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Effects of YC-1 on Learning and Memory Functions of Aged Rats

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Background: The aim of this study was to investigate the effects of a potent nitric oxide-guanylate cyclase activator, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1), on learning and memory functions in aged rats.

Material/Methods: Rats were divided into 2 groups as 4-month-old and 24-month-old rats. Rats received YC-1 (1 mg/kg/day) for 2 weeks long-term. Morris water maze (MWM) and passive avoidance (PA) tests were used to determine learning and memory functions.

Results: In the MWM test, there is a significant increase in the acquisition latency (1–4 days) of 24-month-old rats. There is a significant reduction in the "time spent in the escape platform's quadrant" in 24-month-old rats compared to 4-month-old rats in the probe trial of the MWM test. YC-1 treatment reversed the reduction of the "time spent in the escape platform's quadrant" of 24-month-old rats. In the PA test, there was no significant difference in the 1st-day latency of rats in all groups. On the 2nd day, retention latency significantly decreased in the 24-month-old rats compared to 4-month-olds. YC-1 reversed the diminished retention latency in 24-month-old rats. YC-1 treatment and aging did not affect results of the locomotor activity test or the foot-shock sensitivity test, suggesting our results were not due to a change in motor activity or disability of the animals.

Conclusions: Our findings suggest that activation of the NO-sGC-cGMP pathway plays an important role in spatial and emotional learning and memory functions in aged rats.

MeSH Keywords: Avoidance Learning • Behavior, Animal • Guanylate Cyclase • Memory Disorders • Nitric Oxide

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Background

Older age is associated with functional decline in selective aspects of cognitive performance and brain function [1]. One of the most important matters for many individual as they "normally age" is a decline in cognitive functions [2,3]. Learning and memory deterioration affect nearly half of the aged population [4].

Nitric oxide is known to affect synaptic plasticity and is thought to play important roles in a variety of forms of learning and memory [5]. The most relevant intracellular receptor for nitric oxide (NO) is soluble guanylyl cyclase (sGC), a heterodimeric hemoprotein to which NO binds and triggers the synthesis of cyclic guanosine monophosphate (cGMP). The effects of NO occur by the activation of sGC, which causes an increase in cGMP, and the activation of protein kinase G (PKG). cGMP acts on adenylate cyclase, leading to an increase in cAMP and to a prolonged increase in cAMP-dependent protein kinase (PKA), which then causes changes that underlie long-term memory [6]. The sGC is expressed in the cytoplasm of a large number of mammalian cells, and this isoform is mainly presented in cells of the central nervous system, which can be directly activated by NO [7]. The highest expression levels of sGC were found in the cortex, basal ganglia, and limbic system of the human brain; these are the regions that display the most prominent biochemical and histological changes during aging. It has been reported that sGCα1 and sGCβ1 subunits are widely distributed in the human brain, consistent with a major role in NO signaling; the NO/cGMP pathway appears to be affected by aging in the human brain [8]. It has been reported that cGMP concentration in the rat brain decreases during development and aging, and the ability of the cholinergic system to synthesize cGMP decreases during the life span [9]. Also, it has been reported that sGC inhibitors suppress LTP and GC, and PKG contribute to LTP, possibly as activity-dependent presynaptic effectors of retrograde messengers [10]. sGC activity is affected in Alzheimer disease [11] but the role of sGC in the human brain during aging and age-related neurodegenerative diseases is incompletely understood.

YC-1 (3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole) is a potent NO-GC activator reported to improve rodent learning behavior when examined with the Morris water maze (MWM) and avoidance tests [12]. YC-1 enhanced long-term potentiation (LTP) in hippocampal Schafer collateral-CA1 synapse via the NO-cGMP-PKG-dependent pathway and potentiated LTP induction in the amygdala [13], increased the activation of extracellular signal-regulated kinase (ERK), and potentiated the expression of brain-derived neurotrophic factor (BDNF) cAMP response element-binding protein (CREB) in response to fear memory test [14].

Memory, as measured by changes in animal behavior after learning, reflects many processes, including acquisition, consolidation, and retrieval. The time course of different experimental manipulations used to study stages of memory are important [15]. It was reported that 3-Br 7-NI and ODQ disrupts reference and working memory processes by impairing strategies used for solving learning tasks, and, according to our results, nNOS-sGC may be required for emotional learning and reference and working memory [16].

With this background, we aimed to investigate the role of long-term YC-1 treatment on acquisition and retention of memory in aged rats using 4 month-old and 24-month-old rats in the Morris water maze and passive avoidance tests.

Material and Methods

Animals

4-month-old (200–250 g) and 24-month-old (550–600 g) male Wistar-albino rats were used. Rats were kept in an animal colony (Kocaeli University, Experimental Medical Research and Application Center, Kocaeli, Turkey) at a density of approximately 5–6 per cage for 2 weeks before the start of the experiments. Experiments were conducted between 9:00 a.m. and 12:00 p.m. under standard laboratory conditions (22±2°C room temperature; 12-h light/dark cycle with lights on at 7:00 p.m.). Tap water and food pellets were provided ad libitum.

All experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). The experiments reported in this study were conducted in accordance with the Regulation of Animal Research Ethics Committee in Turkey (6 July 2006, Number 26220). The ethics approval was granted by the Kocaeli University Animal Research Ethics Committee (Kocaeli, Turkey, Project number: 11/6).

Drugs and treatments

YC-1 were purchased from Sigma-Aldrich (USA) and dissolved in dimethyl sulfoxide (DMSO). All drugs were prepared immediately prior to use and given intraperitoneally (i.p.) in a volume of 0.1 ml per 100 g body weight. All rats received 1 mg/kg/day of YC-1 for 2 weeks. DMSO was administered to 4-month-old and 24-month-old rats (n=10, for each group). Doses were selected according to previous studies [14] and to confirm the selected doses on locomotor activity; all results were measured.

Foot-shock sensitivity test

The foot shock sensitivity test procedure was designed as previously described by Rubin et al., [17]. Reactivity to shock was evaluated in the same apparatus used for inhibitory avoidance.

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The flinch and jump threshold was determined. Young, older, and YC-1-treated older animals were placed on the grid and allowed a 3-min habituation period before the start of a series of shocks (1 s) delivered at 10-s intervals. Shock intensities ranged from 0.1 to 0.5 mA in 0.1-mA increments. The adjustments in shock intensity were made in accordance with each animal's response. The intensity was raised by 1 unit when no response occurred and was lowered by 1 unit when a response occurred. A flinch response was defined as withdrawal of 1 paw from the grid floor, and a jump response was defined as withdrawal of 3–4 paws. Three measurements of each threshold were made, and the mean of each score was calculated for each animal.

Locomotor activity test

Because old age and compounds altering locomotor activity may give false-positive/negative effects in behavioral tests, an additional test was carried out with the specific aim of monitoring motor activity. The spontaneous locomotor activity of the animals was assessed by monitoring their activity in a locomotor activity cage. Locomotor activity was measured with a computerized system (40×40×35 cm box; May Commat, Ankara, Turkey). Total number of movements was measured for a 5-min period before the behavioral tests and is expressed as the sum of stereotypic, ambulatory, and vertical activity. In this study, the 24-month-old naturally aged rats were chosen, which do not have impaired locomotor activity or any neurological deficit, in order avoid false-positive/negative effects in behavioral tests.

Passive avoidance test

In this type of avoidance learning test, the animals were refraining from making the measured response. A step-down variant passive avoidance apparatus was used (Ugo Basile model 7551, Italy). The apparatus (measuring 22×21×22 cm) consisted of 2 compartments: a light and dark compartment separated by a guillotine door. On Day 1 (training trial), the rats were placed individually into the light compartment and allowed to explore the boxes to become aware of the environment.

1. Pre-acquisition trial: After 30 s, the door between the 2 boxes was opened, and the animal moved into the dark compartment freely.
2. The acquisition (training) trial was conducted 15 min after the pre-acquisition trial. Rats were placed in the light compartment, and after a 30-s adaptation period, the door between the compartments was opened. Having completely entered the dark compartment, the door was automatically closed, and an electric foot-shock (0.5 mA) of 3-s duration was delivered to the animal via the grid floor. The time taken to reenter the dark compartment was recorded (training latency). Any animal failing to cross from the light to the dark compartment within 300 s was discarded from the experiment. Animals were then removed from the dark compartment and returned to their home cages. Between each training session, both chamber compartments were cleaned to remove any confounding olfactory cues.
3. Retention trial: Recall of the inhibitory stimulus was evaluated at 24 h post-training by returning the animals to the light compartment and recording their latency to enter the dark compartment (4 paws in). No foot-shock was applied in this trial. If the animal did not enter the dark compartment within 300 s, it was returned to its cage and a maximum latency of 300 s was recorded. This latency served as a measure of retention performance of step-down avoidance responses (retention latency).

Morris water maze test

The Morris water maze consisted of a circular pool (150-cm diameter) was filled with water (25°C) and rendered opaque by the addition of small white pieces of plastic [17]. The pool was located in a dimly lit and soundproof test room with a camera and the experimenter. The maze was divided into 4 quadrants. Three equally-spaced points around the edge of the pool were used as the release positions. The order of the release positions was varied systematically throughout the experiment. An escape platform (6-cm in diameter and 12-cm high) was located in 1 quadrant, 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions. Video tracking was conducted with a video camera (Sony Dcr-Hc40e) focused on the full diameter of the pool. The rats were trained in the Morris water maze during 5 daily sessions (familiarization session, S1, S2, S3, and S4). The 5 sessions were performed on consecutive days between 9:00 and 12:00. During the acquisition phase of the experiments, each rat participated in 3 trials per day [19]. For each daily trial, the rat was taken from the home cage and placed into the water maze at 1 of 3 randomly determined locations with its head facing the center of the water maze. A trial was started when the rat was released from 1 of 3 randomly chosen start positions. After the rat found and climbed onto the platform, the trial was stopped and the escape latency was recorded. The maximum trial length was 60 s. If the rat had not climbed onto the platform within 60 s, the experimenter guided the rat by hand to the platform and an escape latency of 60 s was recorded. The inter-trial time was 60 s. During this time, the rat was kept on the escape platform before starting the next trial. The rat was then placed in the pool again, but at a different location, and the next trial began upon its release. Normally, the escape latency declines during acquisition as the animal learns the location of the hidden platform. At the end of the third trial, the rat was returned to its cage. Twenty-four hours after the last acquisition session, a 'probe trial' was used to assess the rats' spatial retention of

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the location of the hidden platform. During this trial, the platform was removed from the maze, and each rat was allowed to search the pool for 60 s before being removed. During this trial, animals should spend more time swimming in the quadrant that previously contained the hidden platform than in the other 3 quadrants.

Statistics

All results are expressed as the mean ±S.E. Acquisition (1–4 days) latency scores in MWM test were measured by 2-way analysis of variance (ANOVA), following post hoc Bonferroni test. Scores of the time spent in the escape platform's quadrant in MWM test, first day and retention latencies in the PA test, total locomotor activity, and foot shock sensitivity scores were measured by 1-way ANOVA. Further statistical analysis for individual groups was carried out by Dunnett's test.

Foot-shock sensitivity flinch and jump thresholds were measured by Kruskal-Wallis nonparametric test. Further statistical analyses for individual groups were carried out by Dunn's multiple comparison test. The criterion for statistical significance was P<0.05.

Results

Morris water maze test

Latency (1–4 days) (s) of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and 24-month-old+YC-1 rats to find the platform

Statistical analysis showed a significant effect of day in the data set (2-way ANOVA, effect of day, F(180, 4)=11.80, p<0.0001). In addition, an extremely significant effect of treatment was demonstrated (2-way ANOVA, effect of treatment, F(180,4)=30.27, p<0.0001). Further analysis also revealed that dayXtreatment interaction was not significant (2-way ANOVA, dayXtreatment, F(180, 12)=0.79, p=0.6622). There was a significant reduction in the latency of 4-month-old young rats (1-way ANOVA, Day 1 *vs.* Day 4, p: 0.0023 F(3,36)=5.838), which may indicate that latency for the young rats to find the platform decreased by Day 4. Post-hoc comparisons showed that 24-month-old rats had an increase in their acquisition latency compared to 4-month-old young rats (p<0.05, p<0.01, p<0.01 and p<0.001, 1st, 2nd, 3rd and 4th day, respectively) and 24-month-old rats treated with YC-1 (p<0.05, p<0.01, p<0.01 and p<0.01, 1st, 2nd, 3rd and 4th day, respectively), Bonferroni test, suggesting that YC-1 blocked the effects of age. Additionally, we used DMSO as a carrier for YC-1. DMSO had a significant effect on acquisition latency in the MWM test, first 1–4 days, compared to saline-treated control rats (p>0.05; Figure 1).

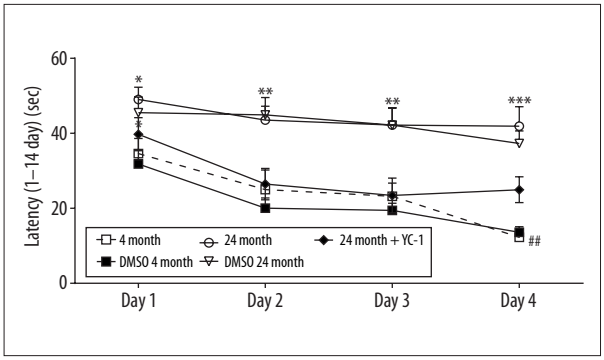

Figure 1. Latency (s) to find the platform of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and 24-month-old+YC-1 rats in the MWM test. ## There is a significant reduction in the latency of 4-month-old rats (1-way ANOVA, Day 1 *vs.* Day 4, p: 0.0023 F(3,36)=5.838). *, **, *** 24-month-old rats had an increase in their acquisition latency compared to 4-month-old rats (p<0.05, p<0.01, p<0.01 and p<0.001) and 24-month-old rats treated with YC-1 (p<0.05, p<0.01, p<0.01 and p<0.01).

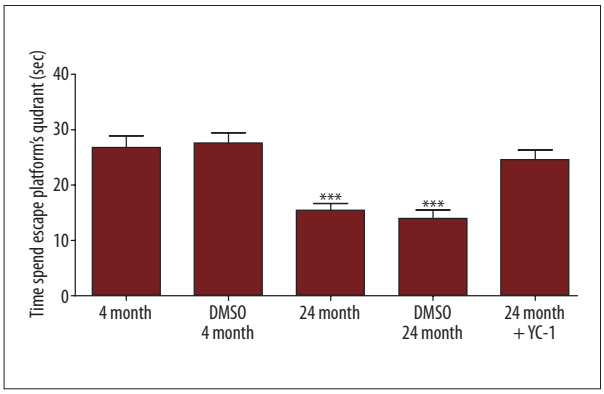

Figure 2. Time spent in the escape platform quadrant (s) of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and YC-1+24-month-old groups in probe trial of MWM test. *** Retention latency of 24-month-old aged rats was significantly shortened compared to 4-month-old young (p<0.0001, Dunnett's test) and YC-1-treated 24-month-old group (p<0.0001, Dunnett's test).

Time spent in escape platform quadrant of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and 24-month-old+YC-1 rats

There was a significant difference between the groups in the probe trial in MWM test (1-way ANOVA, F(4,45)=13.72, p<0.0001, Figure 2). Post-hoc comparisons showed a significant reduction in the time spent in escape platform quadrant of 24-month-old rats compared to 4-month-old young rats (p<0.0001, Dunnett's test). There was no significant difference between 4-month-old rats compared to 24-month-old rats treated with YC-1 group (p>0.05, Dunnett's test), suggesting that

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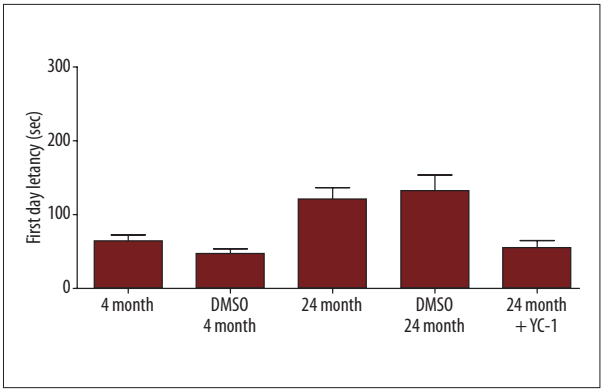

Figure 3. First-day latency of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and YC-1+24-month-old rats in the PA test.

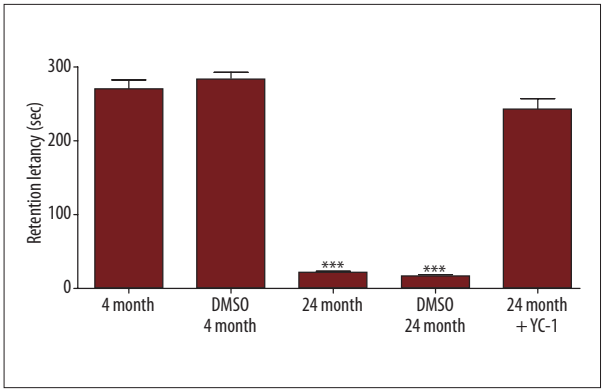

Figure 4. Retention latency (s) of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and YC-1+24-month-old rats in the PA test. *** Retention latency of 24-month-old aged rats was significantly shortened compared to 4-month-old (p<0.0001, Dunnett's test) and YC-1-treated 24-month-old rats (p<0.0001, Dunnett's test).

YC-1 administration reversed the reduction in the time spent in escape platform quadrant of 24-month-old rats. In addition, DMSO had no effect on time spent in escape platform quadrant in MWM test compared to controls (p>0.05, Dunnett's test).

Passive avoidance test

Acquisition latency (Day 1) of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and 24-month-old+YC-1 rats

In the PA test, there was no significant difference in acquisition latency between the groups (1-way ANOVA, F(4,45)=2.84, p>0.05, Figure 3).

Retention latency (Day 2) of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and 24-month-old+YC-1 rats

There was a significant change in retention latency between the groups (1-way ANOVA, F(4,45)=45.61, p<0.0001, Figure 4). Post-hoc comparisons showed that retention latency of 24-month-old aged rats was significantly shortened compared to 4-month-old young rats (p<0.0001, Dunnett's test) and YC-1-treated 24-month-old rats (p<0.0001, Dunnett's test) (Figure 4). The shortened retention latency scores caused by aging is reversed with the administration of YC-1 to aged rats (p<0.0001, Dunnett's test). Also, DMSO had no effect on retention latency in passive avoidance test (p>0.05).

Locomotor activity of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24 month-old, and 24-month-old+YC-1 rats

Because motivational disparities in the training session may account for differences in inhibitory avoidance at testing, experiments were performed to assess whether aging or YC-1

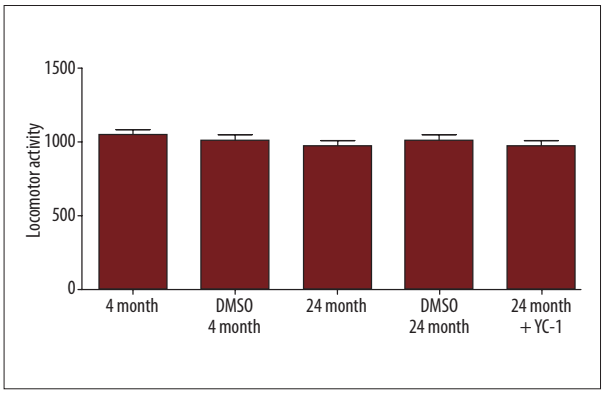

Figure 5. Locomotor activity of 4-month-old, DMSO-4-month-old, 24-month-old, DMSO-24-month-old, and YC-1+24-month-old rats.

affected shock threshold, or locomotor ability of the animals. Statistical analysis of locomotor activity (1-way ANOVA) revealed that pharmacological treatment did not alter the total number of movements (p>0.05) in the locomotor activity test session (Figure 5).

Flinch and jump responses of 4-month-old, DMSO, 24-month-old, and 24-month-old +YC-1 rats in the foot-shock sensitivity (mA) test

Aging did not alter the flinch or jump responses in the foot-shock sensitivity (mA) test in the 4-month-old, DMSO, 24-month-old, and (24-month-old+YC-1) groups as demonstrated by flinch (KW: 2.828, p=0.41) and jump (KW: 0.9041, p=0.82) thresholds exhibited by the animals. Foot-shock sensitivity results suggest that neither aging nor YC-1 treatment caused gross motor disabilities at testing (Figure 6).

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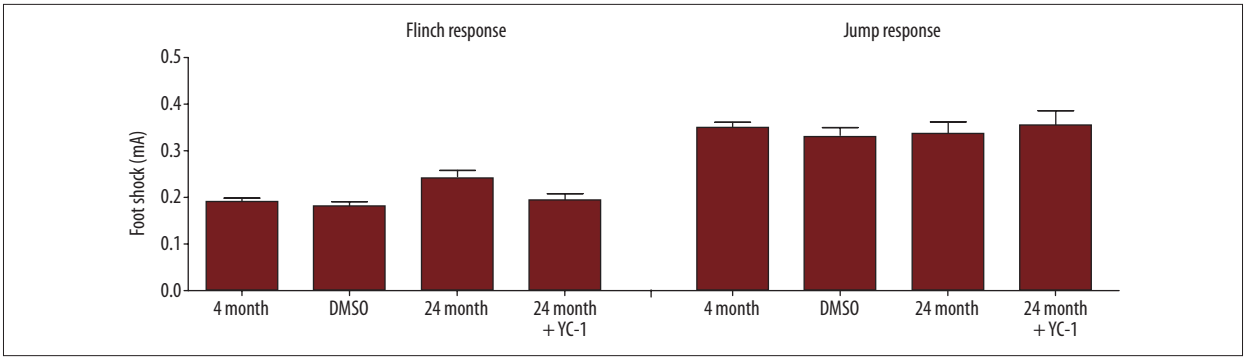

Figure 6. Foot-shock sensitivity of 4-month-old, DMSO, 24-month-old, and 24-month-old+YC-1 rats.

Discussion

This study demonstrates for the first time that chronic YC-1 administration affects learning and memory performance in different learning and memory tasks in aged animals.

In the MWM test, according to the learning curves of each group, latency to find the platform of young rats is significantly reduced by the last day of acquisition session, which may indicate that young rats find the platform faster by training.

Also, interestingly, with the training, we observed an age-dependent learning disability in the latency of 24-month-old aged rats to find the platform through the learning days compared to 4-month-old young and 24-month-old rats-treated with YC-1, suggesting that YC-1 blocked the effects of aging.

In the probe trial of the MWM test, aged rats spent significantly less time in the "escape platform quadrant" compared to younger rats, which indicates aging may affect spatial memory retrieval function.

MWM test results may be interpreted as evidence that long-term YC-1 treatment affects the spatial memory function, which may support the affirmative effect of the activation of the NO-GC pathway in spatial memory.

In the PA test, the first-day latency was not affected by age or YC-1 treatment. The retention latency of rats is significantly reduced by aging. YC-1 treatment reversed the dysfunction of memory retention in the PA test. This finding suggests that cGC may have a role in the formation of emotional memory.

Finally, there was no difference in the locomotor activity between the groups, indicating that the effects on behavioral tests were not due to a change in locomotor activity of the animals or to an exercise inability. To determine if pharmacological treatments affect the motivational aspects of learning (e.g., a passive avoidance test that is a shock-motivated learning task), we assessed the foot-shock sensitivity test. We observed that there was no difference in the foot-shock sensitivity between the groups, indicating that the aging process and YC-1 administration did not affect the flinch and jump thresholds of rats.

Our findings are in agreement with a previous study [12] that demonstrated the positive effect of YC-1 on Morris water maze test and passive avoidance test.

Memory function may be defined as the ability to acquire, process, store, and retrieve information [20]. In this study, we investigated the effects of long-term administration of YC-1 in the PA test and MWM test, finding that YC-1 improved spatial and emotional learning and memory in distinct behavioral tasks involving different brain structures, including the hippocampus and the amygdala. Emotional memory involves the unconscious learning and storage of information about the emotional significance of events. The neural system underlying emotional memory involves the amygdala [21]. Consistently, in a previous behavioral study, it was shown that aged rats required significantly more trials than young rats to learn the maze task [22]. Aged rats' memory functions are generally impaired on a wide variety of navigation tasks (e.g., Morris water maze task, T-maze, and Barnes circular platform corridor mazes) [23]. The MWM task has been used extensively in studying cognitive aging in rodents in part because of its known dependence on the hippocampal formation [24] and spatial cognition is considered an important area in the cognitive neuroscience of aging [25]. Recent studies have shown that older age is associated with functional depletion in spatial cognitive functions, which may restrict daily activities such as retrieving everyday objects or navigating in new environments [26].

Age-related deficits have been reported, showing that older animals take longer to find the hidden platform, travel a longer distance in locating the platform, and may require more trials before reaching a designated criterion performance [1,27].

The underlying mechanisms of cognitive impairment during aging have not been fully explained. Since activation of NMDA

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receptors leads to an increase of calcium in the post-synaptic neurons, several reports have implicated the role of the glutamate/NO/cGMP pathway in learning and memory [28,29]. Learning and memory impairment in aged animals is a consequence of reduced function of the glutamate/NO/cGMP pathway in the aged brain and probably also alteration in cholinergic signaling [22]. A basic question in understanding the role of the NO/c GMP signaling pathway in the naive and diseased nervous system is the regulation of the 2 key enzymes: NOS-1 and sGC. The role of sGC has not been investigated in aging and its mechanism is poorly understood. Age-dependent decreases in sGC activity were observed in rat hippocampus [30]. It has been reported that both sGC types are widely distributed in the human brain and decreased in an age-dependent manner, but no information is available about changes in sGC activity in the course of normal aging in human brains [8]. The increase in PDE expression and activity may lead to more intensive cGMP hydrolysis in the senescent brain. Several findings indicate that NO synthesis is altered in the aged brain [31]. Cognitively impaired aged rats showed significantly higher nNOS mRNA expression than the cognitively unimpaired aged animals [32]. The NO-cGMP pathway in learning and memory had been implicated [33]. The inhibition of PDE5 or PDE2 improves object memory in adult rats by increasing the level of cGMP, and it was reported that the inhibition of PDE2 can improve memory functions via enhancing neuronal plasticity [34]. Previous data indicated that IBMX, a non-specific PDE inhibitor causes an increase in the cGMP level in the aged rat brain [35].

It has been reported that the NO-cGMP-PKG signaling pathway regulates fear memory consolidation in lateral amygdala via activation of ERK/mitogen-activated protein (MAP) [36] and the synaptic integrity in aged brain, indicating that a substantial loss of dendritic spines and spinophilin protein in the hippocampus are unlikely to contribute to age-related impairment in spatial learning [37]. During the aging process, constitutive NOS activity is increased, which leads to increased NO production. The activity of cGMP hydrolyzing PDEs is increased, cGMP levels are decreased, and the LTP process is less efficient in the senescent compared with the adult brain, resulting in worse cognitive performance of aged animals [31].

Our results suggest that improvement of age-related learning and memory deficits via chronic YC-1 treatment may result from the direct effects of YC-1 on sGC. In the present study, YC-1 was used as a tool for investigating sGC and cGMP-mediated pathways on aging. It is well known that the central cholinergic system play an important role in learning and memory processes and also is a prominent hallmark of Alzheimer disease [38]. The decrease of acetylcholine release might be responsible for disturbances of memory. We plan to further investigate the effects of YC-1 on memory disturbances in aged animals induced by the antagonist of cholinergic receptors, scopolamine, in aged animals.

Conclusions

Our findings suggest that aging affects spatial learning, memory, and emotional memory. YC-1 administration may affect age-related learning and memory dysfunction.

In conclusion, activation of NO-GC may play an important role in spatial learning, memory, and emotional memory functions. Because of the important roles of the NO/cGMP signaling pathway in learning and memory functions, sGC is an important factor contributing to age-related memory decline. Alternatively, activation of sGC may be a treatment target for the age-dependent degenerative processes leading to a loss of learning and memory functions.

Conflict of interest

All authors have no conflict of interest to declare.

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