Alpha1-adrenergic receptor antagonist tamsulosin ameliorates aging-induced memory impairment by enhancing neurogenesis and suppressing apoptosis in the hippocampus of old-aged rats

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ABSTRACT
Age-related memory decline is closely associated with decreased neurogenesis and increased apoptosis in the hippocampus (Driscoll and Sutherland 2005; Kim et al. 2010). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family involved in neuronal survival and differentiation. BDNF plays a crucial role in the learning process, and deficit or loss of BDNF in the hippocampus of aged rats contributes to learning and memory impairment (Yang et al. 2014). Aging-related hippocampal susceptibility to apoptosis was demonstrated by increased pro-apoptotic Bax expression, enhanced caspase-3 activity, and reduced anti-apoptotic Bcl-2 expression (Kaufmann et al. 2001; Jin et al. 2008).

1. Introduction
Age-related memory decline is closely associated with decreased neurogenesis and increased apoptosis in the hippocampus (Driscoll and Sutherland 2005; Kim et al. 2010). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family involved in neuronal survival and differentiation. BDNF plays a crucial role in the learning process, and deficit or loss of BDNF in the hippocampus of aged rats contributes to learning and memory impairment (Yang et al. 2014). Aging-related hippocampal susceptibility to apoptosis was demonstrated by increased pro-apoptotic Bax expression, enhanced caspase-3 activity, and reduced anti-apoptotic Bcl-2 expression (Kaufmann et al. 2001; Jin et al. 2008).

Noradrenaline modulates hippocampal synaptic plasticity and deterioration of noradrenaline system may cause learning and memory impairment during aging (Knauber and Müller 2000). Noradrenaline exerts its influence by selectively binding to and activating adrenergic receptors (ARs); alpha1 (α1), alpha2 (α2) and beta (β) subtypes.

The effects of AR on learning and memory are inconsistent and not clearly defined. It was reported that α1-AR stimulation suppressed memory consolidation (Gibbs and Summers 2001), however, other studies reported that activation of α1-AR enhanced learning and memory (Puumala et al. 1998; Sirviö and MacDonald 1999). Even the same α1-AR agonist showed opposite effects depending on the dosage. Low dose of α1-adrenergic agonist improved spatial learning memory and memory consolidation, and high dose impaired spatial learning memory (Gibbs and Bowser 2010; Torkaman-
Boutorabi et al. (2014) suggested that the α₁-AR antagonist, prazosin, impaired the spatial learning memory. In contrast, Katsouri et al. (2013) reported that chronic treatment with prazosin prevented memory impairment in Alzheimer’s disease mice.

Tamsulosin, another α₁-AR antagonist, is also reported to have access to the brain and interact with α₁-AR (Sirviö and MacDonald 1999; Hellstrom and Sikka 2006). Tamsulosin was originally developed for the treatment of arterial hypertension and has been reported to be effective in the treatment of lower urinary tract symptoms, such as benign prostatic hyperplasia (Michel and de la Rosette 2004). In our previous studies, tamsulosin improved voiding function through inhibiting neuronal activity in the neuronal voiding centers (Kim et al. 2012, 2013). Tamsulosin improved short-term and spatial learning memory in the rats under normal conditions (Kim et al. 2015).

In the present study, we evaluated whether α₁-AR antagonist tamsulosin was effective in improving learning and memory impairment by aging. In this study, the effects of tamsulosin on short-term and spatial learning memory in terms of neurogenesis and apoptosis were investigated using rats.

2. Materials and methods

2.1. Animals and treatments

Fisher 344 rats were used in this study. Four-month-old rats (n = 10, 310 ± 10 g) were used as the young-aged control group (YC), and 25-month-old rats (n = 40, 420 ± 20 g) were used as the old-aged groups. The old-aged groups were re-divided into 4 groups (n = 10 in each group): the old-aged control group, the old-aged and 0.01 mg/kg tamsulosin-treated group, the old-aged and 0.1 mg/kg tamsulosin-treated group, and the old-aged and 1 mg/kg tamsulosin-treated group. For the tamsulosin-treated rats, tamsulosin was orally administered at respective dose daily for 4 weeks. All rats received 50 mg/kg 5-bromo-2′-deoxyuridine (BrdU; Sigma Chemical Co., St. Louis, MO, USA) intraperitoneally once a day for 7 days from the starting of the experiment. The experimental design was approved by the Institutional Care and Use Committee of Kyung Hee University Institutional Animal Care and Ethics Committee [KHUASP(SE)-14-047].

2.2. Step-down avoidance test

Short-term memory was determined using step-down avoidance test, as previously described (Kim et al. 2010; Lee et al. 2016). Zoletil 50® (10 mg/kg, i.p.; Vibac Laboratories, Carros, France) was used to anesthetize the rats immediately after radial 8-arm maze test. Zoletil 50® was transcardially perfused with a freshly prepared solution consisting of 4% paraformaldehyde in 100 mM phosphate buffer (pH 7.4). After removing the brains, freezing microtome (Leica, Nussloch, Germany) was used to make 40 μm thick coronal sections.

2.3. Radial 8-arm maze test

Spatial learning memory was determined using radial 8-arm maze test, as previously described (Kim et al. 2010, 2016). Radial 8-arm maze apparatus consisting of a central octagonal plate (30 cm in diameter) and 8 radiating arms (50 cm in length and 10 cm in width) was placed 1 m above the floor and has a small receptacle filled with water (3 × 1 cm in diameter and depth) at the end of the arms. The rats were trained three times before the test. Prior to the training sessions, the rats were deprived of water for 24 h and were able to explore the water for 5 min after each training session. The test was conducted on the 31st day of the starting experiment. The time to find the water at the end of the arm was calculated and the test was terminated when the rat found water in eight arms or exceeded eight min. Re-entry into the previously visited arms was considered as an error and the number of correct number was calculated before the first error occurred.

2.4. Tissue preparation

Tissue preparation was performed, as previously described (Kim et al. 2010; Lee et al. 2016). BrdU immunohistochemistry was performed, as previously described (Kim et al., 2010; Lee et al., 2016). The sections were pretreated in 50% formamide-2 × standard saline citrate (SSC) at 65°C for 2 h, denatured in 2 N HCl at 37°C for 30 min, and rinsed two times in 100 mM sodium borate (pH 8.5). The sections were incubated with BrdU-specific mouse monoclonal antibody (1:600; Roche,
Mannheim, Germany) overnight at 4°C, and the sections were incubated with biotinylated mouse secondary antibody (1:200; Vector Laboratories, Burlingame, CA, USA) for 1 h. The sections were incubated with an avidin-peroxidase complex (1:100; Vector Laboratories) for another 1 h, and then the sections were incubated in 50 mM Tris-HCl (pH 7.6) containing 0.03% 3,3′-diaminobenzidine (DAB), 40 mg/ml nickel chloride, and 0.03% hydrogen peroxide for 5 min for visualization.

The differentiation of BrdU-positive cells was detected on the same section using a mouse anti-neuronal nuclei (NeuN) antibody (1:1000; Chemicon Inc., Temecula, CA, USA). The sections were incubated with a biotinylated anti-mouse secondary antibody. The sections were mounted on gelatin-coated slides. The slides were covered by Permount® (Fisher Scientific, New Jersey, NJ, USA).

2.6. Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL) staining

TUNEL staining was performed using an In Situ Cell Death Detection Kit® (Roche), as previously described (Kim et al., 2010; Lee et al., 2016). The sections were incubated with proteinase K (100 μg/ml), rinsed, incubated in 3% H2O2, permeabilized with 0.5% Triton X-100, rinsed again, and incubated in the TUNEL reaction mixture. The sections were rinsed and visualized using Conver-POD with 0.03% DAB.

2.7. Caspase-3 immunohistochemistry

Caspase-3 immunohistochemistry was performed, as previously described (Kim et al., 2010; Lee et al., 2016). After incubating with mouse anti-caspase-3 antibody (1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA) overnight, the sections were incubated with biotinylated mouse secondary antibody (1:200; Vector Laboratories) for another 1 h. The secondary antibody was amplified with the Vector Elite ABC kit® (1:100; Vector Laboratories). Antibody-biotin–avidin-peroxidase complex was visualized using 0.03% DAB.

2.8. Western blot analysis

Western blot was conducted, as previously described (Kim et al. 2016; Lee et al. 2016). The hippocampal tissues were homogenized on ice, and lysed in a lysis buffer. Protein (20 μg) was separated on SDS-polyacrylamide gels and transferred onto a nitrocellulose membrane. Mouse β-actin antibody (1:500; Santa Cruz Biotechnology), rabbit BDNF antibody (1:1000; Santa Cruz Biotechnology), rabbit tyrosine kinase B (TrkB) antibody (1:1000; Santa Cruz Biotechnology), mouse Bax antibody (1:1000; Santa Cruz Biotechnology), mouse Bcl-2 antibody (1:1000; Santa Cruz Biotechnology), rabbit cAMP-responsive element-binding protein (CREB) antibody (1:1000; Santa Cruz Biotechnology), rabbit phospho-CREB (p-CREB) antibody (1:1000; Santa Cruz Biotechnology), mouse phosphorylatedinositol 3-kinase (PI 3-kinase) p85α antibody (1:1000; Santa Cruz Biotechnology), rabbit phospho-PI 3-kinase p85α (p-PI 3-kinase p85α) antibody (1:1000; Santa Cruz Biotechnology), rabbit protein kinase C alpha (PKCa) antibody (1:1000; Santa Cruz Biotechnology), rabbit phospho-PKCa (p-PKCa) antibody (Merck Millipore Corp., Darmstadt, Germany), rabbit Akt antibody (1:1000; Cell Signaling Technology Inc., Beverly, MA, USA), and rabbit phospho-Akt (p-Akt) antibody (1:1000; Cell Signaling Technology Inc.) were used as the primary antibodies. Horseradish peroxidase-conjugated anti-rabbit antibody (1:2000; Vector Laboratories) for BDNF, TrkB, Akt, p-Akt, CREB, p-CREB, p-PI 3-kinase p85α, PKCo, and p-PKCa, and horseradish peroxidase-conjugated anti-mouse antibody for β-actin, Bax, Bcl-2 and PI 3-kinase p85α (1:2000; Amersham Pharmacia Biothech GmbH, Freiburg, Germany) were used as the secondary antibodies. Band detection was confirmed by enhanced chemiluminescence (ECL) detection kit (Santa Cruz Biotechnology).

2.9. Data analysis

The detected bands were calculated densitometrically using Molecular AnalystTM, version 4.1 (Bio-Rad, Hercules, CA, USA). The numbers of TUNEL-positive, caspase-3-positive, and BrdU-positive cells in the hippocampal dentate gyrus were counted hemilaterally. Statistical analysis was performed using one-way analysis of variance (ANOVA) and Duncan’s post-hoc test. The results were expressed as mean ± standard error of the mean (SEM). Significance was set at p < 0.05.

3. Results

3.1. Short-term and spatial learning memory

Short-term memory was evaluated using step-down avoidance test (Figure 1(A)). The latency in the old-aged rats was shorter than the young-aged rats (p < 0.05). However, tamsulosin treatment increased the latency in the old-aged rats (p < 0.05).

Spatial learning memory was evaluated using radial 8-arm maze test (Figure 1(B)). The old-aged rats spent significantly longer time and made more error than the young-aged rats (p < 0.05). Their correct number was lower than the young-aged rats (p < 0.05). However,
tamsulosin treatment increased the correct number and reduced the error number, resulting in shortening the latency to accomplish this task ($p < 0.05$).

### 3.2. Expressions of p-PKCa, p-CREB, BDNF, TrkB, and neurogenesis

PKCa and p-PKCa expressions were examined (Figure 2(A)). In the old-aged rats, p-PKCa expression in the hippocampus was reduced than the young-aged rats ($p < 0.05$). However, tamsulosin treatment increased p-PKCa expression in the old-aged rats, resulting in increased p-PKCa/PKCa ratio ($p < 0.05$).

p-CREB and CREB expressions were examined (Figure 2(B)). In the old-aged rats, p-CREB expression in the hippocampus was reduced than the young-aged rats ($p < 0.05$). However, tamsulosin treatment enhanced p-CREB expression in the old-aged rats, resulting in increased p-CREB/CREB ratio ($p < 0.05$).

DNF and TrkB expressions were examined (Figure 2(C)). In the old-aged rats, BDNF and TrkB expressions in the hippocampus were reduced than the young-aged rats ($p < 0.05$). However, tamsulosin treatment increased BDNF and TrkB expressions in the old-aged rats ($p < 0.05$).

Photomicrographs of BrdU-positive cells in the hippocampal dentate gyrus are presented in Figure 2(D). The number of BrdU-positive cells in the hippocampal dentate gyrus of old-aged rats were reduced than the young-aged rats ($p < 0.05$). However, tamsulosin treatment increased the number of BrdU-positive cells in the old-aged rats ($p < 0.05$).

### 3.3. Expressions of p-PI 3-kinase p85α, p-Akt, Bcl-2, and Bax

p-PI 3-kinase p85α and PI 3-kinase p85α expressions were examined (Figure 3(A)). Old-aged rats showed reduced p-PI 3-kinase p85α expression in the hippocampus than the young-aged rats ($p < 0.05$). However, tamsulosin treatment increased p-PI 3-kinase p85α expression in the old-aged rats, resulting in increased p-PI 3-kinase p85α/PI 3-kinase p85α ratio ($p < 0.05$).

p-Akt and Akt expressions were examined (Figure 3(B)). Old-aged rats showed reduced p-Akt expression in the hippocampus than the young-aged rats ($p < 0.05$). However, tamsulosin treatment increased p-Akt expression in the old-aged rats, resulting in increased p-Akt/Akt ratio ($p < 0.05$).

Bcl-2 and Bax expressions were examined (Figure 3(C)). Bax and Bcl-2 expressions in the hippocampus of old-aged rats were higher than the young-aged rats. However, the ratio of Bcl-2 to Bax in the old-aged rats was lower than the young-aged rats, because Bax expression was higher than Bcl-2 in the old-aged rats ($p < 0.05$). However, tamsulosin treatment increased Bcl-2 expression and suppressed Bax expression, resulting in increased Bcl-2/Bax ratio in the old-aged rats ($p < 0.05$).

### 3.4. Numbers of caspase-3-positive and TUNEL-positive cells

Caspase-3 expression was examined (Figure 4(A)). Caspase-3 expression was higher in the hippocampus of old-aged rats than the young-aged rats ($p < 0.05$). On the other hand, tamsulosin treatment suppressed caspase-3 expression in the old-aged rats ($p < 0.05$).

The number of TUNEL-positive cells was examined (Figure 4(B)). The number of TUNEL-positive cells was higher in the hippocampus of old-aged rats than the young-aged rats ($p < 0.05$). However, tamsulosin treatment suppressed the number of TUNEL-positive cells in the old-aged rats ($p < 0.05$).
4. Discussion

In this study, short-term and spatial learning memory was impaired in the aged rats. Subchronic treatment of prazosin improved performance of memory task in the aged rats (Knauber and Müller 2000). Previously, we reported that tamsulosin improved memory by activating N-methyl-D-aspartate (NMDA) receptor-mediated ion currents in addition to overactive bladder therapy (Kim et al. 2015). In our study, tamsulosin treatment showed improved short-term and spatial learning memory in the aged rats.

In this study, BDNF expression and neurogenesis in the hippocampus were decreased in the hippocampus of aged rats (Kim et al. 2010; Yang et al. 2014). In our study, tamsulosin treatment increased BDNF and TrkB expressions and also enhanced hippocampal neurogenesis in the aged rats.

In this study, phosphorylation of PKCα, CREB, PI-3 kinase, and Ak in the hippocampus was decreased in the aged rats. PKC is involved in the neurotransmitter release, receptor regulation, cell proliferation, and synaptic remodeling (Pascale et al. 2007). Decreased hippocampal PKC activity deteriorated spatial memory, in contrast, PKC activator improved memory during normal aging process (Govoni et al. 2010). Among PKC isozymes, PKCα is involved in differentiation, regeneration, and learning ability (Pascale et al. 2005). Hongpaisan et al. (2013) reported that reduced PKCα and PKCε expressions in the hippocampus of aged rats correlated with impaired learning and memory retention, and
rescued PKCe and PKCa expressions normalized memory to the level of young rats.

PKC also mediates phosphorylation of CREB, and upregulation of CREB enhanced both short-term and long-term memory (Suzuki et al. 2011). Memory impairment in the aged rats was associated with decreased CREB phosphorylation in the hippocampus (Xu et al. 2010). Gain or loss of CREB function improved or impaired, respectively, the formation of long-term memory (Kida and Serita 2014).

TrkB directly activates PI 3-kinase, which normally presents in cytosol (Yuan and Yankner 2000). Phosphorylation of PI 3-kinase activated Akt, and this signaling pathway inhibited caspase-mediated apoptosis (Zhang et al. 2010). Phosphorylation of Akt promoted cell survival by inactivating apoptosis factors (Yuan and Yankner 2000). Especially, phosphorylation of Akt is known to up-regulate anti-apoptotic proteins such as Bcl-2 and Bcl-xL (Hsu et al. 2010). In our study, tamsulosin treatment facilitated phosphorylation of PKCa, CREB, PI-3 kinase, and Ak in the aged rats.

In this study, Bcl-2 and Bax expressions in the hippocampus were increased in the aged rats. Bax expression was more prominently enhanced, and then Bcl-2/Bax ratio was increased in the aged rats. While Bcl-2 is crucial for the maintenance of neuronal survival, Bax

**Figure 3.** Expressions of phosphatidylinositol 3-kinase p85α (PI 3-kinase p85α), Akt, Bcl-2, and Bax in the hippocampus. (A) Phosphorylated p-PI 3-kinase p85α (p-PI 3-kinase p85α) and PI 3-kinase p85α expressions. (B) Phosphorylated Akt (p-Akt) and Akt expressions. (C) Bcl-2 and Bax expressions. YC: Young-aged control group, OC: old-aged control group, TAM 0.01: old-aged and 0.01 mg/kg tamsulosin-treated group, TAM 0.1: old-aged and 0.1 mg/kg tamsulosin-treated group, TAM 1: old-aged and 1 mg/kg tamsulosin-treated group. ∗ represents $p < 0.05$ compared to the young-aged control group. # represents $p < 0.05$ compared to the old-aged control group.
plays a critical role in neuronal cell death (Yuan and Yankner 2000). The ratio of Bcl-2 to Bax or vice versa is an important factor in deciding whether cells undergo apoptosis (Hsu et al. 2010; Kim et al. 2010). Bcl-2 expression in the hippocampus was increased with aging, and such up-regulation of Bcl-2 exerted neuroprotective effect in the aged rats by decreasing the Bax/Bcl-2 ratio (Kaufmann et al. 2001; Kim et al. 2010). In our study, tamsulosin enhanced Bcl-2 expression and suppressed Bax expression, and consequently increased Bcl-2/Bax ratio in the aged rats.

In conclusion, tamsulosin activated PKC/CREB and PI-3 kinase/Akt pathways. With these pathways, BDNF-TrkB signaling enhanced hippocampal neurogenesis and suppressed apoptosis in the old-aged rats. As the results, tamsulosin improved performance of short-term and spatial learning memory in the aged rats. Tamsulosin can be considered as a new therapeutic agent for improving memory function during aging process.

Disclosure statement
No potential conflict of interest was reported by the authors.

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