Therapeutic Effect of Agmatine on Neurological Disorders as Depression Like Behaviour in Rats and Mice

Poonam R. Pardhi[1], Rupali A. Deshmukh[2], Pranali J. Bhaskar[3], Pragati G. Zalwade[4], Vipin T. Wankhede[5], Nrendra N. Lanjewar[6], Pranita P. Agrawal[7]

[1,2,3,4,5,6,7]*Manoharbhai Patel Institute of Pharmacy, (B. Pharm), Kudwa, Gondia, M.H, 441614, India*

Abstract **- We attempted to undertake our investigation on antidepressant activity of agmatine. Agmatine is chemical substance which is naturally created from the amino acid arginine and its formed by the enzymatic decarboxylation of L-arginine by arginine decarboxylation.[1] It is an endogenous neuromodulator that emerges as a potential agent to manage diverse central nervous system (CNS) disorders. Consistent with its neuromodulatory and neuroprotective properties, there is increasing number f preclinical studies demonstrating the beneficial effects of exogenous agmatine administration on depression, anxiety, hypoxic etc.[2] It has been shown to exert modulatory action at multiple molecular targets, like neurotransmitter system, ion channel, nitric oxide synthesis (NOS) and polyamine metabolism and this provides bases for further research into potential applications[3] The aim of this review is to summarize the knowledge about the effects of agmatine as antidepressant in CNS and point out its potential as new pharmacological treatment for diverse neurological and neurodegenerative diseases.[4]**

Index Terms **- Agmatine, L-arginine, Arginine decarboxylation, Neuromodulator, Neuroprotective, Nitric oxide synthesis, CNS, Neurotransmitter system, Depression, Anxiety, Hypoxia, Ion channels, Antidepressant.**

INTRODUCTION

1.1 Agmatine: A Novel Neurotransmitter in Brain-

The German Scientist Albrecht Kossel discovered agmatine in herring sperm in early 20 th century. Agmatine is a polyamine and endogenous ligand of imidazoline receptor is formed by decarboxylation of L-arginine decarboxylase. [9]

The presence of AGM in plants, bacteria, and invertebrates has been known for a longtime, but its occurrence in mammals was reported for the first time only in the 1990s and since then growing attention has been focused on this polyamine. Agmatine established as a novel neurotransmitter/neuromodulator in CNS synthesized in brain and stored in synaptic vesicles [10]

The concentration of agmatine in various parts of organ like stomach aorta, small intestine, large intestine, sleep lungs, adrenal gland, kidney, heart, liver, muscles and brain.[11]

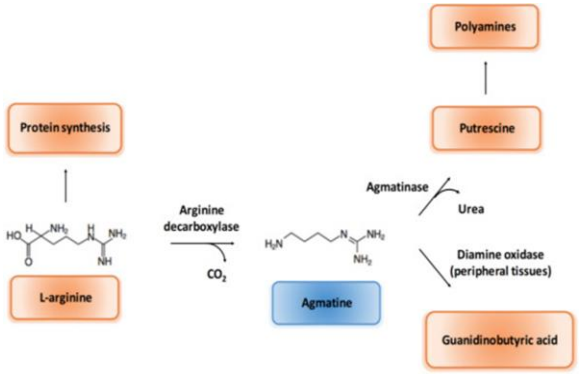

Fig 1:-Schematic illustration of the synthesis and degradation of agmatine. Agmatine is an endogenous polyamine synthesized from L-arginine by the enzyme arginine decarboxylase. It is degraded mainly by hydrolysis, catalyzed by the enzyme agmatinase into urea and putrescine. In an alternative pathway, predominant in the periphery, agmatine is also degraded into guanidinobutyric acid by the enzyme diamine oxidase.

1.2. DEPRESSION

Depression, a kind of mental illness being a state of sadness may be defined as a psychoneurotic disorder characterized by mental and functional activity, sadness, reduction in activity, difficulty in thinking, loss of concentration, perturbations in appetite, sleeping, and feelings of dejection, hopelessness and generation of suicidal tendencies. It is a common and recurrent disorder causing significant morbidity and mortality worldwide. Several workers have described the causes of depression which include genetic,

heterogeneous parental behavior to the siblings, neglect and sexual abuse. In addition, certain conditions like difficulties in job, relationships, natural disasters, finances, child birth, catastrophic injury, loss of life of loved ones and menopause. [5]

1.3. ANTI-DEPRESSANT ACTIVITY

It is known that different brain regions may mediate the onset of variety of symptoms of depression as they regulate emotions, neural security, mood. Antidepressants are medications used to treat major depressive disorder, some anxietydisorders, some chronic pain conditions, and to help manage some addictions. They aim to correct chemical imbalances of neurotransmitters in the brain that are believed to be responsible for changes in mood and behavior. [6] Antidepressants were first developed in the 1950s. Their use has become progressively more common in the last 20 years. Antidepressants may recover the signs of depression, but also exert some side-effects.[7]

1.4. AGMATINE SAFETY AND EFFICACY

Agmatine (decarboxylated arginine) may potentially modulate altered neurochemistry and exerts numerous central nervous system (CNS) dependent pharmacological effects seen in neurological disorders. In preclinical studies, injection has been the predominant route of systemic administration. However, a significant translational step would be the use of oral agmatine treatment at therapeutic doses and better understanding of L-arginine metabolic profiles in the CNS post-treatment. [17]

The present study by following daily oral agmatine sulfate treatment (via gavage) to wild-type (WT) mice up to 900 mg/kg for one week (Experiment 1) or WT and APPswe/PS1ΔE9 transgenic (Tg) mice at 300 mg/kg for fifteen weeks (Experiment 2) systematically investigated the tolerability, safety and brain-plasma neurochemistry. agmatine treatment in both experiments was well tolerated with no marked behavioral impairments, and gross necropsy and organ histology revealed no pathological alterations

after 15-week dosing. In Tg mice exogenous agmatine passes through the blood brain barrier and accumulates in the brain to a greater extent. Furthermore, exogenous agmatine has differential actions in the brain and periphery, and its effect on brain putrescine appears to be dependent on the time post-treatment. Moreover, oral treatment increased agmatine levels in the hippocampus and plasma of WT mice (Experiment 1), and in 6 brain regions examined (but not plasma) of WT and Tg mice (Experiment 2), at 30 minutes or 24 hours post-treatment respectively. This study provides fundamental pre-clinical evidence that daily oral delivery of agmatine sulfate to both WT and Tg mice is safe and well tolerated. This review is aimed to summarize the solid evidence on Anti-depressant activity of agmatine by using the pharmacological animal models like TST, FST and OFT in mice. The participation of NMDA receptor, nitric oxide inhibition and adrenergic pathway in showing antidepressant effect by using oral route administration in mice. [18]

The first preclinical evidence that agmatine has anti-depressant effect in laboratory animals was provided by zomkowski et al that shows agmatine produces an anti immobilite effect in FST and TST.[19] The present study was designed to investigated whether agmatine produces anti depressant like effect on rat or mice by using pharmacological animal models. The possible involvement of neurochemical and neuro receptor modulation in their antidepressant effect by agmatine.

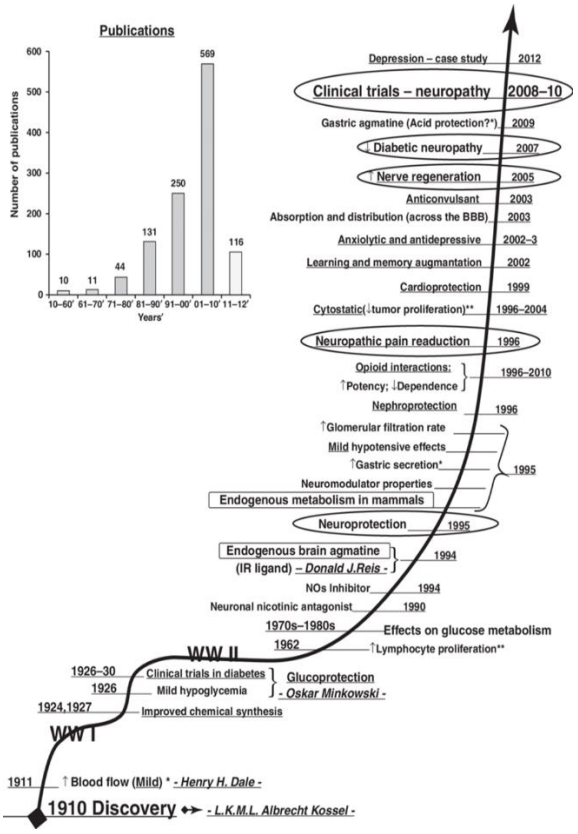

Fig 2:-Milestones in agmatine biomedical research. Key preclinical findings are emphasized by larger or underlined type set, landmark discoveries concerning metabolism in mammals are framed, experimental studies with clinical implications are underlined, and discoveries leading to clinical trials in neuropathy are encircled.

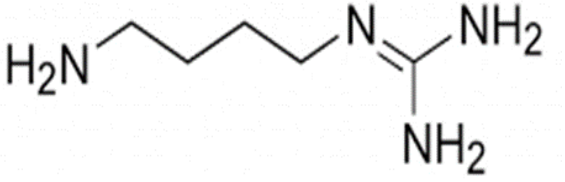

Fig 3:- chemical structure of agmatine

1.1.1 IUPAC name:1-(4-Aminobutyl)guanidine

1.1.2 Properties

Chemical formula	$C_5H_{14}N_4$
Molar mass	130.195 g·mol^{-1}
Density	1.2 g/ml
Melting point	102 °C (216 °F; 375 K)
Boiling point	281 °C (538 °F; 554 K)
Solubility in water	high
Basicity	0.52

1.5. PHARMACOKINETICS:

Agmatine is present in small amounts in plant-, animal-, and fish-derived foodstuff and Gut microbial production is an added source for agmatine. Oral agmatine is absorbed from the gastrointestinal tract and readily distributed throughout the body. Rapid elimination from non-brain organs of ingested (un-metabolized) agmatine by the kidneys has indicated a blood half-life of about 2 hours. Also, agmatine is a neuro-modulator, which means it is a substance that modulates chemical transmission of information between the nerve cells. [23]

1.6. METABOLIC PATHWAY

In all species, agmatine can be metabolized by hydrolysis to putrescine, the precursor of polyamines spermine and spermidine, by the enzyme agmatinase or oxidized by diamine oxidase to γ-guanidinobutyraldehyde, which is then oxidized to γ-guanidinobutyrate and quickly excreted.[24]

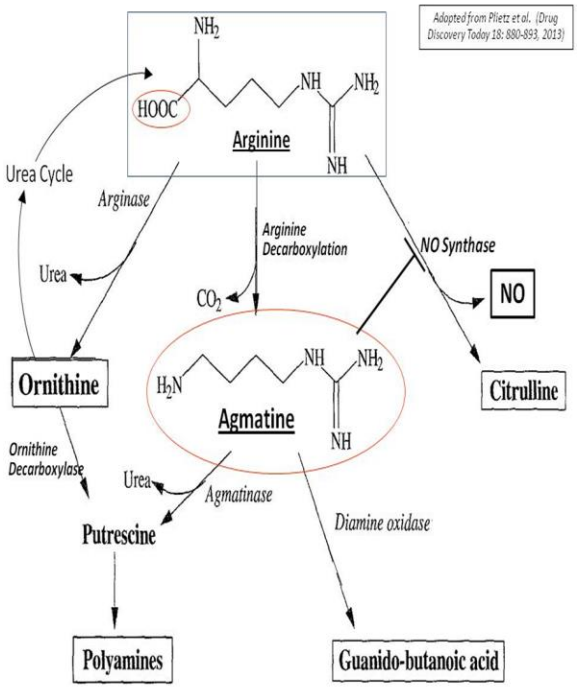

Fig 4:- Synthesis and metabolic pathways of agmatine. Agmatine is synthesized from L-arginine by the action of arginine decarboxylase (ADC). Agmatine can be metabolized to putrescine, the precursor spermine and spermidine, by enzyme agmatinase or oxidised by diamine oxidase to γ-guanidinobutyraldehyde

2. METHODOLOGY

As per the previous research paper studies suggested that the methodology used for anti-depressant effect are as follows-

2.1 SUBJECT

Female Swiss mice (3 months old, 40–45 g) were maintained at constant room temperature (20–22 °C) with free access to water and food, under a 12:12 hr. light: dark cycle (lights on at 07:00 h). The cages were placed in the experimental room 24 h before the test for acclimatization. All manipulations were carried out between 9:00 and 17:00 hr., with each animal used only once. The procedures in this study were per-formed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals and approved by the local Ethics Committee. All efforts were made to minimize animal suffering and the number of animals used in the experiments.

2.2 DRUGS AND TREATMENT

Agmatine (Sigma Chemical Co., St. Louis, U.S.A.) was dissolved in distilled water and was administered by oral route by gavage at doses of 1–100 mg/kg. The dissolution of agmatine was freshly done immediately before its administration. A control group received distilled water as vehicle. In the experiments designed to study the antidepressant-like effect of agmatine in the FST, the immobility time in the FST and the locomotors activity in the open-field were assessed in independent groups of mice 60 min after an acute administration of agmatine by gavage (1–100 mg/kg).[26]

3. BEHAVIORAL TESTS

3.1 Open-field test(OFT) (Depression)

Transport acclimated rodents to the test room singly, if only one test chamber is available, or as a group in the home cage, if several automated chambers are available for testing. Place each mouse in the centre of a chamber. If the experimenter intends to remain in the testing room, care should be taken to be as distant and unmoving as possible once the test session has started. Sudden motion or noise can greatly affect exploratory activity. Rodents are allowed to freely explore the chamber for the duration of the test session. Each line crossed or photocell beam break is scored as one unit of activity. For assessing novel environment exploration, a 5-min test length is typical. If the researcher is interested in examining habituation to an increasingly familiar environment, a 30-min test session is recommended. Upon completion of the test, return the rodent to the home cage. In addition to horizontal units of activity, rearing behaviour, defecation, and grooming activity can also be scored. These parameters provide measures of general physical motor abilities and level of interest in the novelty of the environment. [28]

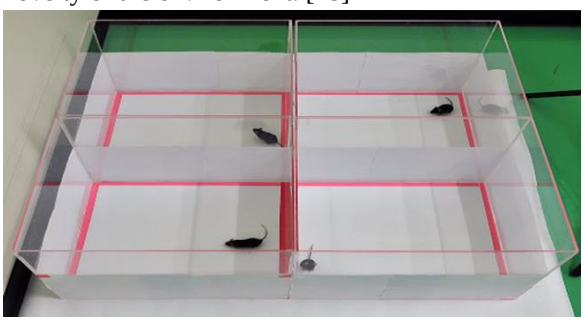

Fig 5 :- Open field test apparatus for behavioral test in rodents

3.2 Forced swimming test (FST)

Mice were individually forced to swim in an open cylindrical container (diameter 10cm, height 25 cm), containing 19 cm of water (depth) at 25 ± 1 °C; the total amount of time each animal remained immobile during a 6-min session was recorded (in seconds) as immobility time, as described previously (Brocardoet al., 2008; Freitas et al., 2010). Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like effect (Porsolt et al., 1977) [30]

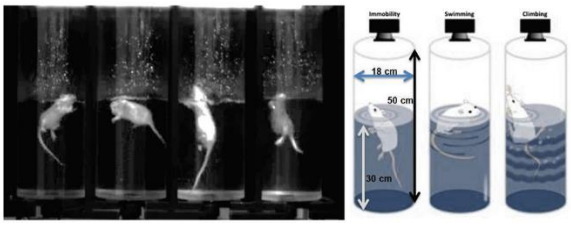

Fig 6:- :-Forcedswimming test for mice

3.3 Tail suspension test(TST)

The total duration of immobility induced by tail suspension was measured according to the method described by Steru et al. (1985).Briefly, mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period.[32]

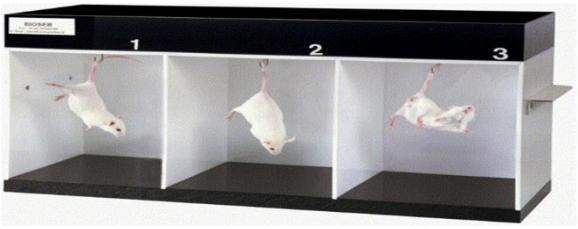

Fig 7:-Tail suspension test for testing immobility time in mice.

4. DISCUSSION

The reason behind using female Swiss mice is may be due to there are rising case of depression mainly in women. In women, the depression arises also due to extra work load, domestic responsibilities, child care, strained relationship, care of aged parents and poverty. In addition to all these indices, the psychological, biological and hormonal factors also significantly contribute in depression. The premenstrual dysphoric

disorder (PMDD) or premenstrual syndrome (PMS) and osteoporosis in women can play important role in development of depression.

The main advantages of this procedure lie in its relatively easy operation and fast results. Moreover, its sensitivity to a broad range of antidepressant drugs that makes it a suitable screening test is one of the most important features leading to its high predictive validity. Agmatine given systemically orally is effective in producing significant antidepressant like effects, when assessed in the FST, a model of depression in mice. Previous findings from our group have shown that agmatine administration by intra-peritoneal (i.p.) and intra cerebroventricular (i.c.v.) routes produces antidepressant-like effect in the FST and TST (Zomkowski et al., 2002, 2004, 2005). In the present study we investigated that an acute agmatine administration by oral route. Produced a significant antidepressant-like effect in the FST, a commonly used behavioral test that predicts the efficacy of antidepressant treatment (Cryan and Holmes, 2005; Porsolt et al., 1977). 1977). Additionally, a consistent antidepressant-like activity of agmatine in mice submitted to the acute restrain stress, a procedure that has been extensively shown to cause behavioral alterations indicative of depressive-like behavior (Kumar and Goyal, 2008; Poleszak et al., 2006; Zafir et al.,2009).

Agmatine blocks the ligand-gated NMDA receptor channel and inhibits all iso forms of nitric oxide synthase (NOS). we also study of mechanism of action of agmatine, in this agmatine act single targeting molecule by binding various receptor like alpha-2 adrenoceptor etc. Since agmatine blocks the NMDA receptors and inhibits all isoforms of NOS and considering the well-known participation of the NMDA receptors. We also study about metabolic pathway of agmatine, in this can be metabolized by hydrolysis to putrescine, the precursor of polyamines spermine and spermidine, by the enzyme agmatinase or oxidized by diamine oxidase to γ-guanidinobutyraldehyde, which is then oxidized to γ-guanidinobutyrate and quickly excreted.

We also investigated when administration of agmatine (dose range 1–100 mg/kg) by oral route produced effect in the locomotor activity in the open-field test.

5. CONCLUSIONS

Agmatine produces antidepressant-like effects after i.p, oral and i.c.v. administration in mice. In this investigation data by indicating some mechanism of underlying the antidepressant-like effect of agmatine in a model of depression induced by restraint stress. The vital finding in this study is that the endogenous amine agmatine, proposed to be a novel neurotransmitter/ neuromodulator in the CNS. Based on the evidence described in this review, it is worth proposing that agmatine is a potentially novel therapeutic drug for depression. Since Giladetal. (1996) showed the first neuroprotective properties of agmatine, a huge amount of studies have corroborated this evidence. More notably is the fact that agmatine produces antidepressant effects by acting on targets related the main hypothesis that explains the pathophysiology of depression and the mechanism of one of antidepressant drugs. Therefore, it is reasonable to suggest agmatine as a promisor antidepressant agent; however more studies, especially in humans, are needed in order to ensure its safety and efficacy.

ABBREVATIONS

CNS	Central nervous system
NOS	Nitric oxide synthesis
5-HT	5-hydroxytryptamine
NMDA	N-methyl-D-aspartate
FST	Forced swimming test
OFT	Open field test
TST	Tail suspension test
AGM	Agmatinase
ADC	Arginine decarboxylase
NIH	National Institute of Health
IACUC	Institutional Animal Care and Use Committee
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
nACh	Nicotinic acetylcholine receptor
I1-R	imidazoline receptors
WT	Wild type
Tg	Transgenic
i.p	Intraperitoneal
i.c.v	Intracerebroventricular

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