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Agmatine's Antidepressant-like Effect in Mice: Possible Contribution of N-Methyl-D-Aspartate (NMDA) Receptors and L-Arginine-Nitric Oxide Pathway

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Abstract. In a mammalian brain, agmatine is an endogenous neurotransmitter and/or neuromodulator which is considered an endogenous ligand for α_2-adrenergic and imidazoline receptors. It blocks N-methyl-D-aspartate subtype of glutamate receptors and inhibits all isoforms of nitric oxide synthases. Both, N-methyl-D-aspartate receptors and nitric oxide system have been implicated in the regulation of various behavioral, cognitive and emotional processes *e.g.* learning, aggression, locomotion, anxiety and depression. This study aimed at investigating the antidepressant-like effect of agmatine and the possible participation of N-methyl-D-aspartate receptors and L-arginine-nitric oxide pathway in this effect. Agmatine (1, 10, 50 mg/kg, i.p.) possessed an antidepressant-like effect in two experimental models of depression; the forced swimming test and the tail suspension test in mice. Agmatine significantly enhanced the anti-immobility effect of imipramine, but did not affect that of ketamine (noncompetitive N-methyl-D-aspartate antagonist). The anti-immobility effect of agmatine assessed in the forced swimming test was completely prevented by pretreatment of mice with ascorbic acid (neuromodulator that antagonizes N-methyl-D-aspartate) or L-arginine (nitric oxide precursor). Agmatine elicited a significant antidepressant-like effect through an interaction with N-methyl-D-aspartate receptors and L-arginine-nitric oxide pathway. A possible synergism between imipramine and agmatine has been detected which may be useful clinically.

Keywords: Agmatine, N-methyl-D-aspartate receptors, L-arginine-nitric oxide pathway, Imipramine.

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Introduction

In mammalian brain, agmatine fulfills the criteria to be established as an endogenous neurotransmitter and/or neuromodulator[1]. It is an amine that is synthesized in the brain (by decarboxylation of L-arginine by arginine decarboxylase), stored in synaptic vesicles in a large number of neurons with selective distribution in the central nervous system (CNS). Agmatine is accumulated by uptake, released by depolarization, and inactivated by selective re-uptake or enzymatically degraded by agmatinase[2]. Agmatine has high affinity to α_2-adrenergic and imidazoline receptors. In addition, agmatine blocks the ligand-gated N-methyl-D-aspartate (NMDA) receptor channel and inhibits all isoforms of nitric oxide synthase[3].

The N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor, is a ligand-gated ion channel complex formed by different subunits[4]. This receptor contains distinct sites for endogenous and exogenous ligands, such as glutamate, glycine, Mg^{2+}, Zn^{2+}, polyamines and channel blockers such as MK801[5]. The NMDA receptors are thought to be involved in the processes such as memory and learning, neuronal plasticity, epileptogenesis, and some forms of acute and chronic neuropathologies[6].

The NMDA receptor complex gates Ca^{2+} entry into neurons, which can interact with calmodulin to subsequently activate nitric oxide synthase (NOS). Nitric oxide synthase catalyzes the conversion of L-arginine to L-citrulline with subsequent release of nitric oxide (NO). Nitric oxide synthase exists in two major forms: Constitutive, which is constitutively expressed in various cells, including neurons and inducible that is expressed only after gene induction. The constitutive form of NOS becomes activated in the presence of calmodulin and increases intracellular Ca^{2+}[7].

Previous studies have reported that NMDA receptor antagonists exhibit antidepressant-like activity in experimental models of depression. They reduce the duration of immobility in forced swim test (FST) and tail suspension tests (TST)[8,9] with efficacies comparable to clinically effective antidepressants[10]. Likewise, several studies have demonstrated that antagonists of voltage operated Ca^{2+} channel produce antidepressant-like effects in forced swim test[11].

It has become generally accepted that nitric oxide (NO) serves as an important neurotransmitter in the nervous system[12]. Nitric oxide (NO) has been suggested to have multiple targets, among which is the soluble guanylate cyclase (sGC), and converts guanosine 5'-triphosphate (GTP) to the important intracellular messenger cyclic guanosine 3',5'-monophosphate[13]. However, some physiological effects of NO are independent of the activation of sGC. It has recently been demonstrated that NO, induced by NMDA receptor stimulation, activates the p21 (ras) pathway of signal transduction with a cascade involving extracellular signal-regulated kinases and phosphoinositide 3-kinase[14]. These pathways are known to be involved in the transmission of signals to the cell nuclei, and may therefore, form a basis of a generation of long-lasting neuronal responses to NO. Other enzymes that constitute cellular targets for NO are cyclooxygenases, ribonucleotide reductase, some mitochondrial enzymes, and NOS itself[15]. Additionally, NO can nitrosylate proteins and damage the DNA[16]. Several *in-vivo* studies have demonstrated that NO modulates the extracellular levels of various neurotransmitters in the central nervous system, *e.g*. serotonin (5-HT), dopamine (DA), γ-aminobutyric acid (GABA), and glutamate[17].

Nitric oxide (NO) has been implicated in the regulation of various behavioral, cognitive and emotional processes, *e.g*.: learning, aggression, locomotion, anxiety and depression[18]. Interestingly, depressed patients have increased plasma levels of nitrate, the end-product of (NO) metabolism[19].

In the light of these studies, the present work was designed to investigate whether agmatine produces antidepressant-like action in the forced swimming test and tail suspension tests in mice compared to that of the classical antidepressant imipramine. This work also investigated the participation of NMDA receptors and the L-arginine-nitric oxide pathway in the antidepressant-like action of agmatine.

Materials and Methods

Materials

A. Test Drugs

The drugs used were: Agmatine sulphate, L-arginine hydrochloride, and imipramine hydrochloride powders (Sigma-Aldrich Co. LLC, St.

Louis, MO U.S.A.), ascorbic acid (Vitamin C) crystal extra pure (Merck KGaA, Darmstadt, Germany), Ketamine vial 50 mg/ml (Amoun Pharmaceuticals Co., Cairo, Egypt).

Agmatine, L-arginine, Imipramine, and ascorbic acid were dissolved separately in saline and administered i.p. 30 min before the test in a volume of 10 ml/kg body weight. All drugs were freshly prepared. Doses of drugs were chosen according to the previous studies [2,24].

B. Animals

Adult albino male mice, weighing 30 ± 5 g, were kept (6 per cage) in an animal house at 22–27°C with free access to tap water and chow pellets, under a 12 h light/dark cycle (lights on at 7 a.m.) for one week before the experiment. All manipulations were carried out between 9:00 and 16:00 h, with each animal used only once. The use of animals was according to the ethical requirements that were approved by the Animals Research Ethic Committee of KAU.

C. Experimental Design

In the experiments that investigated the effects of agmatine, ketamine and imipramine, alone or in combination, on the immobility time in the FST, drugs were injected 30 min before the test.

In a separate series of experiments, to investigate the possible participation of the L-arginine–NO pathway in the anti-immobility effects of agmatine, mice were pretreated with L-arginine, a precursor of NO (750 mg/kg, i.p., a dose that produced no effect in the FST), and after 30 min they received agmatine (10 mg/kg, i.p.). Controls received saline before being tested in the FST 30 min later[8,9].

To assess the possible contribution of ascorbic acid to the action of agmatine, animals were pretreated with ascorbic acid (100 mg/kg, i.p., a dose that produced no effect in the FST) or with saline and, 30 min later, they received agmatine (10 mg/kg, i.p.) before being tested in the FST after 30 min.

The number of animals in each group was 6.

Methods

A. Experimental Procedures

1. Forced swimming test (FST): Mice were individually forced to swim in an open glass cylinder (diameter 10 cm, height 25 cm),

containing water at the height of 19 cm and at 25 ± 1°C. Each animal made vigorous attempts to get out of the glass cylinder during the first two minutes, and thereafter, surrendered to experimental conditions and became immobile with occasional escape attempts. A mouse was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water. The duration of immobility was scored during the last 4 min of the 6-min test period. The depression index is immobility time (in seconds), thus the antidepressive treatment reduces the immobility time. The water was changed after each animal to avoid olfactory cues left by the previous animal[8].

2. Tail suspension test (TST): The total duration of immobility induced by tail suspension was measured according to the method of Steru *et al.*[9]. Mice were transported to the testing room and left there undisturbed for at least 3 h. Thirty minutes after injection, mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Typically, mice demonstrated several escape-oriented behaviors interspersed with temporally increasing bouts of immobility. Mice were considered immobile only when they hung passively and completely motionless. Immobility time was recorded during a 6 min test.

Both, the FST and the TST are accepted as stress models of depression widely used to conduct biological screening of new antidepressant drugs. These tests are quite sensitive and relatively specific for all major classes of antidepressant drugs including tricyclics, serotonin-specific reuptake inhibitors, monoamine oxidase inhibitors, and atypicals[8,9]. In the FST, the immobile behavior is believed to reflect a state of despair or failure to adapt to stress, which is claimed to reproduce a condition similar to human depression[20]. Antidepressant drugs are reported to reduce the immobility time of mice in both tests[8,9]. Correlations are observed between results in these tests and clinical potency, which is not found in any other model[21].

B. Statistical Analysis

Data were analyzed by Statistical Package for Social Sciences (SPSS 11.0) software for Windows (Chicago, IL). Results are presented as the mean ± SD (Standard Deviation). To compare differences between groups, one-way analysis of variance (ANOVA) followed by corrections

for multiple comparisons using the Tukey post-hoc test. For all analyses, p values less than 0.05 were considered statistically significant.

Results

1. Antidepressant-like Effect of Agmatine in Both FST and TST

Agmatine (1, 10, or 50 mg/kg, i.p.) significantly ($p < 0.0001$) decreased the duration of immobility in both the FST by 7.6, 21.6 and 15.5%, respectively, and in the TST ($p < 0.0001$) by 29, 17.9 and 12%, respectively (Fig. 1a, b) in comparison to the control group. The efficacy of agmatine (10 mg/kg, i.p.) in the FST and in the TST (1 mg/kg, i.p.) was comparable to that of the tricyclic antidepressant Imipramine at 15 mg/kg, i.p. ($p = 0.732$ and $= 0.979$, respectively) (Fig. 1a, b).

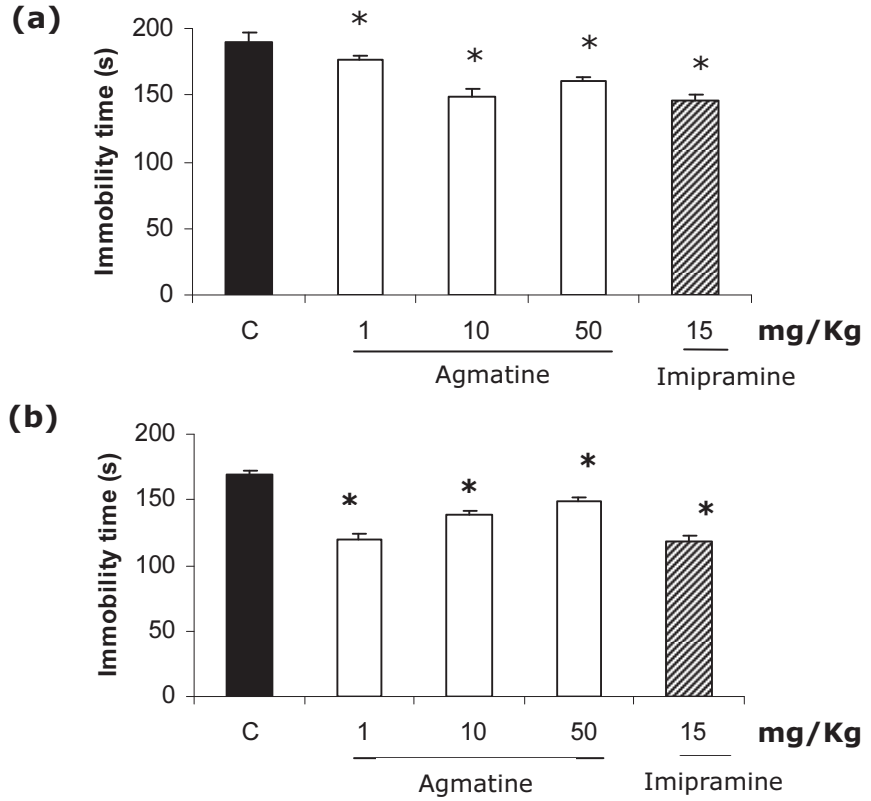

Fig. 1. Effects of acute administration of Agmatine (1, 10, or 50 mg/kg i.p.) and Imipramine (15 mg/kg i.p.) on forced swimming test (a) and tail suspension test (b) in mice. Agmatine and Imipramine were administered 30 min before the test. Values were expressed as mean ± SD (n = 6). *p < 0.0001 *vs.* saline-treated control (C).

2. The Effect of L-Arginine and Ascorbic Acid in FST

Pretreatment of mice with L-arginine (750 mg/kg, i.p., a nitric oxide precursor) and ascorbic acid (100 mg/kg, i.p., a putative neuromodulator that antagonizes NMDA) significantly ($p < 0.0001$) decreased the effect of agmatine (10 mg/kg, i.p.) on the duration of immobility in the FST. Both, L-arginine and ascorbic acid given alone with the same previous dose were without effect in this test (Fig. 2a, b).

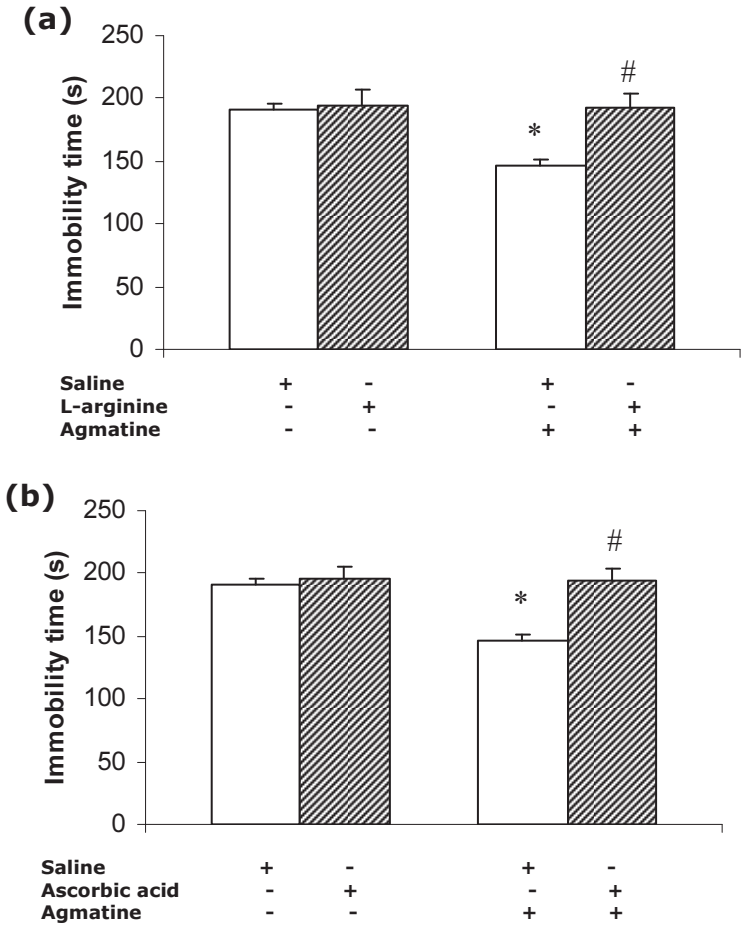

Fig. 2. Effect of pretreatment of mice with L-arginine (750 mg/kg,i.p., A) or ascorbic acid (100 mg/kg, i.p., B) on the agmatine (10 mg/kg, i.p.)-induced reduction in immobility time in the FST. Values were expressed as mean ± SD (n = 6).
***p < 0.0001 for saline-treated control *vs.* agmatine.**
#p < 0.0001 for the agmatine group *vs.* agmatine plus L-arginine or ascorbic acid.

3. The Effects of Agmatine, Ketamine and Imipramine Alone or in Combination on Immobility Time In FST

Table 1 shows that Imipramine (15 mg/kg, i.p.), and the noncompetitive NMDA antagonist ketamine, at a low dose (0.01 mg/kg, i.p.), significantly shortened the immobility time in the FST, similar to agmatine (10 mg/kg, i.p.). The immobility time of mice treated with ketamine plus agmatine was not significantly different from the immobility time of mice treated with ketamine ($p = 0.428$) or agmatine ($p = 0.061$) alone. On the other hand, combined treatment with agmatine plus Imipramine, as well as ketamine plus Imipramine, induced a stronger effect ($p < 0.0001$) in the FST than the administration of either drug alone (Fig. 3).

Table 1. Effect of agmatine (10 mg/kg, i.p.), ketamine (0.01 mg/kg, i.p.) and Imipramine (15 mg/kg, i.p.) alone or in combination on immobility time in FST in mice.

Treatment	Dose (mg/kg, i.p.)	Immobility time (seconds)/4 min
Saline	-/-	190.5 ± 6.0
Agmatine	10/-	149.3 ± 5.1*
Imipramine	15/-	146.2 ± 4.7*
Ketamine	0.01/-	152.8 ± 4.4*
Agmatine + Ketamine	10/0.01	159.7 ± 7.8*,a
Imipramine + Ketamine	15/0.01	118.8 ± 5.6*,b
Agmatine + Imipramine	10/15	109.2 ± 7.0*,c

Drugs were injected 30 min before the test. Values were expressed as mean ± SD (n = 6).
*$p < 0.0001$ *vs.* the saline-treated control; [a]$p < 0.006$ *vs.* Imipramine, and $p < 0.0001$ *vs.* Imipramine+ketamine and agmatine+Imipramine groups; [b]$p < 0.0001$ *vs.* the ketamine and imipramine groups, [c]$p < 0.0001$ *vs.* the Imipramine and agmatine group.

Discussion

The results presented here showed that agmatine given systemically (i.p.) is effective in producing significant antidepressant-like effects comparable to those of the classical antidepressant drug Imipramine, when assessed in the FST, a model of depression in mice. The antidepressant-like action of agmatine administered i.p. was confirmed by a second model, the TST.

A role for agmatine as a modulator of depression has already been suggested from clinical studies, as plasma agmatine concentration was significantly elevated in depressed patients compared with healthy controls and normalized with antidepressants treatment[22].

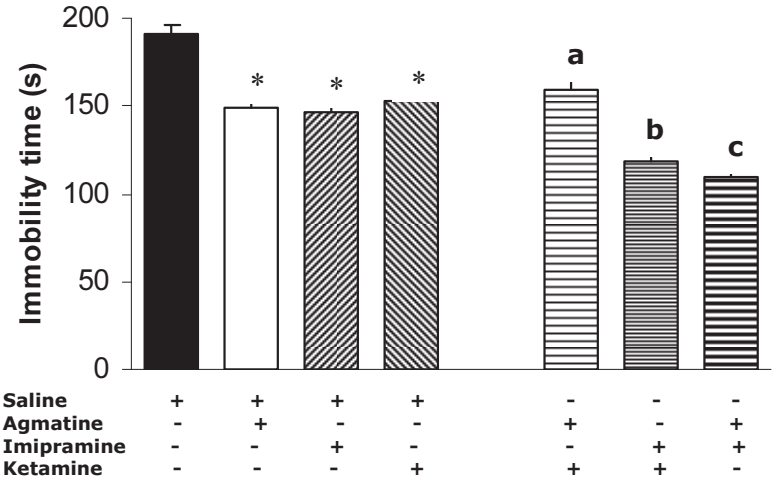

Fig. 3. Effect of agmatine (10 mg/kg, i.p.), Imipramine (15 mg/kg, i.p.) or ketamine (0.01 mg/kg, i.p.) alone or in combination on immobility time in the FST in mice. Values were expressed as mean ± SD (n = 6). *p < 0.0001 *vs.* saline-treated control group; [a]non-significant *vs.* agmatine or ketamine groups; [b]p < 0.0001 *vs.* the ketamine and Imipramine groups; [c]*p* < 0.0001 *vs.* the Imipramine and agmatine groups.

The involvement of NMDA receptors in the anti-immobility effect of agmatine can be shown in the results of the present work where pretreatment of mice with ascorbic acid 100 mg/kg, i.p.; a dose that produced no effect by itself in the FST[24] significantly prevented the antidepressant-like effect of agmatine in the same test. Ascorbic acid is thought to act as a neuromodulator in the brain, where it may alter the redox state of the NMDA receptor and thus, blocks its function[25]. Similarly and in accordance with the results of this work, Zomkowski *et al.*[2] demonstrated that pretreatment of mice with guanosine monophosphate (GMP) completely blocked the agmatine antidepressant-like effect. Guanosine monophosphate (GMP) is an endogenous nucleotide known to be present at a high concentration in the CNS where it has been postulated to decrease NMDA receptor activation[26] and, thus, prevented agmatine binding to NMDA receptors. In the latter study, they used also i.c.v. injection of agmatine (1-100 nmol/site) in the FST. Recently, Eckeli *et al.*[27] demonstrated that acute treatments with GMP, produce a dose-dependent antidepressant-like effect which is probably through inhibition of the NMDA receptors.

Agmatine and imidazoline drugs have been shown to exert *in vitro* modulatory effects on NMDA receptors. This was achieved by their ability to inhibit the binding of dizocilpine ((MK-801); non-competitive NMDA receptor antagonist) in rat cerebral cortex and to be neuroprotective against NMDA-induced cell death[28]. Agmatine applied extracellularly to cultured hippocampal neurons produced a voltage and concentration-dependent block of NMDA currents, by interacting with a site located within the NMDA channel pore[29].

Data of the present work showed the absence of synergistic or additive effects on immobility between ketamine and agmatine reinforce the assumption that agmatine exerts its antidepressant-like effect by blocking NMDA receptor, that may be explained by preventing ketamine binding to NMDA receptors. The results also showed an additive effect for agmatine (or ketamine) and Imipramine in reducing of immobility in the FST. Similarly, findings were previously reported by Eckeli *et al.*[27] with GMP (or MK-801) plus Imipramine. Therefore, agmatine seems to exert its effect in the FST through a similar mechanism to MK-801 and GMP. All these compounds have the same property of acting as neuroprotective agents under excitotoxic conditions[28]. Considering that the major depressive disorders have recently been linked to the impairments in signaling pathways that regulate neuroplasticity and cell survival[30]. The neuroprotective role of these agents might be of pharmacological significance for the modulation of depression.

NMDA receptor antagonists have been proposed as potential antidepressants. It is important to note that even conventional antidepressants that act through the monoaminergic system seem to ultimately affect NMDA receptors, leading to the same functional effects as NMDA antagonists[10]. Li *et al.*[1] found that a high concentration of NMDA induced a decrease of norepinephrine, 5-HT, epinephrine and dopamine in pheochromocytoma (PC12) cells, which was consistent with the changes in the brain of patients with depression. Agmatine or desipramine reversed these changes (at least partially), which also supported the antidepressant-like effect of agmatine.

It is well known that $[Ca^{2+}]_i$ overloading may mediate the NMDA-induced lesion in neurons. Norepinephrine, 5-HT or dopamine also exert a cytoprotective effect and attenuate the $[Ca^{2+}]_i$ overloading induced by NMDA or corticosterone. Similar effects of desipramine or agmatine

were reported, this may suggest that monoamine action may involve the down regulation of NMDA receptor activity caused by agmatine or antidepressants. The monoamines and NMDA receptor are two closely related systems; their interaction probably underlies the antidepressant-like effect of agmatine. Another possibility is that the NMDA blocked by agmatine may cause an increase of monoamine contents in PC12 cells and monoamines, subsequently cascade the cytoprotective effect of agmatine[1].

An involvement of the L-arginine–NO pathway in the modulation of depression has been suggested as NOS inhibitors produce dose-dependent antidepressant-like effects in animal models of depression[31]. Results of the present work showed that pretreatment of mice with L-arginine[31], significantly inhibited the anti-immobility effect of agmatine which may lead to the suggestion that the antidepressant-like effect of agmatine could be due to the inhibition of NOS. There is a general consensus about the fact that the downstream activation of neuronal nitric oxide synthase (nNOS) consequent to stimulation of the NMDA receptor is linked to the calcium influx through the receptor channel[32]. Moreover, agmatine can enter postsynaptic neurons *via* nicotinic and, possibly, NMDA receptor channels to competitively inhibit NOS activity[33].

It could be concluded that the endogenous agmatine, proposed to be a novel neurotransmitter/ neuromodulator in the CNS, produces antidepressant-like effects. These findings also indicate that the antidepressant-like effect of agmatine is dependent on the blockade of NMDA receptors and on inhibition of NOS. In addition, the results also indicate a possible synergism between tricyclic antidepressants and agmatine which might be a useful supplement antidepressant therapy with Imipramine.

References

[1] **Li YF, Gong ZH, Cao JB, Wang HL, Luo ZP, Li J.** Antidepressant-like effect of agmatine and its possible mechanism. *Eur J Pharmacol* 2003; **469**(1-3): 81-88.

[2] **Zomkowski ADE, Hammes L, Lin J, Calixto JB, Santos AR, Rodrigues AL.** Agmatine produces antidepressant-like effects in two models of depression in mice. *NeuroReport* 2002; **13**(4): 387-391.

[3] **Raasch W, Schäfer U, Chun J, Dominiak P.** Biological significance of agmatine, an endogenous ligand at imidazoline binding sites. *Br J Pharmacol* 2001; **133**(6): 755-780.

[4] **Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Burnashev N, Sakmann B, Seeburg PH.** Heteromeric NMDA receptors: molecular and functional distinction of subtypes. *Science* 1992; **256**(5060): 1217-1221.

[5] **Watkins JC, Krogsgaard-Larsen P, Honroe T.** Structure-activity relationship in the development of excitatory amino acid receptor agonist and competitive antagonists. *Trends Pharmacol Sci* 1990; **11**(1): 25-33.

[6] **Choi DW.** Glutamate neurotoxicity and the diseases of the nervous system. *Neuron* 1988; **1**(8):623-634.

[7] **Harkin AJ, Bruce KH, Craft B, Paul IA.** Nitric oxide synthase inhibitors have antidepressant-like properties in mice. 1. Acute treatments are active in the forced swim test. *Eur J Pharmacol* 1999; **372**(3): 207-213.

[8] **Porsolt RD, Bertin A, Jalfre M.** Behavioral despair in mice: A primary screening test for antidepressants. *Arch Int Pharmacodyn* 1977; **229**(2): 327-336.

[9] **Steru L, Chermat R, Thierry B, Simon P.** The tail suspension test: a new method for screening antidepressant drugs. *Psychopharmacology* 1985; **85**(3): 367–370.

[10] **Skolnick P.** Antidepressants for the new millennium. *Eur J Pharmacol* 1999, **375**(1-3): 31-40.

[11] **Czyrak, A.** The effect of chronic nifedipine and ECS in the forced swimming test in rats. *Pol J Pharmacol* 1993; **45**(2): 191–195.

[12] **Baranano DE, Ferris CD, Snyder SH.** A typical neural messengers. *Trends Neurosci* 2001; **24**(2): 99-106.

[13] **Denninger JW, Marletta MA.** Guanylate cyclase and the NO/cGMP signaling pathway. *Biochim Biophys Acta* 1999; **1411**(2-3): 334-350.

[14] **Yun HY, Gonzalez-Zulueta M, Dawson VL, Dawson TM.** Nitric oxide mediates N-methyl-D-aspartate receptor-induced activation of p21ras. *Proc Natl Acad Sci USA* 1998; **95**(10): 5773-5778.

[15] **Garthwaite J, Boulton CL**. Nitric oxide signaling in the central nervous system. *Ann Rev Physiol* 1995, **57**: 683-706.

[16] **Stamler JS**. Redox signaling: nitrosylation and related target interactions of nitric oxide. *Cell* 1994; **78**(6): 931-936.

[17] **Heiberg IL, Wegener G, Rosenberg R.** Reduction of cGMP and nitric oxide has antidepressant-like effects in the forced swimming test in rats. *Behav Brain Res* 2002; **134**(1): 479-484.

[18] **Volke V, Wegener G, Bourin, M, Vasar E.** Antidepressant- and anxiolytic-like effects of selective neuronal NOS inhibitor 1-(2-trifluoromethylphenyl)-imidazole in mice. *Behav Brain Res* 2003; **140**(1-2): 141-147.

[19] **Suzuki E, Yagi G, Nakaki T, Kanba S, Asai M.** Elevated plasma nitrate levels in depressive states. *J Affect Disord* 2001; **63**(1-3): 221-224.

[20] **Willner P.** Animal models as simulation of depression. *Trends Pharmacol Sci* 1991; **12**(4): 131–136.

[21] **Willner P.** The validity of animal models of depression. *Psychopharmacology* 1984; **83**(1): 1-16.

[22] **Halaris A, Zhu H, Feng Y, Piletz JE.** Plasma agmatine and platelet imidazoline receptors in depression. *Ann N Y Acad Sci* 1999; **881**(1): 445-451.

[23] **Yildiz F, Erden BF, Ulak G, Utkan T, Gacar N.** Antidepressant like effect of 7-nitroindazole in the forced swimming test in rats, *Psychopharmacology* 2000; **149**(1): 41–44.

[24] **Mantovani M, Pertile R, Calixtob JB, Santos AR, Rodrigues AL.** Melatonin exerts an antidepressant-like effect in the tail suspension test in mice: evidence for involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide pathway. *Neuroscience Letters* 2003; **343**(1): 1-4.

[25] **Gozlan H, Ben-Ari Y.** NMDA receptor redox sites: are they targets for selective neuronal protection? *Trends Pharmacol Sci* 1995; **16**(11): 368–374.

[26] **Schmidt AP, Lara DR, Maraschin JD, Perla AS, Souza DO.** Guanosine and GMP prevents seizures induced by quinolinic acid in mice. *Brain Res* 2000; **864**(1): 40–43.

[27] **Eckeli AL, Dach F, Rodrigues ALS.** Acute treatments with GMP produce antidepressant-like effects in mice. *Neuro Report* 2000; **11**(9): 839–843.

[28] **Olmos G, DeGregorio-Rocasolano N, Regalado MP, Gasull T, Boronat MA, Trullas R, Villarroel A, Lerma J, García-Sevilla JA.** Protection by imidazol(ine) drugs and agmatine of glutamate-induced neurotoxicity in cultured cerebellar granule cells through blockade of NMDA receptor. *Br J Pharmacol* 1999; **127**(6): 1317–1326.

[29] **Yang XC, Reis DJ.** Agmatine selectively blocks the N-methyl-D-aspartate subclass of glutamate receptor channels in rat hippocampal neurons. *J Pharmacol Exp Ther* 1999; **288**(2): 544–549.

[30] **Manji HK, Drevets WC, Charney DS.** The cellular neurobiology of depression. *Nature Med* 2001; **7**(5): 541–547.

[31] **Da Silva GD, Matteussi AS, dos Santos AR, Calixto JB, Rodrigues AL.** Evidence for dual effects of nitric oxide in the forced swimming test and in tail suspension test in mice. *Neuro Report* 2000; **11**(17): 3699-3702.

[32] **Contestabile A.** Roles of NMDA receptor activity and nitric oxide production in brain development. *Brain Res Rev* 2000; **32**(2-3): 476-509.

[33] **Reis DJ, Regunathan S.** Is agmatine a novel neurotransmitter in brain? *Trends Pharmacol Sci* 2000; **21**(5): 187-193.

مفعول الأجماتين المضاد للاكتئاب في الفئران (الدور المحتمل لمستقبلات ن–ميثيل د–أسبارتات ومحور لـ–أرجينين–أكسيد النيتريك)

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المستخلص. يعتبر الأجماتين موصلاً عصبيًا و/أو معدلاً عصبيًا داخليًا في مخ الثدييات، فهو يعمل على مستقبلات الألفا ٢ الأدرينالينية ومستقبلات الإميدازولين. كذلك يقوم بإغلاق مستقبلات ن–ميثيل–د–أسبرتات (وهي نوع من مستقبلات جلوتامات) وتثبيط جميع أشكال إنزيم أكسيد النيتريك سينثاز. ويدخل كل من مستقبلات ن–ميثيل–د–أسبرتات وأكسيد النيتريك في تنظيم مختلف العمليات الخاصة بالسلوك والإدراك والعواطف مثل التعلم والسلوك العدواني والحركة والقلق والاكتئاب. ولقد صمم هذا البحث لدراسة مفعول الأجماتين المضاد للاكتئاب ومدى إمكانية مساهمة مستقبلات ن–ميثيل–د–أسبرتات ومحور لـ–أرجينين– أكسيد النيتريك في هذا المفعول. ولقد أكد البحث على امتلاك الأجماتين مفعولاً مضادًا للاكتئاب في اختبار العوم الإجباري واختبار التعليق الذيلي للفئران بجرعات ١، ١٠، ٥٠ مج/كجم بالحقن في التجويف البريتوني، وسبب الأجماتين زيادة ذا دلالة إحصائية في مفعول الإمبرامين المضاد للاكتئاب ولكنه لم يؤثر على مفعول الكيتامين، هذا المفعول المضاد للاكتئاب في اختبار العوم الإجباري في الفئران منع تمامًا

بمعالجة الفئران مسبقًا بحمض الأسقربيك (فيتامين ج) أو لـ-أرجينين. ولقد استنتج من هذا البحث أن للأجماتين مفعولاً مضادًا للاكتئاب في الفئران وميكانيكيته تتم من خلال مستقبلات ن-ميثيل-د-أسبرتات ومحور لـ-أرحينين-أكسيد النيتريك. كما أنه وجد للأجماتين مفعول مدعم للإمبرامين قد يكون مفيدًا حال استخدامه إكلينيكيًا.