reported to be effective in reducing hypoxic in brain tissue damage, the exogenous agmatine is also reported to be antiproliferative in the biosynthesis and increase the degradation of cell growth and proliferative in the polyamines synthesis (putrescine spermidine and spermine)(Sumit et al.,2018).

Glutamate induced over stimulation of NMDA receptor leads to a Ca^{2+} overload, the cell have not able to maintnain the osmotic integrity which provoke cell lysis and cell death (Ankarcrona et al.,1995).Agmatine is neuroprotective in brain injuries of necrotic cell death (Maiese et al.,1992; Gilad et al.,1996), in which glutamate-induced neurotoxicity is clearly involved as the mechanism determining cell death. It has been shown to block NMDA currents in rat hippocampal neuron by interacting with a site located within the NMDA channel pore and because the guanidino group of agmatine been identified for blockade of the NMDA receptor channel (Yang and Reis.,1999). The protective effects of the agmatine against NMDA or glutamate induced cell damage are not specific to the cerebellar area only, many reports support neuroprotective roles of agmatine at various doses. Neuroprotective effect against cell damage caused by glucocorticoids in cultured rat hippocampal neurons. From this study we can imply that the neuroprotective effect of agmatine is dose dependent and that agmatine may be neurotoxic at doses higher than 200µM(Tyfun et al.2011). Agmatine is able to block NMDA, glutamate receptor and calcium channel ,

thus agmatine reduced neurotoxicity induced by glucocorticoid through NMDA-receptor and calcium channel blockade, it could protect hippocampal neurons from glucocorticoids-induced neuronal damage in clinical practice(Zhu et al.,2006).

The effect of agmatine on seizure was first investigated by on audiogenic seizures on appearing due to ethanol withdrawl in ethanol dependent rats(Uzbay et al., 2000).

It also has potential applications in the treatment of drug addiction and the prevention of stroke and seizures.

1.Neuroplasticity and Synaptic Plasticity: Agmatine potential role in regulating neuroplasticity and synaptic plasticity could be explored further. Understanding how agmatine influences synaptic remodeling, dendritic spine morphology, and synaptic connectivity could provide insights into its broader effects on brain function and plasticity(Yang et al., 2003).

2.Neuroinflammation and Neurodegeneration: Investigating agmatine effects on neuroinflammatory processes and neurodegenerative diseases could uncover its therapeutic potential in conditions such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Agmatine anti-inflammatory properties and ability to protect against neuronal damage may offer novel strategies for mitigating neurodegeneration (Neurath et al., 2014).

3.Neurotransmitter Release and Reuptake: Elucidating agmatine effects on neurotransmitter release and reuptake mechanisms could provide insights into its modulatory role in synaptic transmission. Understanding how agmatine influences the release and uptake of neurotransmitters such as glutamate, serotonin, and dopamine could shed light on its therapeutic potential in neuropsychiatric disorders characterized by dysregulated neurotransmission (Sulzer et al., 2016).

4.Neuroprotection in Ischemic Stroke and Traumatic Brain Injury: Exploring agmatine neuroprotective effects in ischemic stroke and traumatic brain injury could have significant clinical implications. Agmatine ability to attenuate excitotoxicity, oxidative stress, and inflammation may confer neuroprotection against acute brain injuries and improve long-term functional outcomes in affected individuals (ladecola et al., 2011).

5.Neurogenesis and Cognitive Function: Investigating agmatine influence on neurogenesis and cognitive function could reveal its potential as a cognitive enhancer. Studies examining the effects of agmatine on adult hippocampal neurogenesis, synaptic plasticity in cognitive circuits, and cognitive performance in animal models and humans could provide valuable insights into its cognitive-enhancing properties (Deng et al., 2010).

6.Psychiatric Disorders and Mood Regulation: Exploring agmatine role in psychiatric disorders and mood regulation could offer novel therapeutic avenues. Agmatine interactions with neurotransmitter systems implicated in mood disorders, such as the serotonin and noradrenaline pathways, warrant further investigation to elucidate its potential as a mood stabilizer or antidepressant agent (Nestler et al., 2006).

7.Drug Addiction and Substance Abuse: Investigating agmatine potential role in modulating reward pathways and addictive behaviours could have implications for the treatment of substance abuse disorders. Preclinical and clinical studies examining the effects of agmatine on drug-seeking behaviour, withdrawal symptoms, and relapse propensity could inform the development of adjunctive therapies for addiction treatment (Kalivas et al., 2005).

VIII. CONCLUSION

Agmatine, a derivative of the amino acid L-arginine, has been identified as a novel neurotransmitter with potential neuroprotective effects. It is synthesized in the brain and plays a role in many cellular functions, including the regulation of nitric oxide, a key regulator of cerebral blood flow and neurovascular function. Agmatine has been shown to inhibit certain receptors and activate others, suggesting a complex role in neurotransmission (Regunathan et al., 2016). However, despite these promising findings, the use of agmatine in neuroscience and medicine is still in its early stages. More research is needed to fully understand its mechanisms of action, potential therapeutic applications, and safety profile (Satriano et al., 2001). Agmatine exhibits promising characteristics as a novel neurotransmitter, with its role in modulating various neurotransmitter systems, neuroprotective properties, and potential therapeutic applications in neurological and psychiatric disorders. While further research is needed to fully elucidate its mechanisms of action and clinical efficacy, the accumulating evidence suggests that agmatine holds significant potential for the development of novel treatments targeting the central nervous system (Raasch et al., 1995).

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