SKF83959 Has Protective Effects in the Scopolamine Model of Dementia

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As a worldwide neurodegenerative disease, Alzheimer’s disease (AD) always have cognitive impairments. In this study we investigated whether 6-chloro-7,8-dihydroxy-3-methyl-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (SKF83959) has improvements on cognitive dysfunction. The scopolamine model of dementia was used to investigate the anti-amnesic activities of SKF83959, and then, Western blotting and pharmacological inhibitor were used to assay the anti-amnesic mechanisms of SKF83959. It was found that SKF83959 administration significantly improved the scopolamine-induced memory impairments in the passive avoidance task, Y-maze test, and Morris water maze task. Moreover, SKF83959 treatment significantly antagonized the down-regulating effects of scopolamine on brain-derived neurotrophic factor (BDNF) signaling cascade in the hippocampus, but not cortex. Importantly, the usage of K252a, a selective inhibitor of tyrosine kinase B (TrkB), significantly attenuated the protective effects of SKF83959 in the scopolamine model. Collectively, this study shows that SKF83959 has beneficial effects in the scopolamine model of dementia by modulation of hippocampal BDNF signaling, implying a novel and potential therapeutic agent for treating dementia in AD.

Key words brain-derived neurotrophic factor; memory; scopolamine; SKF83959

MATERIALS AND METHODS

Animals Male ICR male mice of 8 weeks from Nantong University were housed 5 per cage and supplied with food and water freely for one week before experiments. The housing environment was set as described. All the procedures involving mice were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (8th edition, Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington DC, U.S.A.), and approved by the Lab Animal Ethical Committee of Nantong University.

Drugs and Treatments SKF83959 (0.5, 1 mg/kg; Tocris Bioscience, Bristol, U.K.), donepezil (5 mg/kg; Sigma, St. Louis, MO, U.S.A.), scopolamine (1 mg/kg; Sigma) and K252a (25 µg/kg; Alomone Laboratories, Jerusalem, Israel) were all dissolved in 1% dimethyl sulfoxide (DMSO) in 0.9% saline. The dosages of these compounds were chosen according to previous reports. For drug administration, intraperitoneally (i.p.) injected in a volume of 10 mL/kg was employed.

Passive Avoidance Task To perform this task, two trials...
(training trial and test trial) were done.\textsuperscript{15–17} The training trial was performed 24 h before the test trial. The equipment has two identical chambers with one illuminated and the other non-illuminated. The two chambers were separated by a guillotine door. The equipment has an electrifiable grid floor. For the training trial, the test mice were individually placed into the illuminated chamber, and after 10 s, the light was on and the door was opened. The door was closed after the mouse entered the non-illuminated chamber, and a 3 s of electrical foot shock (0.5 mA) was delivered through the electrifiable grid floor. The time taken for the mouse to enter the non-illuminated chamber was recorded as the step-through latency, and it was recorded up to 300 s. The test trial was conducted 24 h after the training trial by returning the mouse to the illuminated chamber, and the time to enter the non-illuminated chamber after door opening was measured again without electric foot shock.

\textbf{Y-Maze Test} The Y-maze equipment has three arms (40 cm long $\times$ 10 cm wide $\times$ 20 cm high) which are disposed at 120° angles from each other.\textsuperscript{15–17} The test mice were individually placed at the end of one arm, and the test period was 8 min. During the period, the sequence and number of arm entries for each mouse was recorded. The spontaneous alternation behavior was defined as entry into all three arms on consecutive choices. For each test period, the arms were thoroughly cleaned. The alternation score (%) for each mouse was defined as described in previous reports\textsuperscript{15–17}: % Alternation = [(Number of alternations)/(Total arm entries $-$ 2)] $\times$ 100.

\textbf{Morris Water Maze} This procedure was also performed according to previous reports.\textsuperscript{15–17} A circular pool divided into four equal quadrants was used. The diameter and height of this pool were 90 and 45 cm, respectively. The pool was filled with water containing milk and placed a platform in one quadrant. This experiment last for six days. On the first day, the test mice were individually forced to swim for 120 s without the platform. During the four subsequent days, the test mice were individually given four trials per day with the platform in place. For each trial, the time taken by mice to locate the platform (latency time) was recorded. On the sixth day, the test mice were individually subjected to the spatial probe test. The platform was removed, and the mice were allowed to swim for 60 s searching it. The swimming time in the quadrant where the platform had been recorded was reported for each mouse.

\textbf{Western Blotting Analysis} As described in previous reports,\textsuperscript{15–17} briefly, the hippocampal tissues of mice used for Morris water maze were rapidly dissected and homogenized in lysis buffer (Beyotime Biotechnology, China). The homogenates were centrifuged, and the supernatants were collected. After denaturation, 30 $\mu$g of protein samples were loaded in sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gels and then transferred to polyvinylidene difluoride (PVDF) membranes. After that, the membranes were blocked in 5% bovine serum albumin (BSA) and then incubated in diluted various primary antibodies [as described in previous studies\textsuperscript{12,15,16}] overnight at 4°C. Next, the membranes were washed and incubated in diluted horseradish peroxidase-conjugated secondary antibodies (1: 5000) for 2 h at room temperature. Lastly, the membranes were washed again and detected using enhanced chemiluminescence.

\textbf{Statistical Analysis} All the data are analyzed by two-way ANOVA followed by Bonferroni’s test or three-way ANOVA followed by Tukey’s test using the SPSS 13.0 software (SPSS Inc., U.S.A.), $p<0.05$ was considered statistically significant.

\textbf{RESULTS} SKF83959 Administration Fully Reverses the Effects of Scopolamine on Memory Behavior in Mice Firstly, the passive avoidance task was used to assess the ameliorating effects of SKF83959 on scopolamine-induced cognitive dysfunction. SKF83959 (0.5, 1 mg/kg)/donepezil (positive control, 5 mg/kg)/vehicle (1% DMSO in 0.9% saline) and scopolamine (1 mg/kg) were administrated 60 and 30 min prior to the training trial, respectively. For the training trial, the step-through latency time was nearly the same among all the groups ($n=10$, Fig. 1A). For the test trial, the step-through latency in the scopolamine group was significantly lower than that in the control group ($n=10$, Fig. 1A), and interestingly, the scopolamine-reduced step-through latency was fully restored by SKF83959 ($n=10$, Fig. 1A). Detailed data analysis showed that the effects of 1 mg/kg SKF83959 were even better than that of donepezil. ANOVA analysis showed the effect of scopolamine [$F(1, 34)=12.532, p<0.01$], the effect of SKF83959 [$F(2, 34)=23.643, p<0.01$], and their interaction [$F(2, 34)=18.053, p<0.01$].

Secondly, the Y-maze task was used. SKF83959/donepezil/vehicle and scopolamine were administrated 60 and 30 min before the task, respectively. Compared to the control group, mice in the scopolamine group displayed abnormal spontaneous alternation behavior ($n=10$, Fig. 1B). However, the numbers of arm entries were similar between all the groups ($n=10$, Fig. 1B), indicating that SKF83959 does not affect the general locomotor activity of mice. ANOVA analysis reported the effect of scopolamine [$F(1, 34)=17.242, p<0.01$], the effect of SKF83959 [$F(2, 34)=28.532, p<0.01$], and their interaction [$F(2, 34)=21.522, p<0.01$].

Furthermore, the Morris water maze task was performed. SKF83959/donepezil/vehicle and scopolamine were administrated 60 and 30 min before the first learning trial of each training day, respectively. As shown in Fig. 2A, mice in the scopolamine group exhibited significantly longer escape latency than mice in the control group throughout the training days ($n=10$). However, our data showed that the effects of scopolamine on escape latency of mice were significantly restored by SKF83959 ($n=10$). ANOVA analysis showed the effect of scopolamine [$F(1, 36)=23.642, p<0.01$], SKF83959 [$F(2, 36)=27.533, p<0.01$], Day [$F(3, 36)=37.892, p<0.01$], and their interaction: scopolamine $\times$ Day [$F(3, 36)=32.365, p<0.01$], SKF83959 $\times$ Day [$F(6, 36)=21.672, p<0.01$], scopolamine $\times$ SKF83959 [$F(2, 136)=26.321, p<0.01$], and scopolamine $\times$ SKF83959 $\times$ Day [$F(6, 136)=29.115, p<0.01$].

For the probe test, the scopolamine-induced decreasing effects on swimming time of mice within the target quadrant were significantly restored by SKF83959 ($n=10$, Fig. 2B). ANOVA analysis also reported the effect of scopolamine [$F(1, 34)=15.295, p<0.01$], the effect of SKF83959 [$F(2, 34)=32.289, p<0.01$], and their interaction [$F(2, 34)=25.209, p<0.01$]. Besides, the positive control, donepezil, also reversed the scopolamine-induced dementia in all the tasks ($n=10$), as
expected. The donepezil results imply that the experiments we have done are reliable and dependable. Taken together, SKF83959 has anti-amnesic activities in mice. Then we examined the levels of BDNF, pTrkB/TrkB, and SKF83959 Treatment Restores the Scopolamine- Decreased BDNF Signaling Pathway in the Hippocampus.
pCREB/CREB in the cortex and hippocampus after SKF83959 and scopolamine administration. The hippocampus data are summarized in Fig. 3A. It was found that scopolamine administration significantly decreased the BDNF, pTrkB and pCREB expression in the hippocampus (n=5), and importantly, these molecular changes were fully reversed by...
SKF83959 treatment (n=5). For hippocampal BDNF [scopolamine: F(1, 14)=24.263, p<0.01; SKF83959: F(2, 14)=38.632, p<0.01; scopolamine×SKF83959: F(2, 14)=30.259, p<0.01], pTrkB [scopolamine: F(1, 14)=21.297, p<0.01; SKF83959: F(2, 14)=35.298, p<0.01; scopolamine×SKF83959: F(2, 14)=27.521, p<0.01] and pCREB [scopolamine: F(1, 14)=23.056, p<0.01; SKF83959: F(2, 14)=37.239, p<0.01; scopolamine×SKF83959: F(2, 14)=34.109, p<0.01] data, ANOVA analysis all showed significant interactions with significant effects for scopolamine and SKF83959. The cortex data are summarized in Fig. 3B. Although scopolamine administration reduced the BDNF, pTrkB and pCREB expression in the cortex (n=5), similar to hippocampus, SKF83959 treatment had no influence on these changes. Thus, promotion of hippocampal BDNF signaling cascade may contribute to the anti-dementia effects of SKF83959.

The Memory Enhancing Effects of SKF83959 Was Prevented by BDNF System Blockade To determine whether hippocampal BDNF system is really necessary for the anti-dementia effects of SKF83959, we used K252a, an acknowledged TrkB inhibitor, and the behavioral tests were performed again. For the passive avoidance task and Y-maze task, mice were first injected with K252a (25 µg/kg) first, and then SKF83959 (1 mg/kg, 30 min later) and scopolamine (1 mg/kg, 60 min later), and finally subjected to the tasks (90 min later). As shown in Fig. 4A [SKF83959: F(1, 36)=27.561, p<0.01; K252a: F(1, 36)=16.329, p<0.01; SKF83959×K252a: F(1, 36)=22.671, p<0.01] and Fig. 4B [SKF83959: F(1, 36)=24.927, p<0.01; K252a: F(1, 36)=14.312, p<0.01; SKF83959×K252a: F(1, 36)=19.337, p<0.01], the SKF83959+K252a+scopolamine mice showed significantly less step-through latency and spontaneous alternation behavior of mice in the Y-maze test. Data are expressed as means±S.E.M. (n=10); **p<0.01 vs. Control; *p<0.05, ***p<0.01 vs. Scopolamine.

**Fig. 4. The Usage of K252a Antagonizes the Effects of SKF83959 against Scopolamine in the Passive Avoidance Task and Y-Maze Test**

Mice were injected with K252a (25 µg/kg) first, and then SKF83959 (1 mg/kg, 30 min later) and scopolamine (1 mg/kg, 60 min later), and finally subjected to the tasks (90 min later). (A) The preventing effects of K252a on the SKF83959-induced increase in step-through latency of mice in the passive avoidance task. (B) The preventing effects of K252a on the SKF83959-induced increase in spontaneous alternation behavior of mice in the Y-maze test.
Fig. 5. The Usage of K252a Blocks the Anti-dementia Effects of SKF8359 in the Morris Water Maze Test

K252a was injected 90 min prior to the first learning trial of each training day, then SKF83959 (60 min prior) and scopolamine (30 min prior) were administrated. (A) The blocking effects of K252a on the SKF83959-induced decrease in mean escape latency of mice during the training trials. (B) The blocking effects of K252a on the SKF83959-increased swimming time of mice in the target quadrant. Data are expressed as means±S.E.M. (n=10); **p<0.01 vs. Control; #p<0.05, ##p<0.01 vs. Scopolamine.

Fig. 6. The Usage of K252a Also Prevents the Restoring Effects of SKF83959 on Hippocampal BDNF Signaling Pathway

The samples were got from the mice used for morris water maze. (A) Representative Western blotting images of BDNF/β-actin, pTrkB/TrkB and pCREB/CREB in the hippocampus. (B) Detailed analysis revealed that the scopolamine+SKF83959+K252a mice displayed significantly less BDNF, pTrkB and pCREB expression in the hippocampus than the scopolamine+SKF83959 mice. Data are expressed as means±S.E.M. (n=5); **p<0.01 vs. Control; #p<0.05, ##p<0.01 vs. Scopolamine.

p<0.01; SKF83959×K252a: F(1, 36)=25.356, p<0.01] than the SKF83959+scopolamine mice (n=10, Fig. 5A and 5B). After that, Western blotting experiments were performed again. Figure 6 showed that the SKF83959+K252a+scopolamine mice had significantly less BDNF [SKF83959: F(1, 16)=39.672, p<0.01; K252a: F(1, 16)=27.554, p<0.01; SKF83959×K252a: F(1, 16)=32.572, p<0.01], pTrkB [SKF83959: F(1, 16)=36.772, p<0.01; K252a: F(1, 16)=24.192, p<0.01; SKF83959×K252a: F(1, 16)=30.927, p<0.01] and pCREB [SKF83959: F(1, 16)=40.023, p<0.01; K252a: F(1, 16)=29.687, p<0.01; SKF83959×K252a: F(1, 16)=34.962, p<0.01] expression in the hippocampus than the SKF83959+
scopolamine mice (n=10), in parallel with the behavioral results. Therefore, hippocampal BDNF signaling cascade is necessary for the anti-amnesic effects of SKF83959.

**DISCUSSION**

In this study, it was found that SKF83959 produced beneficial effects against the scopolamine-induced cognitive impairments, as measured by several behavioral tasks. In addition, activation of hippocampal BDNF system is relevant to the anti-amnesic effects of SKF83959 in mice.

The pathophysiology of AD is complex and still remains elusive. One common pathological phenomenon of AD is dysfunction of the cholinergic neurotransmitter system. Thus, based upon this ‘cholinergic hypothesis,’ scopolamine, a muscarinic receptor antagonist, was widely used to create a model of dementia in rodents. Owing to its anti-cholinergic activity, scopolamine was found to induce a pattern of learning and memory deficits in young volunteers that was markedly similar to the performance of elderly subjects. Since SKF83959 was found to activate the BDNF signaling pathway, and the role of BDNF in learning and memory is well-known, we chose it in this study. Here, we investigated the anti-AD potential of SKF83959 in the scopolamine model, and conducted a series of behavior tests. As expected, SKF83959 injection fully antagonized the disturbing effects of scopolamine on memory in the passive avoidance task, Y-maze task and Morris water-maze task. The effects of 1 mg/kg SKF83959 were even superior to 5 mg/kg donepezil, the positive control. The subsequent Western blotting detection indicated that the hippocampal BDNF system may be involved in the memory-enhancing effects of SKF83959, and this assumption was finally confirmed by the usage of K252a. Collectively, SKF83959 could be a novel anti-AD compound.

It is well known that dopamine receptor signaling plays an important role in the process of memory. For example, dysfunction of D1 receptor in lateral habenula nucleus affects the acquisition of contextual fear memory in rats. Ventral pallidal D2 dopamine receptor plays a role in the consolidation of spatial memory. Intra-CA1 administration of the D1/D5 receptor agonist SKF3893 promotes spatial memory processing in the water maze. As SKF83959 is an agonist of D1–D2 heteromer, the results of our study may imply a role of this heteromer in memory, which shall be very interesting. It is also interesting that SKF83959 treatment reverses the scopolamine-induced BDNF dysfunction in the hippocampus, but not cortex, and this is consistent with Jiang et al. For this finding, currently there are no exact explanations, perhaps D1–D2 heteromer has no distributions in the cortex. How does SKF83959 affect the expression of hippocampal BDNF? It has been demonstrated that SKF83959 stimulates phosphatidylinositol (PI)-hydrolysis via phospholipase Cβ and results in the production of inositol phosphate 3 (IP3), which subsequently induces intracellular Ca2+ release and the transient activation of Ca2+/calmodulin-dependent kinase II (CaMKII). Several reports have shown that CaMKIIα activation leads to BDNF production, and so, it is very possible that the phospholipase C (PLC)/IP3/CaMKIIα pathway underlies the effects of SKF83959 on BDNF synthesis. This assumption can be confirmed if using the PLC/IP3/CaMKIIα pathway inhibitors (U73122, 2-APB, BAPTA-AM) could prevent the effects of SKF83959 in the scopolamine model, and for this we will perform more studies in the future.

Until now, there are few useful medications in clinical for treating AD. Although donepezil has been approved by U.S. Food and Drug Administration (FDA) and Medicines Control Agency (MCA) to treat mild to moderate AD, its efficacy is not very good, and has many side effects due to AChE inhibition, including nausea, anorexia, depression, drowsiness, and so on. For SKF83959, currently there are no guarantee that it will be superior to donepezil, possessing better efficacy and less side effects, after all it is a potential compound for treating dementia. The neurobiology of AD is very complex, involving numerous pathological changes, while cholinergic dysfunction is just one of them. Here we are considering that to develop new anti-dementia drugs in the future, aiming at the BDNF system may be more effective than the cholinergic system, as the former is more related to consolidation of memory compared with the latter. As we have known, by now a lot of compounds have been found to have anti-dementia effects in rodents via enhancing the BDNF signaling cascade, like arabinoxylan, WY14463, P7C3, and so on.

In conclusion, this study suggests that SKF83959 has protective effects in the scopolamine model of dementia, extending the knowledge of SKF83959’s pharmacological effects, and may provide a novel candidate drug for developing novel anti-dementia medications.

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**Conflict of Interest** The authors declare no conflict of interest.

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