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Protective Effects of Dapsone on Scopolamine-Induced Memory Impairment in Mice: Involvement of Nitric Oxide Pathway

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Keywords
Memory · Dapsone · Nitric oxide · Scopolamine · Mice

Abstract
Introduction: The leading cause of memory impairment is dementia-related disorders. Since current treatments for memory impairment target the neuroinflammatory pathways, we selected dapsone, an anti-inflammatory agent, to evaluate its effects on scopolamine-induced memory impairment in mice and the underlying role of nitric oxide (NO). ***Methods:*** Scopolamine (1 mg/kg, intraperitoneal [i.p.]) was used for induction of memory impairment. The animals received various doses of dapsone (0.1, 0.3, 1, 5, and 10 mg/kg, i.p.). Duration and number of arms visits in the Y-maze and step-through latency in the passive-avoidance were documented. To evaluate the underlying signaling pathway, N(ω)-nitro-L-arginine methyl ester (a nonspecific NO synthase [NOS] inhibitor), aminoguanidine (a specific inducible NOS inhibitor), and 7-nitroindazole (a specific neuronal NOS inhibitor) were administered 30 min after dapsone administration. ***Results:*** Dapsone (5 mg/kg) substantially improved memory acquisition in scopolamine-induced memory impairment. Additionally, NOS inhibitors considerably reversed the observed neuroprotective effects of dapsone, accompanied by the elevation of NO levels. ***Conclusion:*** Dapsone revealed a neuroprotective effect against scopolamine-induced memory impairment in mice, possibly through the nitrergic pathway.

Introduction

Neuroinflammation can deteriorate memory and impair cholinergic activities. The cholinergic system is a critical pathway associated with brain functions such as learning and memory [1]. This pathway gained a lot of attention as a target to treat dementia-related disorders. Scopolamine, a muscarinic receptor antagonist, can cause memory impairment by blocking the central cholinergic neurotransmission. Cholinergic fibers release nitric oxide (NO), a free radical gas that modulates the cholinergic

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activity and memory formation processes [2]. Studies are trying to find better options to treat memory impairment and prevent neuronal damage. Animal studies have confirmed scopolamine-induced memory impairment as a validated model for inducing memory deficits in rodents [3].

Dapsone (diamino diphenyl sulfone) is an anti-inflammatory drug that has recently shown neuroprotective effects. It has been suggested that dapsone has neuroprotective effects in different animal and clinical studies, e.g., treatment of memory disturbance by administration of dapsone and corticosteroids in a patient with relapsing neuro-Sweet's disease [4], neuroprotective effects against ischemic strokes by administration of dapsone alone [5], and against kainic acid-induced neurotoxicity by administration of dapsone and phenobarbital [6]. In this study, we aimed to assess the protective effects of dapsone in scopolamine-induced memory impairment in mice and speculate NO's role, using NO synthase (NOS) inhibitors.

Materials and Methods

Animals and Housing Condition

A total of 230 male naval medical research institute mice (30 ± 2 g, 7–8 weeks) were purchased from the Tehran University of Medical Sciences. Rodents were maintained on standard housing conditions (23°C, 60% humidity, adjusted light cycle) with unrestricted access to food and water. Animals were housed in groups of 5 mice per cage. The behavioral tests were done between 9 a.m. and 3 p.m. in a group consisting of 10 mice, and each mouse was used only once [7, 8]. The rodents were allowed 1-week habituation in the experimental environment. In Y-maze, mice were acclimated to the maze 5 min before the test [9]. In passive-avoidance, mice were placed in the lit compartment for 60 s to acclimate to the device before opening the gate [10].

Drugs

Dapsone, from Gilaranco Pharmaceuticals (Rasht, Iran), was dissolved in 4% dimethyl sulfoxide. N(ω)-nitro-L-arginine methyl ester (L-NAME), aminoguanidine (AG), 7-nitroindazole (7-NI), and scopolamine hydrobromide were obtained from Sigma Corporation and were dissolved in normal saline except for 7-NI, suspended in 1% Tween 80. All drugs were administered intraperitoneally. The administered dosage of our drugs was as follows: dapsone (0.1, 0.3, 1, 5, or 10 mg/kg), scopolamine (1 mg/kg), L-NAME (nonselective NOS inhibitor 10 mg/kg), AG (inducible NOS inhibitor, 100 mg/kg), and 7-NI (neuronal NOS inhibitor, 15 mg/kg) [11–14].

Study Design and Experimental Procedures

Animals were divided into 23 groups consisting of 10 mice. Drugs were administered as demonstrated in Figure 1. The experimental groups and study design are summarized in Table 1. We evaluated the spatial short-term memory and fear memory via Y-maze and passive-avoidance (P-A) tests.

Y-Maze

Y-maze is based on rodents' natural interest and willingness to discover novel territories. This test is useful for studying rodent memory since it does not need rule learning [15, 16]. Rodents instinctively favor the novel territories instead of returning to the previously visited sites. Various areas of the brain, including the hippocampus, are stimulated in this experiment. Y-maze has three horizontal arms (40 cm length × 8 cm width ×12 cm height) placed at 120° angle. For differentiation between arms, the walls had different colors (white, green, and pink). The experiment consists of an acclimation phase, a train, and a trial session divided by a 60-min gap. In the train session (10 min), rodents were placed in the middle of the maze and were permitted to freely move around between the arms (start and other), while the novel arm was obstructed. After 60 min, rodents were positioned in the middle of the maze for the trial session (8 min), while moving between the arms was unrestricted. The behavioral evaluations were recorded and then analyzed by a blind inspector to determine the duration and number of arms visits during the trial session [17]. In addition, the total number of arm entries over the total experiment period of the trial phase was considered as the locomotor movement index. To exclude sensory stimulation, we layered the maze floor with sawdust, which was changed between trials, and the walls were thoroughly cleaned using a water spray. The maze was placed in a quiet environment with natural light, and all the experiments were performed under the same condition. The animals' behavior in the Y-maze was measured using the following indexes: (1) duration of arms visits (seconds) and (2) number of arms visits (%). Identifying the new arm from the previously visited arms and increasing the duration and number (%) of arms visits in the novel arm were measured as an index for spatial memory determination [18].

Passive-Avoidance

A step-through P-A is a fear-based memory test [19]. The passive-avoidance chamber is divided into two illuminated and nonilluminated similar sections (20 cm^3), divided with a gate between two chambers. The lit section had a 40-W lamp, and the surface of the other area was framed with steel bars placed 1 cm aside. The passive avoidance consists of an acclimation phase, a train, and a test session. Throughout the train session (first day), rodents were located in the lit section, and when rodents crossed the gate toward the dark section, the gate closed behind them, and the mouse received a mild foot shock (0.5 mA, 1 s). In the test session (second day), rodents were positioned in the lit section where no shock was delivered, and the latency time to cross the gate was documented. The mice with intact memory averted entering the dark compartment where they were formerly shocked. The cutoff time was set to 5 min. Step-through latency (STL, seconds) was used as a behavioral index in the P-A. Step-through latency is defined as the delay of entering the dark chamber from the lit chamber. An increase in the STL time is measured as an index of fear memory determination [12].

Biochemical Analysis

Tissue Preparation

To decrease the excessive stress caused by behavioral tests, 24 h after the procedures, rodents were sacrificed by cervical decapitation, and their brain was promptly extracted and washed with cold saline [20]. The hippocampi tissues were extracted on the ice-cold surface, instantly put in a liquid nitrogen tank, and stored in a −80 freezer for biochemical analyses [14].

Table 1. The description of experimental groups involved in this study and all the administered drugs and behavioral tests

Experimental groups	Pretreatment injections	Treatment injections	Behavioral experiment
Sham	4% DMSO (ip)	–	Y-maze
Control	–	Scopolamine (1 mg/kg, ip)	Y-maze
Dapsone	Dapsone (0.1, 0.3, 1, 5, or 10 mg/kg, ip)	Scopolamine (1 mg/kg, ip)	Y-maze
Intact memory	Dapsone (5 mg/kg, ip)	–	Y-maze
NOS inhibitors per se	–	L-NAME (10 mg/kg, ip) or AG (100 mg/kg, ip) or 7-NI (15 mg/kg, ip) + scopolamine (1 mg/kg, ip)	Y-maze
NOS inhibitors plus dapsone	Dapsone (5 mg/kg, ip)	L-NAME (10 mg/kg, ip) or AG (100 mg/kg, ip) or 7-NI (15 mg/kg, ip) + scopolamine (1 mg/kg, ip)	Y-maze
Sham	4% DMSO (ip)	–	P-A
Control	–	Scopolamine (1 mg/kg, ip)	P-A
Dapsone	Dapsone (5 mg/kg, ip)	Scopolamine (1 mg/kg, ip)	P-A
NOS inhibitors per se	–	L-NAME (10 mg/kg, ip) or AG (100 mg/kg, ip) or 7-NI (15 mg/kg, ip) + scopolamine (1 mg/kg, ip)	P-A
NOS inhibitors plus dapsone	Dapsone (5 mg/kg, ip)	L-NAME (10 mg/kg, ip) or AG (100 mg/kg, ip) or 7-NI (15 mg/kg, ip) + scopolamine (1 mg/kg, ip)	P-A

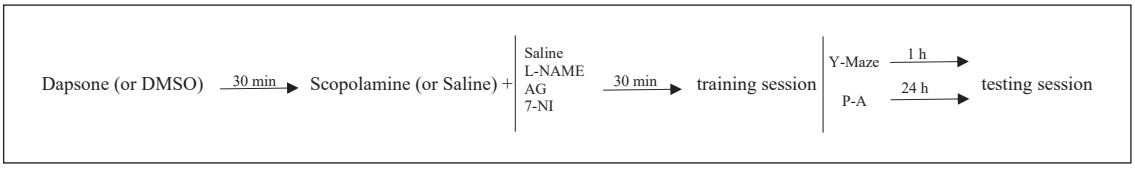

Fig. 1. Timeline of the memory impairment induction, treatment, and behavioral experiments.

NO Assay

The Griess reaction method (Griess reagent [modified], catalog number: G4410, Sigma-Aldrich) was utilized to measure NO levels. The frozen hippocampi samples were homogenized using lysis buffer solution (pH = 8), then incubated for 10 min at room temperature, followed by centrifugation for 10 min (10,000 rpm). The absorbance was determined at 540 nm after 15 min using an automated plate reader. The final concentrations were adjusted for the protein concentration of the samples, and the final results were stated as nmol/mg-protein [2, 21].

Statistical Analysis

Statistical analyses were assessed by GraphPad Prism (v.8.2.1 for macOS). The differences in duration of arms visits, number of arms visits (%), STL, and the NO concentration were analyzed by a one-way analysis of variance accompanied by Tukey's post hoc test in dapsone administered groups. A two-way analysis of variance test was used to analyze the data in dapsone + NOS inhibitors groups. All the values exhibited as mean ± standard error of the mean (SEM). It was considered statistically significant when a p value was less than 0.05. In reporting results, degree of freedom was set as (n-1) while "n" indicates the number of groups involved in the related analysis. The normal distribution of the data was first confirmed via the Shapiro-Wilk test.

Results

Effect of Dapsone on Scopolamine-Induced Memory Impairment in Mice

Y-Maze

Rodents in the saline-treated group distinguished the novel arm from the other arms ($p < 0.001$, Fig. 2a). While after scopolamine injection, rodents were incapable of distinguishing the new arm from previously visited arms in both duration of arms visits ($F_{[2, 27]} = 10.62$, $p > 0.05$, Fig. 2a) and number of arms visits (%) ($F_{[2, 27]} = 0.996$, $p > 0.05$, Fig. 2a) in the trial phase. We observed that scopolamine-treated mice had a significantly lower duration of novel arm visits ($F_{[1, 9]} = 102.4$, $p < 0.001$, Fig. 2a) and a lower number of novel arm visits (%) ($F_{[1, 9]} = 118.8$, $p < 0.001$, Fig. 2b) in comparison with the saline-treated group. Regarding dapsone dose-response, dapsone at a 5-mg/kg dose prevented memory impairment and was selected as the effective dose for further investigations.

In the Y-maze, administration of dapsone (5 mg/kg) 1 h before the training phase notably increased duration

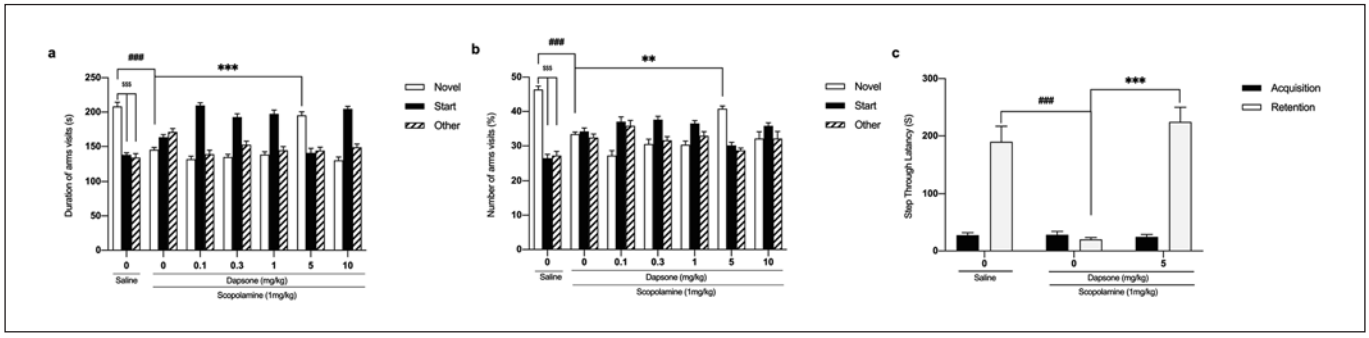

Fig. 2. Effects of different doses of dapsone (0.1, 0.3, 1, 5, and 10 mg/kg, i.p.) on scopolamine-induced memory impairment in mice. **a** Exploration time in each arm (Y-maze). **b** Number of arm entries % (Y-maze). **c** STL time (passive-avoidance). Values are represented as mean ± SEM from 10 animals and were analyzed using a one-way ANOVA accompanied by Tukey's post hoc test. $^{###}p < 0.001$ shows the comparison between the scopolamine-control versus sham (saline) groups. $^{**}p < 0.01$, and $^{***}p < 0.001$ shows the comparison between scopolamine + dapsone (5 mg/kg, i.p.) versus scopolamine-control groups. $^{\$\$\$}p < 0.001$ shows the comparison between all three arms of saline-treated groups. ANOVA, analysis of variance.

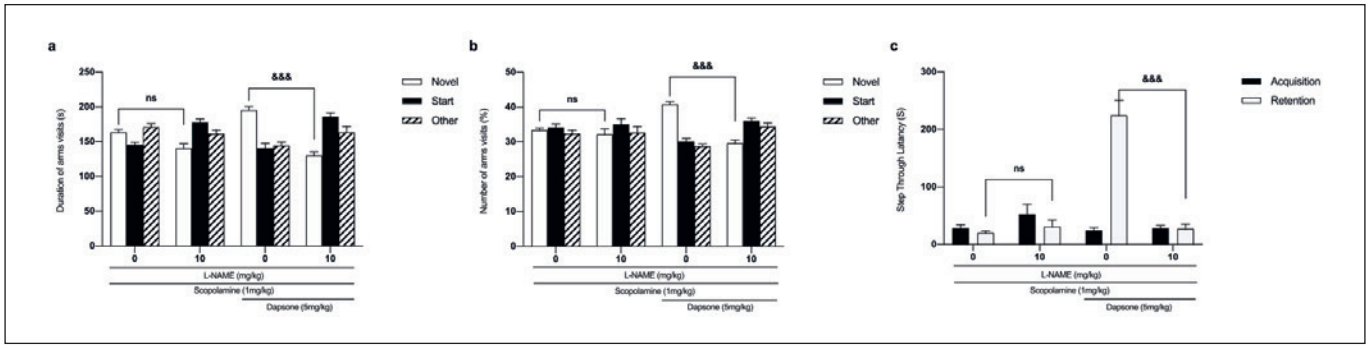

Fig. 3. Effects of L-NAME (10 mg/kg, i.p.) on memory enhancement by dapsone. **a** Exploration time in each arm (Y-maze). **b** Number of arm entries % (Y-maze). **c** STL time (passive-avoidance). Values are represented as mean ± SEM from 10 animals and were analyzed using a two-way ANOVA accompanied by Tukey's post hoc test. ns shows the comparison between scopolamine + L-NAME (10 mg/kg, i.p.) versus scopolamine-control groups. $^{\&\&\&}p < 0.001$ shows the comparison between scopolamine + dapsone (5 mg/kg, i.p.) + L-NAME (10 mg/kg, i.p.) versus scopolamine + dapsone (5 mg/kg, i.p.) groups. ns, non-significant; ANOVA, analysis of variance.

of novel arm visits ($F_{[1, 9]} = 70.32$, $p < 0.001$, Fig. 2a) and number of novel arm visits (%) ($F_{[1, 9]} = 45.46$, $p < 0.01$, Fig. 2b) compared to the control group. In addition, dapsone (5 mg/kg) led to a prominent increase in the duration of novel arm visits ($F_{[2, 27]} = 28.96$, $p < 0.001$) and number of novel arm visits (%) ($F_{[2, 27]} = 71$, $p < 0.001$) compared to the start and the other arm. The total number of arm entries over the total experiment period of the trial phase was similar among the experimental groups, proving that the locomotor movement was not affected by dapsone either in scopolamine or saline-treated groups ($p > 0.05$).

Passive-Avoidance

In the P-A, scopolamine remarkably reduced the STL time in comparison with the saline-treated groups ($F_{[1, 9]} = 38.18$, $p < 0.001$, Fig. 2c). On the other hand, administration of dapsone (5 mg/kg) 1 h before the training session dramatically enhanced the latency time in comparison to the scopolamine-treated mice ($F_{[1, 9]} = 51.37$, $p < 0.001$, Fig. 2c).

Interaction of NOS Inhibitors with the Effect of Dapsone on Scopolamine-Induced Memory Impairment in Mice

Y-Maze

Administration of L-NAME, AG, and 7-NI with dapsone completely reversed the observed protective effects of dapsone in duration of novel arm visits ($F_{[1, 9]} = 71.87$, $p < 0.001$, Fig. 3a; $F_{[1, 9]} = 48.82$, $p < 0.001$, Fig. 4a; and $F_{[1, 9]} = 68.39$, $p < 0.001$, Fig. 5a, respectively) and number of novel arm visits ($F_{[1, 9]} = 58.31$, $p < 0.001$, Fig. 3b; $F_{[1, 9]} = 55.51$,

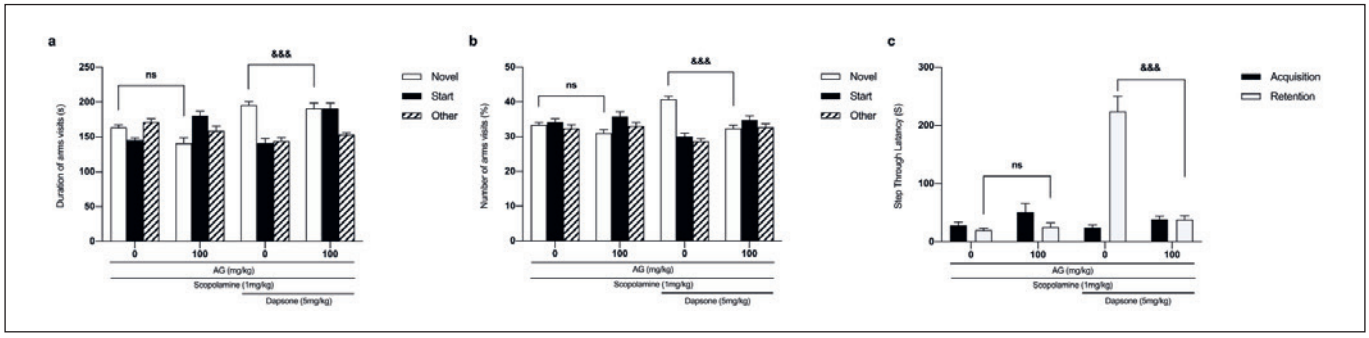

Fig. 4. Effects of AG (100 mg/kg, i.p.) on memory enhancement by dapsone. **a** Exploration time in each arm (Y-maze). **b** Number of arm entries % (Y-maze). **c** STL time (passive-avoidance). Values are represented as mean ± SEM from 10 animals and were analyzed using a two-way ANOVA accompanied by Tukey's post hoc test. ns shows the comparison between scopolamine + AG (100 mg/kg, i.p.) versus scopolamine-control groups. $^{\&\&\&}p < 0.001$ shows the comparison between scopolamine + dapsone (5 mg/kg, i.p.) + AG (100 mg/kg, i.p.) versus scopolamine + dapsone (5 mg/kg, i.p.) groups. ns, non-significant; ANOVA, analysis of variance.

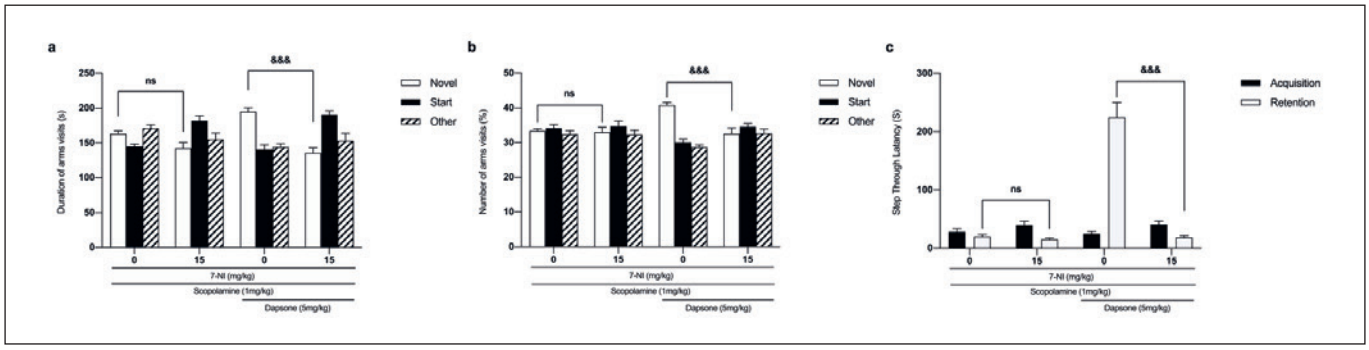

Fig. 5. Effects of 7-NI (15 mg/kg, i.p.) on memory enhancement by dapsone. **a** Exploration time in each arm (Y-maze). **b** Number of arm entries % (Y-maze). **c** STL time (passive-avoidance). Values are represented as mean ± SEM from 10 animals and were analyzed using a two-way ANOVA accompanied by Tukey's post hoc test. ns shows the comparison between scopolamine + 7-NI (15 mg/kg i.p.) versus scopolamine-control groups. $^{\&\&\&}p < 0.001$ shows the comparison between scopolamine + dapsone (5 mg/kg, i.p.) + 7-NI (15 mg/kg, i.p.) versus scopolamine + dapsone (5 mg/kg, i.p.) groups. ns, non-significant; ANOVA, analysis of variance.

$p < 0.001$, Fig. 4b; and $F_{[1, 9]} = 36.11$, $p < 0.001$, Fig. 5b, respectively). However, injection of NOS inhibitors per se did not impact the memory-impaired mice ($F_{[1, 9]} = 0.4588$, $F_{[1, 9]} = 0.1970$, $F_{[1, 9]} = 0.1228$, $p > 0.05$, Fig. 3a, 4a, 5a, respectively). There was no difference in the overall amount of arm entries in NOS inhibitors treated groups, indicating no interference with locomotor activity ($p > 0.05$).

Passive-Avoidance

Administration of L-NAME, AG, and 7-NI + scopolamine 30 min after dapsone (5 mg/kg) treatment showed a decrease in the STL time ($F_{[1, 9]} = 53.44$, $p < 0.001$, Fig. 3c; $F_{[1, 9]} = 63.3$, $p < 0.001$, Fig. 4c; and $F_{[1, 9]} = 67.93$, $p < 0.001$, Fig. 5c, respectively). Injection of NOS inhibitors alone did not impact the STL time compared to the control group ($p > 0.05$, Fig. 3c, 4c, 5c).

NO Levels in the Hippocampus

As displayed in Table 2, an intensification in the NO levels was noticed in the dapsone (5 mg/kg)-treated groups in comparison with the control group ($p < 0.001$). Concurrent administration of L-NAME, AG, and 7-NI with dapsone substantially reduced the NO levels compared to the dapsone-treated animals ($p < 0.001$; $p < 0.01$; and $p < 0.001$, respectively).

Discussion

The present study was aspired to determine whether dapsone can prevent memory impairment in rodents. We discovered that administration of dapsone improved the scopolamine-induced memory impairment in the Y-maze

Table 2. Nitrite concentration (nmol/mg protein) in the hippocampus of the experimental groups

Treatment groups	Nitrite concentrations	Significance
Sham	14.20±1.96	–
Control$^{\&\&\&}$	12.24±1.96	$p < 0.001$
L-NAME (10 mg/kg)	12.70±0.22	NS
AG (100 mg/kg)	12.17±0.22	NS
7-NI (15 mg/kg)	12.73±0.22	NS
Dapsone (5 mg/kg)***	14.58±2.33	$p < 0.001$
Dapsone (5 mg/kg) + L-NAME (10 mg/kg)$^{\#\#\#}$	11.23±3.35	$p < 0.001$
Dapsone (5 mg/kg) + AG (100 mg/kg)$^{\#\#}$	11.82±2.75	$p < 0.01$
Dapsone (5 mg/kg) + 7-NI (15 mg/kg)$^{\#\#\#}$	9.94±4.63	$p < 0.001$

Each group consisted of ten mice. NS, non-significant. $^{\&\&\&}$ $p < 0.001$ compared to the sham group. *** $p < 0.001$, NS compared to the control group. $^{\#\#}$ $p < 0.01$, $^{\#\#\#}$ $p < 0.001$ compared to the dapsone (5 mg/kg) group.

and P-A tests. Based on our results, solo injection of NOS inhibitors did not change the memory performance, but co-administering NOS inhibitors with dapsone significantly reversed the protective effects of dapsone. Our research uncovered that the protective effect of dapsone seems to be modulated through the NO pathway. Biochemical measurements of NO levels showed that dapsone improved cognitive performance by increasing the NO levels in the hippocampus of scopolamine-treated mice.

The cholinergic hypothesis indicates that losing cholinergic activity alters cognitive performance and memory impairment [22]. Scopolamine causes short-term and long-term memory loss by blocking the muscarinic cholinergic receptors in the brain and interfering with learning and memory. Therefore, we used scopolamine as a validated model of memory impairment in mice [3, 23].

Current treatments for memory dysfunction target the cholinergic pathway to increase cholinergic activity. Researchers suggest that the cholinergic agonists, which are currently one of the available treatments for memory dysfunctions, display anti-inflammatory activities. Inflammation is one of the many mechanisms responsible for memory deterioration [24]. Given that dapsone exerts anti-inflammatory properties [25], we hypothesized that dapsone is likely able to prevent memory impairment caused by neuroinflammation.

Dapsone exerts anti-inflammatory properties in different organs such as skin and lungs. For instance, (i) combination therapy of dapsone + ivermectin + metronidazole + azelaic acid leads to strengthening the anti-inflammatory effects of each compound per se [26]. (ii) Combination therapy of dapsone + doxycycline resulted in better outcomes to block inflammatory cascade in COVID-19 [27]. In addition, reports have investigated the neuroprotective effects of dapsone in neuronal disorders, such as (i) inflammatory-associated neuro-Sweet's disease (in combination with corticosteroids) [4], (ii) neurotoxicity associated with kainic acid (in combination with phenobarbital) [6], (iii) propofol-induced cognitive alterations [28], (iv) surgical stress-induced brain oxidative damage [13], and (v) different types of brain ischemia in animal and clinical reports [5].

Moreover, a 1-year, randomized, double-blind, placebo-controlled clinical trial in 201 patients with mild to moderate Alzheimer's disease reported an unambiguous effect of efficacy exerted by dapsone (100 mg/day, oral, 52 weeks) [29]. These negative results are due to extensive neuronal death in patients with mild to moderate Alzheimer's disease. The Seoul study showed that dapsone treatment with the same dose prevents mild cognitive impairment (MCI) progression to dementia syndrome [30, 31]. Parallel to our results, we revealed that prophylactic treatment with dapsone could prevent memory impairment in rodents.

Dapsone stimulates an anti-inflammatory response through regulating NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome activators that are critical in MCI and Alzheimer's disease. Dapsone can attenuate nuclear factor kappa-light-chain-enhancer of activated B cells signaling and inflammatory cytokines release such as IL-1β, IL-8, and IL-18. Dapsone decreases the production of oxidative markers in different in vivo studies [31]. In a model of brain ischemia-reperfusion injury, dapsone exerted NO regulatory properties [25]. These anti-inflammatory, anti-oxidative, and NO modulatory effects of dapsone may be beneficial as an alternative therapy in MCI patients.

NO acts as a retrograde modulator in synaptic transmissions and stimulates synaptic plasticity in learning and memory function. NO influences various brain sections involved in memory formation, such as the CA1 region of the hippocampus. This region plays a prominent role in learning and memory, including short- and long-term memory [32]. Suppressing NO by NOS inhibitors contributes to memory malfunction [12]. L-NAME per se did not affect memory; however, pretreatment with L-NAME nullified the beneficial effect of pioglitazone on memory impairment in the Y-maze test [23]. AG provokes memory dysfunction in the P-A [33]. 7-NI causes memory deficiency in water maze and 8-arm radial maze tests [34]. Consistent experimental evidence revealed that administration of the noneffective dose of NOS inhibitors substantially reversed the favorable effects of various medications on poor memory function [23, 33, 34]. Our experiment also revealed that the observed inhibitory effect of dapsone on memory impairment in mice was probably modulated via the NO pathway.

NO influences memory function and plasticity in different brain regions, e.g., the cerebral cortex and hippocampus, via regulating neurotransmitters such as acetylcholine (Ach) and glutamate. Suppressed NO production leads to decreasing Ach release from cholinergic nerve fibers. Glutamate antagonists prohibit the NO-induced release of Ach. Therefore, reduced glutamate and Ach neurotransmission worsen memory impairment [32]. We revealed that dapsone exerts its neuroprotective role against scopolamine-induced memory impairment in mice via NO augmentation. Further studies are needed to elucidate the different signaling pathways behind the neuroprotective effects of dapsone.

Conclusion

This experiment revealed that dapsone could enhance scopolamine-induced memory impairment in mice, and this improvement might be through increasing the NO levels. The current study signifies the neuroprotective role of dapsone in memory and dementia alleviation.

Acknowledgement

We would like to express our gratitude to the Gilaranco Pharmaceutical Co. (Rasht, Iran) for providing dapsone powder during the course of this research.

Statement of Ethics

All the experimental procedures were done based on the ARRIVE guidelines for animal research and also approved by the Ethics Committee of Tehran University of Medical Sciences (Ethical Code: IR.TUMS.MEDICINE.REC.1398.026).

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Study conception and design: A.D.; acquisition of data: N.N., M.S., F.E., A.M., N.R., and R.Z.; analysis and interpretation of data: N.N. and M.S.; drafting the manuscript: N.N. and M.S.; critical revision: N.N., M.S., F.E., Z.A., and A.D.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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