RESEARCH PAPER

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The effect of clozapine and $GABA_A$ receptor drugs on scopolamine-induced amnesia in male mice

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Scopolamine, a muscarinic acetylcholine receptor antagonist, disturbs learning and memory processes. Clozapine, an atypical antipsychotic, has beneficial predictive validity for confirming principles to help new treatment approaches. It could improve the cognitive deficit. Furthermore, clozapine has affinity for the cholinergic and GABAergic receptors. This investigation examined the effects of clozapine and/or $GABA_A$ receptor drugs on scopolamine-induced memory impairment in male mice. Step-down passive avoidance and open-field tests were utilized for assessing memory acquisition and locomotor activity, respectively. The results exhibited that pre-training administration of muscimol but not bicuculline induced amnesia without affecting locomotor activity. Moreover, pre-training administration of clozapine did not significantly modify memory acquisition, but co-administration of scopolamine and clozapine improved the amnesia produced with scopolamine. Also, co-administration of muscimol along with clozapine potentiated memory impairment induced by scopolamine, whereas co-injection of bicuculline along with clozapine reversed memory impairment produced by scopolamine. These treatments did not significantly change locomotor activity. Based on the findings, it is concluded that the GABAergic system modulates memory acquisition, and clozapine interacts with both muscarinic and GABAergic systems to bidirectionally regulate scopolamine-induced amnesia. These results suggest the potential involvement of GABAergic mechanisms in the memory-impairing effects of scopolamine and highlight the therapeutic potential of clozapine in mitigating cholinergic dysfunction-related memory deficits.

Key words: scopolamine; clozapine; $GABA_A$ receptor drugs; memory; mice

INTRODUCTION

Acetylcholine is a neurotransmitter broadly distributed in the brain that participates in cognitive and memory, cortical development, and activity (Addy et al., 2005; Tang, 2019; Belardo et al., 2023). Scopolamine, a muscarinic cholinergic antagonist, disturbs memory function in animals and humans (Broks et al., 1988; Hasselmo & Wyble, 1997; Lee et al., 2017; Tang, 2019; Cheon et al., 2021). Evidence indicated that pre-training or post-training injection of scopolamine impairs learning and memory processing (Flood & Gherkin, 1986).

To treat cognitive deficiency, the usage of a "drug repositioning" or "repurposing" plan with potential illness-modifying substances has been raised (Meyer et al., 2010; Choi et al., 2017). Clozapine, an atypical antipsychotic, improves the cognitive deficit and

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ameliorates anxiety and depression (Hagger et al., 1993; Buchanan, 1995; Sharma et al., 2003; Galletly et al., 2005). Clozapine was withdrawn from clinical usage because of agranulocytosis; however, it was then reintroduced because of its efficacy in treating resistant schizophrenia (Kane et al., 1988; Youngren et al., 1999; Naheed & Green, 2001). Studies revealed that clozapine indicates an antagonistic characteristic for both excitatory muscarinic M1, M3, and M5 receptors as well as the inhibitory M2 receptor. It indicates an agonist characteristic for the inhibitory muscarinic M4 receptor and the excitatory muscarinic receptors. Evidence also indicated the effect of clozapine on the GABA system. For example, disease models on the impact of sudden withdrawal of clozapine on the GABA release are reported (O'Connor & O'Shea, 2015).

Gamma-aminobutyric acid, GABA, is the principal inhibitory neurotransmitter in the brain (Wassef et al., 2003; Xu & Wong, 2018; Murari et al., 2020). This neurotransmitter plays a main role in numerous pathophysiological processes, such as the control of the cortical and hippocampal neural pathways and functions, cognitive activity-correlated neural oscillations, as well as data integration and processing (Xu & Wong, 2018). GABA induces its inhibitory effect *via* coupling to $GABA_A$ and $GABA_B$ receptors (Makkar et al., 2010; de Jonge et al., 2017; Xu & Wong, 2018). The $GABA_A$ receptors modulate mood, muscle tension, vigilance, and memory actions, whereas $GABA_B$ receptors modulate the cerebral reward activity and behavior (Tınok et al., 2023). It has been reported that selective inhibition of astrocytic GABA synthesis or release might help as an effective therapeutic approach for treating memory impairment (Jo et al., 2014; Govindpani et al., 2017; Neugebauer et al., 2018).

Regarding the role of clozapine in the improvement of the cognitive deficit (Hagger et al., 1993; Buchanan, 1995; Sharma et al., 2003; Galletly et al., 2005) and the affinity of clozapine on the cholinergic and GABAergic receptors (O'Connor & O'Shea, 2015), this study was designed to validate the possibility of clozapine involvement in modulating the memory process *via* affecting the cholinergic and GABAergic receptors in scopolamine-treated mice.

METHODS

Animals

Adult male NMRI mice (weighing 25–30 g, aged 6–8 weeks) were sourced from the Tehran University of Medical Sciences (Tehran, Iran). The animals were housed in groups of seven per cage under a controlled 12-hour light/dark cycle (lights on at 07:00) and maintained at a constant temperature of 22 ± 1°C. Food and water were provided *ad libitum* except during experimental procedures. All behavioral testing was conducted during the light phase. The experimental protocols were approved by the Ethics Committee of Tehran University of Medical Sciences and strictly adhered to institutional animal care guidelines, in accordance with both the NIH Publication No. 80-23 and the Guide for the Care and Use of Laboratory Animals (10th edition).

Drugs

The following pharmacological agents were employed in this study: muscimol hydrobromide (a $GABA_A$ receptor agonist; Tocris, Bristol, UK), bicuculline (a $GABA_A$ receptor antagonist; Tocris, Bristol, UK), clozapine (Sigma, St. Louis, MO, USA), and scopolamine hydrobromide (a non-selective muscarinic acetylcholine receptor antagonist; Sigma, Poole, Dorset, UK). Muscimol, clozapine, and scopolamine were dissolved in 0.9% saline. Bicuculline was first dissolved in a minimal volume of glacial acetic acid before being diluted to its final volume with 0.9% saline. All compounds were administered *via* intraperitoneal (i.p.) injection at a volume of 10 ml/kg. The selected doses for all drugs were based on established efficacy and protocols from previous scientific literature (Malekmohamadi et al., 2007).

Memory testing and apparatus

The inhibitory avoidance apparatus consisted of a black Plexiglas chamber (30 × 30 × 40 cm) equipped with a grid floor composed of parallel stainless-steel rods (diameter: 0.3 cm, spaced 1 cm apart). A wooden platform (4 × 4 × 4 cm) was positioned at the center of the grid. Electrical foot shocks (50 V DC, 1 Hz, 0.5 s duration) were delivered to the grid floor *via* a stimulator (Borj Sanat Co., Tehran, Iran). Memory assessment was conducted using a step-down passive avoidance paradigm. During the training session (conducted between 08:00 and 12:00 hours), each mouse was gently placed on the wooden platform. Upon stepping down and placing all four paws on the grid floor, the animal received a foot shock after a 15-second delay. Twenty-four hours post-training, a retention test was administered under identical conditions without shock delivery. Step-down latency was recorded over a 5-minute period as a measure of memory retention.

Open-field test (OFT)

Locomotor activity was assessed using an open-field test (OFT). The apparatus consisted of a wooden chamber (40 × 60 × 50 cm) with its floor divided into 12 equal-sized squares. Each mouse was placed in the center of the arena and allowed to explore freely for a 5-minute session. Locomotor activity was quantified by counting the number of squares crossed with all four paws during the testing period. This measurement was recorded manually by the experimenter in real time.

Experimental design

A sample size of seven mice was used per experimental group, with each animal being tested only once to prevent carry-over effects. All behavioral tests were conducted 15 minutes following intraperitoneal (i.p.) drug administration. In experiments requiring consecutive drug injections, a 15-minute interval was maintained between administrations.

Experiment 1

Six experimental groups were established to evaluate the effects of pre-training intraperitoneal (i.p.) administration of $GABA_A$ receptor modulators on learning and locomotor activity. Three groups received injections of either saline (10 ml/kg) or muscimol (0.01 and 0.05 mg/kg) 15 minutes prior to training. The remaining three groups were administered either vehicle (10 ml/kg) or bicuculline (0.1 and 0.5 mg/kg) following the same pre-training timeline.

Experiment 2

Sixteen experimental groups (n=7/group) were employed to assess the effects of pre-training intraperitoneal (i.p.) administration of clozapine, both alone and in combination with subeffective doses of GABAergic drugs, on scopolamine-induced amnesia and locomotor activity. The treatments were designed as follows:

1. Clozapine alone: Four groups received either saline (10 ml/kg) or clozapine (0.1, 0.3, and 0.9 mg/kg) 15 min before training.
2. Clozapine + Scopolamine: Four groups received scopolamine (1 mg/kg) co-administered with either saline or clozapine (0.1, 0.3, and 0.9 mg/kg) 15 min before training.
3. Clozapine + $GABA_A$ modulators + Scopolamine: Eight groups received scopolamine (1 mg/kg) in combination with clozapine (0.1, 0.3, or 0.9 mg/kg) and either a sub-threshold dose of muscimol (0.01 mg/kg) or bicuculline (0.1 mg/kg) prior to training.

All drug administrations were performed intraperitoneally 15 min prior to the behavioral training session.

Statistical analysis

Due to the non-normal distribution of step-down latency data, non-parametric statistical methods were employed for analysis. The Kruskal–Wallis one-way analysis of variance was first applied, followed by pairwise comparisons using two-tailed Mann–Whitney U-tests. The family-wise error rate was controlled using the Holm-Bonferroni sequential correction method for multiple comparisons. Data are presented as median and interquartile range for all seven mice per experimental group. For analysis of locomotor activity data, which exhibited normal distribution, either one-way or two-way analysis of variance (ANOVA) was applied as appropriate, followed by *post hoc* testing for detailed group comparisons. A probability value of $P<0.05$ was considered statistically significant for all analyses.

RESULTS

Influences of pre-training i.p. administration of $GABA_A$ receptor drugs on the learning process and locomotor activity

Kruskal–Wallis ANOVA exhibited that pre-training injection of muscimol ($H_{(2)}=6.034$, $P<0.05$, Fig. 1A) but not bicuculline ($H_{(2)}=3.212$, $P>0.05$, Fig. 1B) decreased the step-down latency in the passive avoidance test. The *post hoc* analysis using Mann–Whitney's U-test showed that muscimol (0.05 mg/kg) impaired memory acquisition, thus presenting an amnesic impact. Furthermore, one-way ANOVA indicated that muscimol ($F_{(2,18)}=0.237$, $P>0.05$, Fig. 1C) and bicuculline ($F_{(2,18)}=0.562$, $P>0.05$, Fig. 1D) did not alter locomotor activity.

Influences of pre-training i.p. administration of clozapine and/or $GABA_A$ receptor drugs on the learning process and locomotor activity with the amnesia induced by scopolamine

Fig. 2A displayed that different dosages of clozapine had no significant effect on the learning process [Kruskal–Wallis analysis ($H_{(3)}=0.162$, $P>0.05$) followed by

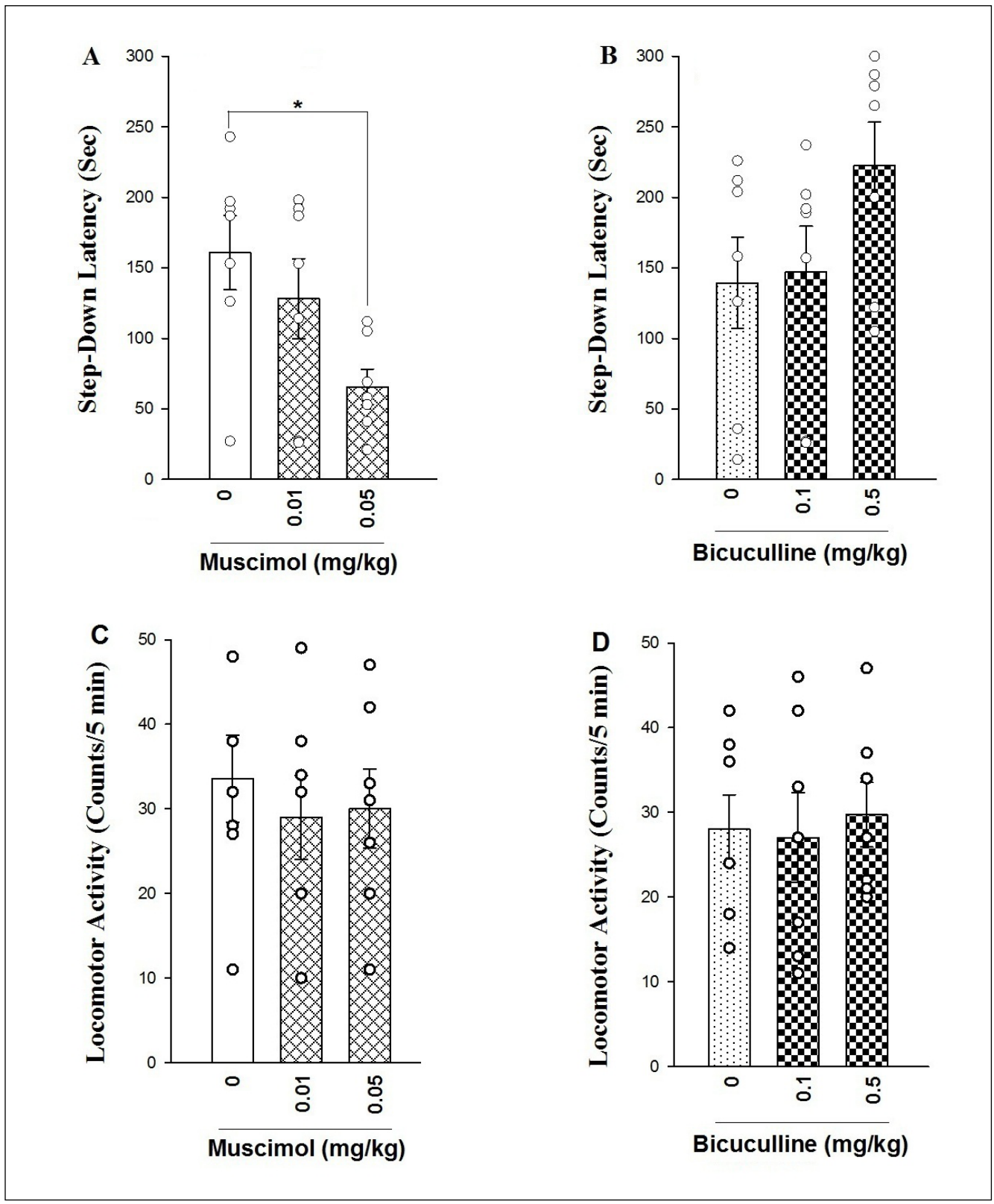

Fig. 1. The effects of pre-training i.p. injection of muscimol and bicuculline on the step-down latency and locomotor activity. Data indicated as mean ± S.E.M. (n=7). Kruskal–Wallis ANOVA followed by Mann–Whitney's U-test was performed to evaluate the data on step-down latency (Panels A and B). Moreover, one-way ANOVA followed by Tukey's *post hoc* test was performed to evaluate the data on locomotor activity (Panels C and D). * P<0.05 compared with saline group.

Mann–Whitney's U-test]. Additionally, one-way ANOVA revealed that clozapine had no significant impact on locomotor activity ($F_{(3,24)}$=0.304, P>0.05; Fig. 2B).

Also, Kruskal–Wallis analysis exhibited that co-treatment of scopolamine and clozapine ($H_{(3)}$=11.176, P<0.01; Fig. 2A) increased the step-down latency in the passive avoidance test. Mann–Whitney's U-test analysis showed that treatment with different dosages of clozapine (0.1, 0.3, and 0.9 mg/kg) reversed amnesia produced by scopolamine (1 mg/kg). Also, one-way ANOVA displayed that co-treatment of clozapine and scopolamine did not change locomotor activity ($F_{(3,24)}$=0.115, P>0.05; Fig. 2B).

Fig. 2A shows the influences of muscimol and clozapine on memory impairment produced by scopolamine (Kruskal–Wallis ANOVA, $H_{(3)}$=3.860, P>0.05). Mann–Whitney's U-test analysis exhibited that co-treatment of an ineffective dosage of muscimol along with clozapine (0.9 mg/kg) potentiated amnesia produced by scopolamine (1 mg/kg). Furthermore, one-way ANOVA exhibited that these treatments did not change locomotor activity ($F_{(3,24)}$=0.089, P>0.05; Fig. 2B).

The results of Fig. 2A indicated the effects of bicuculline and clozapine on memory impairment produced by scopolamine (Kruskal–Wallis ANOVA, $H_{(3)}$=4.958, P>0.05). Mann–Whitney's U-test analysis displayed that co-administration of a non-effective dosage of bicuculline (0.1 mg/kg) along with clozapine (0.9 mg/kg) reversed amnesia induced by scopolamine (1 mg/kg). Also, one-way ANOVA indicated that these treatments did not alter locomotor activity ($F_{(3,24)}$=0.423, P>0.05; Fig. 2B).

DISCUSSION

This study was designed to assess the influence of clozapine in modulating memory acquisition by targeting the cholinergic and GABAergic receptors in male mice. For this, we were selected only not-effective doses of $GABA_A$ receptor drugs due to avoid the dose effect of muscimol and bicuculline. Because treatment of the high doses of the drug induced an effect, however, alone treatment of the not-effective doses of the drug could not induce an effect. Hence the significant results obtained from the co-treatment of the not-effective doses of muscimol and bicuculline along with clozapine and scopolamine revealed the affinity of clozapine on the cholinergic and GABAergic receptors.

First, we assessed the effect of $GABA_A$ receptor drugs on the learning process. Considerable investigations have revealed the influence of the $GABA_A$ receptors in memory processes and neurodegenerative disorders (Chapouthier & Venault, 2002; Makkar et al.,

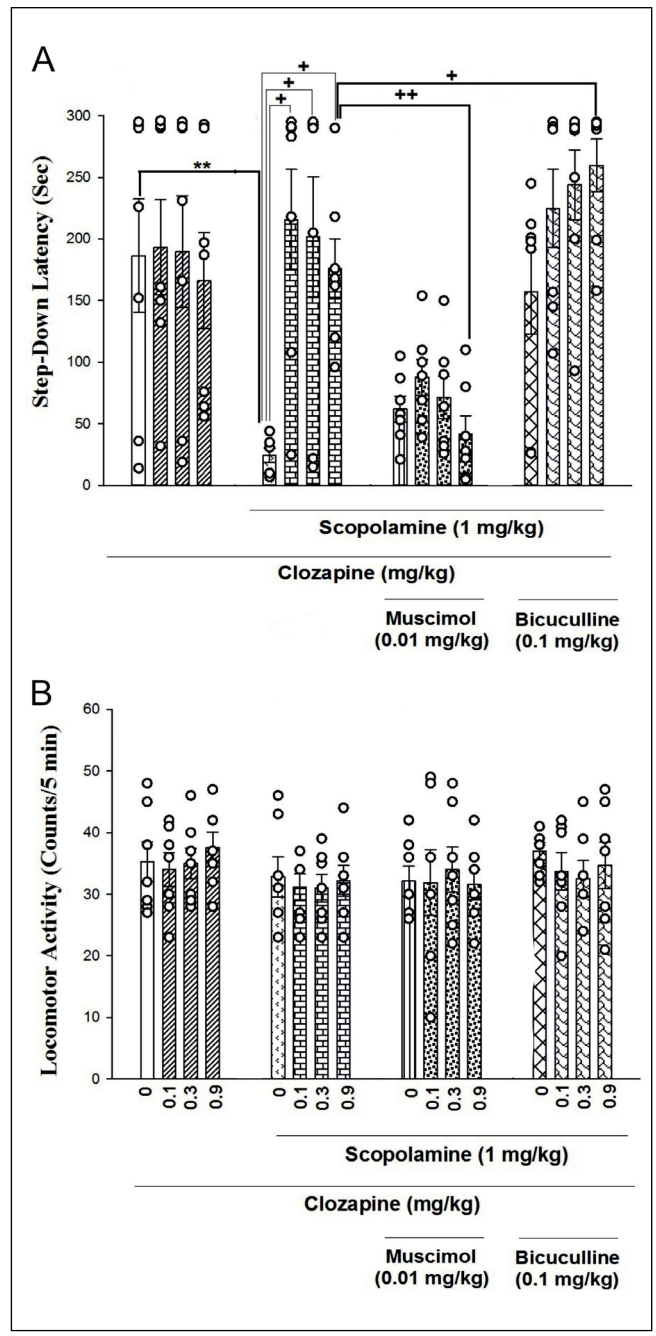

Fig. 2. The effect of pre-training i.p. injection of clozapine and/or $GABA_A$ receptor drugs on learning process and locomotor activity under the amnesia induced by scopolamine. (A) Data indicated as mean ± S.E.M. (n=7). Kruskal–Wallis ANOVA followed by Mann–Whitney's U-test was performed to evaluate the data on step-down latency. (B) Moreover, one-way ANOVA followed by Tukey's *post hoc* test was performed to evaluate the data on locomotor activity. ** P<0.01 indicated statistical significance between saline and scopolamine (1 mg/kg) group. $^+$ P<0.05 indicated statistical significance between clozapine (0.1, 0.3, and 0.9 mg/kg) plus scopolamine (1 mg/kg) group with the scopolamine (1 mg/kg) group. $^+$ P<0.05 and $^{++}$ P<0.01 indicated statistical significance between clozapine (0.9 mg/kg) plus scopolamine (1 mg/kg) plus muscimol (0.01 mg/kg) or bicuculline (0.1 mg/kg) with the clozapine (0.9 mg/kg) plus scopolamine (1 mg/kg) group.

2010; Gasbarri & Pompili, 2014; Murari et al., 2020). Our data showed that muscimol caused an amnesic effect, as evidenced by the reduction in step-down latency in the passive avoidance test. However, bicuculline had no significant impact on memory acquisition. Neither drug altered locomotor activity. We proposed that muscimol binds to the α- and β-subunits of the $GABA_A$ receptor. Hence, chloride channels open, which leads to the entry of chloride ions. Thus, inhibition of neuronal functions was enhanced, resulting in impaired memory acquisition (Makkar et al., 2010; Neugebauer et al., 2018; Xu & Wong, 2018). Moreover, bicuculline occupies the GABA-binding site, inhibiting GABA from coupling to and stimulating the receptor (Makkar et al., 2010). Evidence in rodents has revealed the influence of $GABA_A$ receptors in cognition *via* diverse genetic and pharmacological plans (Collinson et al., 2002; Michels et al., 2012; Xu & Wong, 2018). Substances that increase the function of GABA, for example, benzodiazepines, impair memory processing. On the other hand, substances that decrease the function of GABA, for example, pentylenetetrazol or picrotoxin, increase memory processing (Chapouthier & Venault, 2002). Evidence has confirmed the relation between cognitive function and GABA dysfunctions (Enomoto et al., 2011; Chen et al., 2014). Also, evidence has indicated that GABAergic inhibition plays a main role in numerous processes, including sensory processing, neuroplasticity, attention, memory, and learning (Jung et al., 2025). According to these findings, some evidence indicated that the injection of $GABA_A$ receptor agonists disrupts fear memory. While $GABA_A$ receptor antagonists improve fear memory acquisition and retention, showing that GABAergic neurotransmission is harmful to the acquisition and consolidation of fear memories (Makkar et al., 2010).

Additionally, there is evidence suggesting that clozapine improved cognitive deficit (Hagger et al., 1993; Buchanan, 1995; Sharma et al., 2003; Galletly et al., 2005), which might be *via* interacting with other neurotransmitters, such as acetylcholine and GABA (O'Connor & O'Shea, 2015). The obtained data indicated that i.p. treatment with different dosages of clozapine did not meaningfully change memory acquisition, but co-administration of scopolamine and clozapine improved memory impairment induced by scopolamine *via* enhancement of the step-down latency in the passive avoidance test. In combination treatments, injection of muscimol along with clozapine potentiated amnesia induced by scopolamine, while injection of bicuculline along with clozapine reversed amnesia produced by scopolamine. These treatments did not change locomotor activity. Studies exhibited that counteracting scopolamine-induced amnesia, by either pre-training or post-training drug administration, is not specific to the cholinergic system (Flood & Gherkin, 1986). In agreement with our findings, preclinical and clinical investigations showed that scopolamine can impair memory function in rodents and humans, mainly the short-term memory and learning acquisition (Tang, 2019). Previous studies have revealed that scopolamine enhances the accumulation of reactive oxygen species, which causes oxidative stress resulting in memory impairment (Pushpalatha et al., 2013). A large body of studies reported that clozapine improves cognitive deficiency, anxiety, and depression (Hagger et al., 1993; Buchanan, 1995; Sharma et al., 2003; Galletly et al., 2005). It also improves quality of life and reduces suicidal ideation (Meltzer & Okayli, 1995). Clozapine quickly crosses the blood–brain barrier. It is removed more quickly in small mammals (half-life of about 1.5 h) in comparison to being detected in humans (half-life of about 14–16 h) (Baldessarini et al., 1993). Clozapine shows agonist and antagonist functions for several neurotransmitter receptors and mainly for receptors located in the mesocorticolimbic circuits (Roth et al., 2003). Studies revealed the effect of clozapine on the cholinergic and GABAergic receptors (O'Connor & O'Shea, 2015). The obtained results might be because of the crossing of clozapine from the blood–brain barrier and binding to the acetylcholine and GABA receptors located in a variety of brain areas, for instance, the prefrontal cortex and hippocampus, which are important for the memory process (Addy et al., 2005). One of the limitations of this research is that we did not assess the potential neurobiological mechanisms underlying interaction between scopolamine, $GABA_A$ receptor drugs, and clozapine. Also, we did not assess the possible pathways involved in this interaction. So, the future perspectives of the research are valuation of the neurobiological mechanisms which describe the exact pathways and mechanisms of interaction between scopolamine, $GABA_A$ receptor drugs, and clozapine upon the mediation of memory acquisition in mice.

CONCLUSION

In conclusion, because of the impacts of injection of muscimol (significant reduction of memory acquisition), co-administration of scopolamine and clozapine (significant increase in memory acquisition), and co-injection of scopolamine, muscimol, and clozapine (potentiation of amnesia), as well as co-administration of scopolamine, bicuculline, and clozapine (enhancement of memory acquisition), it can be suggested that there is crosstalk between scopolamine, $GABA_A$

receptor drugs, and clozapine in the control of memory acquisition. Based on the findings of the current investigation, it can be suggested that the application of clozapine along with $GABA_A$ receptor antagonists, for example, bicuculline, reversed amnesia produced by scopolamine in male mice. Nonetheless, additional experiments are needed to describe the exact mechanisms of action of clozapine, acetylcholine, and $GABA_A$ receptor drugs on the control of memory acquisition.

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