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ORIGINAL ARTICLE

Neuroprotective Effect of Famotidine in Mouse Models of Alzheimer's Disease

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SUMMARY

Background: **Famotidine is a competitive histamine H-receptor antagonist that reduces the formation of stomach acid and is used to treat gastrointestinal disorders associated with acid reflux, gastroesophageal reflux disease, duodenal ulcer, gastric ulcer, and pathological hypersecretory disorders. This study is designed to investigate the possible neuroprotective effects of the ranolazine scopolamine-induced Alzheimer's disease-like feature in a mouse model.**

Methods: **Mice were divided equally into five groups (ten mice per group), including control group and induction group. The mice in the induction group were administered scopolamine 1 mg/kg i.p., once daily for 7 days, to induce features similar to Alzheimer's disease. The mice in the remaining three treatment groups were given tested medications prophylactically for 14 days. After that the induction was carried out with scopolamine 1 mg/kg i.p., once daily, while the tested medication dosages were continued for an additional 7 days. These treatment groups included: the donepezil group (5 mg/kg/day), the famotidine group (40 mg/kg/day) and the combined group with donepezil (5 mg/kg/day) and famotidine (40 mg/kg/day); all were administrated i.p., once daily. Behavioral parameters were assessed, among others with the Y-maze test and novel object recognition test, and the inflammatory cytokines and oxidative stress parameters were assessed as well.**

Results: **Famotidine exhibits significant improvements in behavior and memory, level of oxidative stress parameter, and inflammatory cytokines.**

Conclusions: **Famotidine and its combination at prescribed doses in the current study improved learning and memory impairments in mice model of Alzheimer's disease probably via their antioxidant and anti-inflammatory properties confirmed by a significant increase in antioxidant mediator and a significant decrease in oxidative stress marker and inflammatory cytokines.**

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KEYWORDS

Alzheimer’s disease, famotidine, donepezil, inflammatory cytokines, oxidative stress

LIST OF ABBREVIATIONS

NOR - Novel object recognition
IL-1β - Interleukin-1beta
MDA - Malondialdehyde
SOD1 - Superoxide dismutase 1
TNF-α - Tumor necrosis factoralpha

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INTRODUCTION

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease that often starts slowly and gets worse over time, as more areas of the brain are affected and more symptoms appear. The buildup of beta amyloid protein fragments outside of neurons and the twisting of tau protein fibers inside of neurons are the main characteristics of AD pathogenesis [1].

Numerous hypotheses about AD have been suggested, including those involving amyloid-β (Aβ), Tau, cholinergic neuron destruction, oxidative stress, inflammation, etc. On the basis of these hypotheses, numerous efforts have been made to create anti-AD medications [2]. Six medications have received FDA approval to be used in the treatment of Alzheimer's disease. Four of these medications, donepezil, rivastigmine, galantamine, and memantine in combination with donepezil, treat Alzheimer's symptoms only temporarily; they have no effect on the underlying brain abnormalities associated with the illness [3].

The brain is especially prone to oxidative stress due to its high oxygen consumption, which uses 20% more oxygen than other mitochondrial respiratory tissues [4]. The fundamental functional unit of the brain is the neuron, which is rich in polyunsaturated fatty acids. Less glutathione in neurons is another factor contributing to oxidative stress injury. It can interact with ROS, causing the lipid peroxidation reaction and molecular apoptosis [5].

Famotidine is a competitive histamine H-receptor antagonist that reduces the formation of stomach acid and is used to treat gastrointestinal disorders associated with acid, including gastroesophageal reflux disease (GERD), duodenal ulcer, gastric ulcer, and pathological hypersecretory disorders [6]. Famotidine efficiently inhibits the effects of histamine by attaching to the H-receptors, found on the basolateral membrane of the parietal cell in the stomach [7]. *In vitro* studies using SARS-CoV-2 infected cells have shown that famotidine inhibits histamine-induced toll-like receptor 3-mediated inflammatory signaling [8]. Famotidine may contribute to the decreased histamine-induced inflammation and cytokine release, which may improve the outcome for COVID-19 patients, according to pharmacokinetic studies that show that it can reach blood levels sufficient enough to antagonize histamine H2 receptors expressed on mast cells, neutrophils, and eosinophils [8].

Snyderetal 2022 [9] demonstrated famotidine's antioxidant properties and its protective effects. During ischemia, famotidine prevented drops in antioxidant levels and rises in oxidative stress indicators.

The current study aimed to investigate and evaluate the possible neuroprotective effects of ranolazine against scopolamine-induced AD-like features in mouse model.

MATERIALS AND METHODS

Fifty male mice, with an age range of 2 - 3 months and a weight range of 25 - 35 g, were housed under standard laboratory conditions, with a temperature of 20 - 22℃. The following drugs were used: scopolamine (hyper chem, China), famotidine (hyper chem, China), and donepezil (hyper chem, China) are dissolved normal saline. Y-maze and open field box are locally made in Baghdad.

The animals were divided equally into 5 groups of 10 mice each. Group 1: negative control group. Group 2 (induction group): mice received scopolamine i.p., 1 mg/kg, once daily for 7 days, to induce AD-like features (Yadanget al., 2020) [10]. The other three treatment groups included mice that received tested drugs prophylactically for 14 days, then the induction with scopolamine i.p., 1 mg/kg, once daily, together with the continuation of the same doses of the tested drugs for further 7 days. These treatment groups included group 3 (donepezil group): donepezil 5 mg/kg i.p., once daily (Eskandary et al., 2019) [11], group 4 (famotidine group): famotidine 40 mg/kg i.p., once daily (Ahmadiet al., 2011) [12], and group 5 (combined group)(donepezil + famotidine): donepezil 5 mg/kg and famotidine 40 mg/kg; both were administrated i.p., once daily. Behavioral tests, including cognitive examination by using Y maze and novel object recognition (NOR), were done on day 25 for three successive days.

Behavioral tests

Y-maze test

This device is designed like a Y, with three equal arms, that were conveniently denoted by the letters A, B, and C. The arms had the following measurements: 15 cm high, 6 cm wide, 20 cm long, and a 120° angle connecting them to one another (Nazir et al., 2020) [13].

Each animal was subjected to this test for a total of 10 minutes. Each animal was placed in one arm, and the sequence and number of arms it entered after that was noted. Complete arm entrance was defined as the hind paws fully enclosing any given arm, while alternation was defined as each mouse making three consecutive arm entries into different arms. To prevent olfactory cues between tests, the Ymaze arena was cleaned with an ethanol 70% v/v solution (Kirshenbaum et al., 2015) [14].

The spontaneous alternation (%) was computed by multiplying the number of arm entries minus two divided by the sum of all the alternations, which resulted in the following equation (Lee et al., 2017) [15]:

$$\text{Alternations \%} = \frac{\text{No. of Alternations}}{\text{Total No. of Arm Entries} - 2} \text{ x } 100$$

Novel object recognition (NOR)

The experimental tool was a white plastic open field box measuring 40 cm x 40 cm x 20cm.

Three phases make up this evaluation: 1) habituation; on the first day, each mouse was permitted to recognize the open field box for around 15 minutes without an object present. 2) training; each mouse was left in an open field for 10 minutes on the second day and was free to explore the two comparable objects. 3) test; 90 minutes following the training session, one of the familiar objects was swapped out for a novel one, and the mice ran for 5 minutes while the duration of the time consumed with both objects was noted (Ghias et al., 2019) [16]. The recognition index was determined by using the following formula: [TB/(TA + TB)* 100]. Object exploration was described as active involvement with the object, such as smelling or touching the object with the nose and/or forepaws, where TA and TB are the times spent investigating familiar object A and novel object B, respectively (Batool et al., 2016) [17].

After the behavioral tests, animals were anesthetized by inhaled diethyl ether. The animals were sacrificed, and their brains were immediately removed and washed in cold phosphate -buffered saline. One hemisphere of the brain was rinsed in ice-cold PBS (0.02 mol/L, pH 7.2 - 7.4). The homogenized tissue of mouse brain was used to assess the oxidative stress indices (levels of MDA and SOD1) and the inflammatory cytokines (levels of IL-1β, IL-6, and TNF-α) in mouse brain tissues, with aid of ELISA (BT LAB), according to the manufacturer's recommendations accordingly.

Statistical analysis

All data were presented as mean ± standard deviation. Independent *t*-test and a one-way ANOVA (analysis of variance) test were used for the statistical comparisons, and p-values equal 0.05 or less were considered statistically significant. The data were analyzed by using the statistical package for social sciences (SPSS), version 23, and Excel 2010.

RESULTS

Ymaze test

The spontaneous alteration highly significantly decreased ($p \leq 0.001$) in scopolamine (induction group) when being compared to the control group, while each of the donepzil, famotidine, and combined (donepzil + famotidine) groups showed a highly statistically significant increase in the spontaneous alteration in comparison to the induction group, and there was no statistically significant change ($p > 0.05$) when being compared with the control group (Table 1).

NOR test

The recognition index highly significantly decreased in scopolamine (induction group) when being compared to the control group. While each of the donepzil, famotidine, and combined (donepzil + famotidine) groups showed a highly statistically significant increase in the recognition index when being compared to the induction group, and there was no statistically significant change when being compared with control group (Table 1).

Assessment of oxidative stress

Compared to the control group, the induction group showed a highly significant increase in MDA level and a highly significant decrease in SOD1. Each of the donepezil, famotidine, and combined (donepezil + famotidine) groups showed a highly significant decrease in MDA levels and a significant increase in SOD1 levels compared to the induction group. Compared to MDA and SOD1 level of the control group, the donepezil, famotidine, and combined (donepezil + famotidine) groups showed a statistically non-significant change ($p > 0.05$) (Table 2).

Assessment of inflammatory cytokines

Compared to the control group, there were highly significant increases in IL-1β, IL-6, and TNFα levels in the induction group, while in comparison to the induction group, each of the donepzil, famotidine, and combined (donepezil + famotidine) groups showed highly significant decreases in IL-1β, IL-6, and TNFα levels. There were non-significant changes in IL-1β, IL-6, and TNFα levels in the donepzil, famotidine, and combined (donepezil + famotidine) groups when being compared to the control group (Table 3).

DISCUSSION

Alzheimer's disease is one of the most prevalent, progressive neurodegenerative disorders that results in serious suffering for patients and their relatives (Scheltenset et al.,2021) [17]. Although there is mounting evidence that AD is a complicated illness resulting from several causes with different molecular targets, the precise pathophysiology of AD is still unknown. Thus, while developing a novel medication, synaptic malfunction, oxidative stress, or the early stages of neuroinflammation must be considered [18].

Scopolamine hydrochloride has been used in the current study to induce memory impairment in a mouse model. In experimental models, it's frequently used to induce dementia-like AD. Scopolamine-induced amnesia has been used to assess the therapeutic efficacy of medications in the experimental model of neurodegenerative disease in an effort to identify anti-dementia medications, since it is linked to oxidative stress and synapse loss throughout the brain [19].

The Y-maze was applied, and novel object recognition (NOR) tests were conducted to evaluate the cognitive performance (memory and learning). In accordance with earlier research, scopolamine (induction groups) demonstrated the lowest level of motion in the Y-maze behavioral test, in terms of the percentage of spontaneous alternations and total arm entries, when compared with the control group [20]. In the NOR test, the scopol-

Table 1. Effects of famotidine and donepezil on behavioral tests.

Groups	Y-maze	NOR
Control	66.58 ± 2.82	63.58 ± 2.81
Induction (scopolamine)	53.72 ± 4.32 ##	50.16 ± 4.0 ##
Donepezil	67.58 ± 4.0 **	64.77 ± 5.35 **
Famotidine	65.12 ± 4.58 **	61.02 ± 3.92 **
Donepezil + famotidine	65.97 ± 3.95 **	63.54 ± 6.21 **

n = 10 mice/group, data are expressed as mean ± SD, # statistically significant ($p \leq 0.05$), ## highly statistically significant ($p \leq 0.001$) compared with the control group, * statistically significant ($p < 0.05$), ** highly statistically significant ($p \leq 0.001$) compared with the induction (scopolamine) group.

Table 2. Effects of famotidine and donepezil on oxidative stress parameters.

Groups	MDA (ng/mL)	SOD1 (ng/mL)
Control	1.74 ± 0.21	16.93 ± 2.55
Induction (scopolamine)	2.57 ± 0.29 ##	10.87 ± 2.32 ##
Donepezil	1.65 ± 0.21 **	14.51 ± 3.59 *
Famotidine	1.64 ± 0.24 **	17.99 ± 2.39 **
Donepezil + famotidine	1.94 ± 0.77 **	14.79 ± 2.91 *

n = 10 mice/group, data are expressed as mean ± SD, # statistically significant ($p \leq 0.05$), ## highlystatistically significant ($p \leq 0.001$) compared with the control group, * statistically significant ($p < 0.05$), ** highly statistically significant ($p \leq 0.001$) compared with the induction (scopolamine) group.

Table 3. Effects of famotidine and donepezil on inflammatory cytokines.

Groups	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)
Control	130.77 ± 18.32	693.56 ± 150.18	156.45 ± 39.04
Induction (scopolamine)	189.89 ± 33.93 ##	983.69 ± 109.73 ##	227.51 ± 35.19 ##
Donepezil	125.91 ± 21.21 **	744.48 ± 34.39 **	158.68 ± 15.92 **
Famotidine	133.41 ± 17.84 **	577.16 ± 131.7 **	145.31 ± 21.1 **
Donepezil + famotidine	127.42 ± 14.32 **	674.41 ± 170.65 **	157.98 ± 22.61 **

n = 10 mice/group, data are expressed as mean ± SD, # statistically significant ($p \leq 0.05$), ## highly statistically significant ($p \leq 0.001$) compared with the control group, * statistically significant ($p < 0.05$), ** highly statistically significant ($p \leq 0.001$) compared with the induction (scopolamine) group.

amine group's recognition index significantly decreased in comparison to the control group, indicating a potential impairment in the process of learning and recognition. The results revealed that scopolamine, an anticholinergic medication that blocks muscarinic receptors, interfered with learning and both short- and long-term memory performance, as previously reported by (Lizethet et al. in 2024) [21].

The current study's findings confirm the previous suggestion that there was a collapse in the brain's antioxidant defense mechanism, as seen by a higher level of MDA in the group receiving scopolamine medication than in the control group [10]. In the present study, superoxide dismutase (SOD1) was significantly decreased in the brain homogenate when compared to the control group. Among all the antioxidant enzymes, superoxide dismutase (SOD1) is the most important enzyme as the SOD1 detoxifies superoxide anions which have harmful

effects on the cell membrane [22]. The current study's findings confirm that the oxidative stress state following scopolamine administration resulted from the elevated MDA level and decreased SOD1 level in the induction group's brain homogenate.

Behavioral anomalies and memory impairments produced by scopolamine are demonstrated by spatial memory and learning. Significant impairment of cognitive function is caused by scopolamine, which has been associated with elevated levels of AChE, oxidative stress, neuroinflammatory markers, IL-1β, TNF-α, IL-6, and IFN in the brain [23]. The abnormal productions of inflammatory cytokines induce neuronal damage, preceding the progression of AD. According to earlier research, administering scopolamine for experimental animal model significantly raised the neuroinflammatory markers, which lead to neuronal damage [20].

The present study demonstrated that scopolamine administration increases inflammatory mediators and neurotoxic cytokines, including IL-1β, TNF-α, and IL-6, as previously reported by (Muhammad et al., 2019) [24]. This study shows that famotidine significantly improves the recognition index and the average of spontaneous alteration, suggesting that the drug may have a protective effect against the cognitive impairment brought on by scopolamine. The current study's findings are in agreement with those of Unal, 2020 [25], who demonstrated that famotidine pretreatment inhibited ketamine's disruptive effect on sensorimotor gating in rodents and enhanced the recognition index when NOR test was performed. Furthermore, when rats were given famotidine alone, their memory performance remained unchanged. Nikiforuket et al. (2016) [26] demonstrated that famotidine therapy corrected the majority of behavioral impairments, involving visual recognition memory, learning and memory, and social performances, in a rat model of schizophrenia-like behavior induced by ketamine, proposing its molecular effects on the signaling pathway Akt/GSK-3/-Catenin. One case report, published in 2020, by Alper [27], found that a young patient's neuropsychiatric problems, which had emerged after COVID-19, were relieved by 20 mg of oral famotidine administered two times daily; the anti-inflammatory effect of famotidine resulting from the stimulation of the vagus nerve inflammatory reflex.

The present study revealed that famotidine exhibited a significant reduction in MDA level and a significant elevation in SOD_1 level, indicating its powerful antioxidant effects. These findings appear to be consistent with Kurt et al. (2011) [28], who demonstrated famotidine's preventive effect against ovarian damage resulting from ischemia-reperfusion in rats, via reducing oxidative stress marker (MDA) and maintaining tGSH, SOD levels, suggesting that famotidine inhibits a drop in enzymatic and non-enzymatic anti oxidation levels. In the present study, famotidine exhibited significant reduction in pro-inflammatory cytokines (TNF- α, IL-1β, and IL-6).

Yang et al. (2022) [29] showed that in severe viral infection, such as COVID-19, famotidine has a potential role in reducting the inflammation by lowering TNF-α and IL-6 and by preventing cytokine storm, since it inhibits the synthesis of histamines that might worsen immunological reaction and trigger cytokine storm. Furthermore, by stimulating the immunological response, famotidine stimulates the activity of specific immune cells, including T cells and natural killer cells. In SARS-CoV-2-infected cells, it was discovered that famotidine decreased the amounts of specific proteins linked to the NF-B pathway, the interferon pathway, and TLR signaling [8].

Calabrese et al. (2020) [30] showed that famotidine may avert cytokine storms and suppress inflammatory biomarkers such as IL-6, TNF-α, ferritin, CRP (c-reactive protein), and procalcitonin. This is in agreement with the findings in this study.

Tanriverdi et al. (2021) [31], who investigated the antioxidant effect of famotidine on testicular torsion, showed that famotidine protects against ischemia reperfusion damage by suppressing an upsurge in oxidative stress indicators MDA and NO and by stimulating the formation of antioxidants. This is in line with the current study. The potent antioxidant effects of famotidine have been shown *in vitro*, especially when it involves scavenging hydroxyl radicals, nitric oxide (NO), and myeloperoxidase-catalyzed processes; all of these could contribute to a significantly reduced inflammation [31].

CONCLUSION

1) Famotidine has a neuroprotective effect against scopolamine-induced AD-like features in mouse model.
2) Famotidine and its combination at prescribed doses in the current study improved learning and memory impairments in mice model of Alzheimer's disease induced by scopolamine probably via their antioxidant and anti-inflammatory properties confirmed by a significant increase in antioxidant mediator (SOD_1) and a significant decrease in oxidative stress marker (MDA) and inflammatory cytokines (TNF-α, IL-1β, and IL-6).
3) Further detailed studies are recommended to determine the effective doses and to elucidate the precise mechanisms of the preventive actions of famotidine and the famotidine against scopolamine-induced AD-like features in laboratory animals.

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Ethical Approval:
Ethical approval for conducting this study was issued and approved by the Department of Pharmacology of the College of Medicine, Al-Nahrain University, Iraq. (https://www.colmed-alnahrain.edu.iq/?&lang=en), according to the letter no. 2/3/1970 dated in December 12, 2021.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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