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NORADRENERGIC AND NITRIC OXIDE MODULATORS INFLUENCE ANTIDEPRESSANT EFFECTS OF AGOMELATINE IN MICE

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Agomelatine is a synthetic analog of melatonin that is receiving attention as an alternative for the treatment of depression. The current study aimed to evaluate the involvement of the noradrenergic and nitric oxide (NO) pathway in the antidepressant effect of agomelatine. Male Swiss mice (26±3 g) were used. Agomelatine (40 mg/kg), imipramine (10 mg/kg, a tricyclic antidepressant), bupropion (10 mg/kg, dopamine /norepinephrine-reuptake inhibitor), prazosin (1 mg/kg, an α1-adrenoceptor antagonist), yohimbine (1 mg/kg, an α2-adrenoceptor antagonist), and propranolol (2 mg/kg, a β-adrenoceptor antagonist), L-arginine (100 mg/kg, NO precursor), L-NAME (10 mg/kg, NO synthetase inhibitor), methylene blue (5mg/kg, guanylate cyclase inhibitor) were injected 30 min before administration of agomelatine, α-methyl-p-tyrosine (100 mg/kg, an inhibitor of tyrosine hydroxylase) was administered 3 h before agomelatine. All treatments were injected intraperitoneally, 1 ml/100g. Locomotor activity test, and forced swim test (FST) were performed an hour after agomelatine injection. The locomotor activity was reduced after imipramine or propranolol administration compared with the control group. Agomelatine decreased the immobility time during FST, but following its administration with imipramine it increased significantly compared with agomelatine alone. Agomelatine-prazosin, or AMPT significantly reduced immobility time compared with agomelatine alone. Immobility time decreased significantly after agomelatine and L-arginine were administered compared with agomelatine alone. While agomelatine with yohimbine, propranolol, L-NAME, or methylene blue insignificantly changed the results. Agomelatine proved to have potential antidepressant effects, that were enhanced by adrenergic or nitric oxide pathway modulation. Further research is warranted to determine the precise molecular mechanisms and optimize clinical applications.

***Keywords**: Adrenergic system; Agomelatine; Depression; Animal sciences; Nitric oxide*

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders with a high economic burden. According to the monoamine hypothesis of depression, the insufficiency of monoamine neurotransmitters, i.e. serotonin (5-HT), norepinephrine (NE), and dopamine (D) in specific structures of the central nervous system (CNS) may lead to depression. Most of the current antidepressants, interact with monoaminergic systems, by inhibition of the transporters or inhibition of the metabolizing enzymes (monoamine oxidase)[1]. Despite different mechanisms of antidepressant action, all antidepressants share a slow onset of action in humans, resulting in a delay of several weeks before maximal antidepressant effect is achieved[2].

Agomelatine (Ago) is a synthetic analog (beta-methyl-6-chloro melatonin) of melatonin. Melatonin is a hormone secreted by the primary pineal gland in the brain and plays a role in regulating the circadian rhythm[3].

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Melatonin interacts with various neurotransmitter systems through its two main receptors, MT1 and MT2. Melatonin modulates the serotonergic system in the body, altering circadian phase regulation, sexual behavior, sleep-wake cycles, and neuroendocrine effects. Similarly, melatonin affects the dopaminergic, GABAergic, opioid, and cholinergic systems in the body[4-6]. It is now proven that one of the factors that can cause emotional disorders such as depression is the disturbance in the circadian rhythm of the body[7].

Previous evidences from preclinical and clinical studies have shown that Ago, a specific agonist of MT1 and MT2 receptors and a selective antagonist of 5-HT2c receptors, has antidepressant properties[3,8]. Preclinical studies show that the administration of Ago improves behaviors such as disruption of the circadian rhythm, anxiety, and depression[9]. Clinical trials have confirmed the efficacy and safety of Ago for the treatment of depression, but there is insufficient evidence for its use in long-term treatment [10]. Other promising therapeutic effects of Ago could be in obsessive-compulsive disorder, menopausal osteoporosis, migraine, fibromyalgia, and alcohol-related sleep disorders[11-13].

Nitric Oxide (NO) not only has important roles in the cardiovascular system, but also has been proven to have an important role in the nervous system. Many physiological activities demonstrated that NO serves as a messenger molecule, including activities related to the major psychiatric diseases[14,15]. In the brain NO is synthesized from the amino acid L-arginine by nitric oxide synthase (n NOS), which is the enzyme identified in neurons and is dependent on high Ca2+. Several behavioral animal studies have proven that NOS inhibition causes antidepressant-like and anxiolytic effects[15].

The evidence indicates that the antidepressant effects of Ago include different mechanisms, typically the serotonergic and dopaminergic systems[3,6]. However, the involvement of the adrenergic system in the antidepressant efficacy of Ago is yet to be investigated.

The current study emphasizes the antidepressant efficacy of Ago through its interaction with adrenergic, and NO pathways and provides insights into its pharmacodynamics. This goal was achieved by the help of imipramine (a tricyclic antidepressant), bupropion (Dopamine and NE reuptake inhibitor), prazosin (α1 adrenoceptor antagonist), yohimbine (α2 adrenoceptor antagonist), propranolol (β1 and β2 adrenoceptor antagonist), and a selective inhibitor of tyrosine hydroxylase α-methyl-para-tyrosine or metyrosine, which inhibits the production of NE and D[16,17]. To evaluate the NO messenger role in Ago antidepressant efficacy L-NG-nitroarginine methyl ester typically NOS inhibiting amino acid related to L-arginine binding site, methylene blue inhibiting the stimulation of soluble guanylyl cyclase (GC) by NO, and L-arginine (NO precursor) were used [18]. The primary outcomes measured included the locomotor activity, immobility time and the mobile phase in the forced swim test (FST).

MATERIALS AND METHODS

Chemicals

Agomelatine (Ago) was obtained from MSN Corporate, Telangana, India, L-NG-nitroarginine methyl ester (L-NAME), and L-arginine, Imipramine (Imi), yohimbine (Yoh), and α-methyl-para-tyrosine (AMPT) were purchased from Sigma company USA, methylene blue (MB) Merck Pharmaceutical company, Germany, prazosin (Prz) was received as a gift from Amin industry, Iran, and propranolol (Prp) (1 mg/ml) POLFA, Poland ampule was used.

Animals

A total of 120 male white NMRI mice, aged 6 weeks and weighing between 23-29 g, were housed in the animal facility of the School of Pharmacy in Isfahan University of Medical Science. The mice were maintained under standard conditions of humidity, temperature, and light/dark cycle. The supply of food and water were *ad libitum*. Each cage included six mice, and all animal studies were conducted in accordance with the standards for the care and use of laboratory animals provided by The National Ethical Committee of Iran (Ethics code IR.MUI.AEC.1402.018). Every possible effort was made to minimize the quantity of animals and the animal distress.

Experimental design

Ago 40 mg/kg was administered after dissolving in 0.1% tween 80 in normal saline[19]. To investigate the involvement of the adrenergic system, AMPT 100 mg/kg was administered three hours before Ago[16]. Treatment with all other drugs was half an hour before Ago injection. Prazosin with a dose of 1 mg/kg, yohimbine 1 mg/kg, propranolol 2 mg/kg, imipramine 10 mg/kg, and bupropion 10 mg/kg[16,20]. To evaluate the role of NO system, arginine 100 mg/kg, L-NAME 20 mg/kg, and methylene blue 5 mg/kg were administered[21]. All these drugs after dissolving in normal saline were injected intraperitoneally at a volume of 1 ml/100g. The behavioral tests [locomotor test, and force swim test (FST) serially] were given an hour after Ago administration.

Six mice were studied in each group, the animal groups were as follow: 1) The control group injected 0.1% tween 80 in normal saline or normal saline alone (1 ml/100g) 2) Ago alone group,
3) and 4) bupropion alone, Ago-Bup groups, respectively
5) and 6) imipramine alone, Ago-Imi groups, respectively
7) and 8) prazosin alone, Ago-Prz groups, respectively
9) and 10) yohimbine alone, Ago-Yoh groups, respectively
11) and 12) propranolol alone, Ago-Prp groups respectively,
13) and 14) AMPT alone, Ago-AMPT groups, respectively,
15) and 16) L-NAME alone, Ago-LN groups, respectively,
17) and 18) methylene blue alone, Ago-MB groups, respectively,
19) and 20) L-arginine alone, Ago-Arg groups, respectively.

Locomotor test

Prior to behavioral tests, this baseline test is administered to determine the animals' baseline locomotor activity. The test was performed in an open arena (40×40×40 cm) manufactured by Borj-Sanat, Iran. The arena is separated into fifteen equal sections by infrared beams. After being carefully positioned in one corner, the mice were allowed to roam about for three minutes. The number of times the mice walked over the beams was counted by automated sensors, and the number of times they stood on their hind legs was manually recorded. The total activity level was determined by adding the zone entrances and hind-leg raising occurrences[22,23].

Forced swim test

This test was performed as previously mentioned by Can et al.(2012)[24]. For six minutes, mice were made to swim in 12 centimeters of water at 25 °C in a cylindrical beaker. The first two minutes were regarded as the habituation period, while the latter four minutes were used to record every movement the animal made using a camera (Canon PowerShot ELPH 115, Japan). Later, the immobility duration was quantified and compared across the various groups. Additionally, the amount of time spent swimming and scaling the container walls were recorded. At last, the mice were taken out of the water and thoroughly dried to prevent hypothermia.

Statistical analysis

All results are presented as mean ± SEM, and were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Swimming and climbing time during FST were analyzed by two-way ANOVA. The significant differences were considered for *P* values lower than 0.05. The software programs that were used for data analysis and making graphs were GraphPad Prizm 10 and Excel 2020 respectively.

RESULTS AND DISCUSSION

The effect of agomelatine alone and following bupropion and imipramine administration on depressive behavior

According to the data shown in **Table 1**, there was only a significant drop in the total activity count when imipramine was administered alone and concurrently with Ago compared with the control group (Ago-Imi $p<0.001$). However, this decrease did not have an impact on the FST results.

Table 1: The effect of agomelatine, antidepressants, adrenergic and NO system drugs on the locomotor activity test.

.Groups(n=6)	Total activity number	Groups(n=6)	Total activity number
Control	181.3±20.3	AMPT	127.8±13.5
Agomelatine	187.3±9.9	Ago-Bup	131.0±13.7
Bupropion	145.8±17.6	Ago-Imi	76.7±15.9 ***
Imipramine	123.9±8.5 *	Ago-Yoh	140.0±13.7
Prazosin	124.9±6.2	Ago-Prp	76.5±8.3 *
Yohimbine	135.7±28.4	Ago-Prz	117.0±25.0
Propranolol	131.7±10.2	Ago-AMPT	119.0±9.3
L-NAME	116.0±11.8	Ago-LN	183.3±27.7
Methylene Blue	159.1±18.1	Ago-MB	127.7±26.3
Arginine	118.3±12.8	Ago-Arg	167.3±22.3

Total activity during locomotor test= (horizontal +vertical) exploration. Control groups received NS. Agomelatine (Ago) and bupropion (Bup) prazosin (Prz), yohimbine (Yoh) and propranolol (Prp), imipramine (Imi), L-NAME (LN), methylene blue (MB), L-arginine (Arg) and AMPT were IP injected. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test. *p<0.05 and ***p<0.001 compared to control group.

Fig. 1a displays the immobility time findings of the FST. The possible mood-enhancing effect of Ago following administration was investigated, and there was a significant reduction in immobility time (93.7±10.5 s vs. control 178.1±9.8 s, p<0.01). The administration of Bup or Imi alone also decreased the duration of immobility (84.1±14.3 s and 71.1±14.5 s compared to control, p<0.01 and p<0.001 respectively) which in accordance with the antidepressant effects. While the combination Ago-Bup showed similar results as Ago alone Ago-Imi co-administration reversed the antidepressant effects (157.0±10.3 s, p<0.05 vs Ago alone group).

The length of time that the mobile phase was noted during the FST is shown in **Fig. 1b**. The swimming time in all the treatments except Ago-Imi group was significantly higherthan the control group (105.3±13.3 s, at p<0.01). While only in Imi alone group the climbing activity is significantly more than the control group (75.6±15.0 s, vs 13.6±6.0 s, p<0.01). The climbing time is significantly lower than the swimming duration (at p<0.01) in all drug treatment groups except Imi alone group.

The effect of agomelatine alone and following administration of adrenergic inhibitors on depressive behavior

In the locomotor test, the total number of movements of mice in the prazosin, yohimbine, propranolol, and AMPT groups had no significant difference compared to the control group. Although, the combination of Ago-Prp significantly decreased the movements compared to the control group (p<0.01) (**Table 1**), it did not influence other behavioral tests.

The length of time that immobility was measured during the FST is shown in **Fig. 2a**, there was insignificant difference when Prz,

Prp, or AMPT alone were administered versus control group. While Yoh significantly decreased the immobility time (105.7±13.8 s, p<0.05 vs control). The immobility period decreased significantly when Ago-Prz (29.6±12.3 s, p<0.05), and Ago-AMPT (27.5±9.4 s, p<0.01) were given against Ago alone group. While the changes in Ago-Yoh and Ago-Prp groups were insignificant compared with the Ago alone group. All the combination of drugs administered with Ago significantly decreased the immobility time compared with the control group (at least p<0.05).

The swimming and climbing times during FST are compared in **Fig. 2b**. All the combination of drugs administered with Ago significantly increased swimming time compared with the control group (50.3±9.0 s, at least p<0.05). The climbing time for Ago-Prz and Ago-AMPT was significantly higher than the control group (13.6±5.9 s, at least p<0.05). As for Ago alone in the combination groups, Ago with Prz, Yoh, and Prp swimming time was more than climbing time (p<0.05).

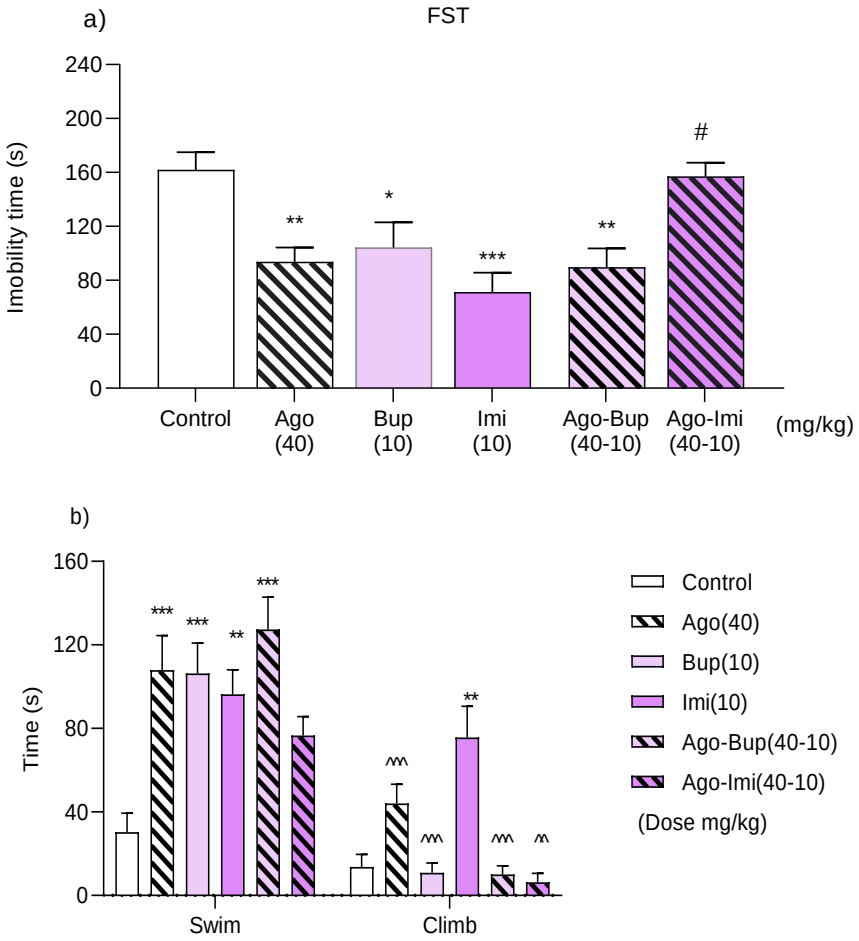

Fig.1: The effect of agomelatine and the antidepressant drugs on behavior during forced swim test. a) Immobility time, and b) swimming and climbing time. The control group received normal saline. All the treatments were injected IP. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison test (a) and two-way ANOVA (b). *p<0.05,**p<0.01 and ***p<0.001 compared to the control group. # p<0.05 compared to Ago alone group^^p<0.01, ^^^p<0.01 compared with the swimming time in the same group. Agomelatine (Ago), Bupropion (Bup) and imipramine (Imi).

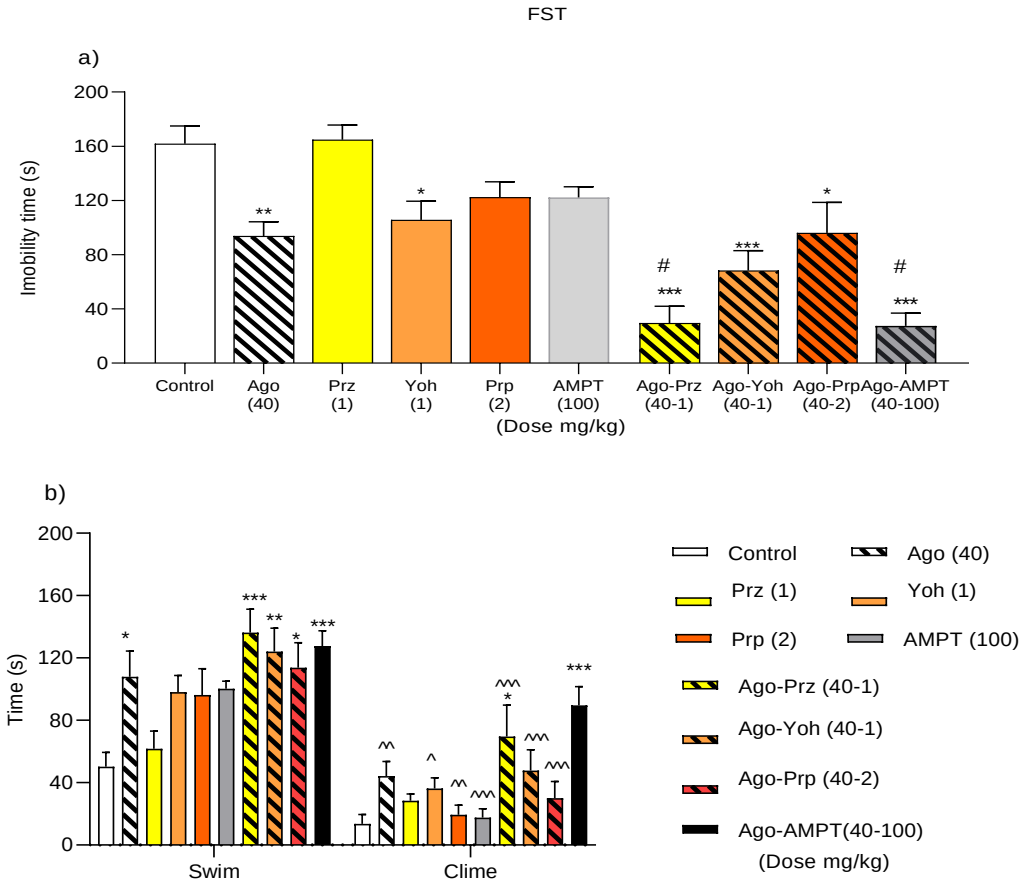

Fig. 2: The effect of agomelatine alone and following administrating adrenergic inhibitors on behavior during forced swim test. a) Immobility time, and b) swimming and climbing time. Control group received normal saline. All the treatments were injected IP. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison test (a) and two-way ANOVA (b). *p<0.05,**p<0.01 and ***p<0.001 compared to the control group. # p<0.05 compared to Ago alone group. ^p<0.05, ^^p<0.01, ^^^p<0.01 compared with the swimming time in the same group. Agomelatine (Ago), prazosin (Prz), yohimbine (Yoh) and propranolol (Prp) and AMPT.

The effect of agomelatine alone and following administrating nitric oxide pathway drugs on depressive behavior

In the locomotor test, none of the groups had a significant difference in the total number of movements compared to the control group (**Table 1**).

The length of time that immobility was noted during the FST is shown in **Fig. 3a.** Following the administration of MB, or Arg alone immobility time was significantly lower than the control group (50.5±7.1 s, 44.8±5.1 s respectively, p<0.001). The immobility period decreased significantly (at least p<0.05) when Ago was given in addition to LN, MB and Arg compared with the control group. But only in Ago-Arg group the value differed significantly compared with Ago alone group (p<0.05).

The length of time that the mobile phase was noted during the FST is shown in **Fig. 3b**. The swimming period increased significantly when Ago, LN, MB and Arg were administered alone and following their combinations compared with the control group (at least p<0.01). Regarding Ago-Arg group this period was significantly higher than Ago alone group (174.6±9.1 s vs 46.3±8.6 s, p<0.001). The climbing duration only in Ago-LN group was significantly higher than the control group (p<0.05). The climbing time was significantly lower than the swimming time in all the drug treatment groups (p<0.001).

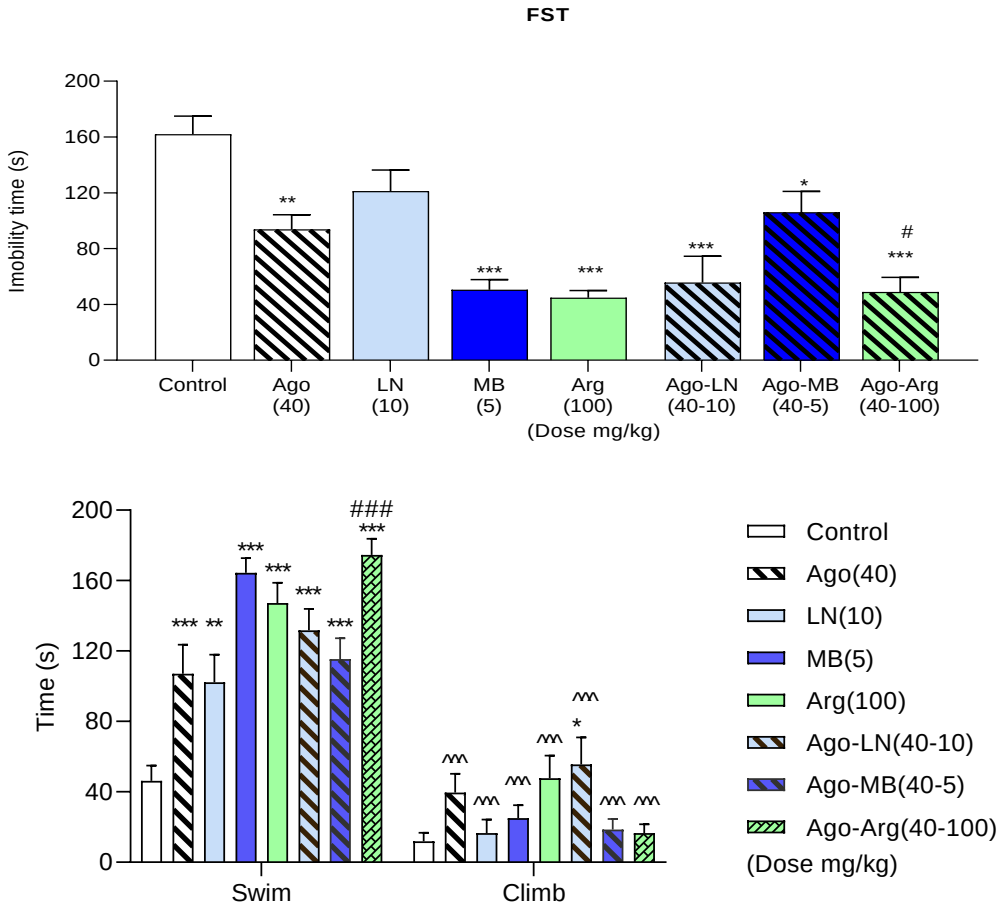

Fig.3: The effect of agomelatine alone and following administrating NO pathway drugs on behavior during forced swim test. a) Immobility time, and b) swimming and climbing time. Control group received normal saline. All the treatments were injected IP. Results are expressed as group mean ± SEM and analyzed by one-way ANOVA followed by Tukey's comparison test (a) and two-way ANOVA (b). **p*<0.05,***p*<0.01 and ****p*<0.001 compared to the control group. # *p*<0.05, ### *p*<0.01 compared to Ago alone group. ^^^*p*<0.01 compared with the swimming time in the same group. Agomelatine (Ago), L-NAME (LN), methylene blue (MB) and L-arginine (Arg).

Discussion

The findings of this study provided important insights into the pharmacodynamics of Ago and its potential mechanisms of action. Ago, administered at 40 mg/kg, significantly reduced immobility time in the FST compared to the control group, indicating a robust antidepressant-like effect. This reduction in immobility is consistent with Ago's ability to enhance active coping mechanisms and alleviate behavioral despair, which are hallmark symptoms of depression[25]. Notably, Ago did not significantly alter locomotor activity, suggesting that the observed effects are specific to antidepressant action rather than general stimulation. Previouly an animal study have also proven the antidepressant effect of Ago after neuronal injury imposed by lipopolysaccharide in rats[26]. According to the molecular–cellular investigations, Ago antidepressant activity could be related to the synergistic action as MT1/MT2 agonism and 5-HT2c receptors antagonist. This synergistic action is responsible for Ago efficacy on brain-derived neurotrophic factor, and neurogenesis[27]. This mechanism of action could also describe the chief efficacy of Ago on improving interest and reactivity to pleasurable stimuli (hedonic efficacy), which is vital in the treatment of MDD with anhedonia[28].

There was no synergistic effect following Ago-Bup administration, since there was no change in the immobility time during FST

compared to Ago alone group. Bupropion has similar antidepressants efficacy to SSRIs and TCAs. However, it is a drug with unique pharmacologic properties in contrast to other antidepressants it does not affect serotonin transporter or postsynaptic receptors[29]. The NE and dopamine reuptake inhibition of bupropion is responsible for its unique property[29]. The similar antidepressant response observed following Ago-Bup administration could indicate their similar antidepressant mechanism. Ago as a 5-HT2c receptor antagonist could also enhance NE and dopamine release[30]. Following the co-administration of Ago-Imi the immobility time increased in FST, since the locomotor activity in Ago-Imi group also declined significantly, this could be related to the sedation effects of the two agents administered concomitantly. It has been denoted that swimming and climbing time in FST are differentially produced by serotonergic and noradrenergic antidepressants respectively[31]. After Ago-Imi administration climbing time declined in contrast to the imipramine alone group, probably due to the antagonistic effect of the combination.

The involvement of the adrenergic system in the antidepressant effects of Ago was further clarified through its co-administration with various adrenergic regulators including AMPT, that inhibits the tyrosine hydroxylase enzyme and reduces the synthesis of NE and dopamine[17]. This substance helped to evaluate the role of central catecholamine transmission in mediating the effects of Ago.

According to the reported studies, AMPT alone does not reduce the immobility time[32,33], but, co-administration of Ago-AMPT significantly reduced the immobility time. This indicates an additive effect on the antidepressant action of Ago. Swimming and climbing behavior during FST both increased after Ago-AMPT administration. This raises the possibility of a compensatory increase of serotonergic activity in case of suppression of NE and dopamine synthesis[34]. Pharmacological and genetic studies to the function of 5-HT2c receptor reveal that it mainly controls serotonergic system of various behavioral and mental activities[35]. While, AMPT alone or Ago-AMPT did not significantly alter locomotor activity. This supports the hypothesis that the interaction between Ago and AMPT is specifically related to mood regulation rather than changes in general motor activity.

In addition to AMPT, the effects of specific antagonists of adrenergic receptors were also investigated. Prazosin and propranolol alone did not alter immobility time in the FST test, in contrast to yohimbine that reduces the immobility time. This result was consistent with previous results that used a similar dose of these agents to understand the possible mechanism for the anti-immobility effect of resveratrol during FST[17].

Prazosin with Ago significantly reduced immobility time in FST compared with Ago alone. This finding suggests that blocking the α1 receptor may synergize the antidepressant effects of Ago. Yohimbine and propranolol did not produce significant changes in immobility time while administrated with Ago, suggesting that α2 and β-adrenergic receptors have a limited role in the main mechanism of action of Ago. Swimming and climbing time both increase in Ago-Prz group, while the swimming time was significantly higher than the climbing time which could be related to diversity changes in the neurotransmitters.

Although prazosin or yohimbine administration with Ago did not change the locomotor activity, Ago-Prp administration reduced the locomotor activity compared to the control group denoting the possible sedating effect of the two drugs together.

Normally, α1- and β- adrenergic receptors stimulate cell signaling, by increasing intracellular phospholipase C and cyclic adenosine monophosphate (cAMP), respectively, whereas α2-receptores have an inhibitory influence on signaling by suppressing intracellular cAMP[36]. It has been realized previously that α1- receptors in the brains of MDD patients are desensitized[36]. On the other hand, the affinity and density of inhibitory α2-receptores are increased in the locus coeruleus and prefrontal cortex in these patients that indicates a compensatory response related to high NE levels[37]. It was reported that prazosin administration following pyridoxine therapy significantly reduced the immobility time compared to pyridoxin alone, indicating a synergic antidepressant effect while yohimbine did not change the immobility time during FST[32]. On the contrary, the antidepressant

efficacy of lamotrigine, folic acid, or magnesium in mice was antagonized by prazosin and yohimbine administration[16,33,38]. These results showed that adrenergic system has limited contribution to Ago antidepressant effects.

The role of the NO pathway on Ago antidepressant effect was also examined using L-NAME, methylene blue, and L-Arginine. These interventions did not cause important alterations in the locomotor activity. As a GC inhibitor, methylene blue reduces cGMP levels, which decreased the immobility time during FST. It has been reported that methylene blue (7.5-30 mg/kg) administered in rats increased time spent in open arms in the elevated plus-maze, suggesting its antianxiety effect. While in higher doses it has reduced rat immobility time during FST, ie. reduction of cGMP causes antidepressant effects[39]. L-arginine (100 mg/kg) which is a precursor of NO, also reduced immobility time in FST. Evidently, L-arginine has no change in the immobility of mice in doses less than 30 mg/kg, it has an antidepressant effect in doses slightly higher than 100 mg/kg, and again it causes no alteration in doses higher than 1000 mg/kg[40].

The Co-administration of Ago-MB resulted in a slight enhancement in immobility time compared to Ago alone but remains significantly lower than the control group. While Ago-LN insignificantly reduced immobility time during FST. This may indicate a complex interaction where excessive inhibition of the NO-cGMP pathway could alter Ago's balance in neurotransmitters.

Surprisingly, when L-arginine was administered simultaneously with Ago, immobility time was reduced and swimming time was increased significantly during FST. Evidently, higher NO level increases neurotransmitter release, although decreasing effects have also been observed[41]. It was emphasized that, in all brain structures investigated, endogenous NO regulates the release of some neurotransmitters, such as NE, 5-HT, acetylcholine, histamine, excitatory and inhibitory amino acids[41].

Antidepressant-like effects can be produced in the brain by reducing NO levels or inhibiting its production (blocking NOS)[42]. 7-nitroindazole (a nNOS inhibitor) microinjections in rat dorsal hippocampus has been shown to exhibit antidepressant-like effects by shortening the immobility period and promoting swimming behavior during FST[43]. Patients with significant depression have been reported to have higher amounts of NO[44]. So, more investigations are needed in order to determine the NO–cGMP pathway and its influence on Ago antidepressant efficacy.

Clinical studies demonstrate that agomelatine is well-tolerated, primarily because it does not impact sexual functioning or weight. Its favorable adverse effect profile contributes to low discontinuation rates. The only drawback of using agomelatine is the need to monitor liver enzymes, as it can elevate hepatic enzyme levels[45].

Conclusions

The findings demonstrate that Ago exerts significant antidepressant effects, which are enhanced by adrenergic and nitric oxide pathway modulation. However, it may halt the efficacy of the simultaneous antidepressant drug (ex, imipramine). The potentiation of effects by AMPT suggests that reduced catecholamine synthesis may facilitate a compensatory increase in serotonergic activity, augmenting Ago's efficacy. On the other hand, L-arginine administration with Ago also significantly increased swimming time which could be related to the NO effect on neurotransmitter release. This highlights the complex interplay between adrenergic and serotonergic systems in mediating antidepressant responses. Future research should explore the therapeutic potential of combining Ago with other antidepressant drugs, α1 blockers, and NO enhancers.

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مُعدِّلات النورأدرينالين وأكسيد النيتريك تؤثر في التأثيرات المضادة للاكتئاب لعقار أجوميلاتين في الفئران

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يعد أجوميلاتين نظيراً اصطناعياً لهرمون الميلاتونين، و يحظى هذا العقار باهتمام متزايد كعلاج بديل للاكتئاب. و قد هدفت الدراسة الحالية إلى تقييم دور المسار النورأدرينالييني ، بالإضافة إلى مسار أكسيد النيتريك (NO)، في التأثير المضاد للاكتئاب لعقار أجوميلاتين. تم استخدام فئران سويسرية من الذكور (بوزن ٢٦±٣ جرام) فى هذه الدراسة. و قد تم حقن أجوميلاتين (٤٠ ملجم/كجم)، إيميبرامين (١٠ ملجم/كجم)، وهو أحد مضادات الاكتئاب ثلاثية الحلقات، بوبروبيون (١٠ ملجم/كجم)، و هو دواء مثبط لعملية إعادة التقاط الدوبامين/النورأدرينالين، و برازوسين (١ ملجم/كجم، مضاد مستقبلات-α1 الأدرينالية)، و يوهيمبين (١ ملجم/كجم، عقار مضاد لمستقبلات الأدرينالين α٢)، و كذلك بروبرانولول (٢ ملجم/كجم، مضاد مستقبلات-β الأدرينالية)، و إل-أرجينين (١٠٠ ملجم/كجم)، و هو مادة أولية مُولدة لأكسيد النيتريك، و إل-نيم (١٠ ملجم/كجم)، و هو مثبط للانزيم المحفز (القابل للتولد) المخلق لأكسيد النتريك، بالإضافة إلى أزرق الميثيلين "الأزرق المثيلي" فى جرعة ٥ ملجم/كجم، و هو مثبط لإنزيم جوانيلات سيكليز. حقنت هذه المواد ٣٠ دقيقة قبل حقن أجوميلاتين، بينما تم إعطاء-α ميثيل-ب-تيروسين، مثبط انزيم التيروزين هيدروكسيلاز، فى جرعة ١٠٠ ملجم/كجم قبل ٣ ساعات من حقن أجوميلاتين. تم حقن جميع العلاجات فى التجويف البريتونى، بمقدار ١ مل لكل ١٠٠ جرام من وزن الفأر. و بعد ساعة واحدة من حقن أجوميلاتين، أجريت اختبارات النشاط الحركي واختبار السباحة القسرية (FST).

و قد أظهرت نتائج الدراسة انخفاض النشاط الحركي بعد إعطاء كل من إيميبرامين أو بروبرانولول مقارنة بالمجموعة الضابطة. كما تبين أن أجوميلاتين قلل من مدة الثبات (وقت الجمود أو عدم الحركة) أثناء اختبار السباحة القسرية، بينما زادت هذه المدة (مدة الثبات) بشكل ملحوظ عند إعطائه مع إيميبرامين، مقارنة بالفئران التى تم حقنها بأجوميلاتين بمفرده. كما قلل أجوميلاتين و برازوسين مجتمعين، أو AMPT من مدة الثبات بشكل ملحوظ، مقارنة بأجوميلاتين وحده. كذلك انخفضت مدة الثبات بشكل ملحوظ بعد إعطاء أجوميلاتين مع إل-أرجينين مقارنة بأجوميلاتين بمفرده، في حين أن علاج الفئران بأجوميلاتين مع كل من يوهيمبين، بروبرانولول، إل-نيم، أو أزرق الميثيلين لم يؤثر بشكل كبير على النتائج.

أثبتت نتائج الدراسة أن أجوميلاتين له تأثيرات مضادة للاكتئاب، والتي تعززت من خلال تعديل المسارات الأدرينالية أو مسار أكسيد النيتريك. كما أن هناك حاجة إلى مزيد من الأبحاث لتحديد الآليات الجزيئية الدقيقة و تحقيق أقصى استفادة فى التطبيقات السريرية.