Chronic agmatine treatment modulates behavioral deficits induced by chronic unpredictable stress in wistar rats

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Abstract

Aim: Stressful life events modifies brain neuronal structure that impairs normal brain functions and leads to behavioral deficiencies. Agmatine is a well-recognized neurotransmitter and has been reported to be released as a response to several stressful stimuli. Chronic mild stress model induces depressive like behaviors in rats which simulates human depression.

Material and Method: 36 Albino Wistar rats were equally divided in controls and CMS exposed groups that further divided into three groups (n=6). Agmatine (100 mg/Kg/day) and mirtazapine (30 mg/Kg/day) were administered to respective animals while controls with 0.9% saline orally. Test rats were exposed to CMS after one hour of drugs administration and behaviors were observed in different paradigms post 24 hours of drugs monitoring for 28 days.

Results: Agmatine significantly increased the time spent and entries of stressed rats in light/ dark transition box test and elevated plus maze test while struggling and mobility in forced swim test was also improved in rats treated with agmatine.

Conclusion: All the data collected and results obtained clearly validated the antidepressant and anxiolytic activities of agmatine in CMS induced depression in rats. Thus, drug development based on brain agmatine levels may leads to novel approach for stress related mood disorders therapeutics.

Keywords: Chronic mild stress; Agmatine; Mirtazapine; Antidepressant; Behaviors.

Introduction

Persistent stressful life events may result in anxiety and depression and other psychiatric illnesses (Miller D et al., 2002, Stetler C et al., 2011). Constant recurring of stress in humans may leads to depression in vulnerable individuals (De Kloet E et al., 2005, Siegrist J 2008). Peripheral and interior stress factors for example exposure to traumatized events and prolonged inflammation that may cause oxidative and nitrosative stress pathways that causes depression in a person (Maes et al., 1995, 2008, 2012). Effects on neuroendocrine responses may also observed in individuals exposed to constant stress (Mattews K et al., 2001). Willner et al in 1987 (Willner et al., 1987) developed an animal model of unpredictable chronic mild stress (UCMS) that interconnects chronic stressors and depression. Rodents are constantly introduced to mild unpredictable stresses such as deprivation of food or water, restraint or temperature fluctuation. More commonly after 14 days for UCMS treatment, animals grow various signs of depression similar to humans for instance loss of weight, sleep deprivation and anhedonia (Willner P et al., 1987, 1991, 1992, 2005). A number of antidepressants revealed efficiency in UCMS (Willner Pet al., 1987, Monleon et al., 1995).

Agmatine (4-Aminobutyl) guanidine) also called decarboxylated arginine is a metabolite located endogenously among metabolism of polyamine, production of nitric oxide and urea cycle pathway (Reis and regunathan, 2000). Agmatine described as a neuromodulator in CNS, since it:

i) Is produced in a Ca^{2+} way from synaptosomes (Sastre et al., 1997),
ii) Is deactivated by selective reuptake (Sastre et al., 1997),
iii) Is deposited in billions of neurons with selectivity in the brain (Otake et al., 1998),
iv) Is degraded enzymatically in synaptosomes by agmatinase (Tabor and Tabor, 1984),
v) Has a number of molecular targets such as I1R, and α2-adrenergic receptors, $5HT_3$ receptors, antagonized membrane Ca^{+2} channels and isoforms of NOS (nitric oxide synathase) and blocks NMDA receptors inside brain (Reis and Regaunathan, 1998, 1999, 2000).

Additionally, agmatine has been evolving as a reputed unconventional therapeutic implements that could assist traditional pharmacotherapy of depression. It has been observed that agmatine exhibited an antidepressant like outcomes in tail suspension test (TST) and forced swim test (FST), which was coordinated by modulation of NMDA receptors, opioids and monoaminergic systems and pathway of L-arginine nitric oxide (Zomkowski et al., 2002, 2004, 2005). Notably,

Shopsin (2013) recently described a clinical antidepressants therapeutics of agmatine in subjects effected by depression.

Mirtazapine 2-Methyl-1,2,3,4,10,14b-hexahydrobenzo[c] pyrazino[1,2-a] pyrido[3,2-f] azepine used as an antidepressant in humans (Berton and Nestler, 2006). A convincible mechanism of antidepressant action of mirtazapine is blockade of 2-adrenergic presynaptic receptors (Rauggi et al., 2005). In vivo, various studies determine the interconnection of 5 HT subtype receptors and mirtazapine and mediated behaviors (Dazzi L et al., 2008).

The present study was conducted to investigate the anxiolytic and antidepressant role of agmatine, whether it modulates the behavioral inadequacies affected by chronic unpredictable mild stress rat model induced despair and fear and comparison of agmatine with classical antidepressant mirtazapine.

Materials and Methods

Animals

Male Albino wistar rats, approximately 6-8 months old and weighing between (120-180 gm) were purchased from Dow University of health and sciences, Karachi. All the animals used in this experiment were treated accordance to the protocols specified by institutional ethics and care committee. All animals were housed separately under controlled conditions of 12:12 hrs. light /dark cycle, temperature 25 $\pm$ 1^{o}C and free accesses to water and food for 3 days for acclimatization before the experiments.

Drugs and administration

Agmatine and mirtazapine were obtained from Sigma chemicals, Co. St. Louis. USA and were administered orally by stainless steel oral gavage. The selected dose of Agmatine was (100 mg/Kg) and mirtazapine was (30 mg/Kg) per day. Both drugs were dissolved in distilled water at the ratio of 1:1 w/v. Control groups received 0.9% saline.

Experimental protocol

36 rats were divided randomly into control-unstressed and test-UCMS groups (each group = 18 rats) and daily administered with saline and drugs 01 hour before stresses and behavioral tests in various paradigms for 28 days. Both groups were further divided into 3 groups (each group = 6 rats)

a) **Group I**: treated with saline and labeled as control groups.

b) **Group II:** not exposed to stresses in control group but treated with UCMS stressors in tests and both were administered with agmatine (100 mg/Kg) orally.

c) **Groups III**: the division was similar to group II but treated with mirtazapine (30 mg/Kg) orally.

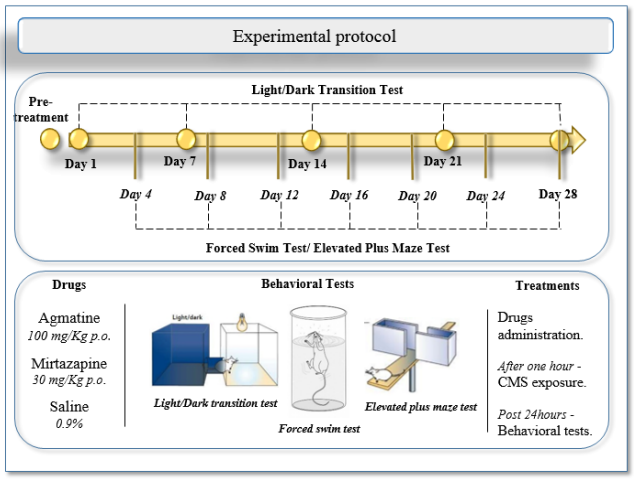


Fig. 1: Schematic representation of experimental protocol and treatments and behavioural evaluations

Elevated Plus-Maze Test (EPM)

Elevated plus maze has been commonly endorsed to observe anxiety in rats (Pellow et al., 1985). The apparatus consists of plus shaped four arms in which two arms are open (50 x 10 cm) and two closed arms (50 x 20 cm) with 15 cm high opaque walls. Open arms edges were .25cm high to avoid fall of rat. The maze was elevated 100 cm above the ground. Each rat is positioned at the center of maze facing enclosed arm. Time spent and entries in open arms were observed in 5 minutes test period (Pellow and file, 1986).

Light Dark Box Testing

Light dark transition test is renowned for analyzing anxiety in rodents. The apparatus consists of two chambers of equal size made up of transparent and black opaque Plexiglas (20 x 30 x 30 cm). the partition is dividing the compartment has a 10 x 10 cm door in the middle of wall through which rat can move from one chamber to another. Single animal was placed in the middle of light chamber facing the opposite side from the middle wall opening. Behaviors measured were entries and time spent in light box for 05 minutes.

The Forced Swim Testing

Forced swim test is known as an authentic test for examine depression-like behavior. The apparatus was a transparent glass cylinder (12 cm diameter and 22 cm height). The cylinder was filled up to 10cm with water (25^{o}C). Each rat was placed into the apparatus and struggling of rat was monitored for 5 minutes. The cylinder was filled with clean water after each test.

Statistics

All the data obtained are exhibiting as mean ± SD (standard deviation) and evaluated as three way ANOVA repeated measured designs SPSS version 17, followed by Newman Keul's post hoc determination. Significance was considered when P value was < 0.05.

Results

Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Light Dark Transition Test (Entries in Lit Area).

The reversal effects of agmatine and mirtazapine on unpredictable chronic mild stress induced depression in unstressed and stress rats are determined by frequency of entries in lit box of light/dark transition paradigm in figure 01. The results obtained were analyzed by III way ANOVA repeated measures design which demonstrated the effects of days ($F(4, 33) = 3.214$) were non-significant however, significant effects of drug ($F(1, 33) = 367.546$ $p<0.05$), stress ($F(1, 33) = 66.124$ $p<0.10$), and interaction of drugs days and stress ($F(4, 33) = 15.882$ $p<0.01$) were attained.

Table 1

Week	Day	Streasors	Duration
1.	Monday	Inversion of Light/Dark Cycle + Overcrowding	1 hour
	Tuesday	Wet Bedding + Cold Stress 4°C	1 hour
	Wednesday	Cage Tilting + Bed Chipping Removed	24 hours
	Thrusday	Soil Bedding +Water Deprivation	24 hours
	Friday	Restraint Stress + Cage Shaking (200 Rpm)	2 hours
	Saturday	Overnight Illumination + Food Deprivation	24 hours
	Sunday	White Noise +Stroboscopic Light	3 hours
2.	Monday	Wet Bedding + Cold Stress 4°C	1 hour
	Tuesday	Cage Tilting + Bed Chipping Removed	24 hours
	Wednesday	Soil Bedding +Water Deprivation	24 hours
	Thrusday	Inversion of Light/Dark Cycle + Overcrowding	1 hour
	Friday	White Noise +Stroboscopic Light	3 hours
	Saturday	Restraint Stress + Cage Shaking (200 Rpm)	2 hours
	Sunday	Overnight Illumination + Food Deprivation	24 hours
3.	Monday	Cage Tilting + Bed Chipping Removed	24 hours
	Tuesday	Restraint Stress + Cage Shaking (200 Rpm)	2 hours
	Wednesday	Soil Bedding +Water Deprivation	24 hours
	Thrusday	Wet Bedding + Cold Stress 4°C	1 hour
	Friday	White Noise +Stroboscopic Light	3 hours
	Saturday	Inversion of Light/Dark Cycle + Overcrowding	1 hour
	Sunday	Cage Tilting + Bed Chipping Removed	24 hours
4.	Monday	Restraint Stress + Cage Shaking (200 Rpm)	2 hours
	Tuesday	Overnight Illumination + Food Deprivation	24 hours
	Wednesday	Inversion of Light/Dark Cycle + Overcrowding	1 hour
	Thrusday	White Noise +Stroboscopic Light	3 hours
	Friday	Soil Bedding +Water Deprivation	24 hours
	Saturday	Wet Bedding + Cold Stress 4°C	1 hour
	Sunday	Overnight Illumination + Food Deprivation	24 hours

Post-hoc analysis by Newman Keul's tests explained that agmatine after 7th ($p<0.05$) and 14th, 21st, 28th ($p<0.01$) administration in unstressed and after 14th, 28th ($p<0.01$) and 21st ($p<0.05$) treatment in stressed rats increased entries in lit area significantly whereas, mirtazapine increased entries in bright area after 7th, 14th, 21st and 28th ($p<0.01$)in unstressed and stress exposed rats when both drugs were compared to saline controls on same day of drug administration. Further comparing drugs to their first treatment, agmatine improved the number of entries in lit compartment after 14th, 28th ($p<0.05$) and 21st ($p<0.01$) in unstressed rats and 14th, 21st and 28th ($p<0.01$) administration in stressed rats 24 hours later and mirtazapine after 14th, 21st and 28th ($p<0.01$) treatment in stressed and unstressed animals individually. Stress significantly decreased frequency of rats arrival in bright box in saline group after 28th ($p<0.05$), agmatine after 7th

(p<0.01) and animals treated with mirtazapine after 21st (p<0.05) day of administration.

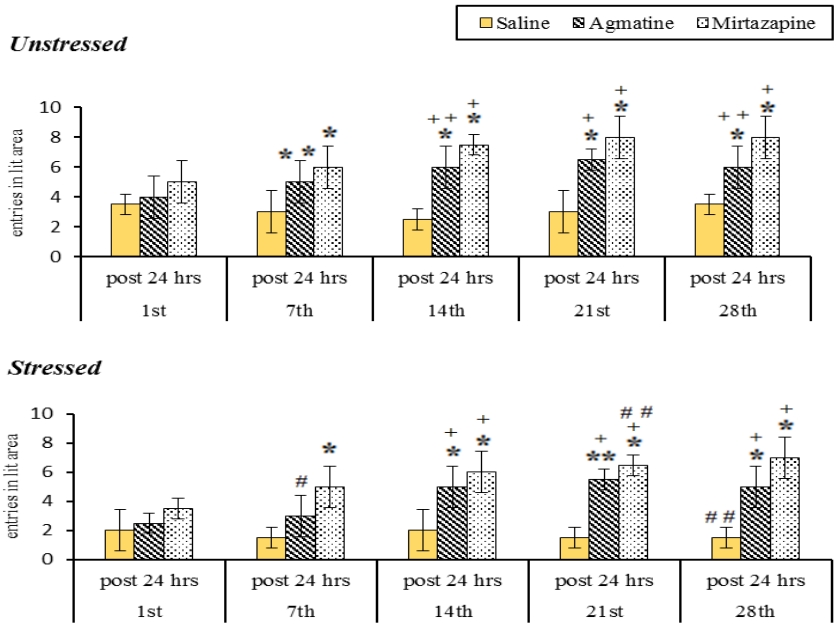


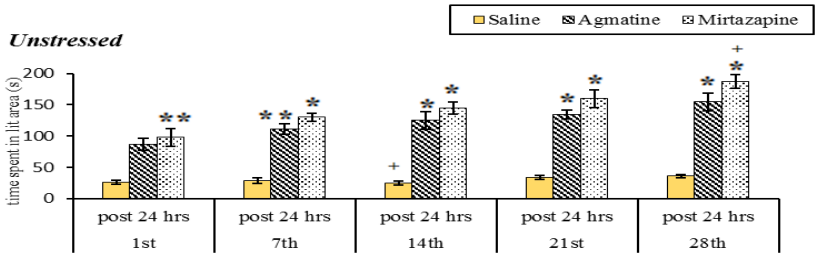
Fig. 2: Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Light Dark Transition Test (Entries in Lit Area)

Values are means ± SD (n=6) as administered post 24 hours of drug administration. Significant differences by Newman-Keul's test: groups that differ significantly from respective saline treated controls *p<0.01, **p<0.05; +similar drug treated groups that significantly differ from 1st administration p<0.01; #p<0.01, ##p<0.05 from similarly administered drug of unstressed to stressed group on same day following three way ANOVA (repeated measure design)

Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Light dark transition test (time spent in lit area)

Assessments of time spent in light box of light dark transition tests by repeated administration of agmatine and mirtazapine in unstressed and stressed rats are explained in Fig. 2. Observed results were analyzed by III way ANOVA (repeated measure design) that described the effects of days (F (4, 33) = 15.891 p<0.01), drugs (F (1, 33) = 175.658 p<0.10) and interaction between days, drug and stress (F (4, 33) = 193.9 p<0.01) were significantly obtained however, effects of stress (F (1, 33) = 43.969) were non-significant.

Post-hoc analysis by Newman Keul's test explained that agmatine after 7th (p<0.05) and 14th, 21st, 28th (p<0.01)administration and mirtazapine post 24 hours of 1st (p<0.05) and 7th, 14th, 21st, 28th (p<0.01) treatment significantly increased the time spent of unstressed rats in light box whereas, a day later of agmatine 28th (p<0.01) administration and mirtazapine after 14th, 21st and 28th (p<0.01) day of treatment significantly improved the duration spent in stress exposed rats when both drugs were compared with saline controls. Additionally, after 14th (p<0.01) day of saline administration, controls exhibited significant increased time spent in unstressed rats. However, agmatine after 28th (p<0.05) in stress affected rats and mirtazapine after 28th (p<0.01) treatment in both unstressed and stressed groups increased the length of time spent in lit compartment when all the drugs were compared from their first administration. Stress caused reduction in time that spent in lit box observed after first treatment of mirtazapine (p<0.01) significantly.



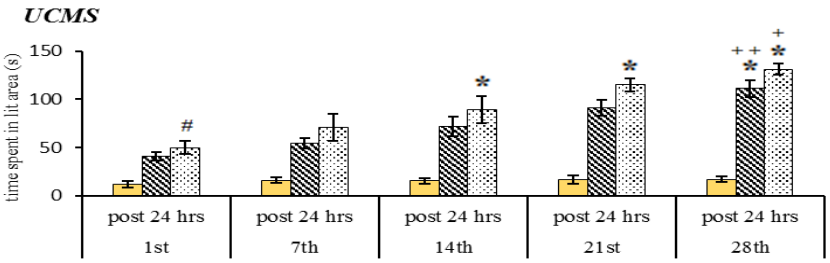


Fig. 3: Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Light dark transition test (time spent in lit area)

Values are means + SD (n=6) as administered post 24 hours of drug administration. Significant differences by Newman-Keul's test: groups that differ significantly from respective saline treated controls *p<0.01, **p<0.05; similar drug treated groups that significantly differ from 1st administration +p<0.01, ++p<0.05;

#p<0.01 from similarly administered drug of unstressed to stressed group on same day following three way ANOVA (repeated measure design).

Antidepressant like activity of Agmatine and Mirtazapine in Forced swim Test (struggling time)

The effects of chronic mild stress and its attenuation by agmatine and mirtazapine are explained in figure 03 in forced swim test experiment. The results were analyzed by III way ANOVA (repeated measure design) which determined the effects of days (F (6, 33) = 0.347) to be non-significant whereas, drugs (F (1, 33) = 218.644 p<0.10), stress (F (1, 33) = 68.134 p<0.10) and interactive effects of days, drugs and stress (F (6, 33) = 51.857 p<0.01) affected significantly. Post-hoc analysis by Newman Keul's test demonstrated that agmatine increased the struggling of unstressed rats after 1st, 4th, 6th, 7th (p<0.01) administration and 5th, 6th and 7th (p<0.01) treatment in stressed group of rats while mirtazapine improved struggling 4th, 5th, 6th and 7th (p<0.01) in unstressed and 4th, 5th (p<0.05) and 6th, 7th (p<0.01) post 24 hours of administration in UCMS exposed rats while both drugs were compared with saline controls. Agmatine after 6th and 7th (p<0.01) management in unstressed controls and mirtazapine after 5th, 6th, 7th (p<0.0) in unstressed and 6th (p<0.05) and 7th (p<0.01) treatment in stressed rats exhibited greater struggling from their first drug administration individually. Agmatine significantly produced antidepressant like activity after 4th (p<0.01) and mirtazapine after 5th (p<0.05) and 6th, 7th (p<0.01) administration in stressed rats.

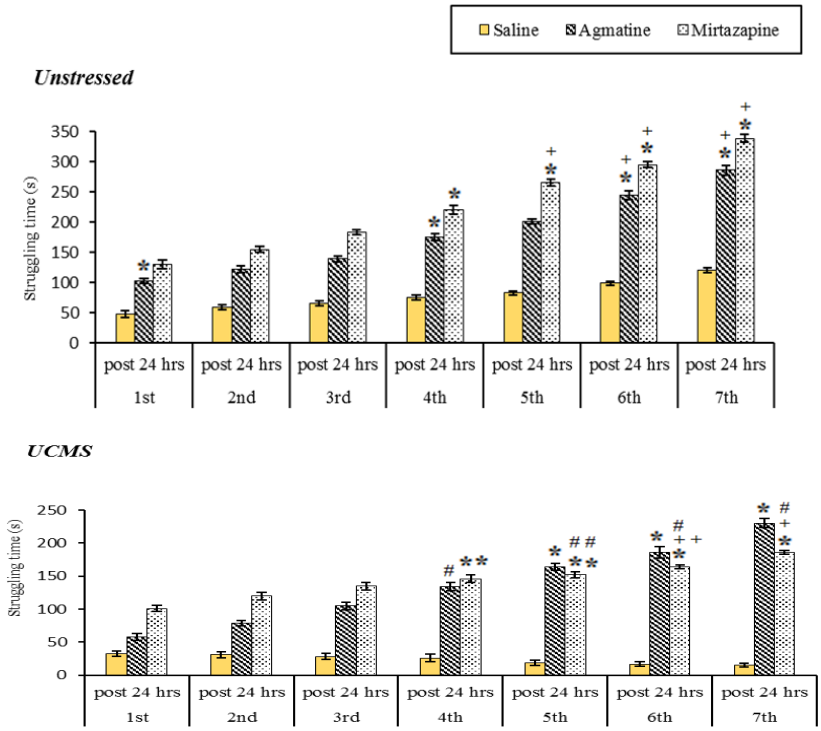


Fig. 4: Antidepressant responses of Agmatine and Mirtazapine in Forced swim Test (struggling time)

Values are means + SD (n=6) as administered post 24 hours of drug administration. Significant differences by Newman-Keul's test: groups that differ significantly from respective saline treated controls *p<0.01, **p<0.05; similar drug treated groups that significantly differ from 1st administration +p<0.01, ++p<0.05;

#p<0.01, ##p<0.05 from similarly administered drug of unstressed to stressed group on same day following three way ANOVA (repeated measure design).

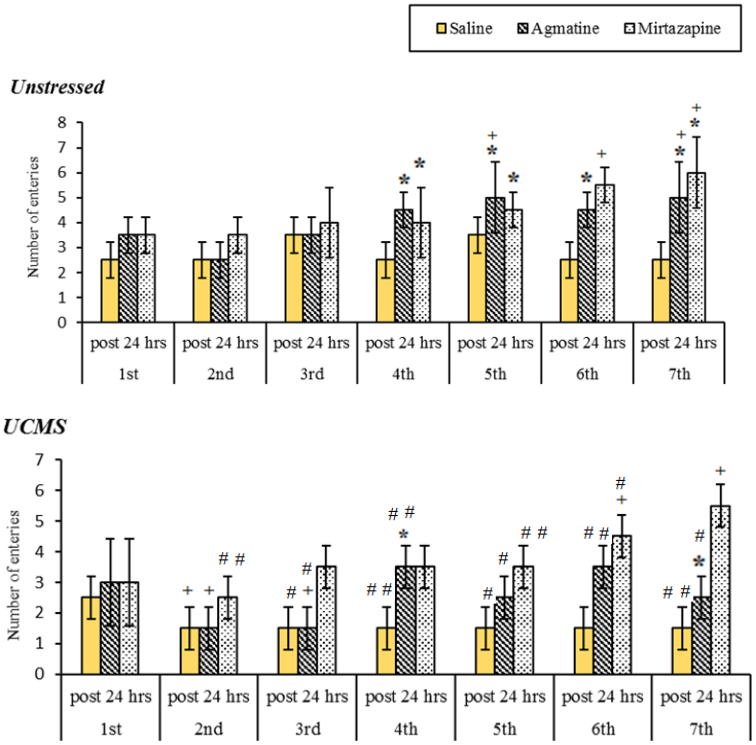


Fig. 5: Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Elevated Plus Maze (Entries in open arms)

Values are means + SD (n=6) as administered post 24 hours of drug administration. Significant differences by Newman-Keul's test: *groups that differ significantly from respective saline treated controls <p 0.01; + similar drug treated groups that significantly differ from 1st administration p<0.01;

#p<0.01, ##p<0.05 from similarly administered drug of unstressed to stressed group on same day following three way ANOVA (repeated measure design).

Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Elevated Plus Maze (Entries in open arms)

Fig. 6 explained the frequency of entries of unstressed and stressed rats exposed to agmatine and mirtazapine in elevated plus maze. Results given by both the drugs and controls were assessed by III way ANOVA (repeated measure designs) that determined the significant effects of days (F (6, 33) = 4.743 p<0.05), drugs (F (1, 33) = 415.677 p<0.05), stress (F (1, 33) = 226.388 p<0.10) and the interaction between days, drugs and stress (F (6, 33) = 15.806 p<0.01). Newman keul's post hoc analysis described the significant effects of agmatine in unstressed after 4th, 5th, 6th, and 7th (p<0.01) and after 4th and 7th (p<0.01) drug administration in stressed group while mirtazapine a day after 4th, 5th, 7th (p<0.01) treatment improved entries occurrence in open arms of unstressed rats in contrast of their saline controls. Stress decreased arrival of saline controls significantly in open arms post 24 hours of 2nd (p<0.01) administration whereas, agmatine increased entries after 5th and 7th (p<0.01) treatment in unstressed and decreased after 2nd and 3rd (p<0.01) administration on the other hand mirtazapine effected arrival of rats in open arms after 6th and 7th (p<0.01) in both unstressed and stressed groups from first administration of all drugs separately. Stressed controls entered less in open arms after 3rd, 5th (p<0.01) and 4th, 7th (p<0.05) treatment while stressed rats treated with agmatine entered less after 3rd, 5th, 7th (p<0.01) and 4th and 6th (p<0.05) administration. Additionally, after 2nd and 5th (p<0.05) and 6th (p<0.01) treatment of mirtazapine, stress exposed rats entered significantly less in open arms in contrast to their unstressed rats.

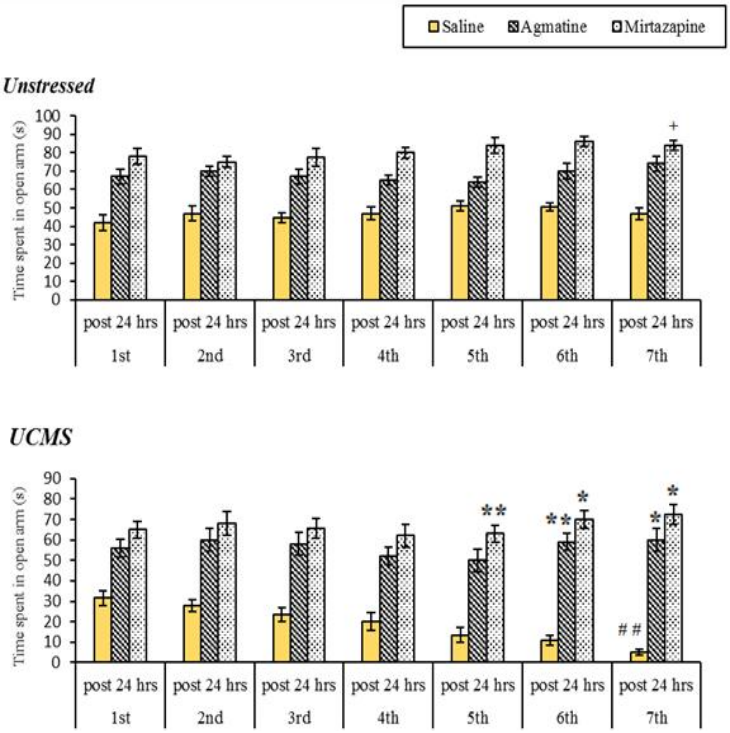


Fig. 6: Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Elevated Plus Maze (Time spent in open arms)

Values are means + SD (n=6) as administered post 24 hours of drug administration. Significant differences by Newman-Keul's test: groups that differ significantly from respective saline treated controls *p<0.01, **p<0.05; + similar drug treated groups that significantly differ from 1st administration p<0.01;

#p<0.01, ##p<0.05 from similarly administered drug of unstressed to stressed group on same day following three way ANOVA (repeated measure design).

Anxiolytic and Antidepressant Responses of Agmatine and Mirtazapine in Elevated Plus Maze (Time spent in open arms)

Time spent in open arms of elevated plus maze resulted by repeated administration of agmatine and mirtazapine in unstressed and unstressed groups of rats are explained in figure 04. All the data obtained was analyzed by III way ANOVA (repeated measure design) that demonstrated the effects of days ($F(6, 33) = 14.054$ $p<0.01$), drugs ($F(1, 33) = 96.164$ $p<0.1$), and interaction of days, drugs and stress to be significant while non-significant effects of stress ($F(1, 33) = 23.111$) were observed. Newman Keul's test post-hoc analysis explained that agmatine increased the duration spent in open arms of EPM after 6^{th} ($p<0.05$) and 7^{th} ($p<0.01$) administration and mirtazapine after 5^{th} ($p<0.05$) and 6^{th}, 7^{th} ($p<0.01$) treatment significantly in stressed rats when both groups of drugs compared from saline controls. Mirtazapine improved duration spent in open arms on 7^{th} ($p<0.01$) administration from first treatment of mirtazapine dose in unstressed rats. Furthermore, Stress decreased time spent in open arms in saline controls after 7^{th} ($p<0.05$) day significantly.

Discussion

The present study was designed to determine the antidepressant and anxiolytic activity of agmatine particularly at the selected dose of 100mg/Kg in chronic unpredictable mild stress induced depressive like behaviors and it's comparison with 30 mg/kg/day mirtazapine administration. Katz and coworkers initially originate the chronic mild stress model (CMS) consisted the etiology of depression (Katz, 1981) (Katz and Sibel, 1982). The classic model involves various mild stresses repetitive experiences during a specific time period that results it in extensive conventional model of depression (Krishnan and Nestler, 2011). Various studies support and recommend CUMS model of depression that it causes alternation in biochemical and behavioral aspects of animals and produces symptoms resemble to clinical depression (Luo et al., 2008).The behavioral paradigms used and results obtained in this particular study expressed the anhedonic, anxiogenic and depressive consequences produced by chronic mild stress. The protocol

was consisted of paired stressors in which one is physical stress accompanied with a psychological mild distress. The protocol was designed in order to recognize the unrevealed impacts of dual stresses on rats and attenuation by agmatine administration.

Light/dark test paradigm is established on the natural behaviors of mice that include aversion of intensely lightened area and exploration in novel environment (Crawley, 1985). The selected two perimeters for light/dark transition tests were frequency of entries and spent time by the animal in lit box during 5 minutes testing session. The results revealed that 4 weeks administration of both agmatine (neuromodulator/neurotransmitter) and mirtazapine (noradrenergic and specific serotonergic antidepressant (NaSSA) produced anxiolytic and antidepressants effects in contrast to saline controls presented in figure 01 and 02. Saline treated rats which were exposed to stress displayed significant reduction in entries and time spent in open arms. Stress leads to anxiety and depression which assessed in light/dark paradigm in rodents. Light/dark transition test extensively used to determine anxiety in animals (Crawley, 2000). Agmatine produces anxiolytic and antidepressant effects in stressed exposed rats when compared to saline controls. After 28th administration, agmatine significantly increased arrival and duration that rats spent in light box in unstressed groups whereas CMS caused anxiogenic and depressive like behaviors that was improved by agmatine is illustrated in present study. Mirtazapine is a well-known antidepressant and was used to reduce depressive like behaviors in rodents in this experimental evaluation. When administered to unstressed and stressed rats, mirtazapine enhanced rat's activity in light/dark transition test. Post 24 hours of 28th day of mirtazapine administration, undressed rats increased time spent and entries significantly whereas, stressed exposure affected both entries and time spent in light box. Mirtazapine improved activity compared to saline and agmatine treated rats. The light/dark test conventionally used to assess behaviors in animals treated with antidepressant and anxiolytic drug (Crawley, 1985).

Chronic mild stress exposed control group displayed decrease in mobility determined the depressive performance in forced swim test apparatus. Studies suggested that rats exposed to chronic mild stress displayed increased immobility and despair in forced swim test (Dalla et al., 2005) (Kompagne et al., 2008). Present study demonstrated the decrease in mobility and struggling as the consequence of CMS in saline controls whereas the rats which were remained unstressed persisted the struggling duration when forced to swim in water at room temperature. Agmatine efficiently increased the struggling ability in unstressed rats comparatively to saline controls whereas, CMS induced despair and melancholy worsen the mobility in rats that was improved by administration of agmatine significantly in four weeks duration. Mirtazapine on the other hand initiated greater mobility time and lessen the despair in unstressed and stressed exposed rats when compared to saline controls. Forced swim test is a paradigm used to evaluate the proficiency and effectiveness of antidepressants and validate the effects of several behavioral and psychological influences in preclinical research (Petit-Demouliere et al., 2005) (Porsolt et al., 1978, Mineur et al., 2006, Millstein et al., 2007). The test is known to interpret a condition in which despair behavior is induced in animal caused hopelessness (Porsolt et al., 1977).

Elevated plus maze is extensively used as a validity model for anxiolytic drugs screening (Rodgers and Dalvi, 1997, Mechiel Korte and De Boer, 2003, Crawley, 2007). The perimeters which are entries in open arms and time spent are assessed in which anxiolytic drugs increase and anxiogenic drugs decreased the activity in elevated plus maze test. Total score is the index of major anxiety in animals evaluated in EPM paradigm (Rodgers and Dalvi, 1997, Mechiel Korte and De Boer, 2003).

The particular study conducted to reveal the effects and impacts of CMS that produce depressive and anxiogenic behaviors in rats. Both stressed and unstressed groups of saline controls were assessed in elevated plus maze apparatus and obtained results determined the less entries and minimal time spent of stressed group of rats in open arms whereas, rats which were kept at normal environmental conditions and administered with saline only illustrated consistent activity in EPM paradigm. Agmatine on the other hand improved the frequency of entrance and time spent of rats that were not exposed to stress. Figure 05 and 06 explained the anxiogenic and anxiolytic efficacy of agmatine in animals acquainted with chronic unpredictable stresses. Stress that leads to anxiety and depression effected the activity in stressed group of rats when compared to saline stressed controls however simultaneous treatment with agmatine moderated the effects of stress and improved the performance of stressed rats. Furthermore investigations with mirtazapine revealed the anxiolytic effects of particular antidepressant of (NaSSA) group which shown the maximum

number of entries and time period spent of unstressed and stressed exposed rats in open arms during 5 minutes test session. CMS influenced animals demonstrated the improved arrivals and consumed time in open arms as a result of the administration of both agmatine and mirtazapine at particular dose of (100 mg/kg) and (30 mg/Kg) respectively.

Conclusion

In conclusion, repetitive administration of agmatine attenuated the distress caused by chronic mild stress paradigm however this effect was developed after chronic treatment compared to conventional antidepressant management such as mirtazapine. Moreover, Agmatine and Mirtazapine are comparable to each other and further evaluation should be carried out before our results and outcomes become an approximate to depression therapy.

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