Pharmacological Profile for the Contribution of NO/cGMP Pathway on Chlorpheniramine Antidepressant-Like Effect in Mice Forced Swim Test

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Abstract- Chlorpheniramine, a first-generation antihistamine, is widely used for allergic reactions. Previous studies showed the interaction between antidepressant activity and nitric oxide and cyclic guanosine monophosphate (NO/cGMP) pathway. Thus, we aimed to assess the possible involvement of NO/cGMP pathway in this effect using forced swim test (FST) in male mice. To evaluate the locomotor activity and immobility time, we performed open field test (OFT) and FST on each mouse. Chlorpheniramine was administered intraperitoneally (i.p.) (0.1, 0.3, 1, 10 mg/kg) 30 minutes before FST. To assess the involvement of NO/cGMP pathway, a non-selective nitric oxide synthase (NOS) inhibitor, L-NAME (10mg/kg, i.p.), a selective inducible NOS (iNOS) inhibitor, aminoguanidine (50 mg/kg, i.p.), a selective neural NOS (nNOS) inhibitor, 7-nitroindazole (7-NI, 30 mg/kg, i.p.), a NO precursor, L-arginine (750 mg/kg, i.p.) and a selective phosphodiesterase-5 (PDE-5) inhibitor, sildenafil (5 mg/kg, i.p.) was co-administered with chlorpheniramine. Chlorpheniramine significantly decreased the immobility time at doses of 1mg/kg (P<0.01) and 10 mg/kg (P<0.001). Administration of L-NAME (P<0.01) and 7-NI enhanced the anti-immobility activity of chlorpheniramine (P<0.001), while aminoguanidine did not have any significant effects on the immobility time (P>0.05). Moreover, pretreatment with L-arginine (P<0.01) and sildenafil (P<0.001) significantly reduced the anti-immobility effect of chlorpheniramine. These treatments did not alter the locomotor activity of mice in OFT. Our results revealed that the antidepressant-like effect of chlorpheniramine is mediated through inhibition of NO/cGMP pathway.

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Keywords: Chlorpheniramine; Nitric oxide; Cyclic guanosine monophosphate; Forced swim test; Mice

Introduction

Depression is one of the most common psychiatric disorders and a public health concern (1) which is associated with high rate of morbidity and mortality (2,3). Therefore, increasing attention must be paid to treat this disease. Among the several routine antidepressant agents which are mainly based on monoamine regulation (4), few have desired effects without causing serious side-effects (2). Thus, finding new antidepressant agents with appropriately pharmacological actions would be of benefit.

Chlorpheniramine prevents reuptake of monoamines like tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (5-7). Accordingly, it has been shown that it is effective against panic attack and phobia and modifies mood and emotional activities (8,9). Therefore, there is little evidence of antidepressant and anxiolytic effects of chlorpheniramine (10).

Chlorpheniramine belongs to the class of organic compounds known as pheniramines, which are histamine H_1 receptor antagonists (11). It has been previously demonstrated that chlorpheniramine exerts antidepressant-like properties in the rat forced swim test (FST) and mouse tail suspension test (TST) (12) not due to anti-histaminergic activity. A similar effect was also observed with administration of Mepyramine and Clemastine, the selective histamine H_1 receptor antagonists, which had no influence in that paradigm (13). It has been claimed that stimulation of dopamine D_1

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receptors is involved in the antidepressant-like activity of chlorpheniramine (14). Considering these results, the monoamine enhancement produced by chlorpheniramine may mediate the antidepressant-like effect in rodents.

Previous reports have shown that neural nitric oxide synthesis (nNOS) is expressed in dopaminergic neurons (15,16). Activation of dopamine D_1 receptors on dopaminergic neurons reduces the intracellular levels of Ca^{2+} (17) which is essential for numerous signaling pathways, including the NO production (18).

NO is synthesized in the brain from L-arginine by nitric oxide synthesis. The three isoforms of NOS that were characterized inducible NOS (iNOS), endothelial NOS (eNOS), and nNOS (19). In the brain the activity of NOS is far apart from other tissues, and widespread distribution of the enzyme in brain indicates that NO could be involved in important CNS functions, such as neurotransmitter release, pain perception, and depression (20). Animal studies have demonstrated that cyclic guanosine monophosphate (cGMP) synthesis is essential signaling involved in the pathogenesis of depression mediated by NO (21). The NO/cGMP pathway is known to be involved in the regulation of various pathophysiologic behavioral and emotional function (22) and now is suggested as a therapeutic target for depression (23). It has been showed that inhibition of NO/cGMP pathway exerts antidepressant properties (24) and also augment the antidepressant-like effects of numerous agents such as lamotrigine (25), pramipexole (26), Tropisetron (26), baclofen (27) gabapentin (28), and topiramate (29). Therefore, we decided to investigate the role of NO/cGMP pathway in the antidepressant-like effect of chlorpheniramine in the mouse FST.

Materials and Methods

Animals

The animals that we used in this study were 20-30 g NMRI male mice purchased from Pasteur Institute, Tehran, Iran. Animals were divided randomly into groups of 4-5 and were kept under standard laboratory conditions (temperature of 21-23° c, under 12-hour regular light/dark cycle and allowed free access to food and water excluding the short period time of examination. All experiments were done during the time between 12:00-16:00. All procedures were performed in agreement with the guide for the care and use of laboratory animals for animal care and use (30). Each mouse was used only once, and each experimental group consisted of 8 to 9 mice.

Drugs

The following drugs were used in this study: chlorpheniramine, N(G)-Nitro-L-arginine methyl ester (L-NAME), aminoguanidine, 7-Nitroindazole (7-NI), L-arginine (L-arg), and sildenafil (All were purchased from Sigma, St Louis, MO, USA). Except for 7-NI which was dissolved in Tween 80 (1%) solution, all drugs were freshly dissolved in physiological saline and were prepared immediately before the experiments. All drugs were injected through intraperitoneal (i.p.) route and with a volume of 5 ml/kg body weight (31).

Open field test (OFT)

The OFT was used to evaluate the locomotor behavior of animals to confirm changes in the immobility time are not resultant of the changes in the locomotor activity (32,33). The open-field apparatus was made of white opaque Plexiglas (50 cm×50 cm×30 cm) with dim light, and the ground of the arena was divided into 12 squares, each mouse was placed gently on the center square, and the number of squares passed with all paws (crossing) was counted in a 6-minute period.

Forced swimming test

The FST was used to study behavioral despair in mice as a standard test for antidepressant activity of the drug (34-36). For conducting the FST, the animals were placed in an open cylinder-shaped flask (diameter 10 cm, height 25 cm) filled with 19 cm water at 24±1° C. Being allowed to swim for 6 minutes, each mouse was assumed immobile when stopped struggling and floated motionless in the water, making only the movements for keeping its head above water. The time of remaining immobile within the last 4 minutes of the test was recorded.

Experimental design

First, we examined the effects of different doses of chlorpheniramine (0.1, 0.3, 1, 3 and 10 mg/kg) administrated to the mice 30 minutes before the behavioral tests to determine the effective and sub-effective doses of this agent. The dose and times of administration were based on our pilot and previous studies (14). The measurement for time of immobility and numbers of crosses were compared with saline-treated animals, saline (5 mg/kg) was injected 30 minutes before the test into the control group.

After defining the effective and sub-effective doses of chlorpheniramine, we assessed the effect of L-NAME (10 mg/kg, 45 minutes prior to behavioral tests),

aminoguanidine (50 mg/kg, 45 minutes prior to behavioral tests), 7-NI (25 mg/kg, 30 minutes prior to behavioral tests), L-arg (750 mg/kg, 45 minutes prior to behavioral tests), and sildenafil (a selective phosphodiesterase (PDE)-5 inhibitor) (5 mg/kg, 30 minutes prior to behavioral tests) on the behavior of mice in the FST and OFT. The doses were based on pilot study and previous reports (25-28).

To investigate the involvement of nitrergic system in the possible antidepressant-like effect of chlorpheniramine, we examined separately co-administration of L-NAME (10 mg/kg), aminoguanidine (50 mg/kg) and 7-NI (25 mg/kg) along with chlorpheniramine. Also, chlorpheniramine along with L-arginine (750 mg/kg) and sildenafil (5 mg/kg) was co-administrated to the animals. To exclude the effect of vehicle administration on behavioral assessment, saline (5 mg/kg) was injected along with chlorpheniramine to control group (37).

Statistical analysis

Statistical analyses were carried out using Graph Pad Prism 6 software (San Diego, CA, USA). The results are presented as mean±standard error of mean (SEM). One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was carried out to evaluate dose-related effects of chlorpheniramine on immobility time and locomotor activity. Two-way ANOVA followed by Bonferroni test was used to analyze the other results. Chlorpheniramine treatment and NO modulator-treatment were considered as the first and second factors, respectively. The analysis method applied in each part of the experiment is stated in Section 3 and "Fig. captions". Data are expressed as mean±SEM. *P* less than 0.05 were considered statistically significant.

Results

Effect of chlorpheniramine in the immobility time during FST and on locomotor activity during OFT

Chlorpheniramine at doses of 1 mg/kg like fluoxetine ($P<0.01$) and 10 mg/kg ($P<0.0001$ F (5, 41) =13.85) significantly reduced the immobility time in the forced swim test compared to vehicle-treated group (Figure 1A). Chlorpheniramine at doses of 0.1 and 0.3 mg/kg could not alter the immobility period in comparison with vehicle control group (Figure 1A). Also, chlorpheniramine at these doses did not alter the locomotor activity of animals ($P>0.05$, Figure 1B).

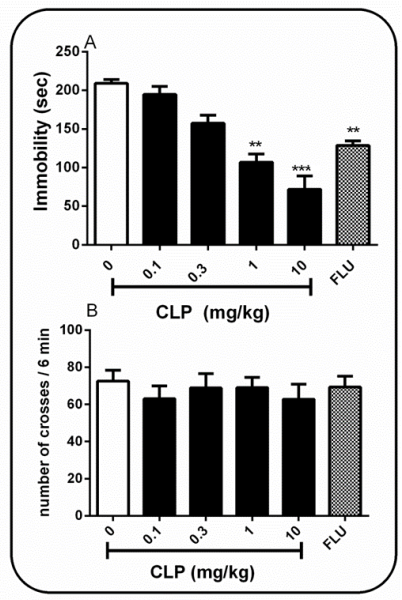

Figure 1. Effect of chlorpheniramine in various doses or fluoxetine (FLU) administration, 30 minutes before forced swim test (A) and open field test (B). Values are expressed as mean±S.E.M. (n=8) and were analyzed using a one-way ANOVA followed by Tukey's post-. *$P<0.01$, *** $P<0.001$ versus saline-treated control

Involvement of nitric oxide in the antidepressant-like effect of chlorpheniramine during FST and effect on locomotor activity during OFT

L-NAME (10 mg/kg) administration 45 minutes before FST did not show antidepressant-like effects. Also, this dose of L-NAME could not significantly change the locomotor activity of animals in the OFT. We administrated the sub-effective dose of L-NAME (10 mg/kg) with sub-effective dose of chlorpheniramine (0.1 mg/kg) for determination of any additive effect. Demonstrated in figure 2A, co-administration of sub-effective doses of chlorpheniramine and L-NAME showed an antidepressant-like effect in animals, significantly ($P<0.01$, F (3, 28)=28.4) compared to comparing with chlorpheniramine (0.1 mg/kg) or L-NAME (10 mg/kg) alone. Co-administration of chlorpheniramine and L-NAME could not change the locomotor activity in OFT ($P>0.05$, Figure 2B).

In another set of experiments, we used L-arginine as a NO precursor for additional determination of NO role in the antidepressant-like effect of chlorpheniramine. As shown in figure 3A, co-administration of sub-effective dose of L-arginine (750 mg/kg) with effective dose of chlorpheniramine (10 mg/kg) reversed the anti-immobility effect of chlorpheniramine in the FST ($P<0.01$, F (3, 28)=21.31, Figure 3A). Co-administration of L-arginine with saline or chlorpheniramine (10 mg/kg) did not change the locomotor activity in the OFT ($P>0.05$, Figure 3B).

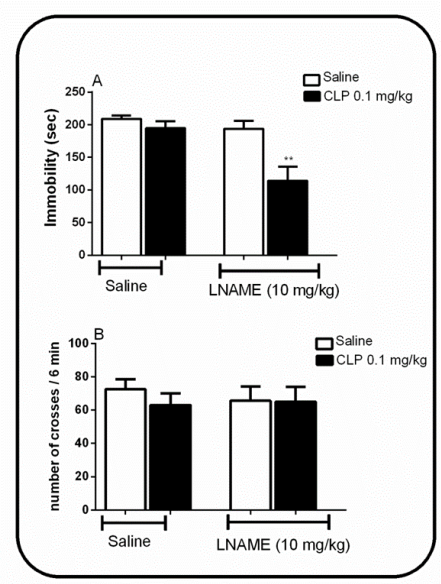

Figure 2. Effect of L-NAME (10 mg/kg) administration 45 minutes prior to FST (A) or OFT (B) on chlorpheniramine treated-mice. The immobility time in forced swim test analyzed for last 4 minutes of the test. B shows the total number of crosses recorded during the open-field test. Data are presented as mean±S.E.M, n=8 animals/group, and were analyzed using a two-way ANOVA followed by Bonferroni post-hoc test. ** *P*<0.01compared with the controls

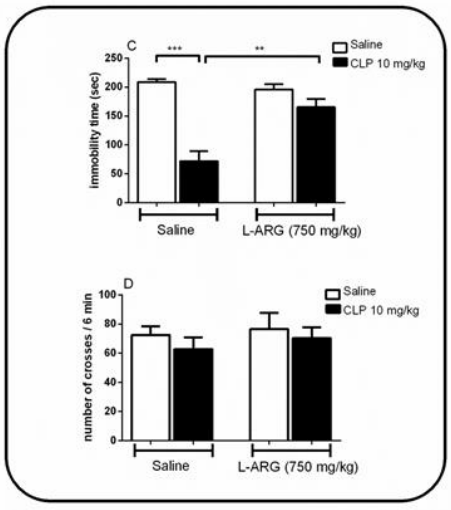

Figure 3. Effect of L-arginine (L-ARG, 750 mg/kg) 45 minutes prior to FST (A) or OFT (B) on chlorpheniramine treated-mice. Total number of crosses recorded during the open-field test. Data are presented as mean ± S.E.M, n=8 animals/group, and were analyzed using a two-way ANOVA followed by Bonferroni post-hoc test. ** *P*<0.01compared with the controls.

Involvement of NOS sub-types in the antidepressant-like effect of chlorpheniramine during FST and its effect on locomotor activity during OFT

To explore the probable modulatory effect of nNOS and iNOS in the anti-immobility effect of chlorpheniramine, 7-NI and aminoguanidine were administrated, respectively, either alone, or in combination with chlorpheniramine. For this purpose, the effect of non-effective doses of chlorpheniramine (0.1 mg/kg) and 7-NI (30 mg/kg) or aminoguanidine (50 mg/kg) was tested on FST.

Co-administration of sub-effective doses of chlorpheniramine (0.1 mg/kg) and 7-NI (30 mg/kg) showed significant antidepressant-like effect ($P<0.001$, $F(3, 28)=8.364$, Figure 4A). Concurrent treatment with sub-effective doses of chlorpheniramine and 7-NI did not change the locomotor activity compared to saline/saline, saline/7-NI, and chlorpheniramine/saline-treated mice in the OFT ($P>0.05$, Figure 4B). Figure 5A shows that co-administration of sub-effective doses of chlorpheniramine (0.1 mg/kg) and aminoguanidine (50 mg/kg) did not produce antidepressant-like effect compared with chlorpheniramine or aminoguanidine groups ($P>0.05$, $F(3, 28)=2.249$). Also, co-administration of sub-effective doses of chlorpheniramine and aminoguanidine could not change the locomotor activity compared to other groups in the OFT ($P>0.05$, Figure 5B).

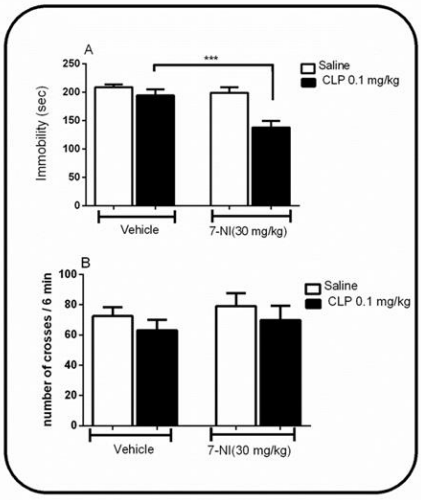

Figure 4. Effect of 7-NI (30 mg/kg) administration, 30 minutes prior to FST (A) or OFT (B) on chlorpheniramine treated mice. The immobility time in forced swim test analyzed for last 4 minutes of the test. B shows the total number of crosses recorded during the open-field test. Data are presented as mean ± S.E.M, n=8 animals/group, and were analyzed using a two-way ANOVA followed by Bonferroni post-hoc test. *** *P*<0.001 compared to saline-treated controls

Involvement of cGMP in the antidepressant-like effect of chlorpheniramine during FST and effect on locomotor activity during OFT

Demonstrating in figure 6A, sildenafil (a PDE5 inhibitor, 5 mg/kg) could not alter the immobility time while reversing the antidepressant-like effect of chlorpheniramine (10 mg/kg) significantly (P<0.001, F (3, 28) =19.61). Also, co-administration of sildenafil with chlorpheniramine did not alter the locomotor activity of mice in OFT (P>0.05, Figure 6B).

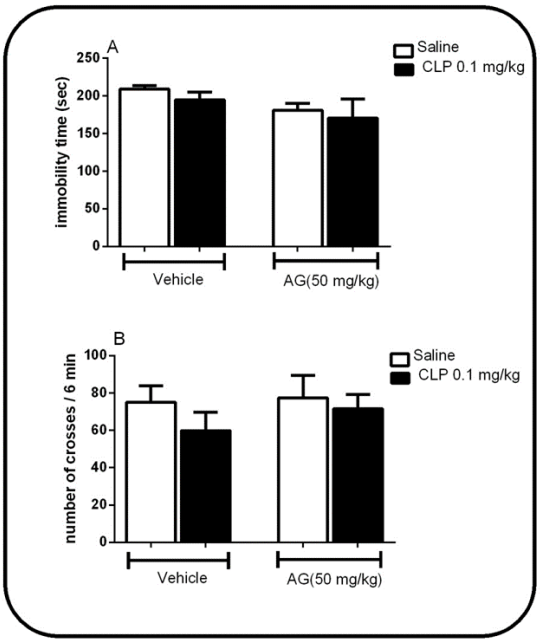

Figure 5. Effect of aminoguanidine (AG 50 mg/kg) administration, 45 minutes prior to FST (A) or OFT (B) on chlorpheniramine treated mice. The immobility time in forced swim test analyzed for last 4 minutes of the test. B shows the total number of crosses recorded during the open-field test. Data are presented as mean±S.E.M. n=8 animals/group and were analyzed using a two-way ANOVA followed by Bonferroni post-hoc test. No significant change was observed.

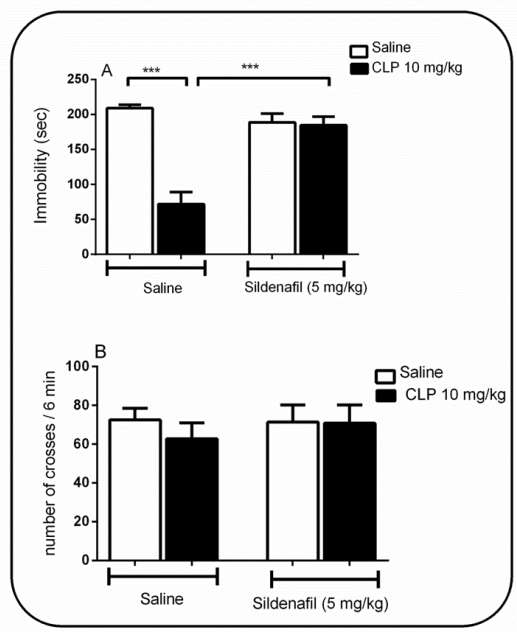

Figure 6. Effect of sildenafil (5 mg/kg) administration, 30 minutes prior to FST (A) or OFT (B) on chlorpheniramine treated mice. The immobility time in forced swim test analyzed for last 4 minutes of the test. B shows the total number of crosses recorded during the open-field test. Data are presented as mean±S.E.M., n=8 animals/group, and were analyzed using a two-way ANOVA followed by Bonferroni post-hoc test. *** P<0.01 compared with saline-treated control or with the chlorpheniramine (10 mg/kg) treated group.

Discussion

The current study demonstrates the effect of acute chlorpheniramine, a first-generation antihistamine, on the immobility time of mice in FST. Chlorpheniramine exhibits antidepressant-like effect comparable to fluoxetine, the standard antidepressant agent. The antidepressant-like behavior of chlorpheniramine was not due to the altered locomotor activity in the OFT. Our results also show that inhibition of NO production potentiates the antidepressant-like effect of chlorpheniramine, while NO precursor and PDE inhibitor reduce it. Additionally, unlike the iNOS inhibitor, co-injection of sub-effective dose of selective nNOS inhibitor, 7-NI, and chlorpheniramine significantly decreased the immobility time in FST. Taken together, these findings suggesting the role for NO/cGMP pathway in the antidepressant-like action of chlorpheniramine.

Histamine H_1 receptor-mediated neurotransmission has modulatory effect on emotional behaviors such as depression. Noguchi *et al*., (1992) revealed that chronic treatment with histamine H_1 receptor antagonists, levoprotiline and mepyramine, exerts antidepressant-like effect in the mouse forced swimming test (38). While, Lamberti *et al*., (1998) reported that the histamine H1 receptor agonist had the antidepressant-like effect in animal models of depression (39). On the other hand, Yanai *et al*., revealed that the immobility time did not alter in mice lacking histamine H_1 receptors (40). These conflicting findings are probably due to the differences in the experimental methods and used drugs (41). While the antidepressant action of chlorpheniramine has been recently established in animal studies. It has been suggested that chlorpheniramine inhibits the reuptake of dopamine, noradrenaline, and serotonin (5-7,42). Current results also reported the involvement of NO/cGMP pathway in chlorpheniramine antidepressant effects. Our data are consistent with the variety of evidence representing the role of NO in major depression and mechanism of action of some other antidepressants (26,43,44). Nitric oxide has neuromodulatory effects in the central nervous system (CNS) which participate in pathophysiology of mood disorders (44). It is established that targeting NO pathway would be a potential therapeutic approach to depression (45). However, previous literature shows a dual effect of NO in depression. Numerous studies have indicated that NOS inhibitors exert antidepressant effects in animal and human studies (46,47). Treatment with antidepressants and antipsychotics, reduces the high serum NO levels during a depressive episode in patients with bipolar type 1 disorder (46). Additionally, it has been shown that plasma level of nitrite, the NO metabolite, increases in depressed patients (48) while some other data representing the reduced plasma NO level in these patients (49). In addition, it has been reported that both stimulating and inhibiting the NO production exert antidepressant properties (50). NO has also double-faceted character in other pathophysiological processes including itch (51), pain, inflammation, seizure, cerebral ischemia, and anxiety (52-56). Overall, the dual effect of NO is dependent on the amount, location, and duration of NO production and the effect of L-arginine and NOS inhibitors are dose-dependent (57).

O Gammoh *et al*., for the first time evaluated the association of NO metabolism with the antidepressant effect of chlorpheniramine in BALB/c mice. They found that 3 weeks of treatment with chlorpheniramine inhibits stress-induced NO in the serum without affecting the elevated superoxide dismutase activity. Considering the association of mood disorders with oxidative stress, they suggested that iNOS would be responsible for NOx synthesis (58). While, our results rule out the involvement of iNOS, since aminoguanidine was not able to alter the effect of chlorpheniramine in behavioral tests. Here, we showed that co-administration of L-NAME or 7-NI with chlorpheniramine significantly increased the immobility time which representing the involvement of nNOS in the antidepressant-like activity of chlorpheniramine. Current findings in line with Gammoh's study indicating that antidepressant properties of chlorpheniramine are mediating through inhibition of NO pathway. However, there are differences between the two methods, as the animals used in our study experienced no stress and thus not have overproduction of baseline NO. In addition, we assessed the effect of acute treatment with chlorpheniramine. The method used in the current study is validated for investigating the mechanism of action of antidepressants (26-28,43). Nevertheless, as the dual effect of NO is related to the amount and duration of NO production by NOS isoforms, further investigations in the setting of acute or chronic stress would be valuable in this regard.

Large body of evidence represents that nNOS inhibitors have selective antidepressant properties. While NO precursors reverse these effects (59). Similar to our findings with chlorpheniramine, Harkin *et al*., have shown that pretreatment with L-arginine attenuates the antidepressant effects of imipramine (60). Moreover, antidepressant properties of substances including

venlafaxine, escitalopram, fluoxetine, and imipramine mediating through nNOS inhibition (28,61,62). Additionally, it has been shown that over-expression of nNOS mostly in hypothalamus induces depressant effects while its inhibition has antidepressant properties (63). Neuronal NOS is the most abundant isoenzyme expressing in the brain (63), while overexpression of iNOS mostly occurs during inflammation or chronic stress (64), which explain our results with aminoguanidine. The H1 receptors are coupled to Gαq G-proteins to result in calcium ion mobilization. It is evident that intracellular Ca^{2+} influx stimulates nNOS activity and NO production (18). Conversely, histamine-induced elevated level of cytosolic Ca^{2+} is inhibited by histamine H1 receptor- antagonists such as chlorpheniramine (65). Thus, it supports the association of inhibited nNOS with the antidepressant role of chlorpheniramine.

We also showed that sildenafil which inhibits cGMP-specific phosphodiesterase type 5, an enzyme that degrades cGMP (66), suppresses the antidepressant activity of chlorpheniramine. Nitric oxide has been proposed to modulate synaptic transmission in several ways; including activation of guanylate cyclase and subsequent cGMP production (67). It has been revealed that depressant effects of NO is dependent on cGMP production in rodents as inhibition of guanylate cyclase induces antidepressant-like behavior (68). While, 5-PDE inhibitors increase the level of cGMP in target tissues, and reverse the antidepressant-like effect of various antidepressants (47).

In summary, our results reveal that the antidepressant-like effect of chlorpheniramine is mediated by inhibition of NO/cGMP pathway and the role of nNOS is more prominent in this process. Our findings along with previous reports thus suggest the NOS inhibitors as augmentation therapy for the management of depression (60). Indeed, additional investigations are needed to verify the exact mechanism of action of chlorpheniramine and prove its practical therapeutic role in clinical setting.

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