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D-Cycloserine, a Novel Cognitive Enhancer, Improves Spatial Memory in Aged Rats

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BAXTER, M. G., T. H. LANTHORN, K. M. FRICK, S. GOLSKI, R.-Q. WAN AND D. S. OLTON. *D-cycloserine, a novel cognitive enhancer, improves spatial memory in aged rats.* NEUROBIOL AGING **15**(2) 207–213, 1994.—D-cycloserine, a partial agonist of the NMDA receptor-associated glycine site, can enhance cognition. The present experiment examines the behavioral effects of D-cycloserine on cognitive deficits in male Fischer-344 rats, 24 months old. Rats 24 months old (n = 42) received either vehicle or one of 3 doses of D-cycloserine prior to testing. Young rats, 4 months old (n = 13), received vehicle prior to testing. Place discrimination and repeated acquisition were tested in the water maze and a variety of sensorimotor tasks were given. Aging impaired performance in all tasks. D-cycloserine improved performance in place discrimination and repeated acquisition. No doses affected sensorimotor function. These results support the hypothesis that D-cycloserine has cognition enhancing properties and that it may be useful in treating disorders involving cognitive impairment.

D-Cycloserine Cognitive enhancer Glycine partial agonist Fischer-344 rats Spatial memory Aging

D-CYCLOSERINE is a partial agonist of the N-methyl-D-aspartate (NMDA) receptor-associated glycine site (7,8). The NMDA receptor is crucial to cellular plasticity underlying learning and memory; administration of NMDA antagonists prevents learning and blocks induction of long-term potentiation (LTP) (1,14). Activation of the NMDA receptor ion channel requires cell depolarization to remove the magnesium channel blocker and simultaneous activation of the glycine and glutamate sites on the receptor (10,19). This activation of the NMDA receptor permits entry of calcium ions into the cell resulting in a cascade of intracellular changes that are correlated with learning (17).

Modulation of the NMDA receptor by action at the glycine site is an attractive option for development of cognitive enhancers. Glycine antagonists blocked induction of LTP in area CA1 of rat hippocampal slices (9) and glycine agonists had cognitive enhancing effects. D-cycloserine reversed deficits in water maze performance induced by scopolamine (3,16), restored performance of hippocampal-lesioned rats in a radial arm maze (15), doubled learning rates of rabbits in a conditioned eyeblink paradigm (18), increased retention of a passive avoidance task in young mice in a dose-dependent manner, improved deficits in pasive avoidance learning in senescent-accelerated mouse strains (2), and enhanced passive avoidance learning and place learning in a T-maze in rats (12). Furthermore, milacemide, which increases brain glycine levels, enhanced retention of a passive avoidance task in rats and reversed deficits induced by scopolamine and AP7 in spontaneous alternation (6).

This experiment used two discrimination tasks in the water maze to assess the ability of D-cycloserine to reduce age-associated memory deficits in aged rats. In the place discrimination, a submerged platform was placed in one location in the water tank. The rat learned to reach the platform based on its relation to the spatial cues present in the environment (13). Aged rats were substantially impaired in performance of this task (4,5). A variable-interval probe trial procedure was included, in which the platform was removed from the maze and the rat's memory of the location was assessed by several measures. This procedure allows for repeated measures of spatial memory with no extinction, because the response-reinforcement contingencies on the variable interval probe trials are the same as those on platform trials (11).

Repeated acquisition assessed spatial working memory. In this procedure, the platform is moved to a new location at the beginning of each session. Learning was assessed within each session, measuring the ability of the rat to learn a new platform location.

Certain measures of performance in the water maze can be affected by factors other than spatial memory. Sensory and motor abilities were measured with a battery of tasks to assess the possible beneficial effects of these compounds on sensorimotor skills, to determine the extent to which changes in water maze performance may have been caused by alterations in gross sensory or motor function.

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METHOD

Subjects

Male Fischer-344 rats were 4 months old (4MO, $n = 13$) or 24 months old (24MO, $n = 42$) at the start of behavioral testing and were housed in pairs in a colony room with a 12L:12D cycle (lights on at 7 a.m.). Food and water were available ad lib. All behavioral testing occurred during the light portion of the cycle.

Apparatus

The tank, made of galvanized metal, was 180 cm in diameter and 60 cm high. Water filled the tank to a depth of 35 cm, and was maintained at 24 ± 2°C by an aquarium heater (Visitherm), which was removed prior to testing. White watercolor paint (Rich Art) was added to the water to make it opaque. The inside of the tank was painted white. The tank was divided into 4 quadrants (NE, NW, SE, SW) by two imaginary perpendicular lines crossing in the center of the tank. A tracking system (HVS Image Analysis VP-112) was used to record data. A camera (Burle) was mounted 1.4 meters above the surface of the water and was connected to a computer which ran the program for the tracking system and stored the data collected. Light was provided by four 40-watt bulbs, mounted in a circle, 1.2 meters above the surface of the water. The tank was located at one end of a small rectangular room, with a variety of visual cues throughout the room. Visual stimuli were both distal (on the walls of the room) and proximal (located on the rim of the maze). Auditory stimuli from a radio were present during all behavioral testing.

The platform was made of transparent plastic (Lucite), 100 cm^2, with 1 cm diameter holes that provided a gripping surface for the rat. The platform could be raised and lowered by a cable that was located beneath the water and ended outside of the tank. In the raised position, the platform was 1 cm below the surface of the water and available to the rat for escape from the water. In the lowered position, it was 19 cm below the surface of the water, unavailable for escape.

For shaping and straight swim (see below), two pieces of transparent plastic (Lucite), 100 cm long and 61 cm high, were placed parallel to each other in the tank to form an alley, 15 cm wide, with edges 26 cm above the surface of the water. One end of the alley was placed against the edge of the tank. A third piece of transparent plastic (Lucite), 15 cm wide and 61 cm long, extended 26 cm above the surface of the water and was placed to block the other end of the alley.

Drug Administration

The drug administered was D-cycloserine. Each rat received the same dose of the same drug on each day of testing. Each drug solution had 1 mg of the drug per ml of vehicle (isotonic saline). A fresh solution of each drug was made each day of testing.

Control. Vehicle was given to each control rat throughout behavioral testing.

D-cycloserine. D-cycloserine was dissolved in isotonic saline and administered by IP injection in the following doses: 1.0, 3.0, and 10.0 mg/kg. Testing began at least 30 min after drug administration and was completed within 120 min of drug administration.

Design

Each 4MO rat was assigned to the young control group (4MO–CON, $n = 13$) and given vehicle before testing. Each 24MO rat was randomly assigned to one of 4 groups, one control group (24MO–CON, $n = 11$) and 3 drug groups, one for each dose: 24MO–CYC1 (1.0 mg/kg, $n = 10$), 24MO–CYC3 (3.0 mg/kg, $n = 10$), and 24MO–CYC10 (10.0 mg/kg, $n = 11$).

Procedure

The general procedure for testing in the water tank was the same for all tasks. The platform was placed in the appropriate location in the tank. Each rat was placed at the start location and allowed to swim to the platform. If the rat did not reach the platform within 60 s, the experimenter led the rat to the platform by hand. Upon reaching the platform, the rat remained there for 10 s, and was then removed from the tank and returned to a holding cage for an intertrial interval (ITI) of approximately 2 min. Signs of hypothermia were monitored throughout testing. Testing proceeded in the following order: shaping, straight swim, place discrimination, repeated acquisition, sensorimotor testing. Two days with no testing occurred between straight swim and place discrimination, place discrimination and repeated acquisition, and repeated acquisition and sensorimotor testing.

Shaping

Shaping was designed to teach rats to swim in the water and to climb onto the platform. No spatial discrimination was involved because the alley was so narrow that the rat went directly to the platform. The Lucite pieces were placed in the tank to form the alley. The platform was placed 25 cm from the end of the alley away from the edge of the tank. Black curtains around the tank eliminated the visual cues that were used for place discrimination on subsequent days of testing. Saline (1 ml/kg) was given before testing to habituate the rat to the method of drug administration.

For each trial, the rat was placed at a specific place in the alley, allowed to reach the platform, and then removed from the tank after 10 s on the platform. Each of five successive start locations, each farther away from the escape platform, was used twice: (a) on the escape platform, (b) with forepaws on the platform, (c) several centimeters from the platform, (d) one body length from the platform, and (e) halfway down the alley, approximately 25 cm from the platform.

Straight Swim

One session took place on the second day. The apparatus was identical to that used in shaping. Each rat was placed at the end of the alley against the edge of the tank and was allowed to swim to the platform. Six trials were given. The time taken by the rat to reach the platform was recorded.

Place Discrimination

One session took place each day for 5 consecutive days. Each session had six trials. For each session, the first five trials were platform trials and the sixth was a variable interval probe trial. For all sessions, the platform was located in the SW quadrant, 40 cm from the edge of the tank.

For platform trials, the platform was in the raised position 1 cm below the water. The rat was lowered by hand into the water near the rim of the tank, facing the center of the tank. The start location was in the center of one of the three quadrants not containing the platform, in a pseudorandom order (so that the same start position was not used twice in a row) differing across sessions but consistent within each session.

For each probe trial, the platform remained in the lowered position for a variable time: 10, 30, 20, 40, 10 s (for sessions 1–5, respectively). At the end of the interval, the platform was raised, making it available to the rat.

Repeated Acquisition

One session took place per day 5 consecutive days. The procedure was identical to that for the place discrimination (i.e., 5 platform trials and 1 probe trial per session), except that for each session the platform was placed in a quadrant and at a distance (20, 40, or 60 centimeters) from the edge of the tank that was different than that used in the previous session. Platform location remained the same within each session.

Measures of Performance

The platform trials had three measures of performance. *Swim time* was the time in seconds to reach the platform. *Swim distance* was the distance, in centimeters, swam between the start location and the platform. *Heading angle* was the angle between the direction when leaving the edge of the tank and a straight line drawn from the start location to the platform. For all three measures, lower scores indicated better performance.

The variable interval probe trials had three measures of performance. *Quadrant time* was the percentage of time spent in the quadrant containing the platform. (Quadrant time was not measured on probe trials during repeated acquisition.) *Annulus–40 time* was the percentage of time spent within a circle with a diameter of 40 centimeters, centered on the location of the platform during the previous platform trials. *Platform crossings* were the number of times the rat crossed the location of the submerged platform. For all three measures, higher scores indicated better performance.

Sensorimotor Tasks

Sensorimotor testing was performed for 3 days. Eight sensorimotor tasks were given in the order in which they are listed on each of the 3 days. The mean of scores for each rat on each task was taken across the three daily sessions; these means were used in the data analysis. Drug or vehicle was administered to each rat, as just described. A maximum of 120 s was allowed for the completion of each task.

Initiation of walking. Each rat was placed on a flat, opaque plastic sheet. The time (in seconds) taken to move one body length was recorded.

Turning around in an alley. The wooden alley was 10 cm wide, 25 cm high, and 32 cm long. Each rat was placed 17 cm from the closed end of the alley facing the closed end. The time (in seconds) to turn around and face the open end of the alley was recorded.

Bridges. A wooden bridge, 48 cm long, was suspended 60 cm above foam padding. At each end of the bridge was a wooden platform, 16 cm × 18 cm. The rat was placed in the center of the bridge. The trial ended when the rat escaped to one of the platforms, fell from the bridge, or when 120 s had elapsed. Time to escape was the amount of time taken to reach one of the platforms and was recorded as 120 s if the rat fell. Time to fall was the time spent on the bridge before falling and was recorded as 120 s if the rat escaped to one of the platforms. If the rat remained on the bridge for 120 s but did not escape or fall, the time to escape and to fall were both recorded as 120 s. Three flat bridges, 6, 4, and 2 cm in width, and one round bridge, 2 cm in diameter, were used. The order of testing for each day was: 6 cm, 4 cm, 2 cm, round.

Turning on an inclined grid. Each rat was placed on a wire grid and the grid was gently rotated until the rat was facing downward at a 45° angle. The time for the rat to turn completely around, facing upright, was recorded.

Falling from a wire. Each rat was placed on a horizontal metal wire 2 mm in diameter, hanging by his front paws 60 cm over a foam cushion. The time to fall from the wire was recorded.

Data Analysis

All data analyses were conducted with the MGLH module of the SYSTAT statistical software package (20).

Place Discrimination

For the place discrimination, the mean of each measure of performance from platform trials was taken across Trials 1–5 in each session for each rat, yielding 5 values for each measure for each rat. The single value for each measure of probe trial performance was used in the data analysis.

An age effect was assessed by repeated-measures analysis of variance (ANOVA) on each measure of performance from control rats (4MO–CON vs. 24MO–CON).

Drug effects on place discrimination performance were analyzed in separate ANOVAs. A one-way repeated-measures ANOVA was performed on data from place discrimination performance, comparing the groups receiving the three doses of D-cycloserine to 24MO–CON rats. The independent variable was the drug condition, the criterion variable was one of the measures of performance, and the repeated measure was the session (Session 1 through Session 5). Individual ANOVAs comparing single dose groups with 24MO–CON rats were performed as planned comparisons to determine if specific doses differed from the control.

Repeated Acquisition

The mean of each measure of performance from platform trials was taken across Sessions 1–5 for each rat, yielding 5 values for each measure for each rat. These data were analyzed in a similar fashion with regard to independent variables and criterion variables. The repeated measure was the trial (Trial 1 through Trial 5) for platform trial measures, and the sessions for probe trial measures (Sessions 1 through 5).

Sensorimotor Skills

The mean score was calculated for each task across the 3 days. An ANOVA identical to that for water maze data was used for each task (except that repeated measures were not necessary).

RESULTS

Straight Swim

Swimming ability was equivalent in young and old rats after the shaping and straight swim procedures; time to reach the platform on the sixth trial of straight swim (mean ± SEM) was 7.6 ± 2.5 s for 4MO rats and 9.1 ± 1.1 s for 24MO rats; this difference was not significant ($p > 0.10$).

Place Discrimination

Age effects. Aging significantly impaired performance (24MO–CON rats performing worse than 4MO–CON rats) on five measures of performance (Table 1).

TABLE 1

PLACE DISCRIMINATION, AGE EFFECTS: 24MO–CON COMPARED TO 4MO–CON

Measure	*F* Statistic	*p*<
Swim time	$F(1, 22) = 35.80$	0.0005
Swim distance	$F(1, 22) = 3.68$	0.068
Heading angle	$F(1, 22) = 7.97$	0.010
Annulus-40 time	$F(1, 22) = 45.71$	0.0005
Quadrant time	$F(1, 22) = 36.63$	0.0005
Platform crossing	$F(1, 22) = 34.32$	0.0005

TABLE 2

PLACE DISCRIMINATION: SOME DOSES OF D-CYCLOSERINE IMPROVED PERFORMANCE OF 24MO RATS.

Comparison	Swim Time	Swim Dist	Heading Angle
Platform trial measures			
24MO–CON vs.: 24MO–CYC3	$p = 0.047$	*ns*	$p = 0.010$
Probe trial measures	**Ann-40 Time**	**Quad Time**	**Num Plat Cross**
24MO–CON vs.:			
24MO–CYC1	$p = 0.018$	$p = 0.022$	*ns*
24MO–CYC3	$p = 0.076$	*ns*	$p = 0.057$

ns = not significant ($p > 0.1$).

Results are presented only for those comparisons in which differences at least approached statistical significance.

Drug Effects. ANOVAs comparing all four 24MO groups reached significance on one behavioral measure and approached significance on two others: swim time, $F(3, 38) = 2.53$, $p = 0.072$; heading angle, $F(3, 38) = 8.12$, $p = 0.029$; annulus-40 time, $F(3, 38) = 2.21$, $p = 0.103$. Comparison of individual doses on several behavioral measures also reached or approached significance; results are summarized in Table 2. Graphs of performance on a platform trial measure (swim time) and a probe trial measure (annulus-40 time) are presented in Figs. 1–2.

Repeated Acquisition

Age effects. Aging significantly impaired performance (24MO–CON rats performing worse than 4MO–CON rats) on all behavioral measures (Table 3).

Drug effects. Overall ANOVAs comparing all four 24MO groups approached significance on two behavioral measures: swim time, $F(3, 38) = 2.36$, $p = 0.087$; swim distance, $F(3, 38) = 2.806$, $p = 0.053$. Comparisons of individual doses to 24MO–CON rats also reached or approached significance for all three doses (Table 4).

Graphs of performance on one platform trial measure (swim time) and one probe trial measure (annulus-40 time) for repeated acquisition are presented in Figs. 3 and 4.

Sensorimotor Skills

Age effects. An effect of age (24MO–CON rats performing worse than 4MO–CON rats) was significant on six measures of sensorimotor skills. Mean scores of 4MO–CON and 24MO–CON rats are also presented (Table 5).

Drug effects. Performance was not affected by D-cycloserine. An effect on time to fall from the wire, in which there was no significant age effect, did approach significance: $F(3, 38) = 2.69$, $p = 0.060$.

DISCUSSION

Aging significantly impaired place discrimination, repeated acquisition, and sensorimotor skills. These behavioral tasks assessed two cognitive abilities: spatial reference memory in the place discrimination and spatial working memory in repeated acquisition,

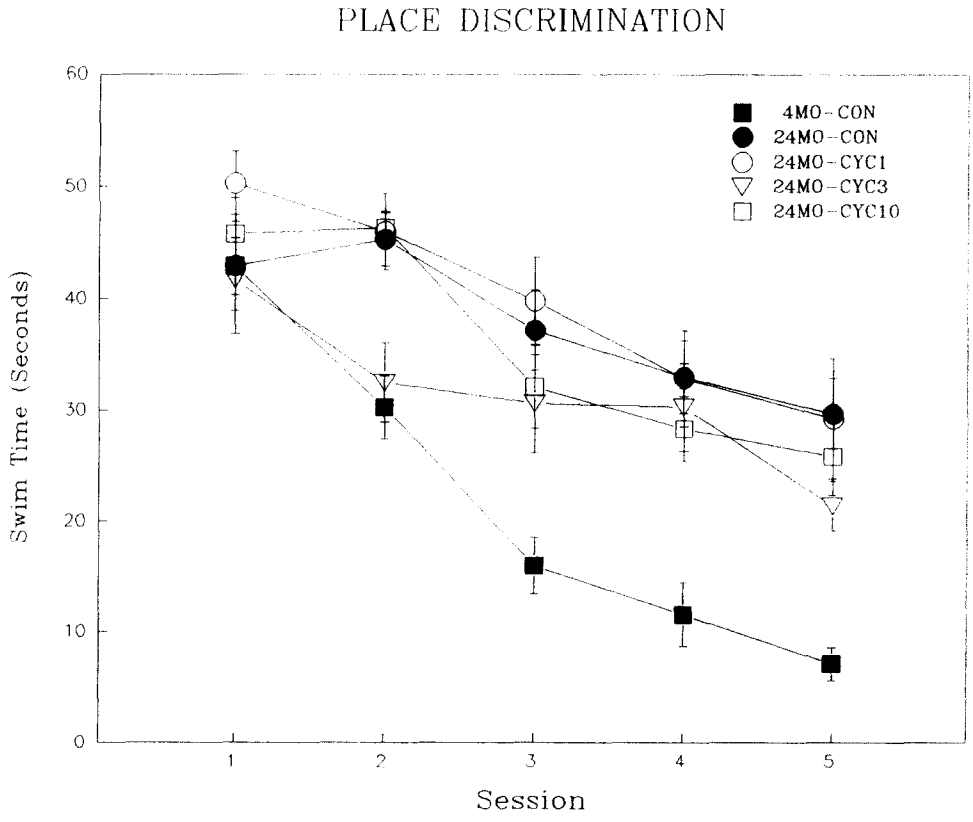

FIG. 1. Place discrimination, swim time. The symbols represent the mean value; the vertical bars represent 1 SEM.

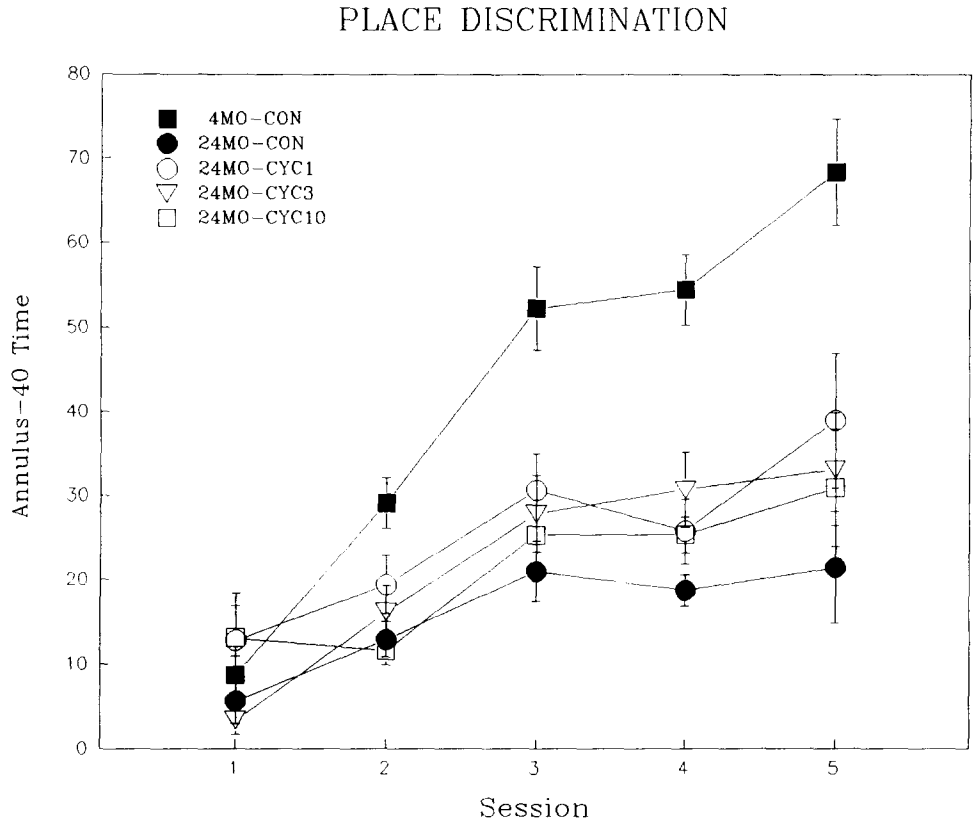

FIG. 2. Place discrimination, annulus-40 time. The symbols represent the mean value; the vertical bars represent 1 SEM.

as well as sensorimotor skills. Young, 4MO–CON rats, learned the discriminations quickly and performed well in all tasks. All these tasks were very sensitive to age-related behavioral impairments as indicated by the impaired performance of 24MO–CON rats as compared to 4MO–CON rats, and are in accordance with other studies indicating age-related behavioral deficits (4,5). Consequently, these procedures are appropriate to assess the beneficial effects of potential cognitive enhancers.

D-cycloserine enhanced place discrimination throughout testing, with a similar pattern of results in repeated acquisition; overall, D-cycloserine lessened the age-related impairment in performance in these tasks. These results agree with those of other studies indicating the capacity of D-cycloserine to reverse cognitive deficits consequent to pharmacological challenges or lesions (3,7,15,16) and suggest that D-cycloserine acts to improve performance through enhancement of spatial memory.

TABLE 3

REPEATED ACQUISITION, AGE EFFECTS: 24MO–CON COMPARED TO 4MO–CON

Measure	*F* Statistic	*p*<
Swim time	$F(1, 22) = 24.44$	0.0005
Swim distance*	$F(4, 88) = 7.91$	0.0005
Heading angle	$F(1, 22) = 4.58$	0.045
Annulus-40 time	$F(1, 22) = 31.60$	0.0005
Platform crossings	$F(1, 22) = 20.43$	0.0005

* Age × Trial interaction.

The lack of effects on sensorimotor skills does not exclude the possibility that D-cycloserine enhances water maze performance through a noncognitive mechanism, as none of the sensorimotor tests given specifically examine the sensory and motor components of spatial learning in the water maze. However, the absence of an age effect in the straight swim given prior to place discrimination suggests that enhanced performance in the water maze is not due to an improvement of a generalized swimming deficit in aged rats, because no such deficit is present. Similarly, the absence of drug effects on the sensorimotor tasks reduces the prob-

TABLE 4

REPEATED ACQUISITION: SOME DOSES OF D-CYCLOSERINE IMPROVED PERFORMANCE OF 24MO RATS

Comparison	Swim Time	Swim Dist	Heading Angle
Platform trial measures			
24MO–CON vs.:	*ns*	$p = 0.043$	*ns*
24MO–CYC1	$p = 0.032$	*ns*	*ns*
24MO–CYC3	$p = 0.017$	$p = 0.008$	*ns*
24MO–CYC10			
Probe trial measures	**Ann-40 Time**	**Num Plat Cross**	
24MO–CON vs.:			
24MO–CYC3	$p = 0.033$	*ns*	

ns = not significant ($p > 0.1$).

Results are presented only for those comparisons in which differences at least approached statistical significance.

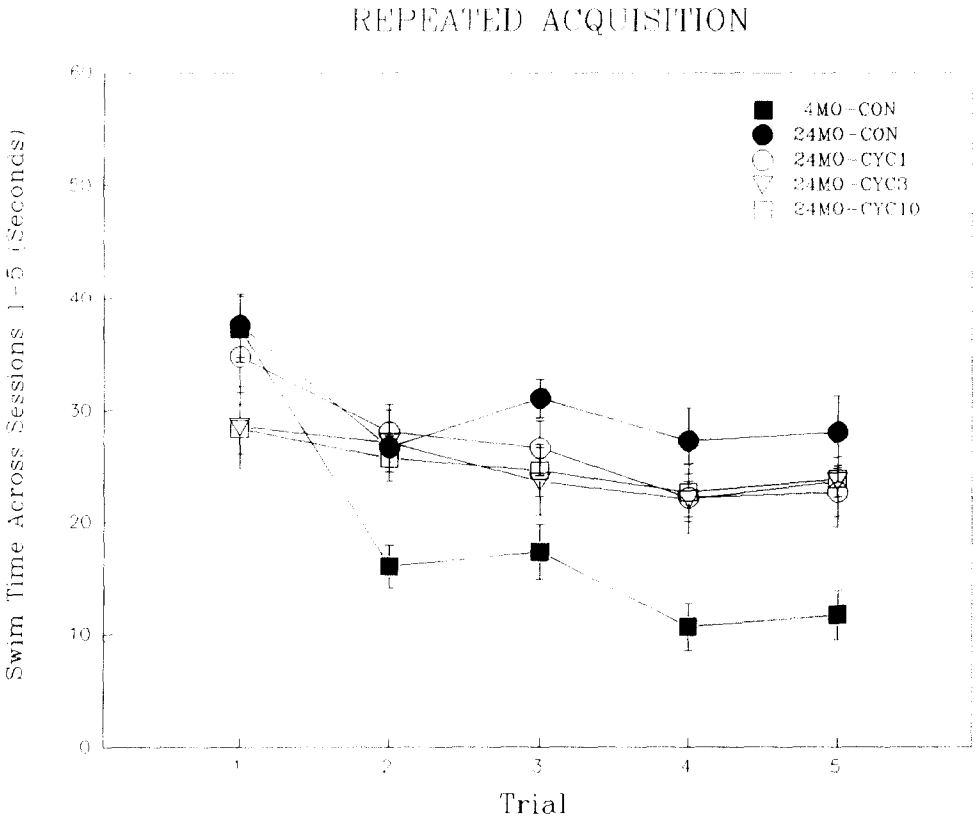

FIG. 3. Repeated acquisition, swim time. The symbols represent the mean value; the vertical bars represent 1 SEM.

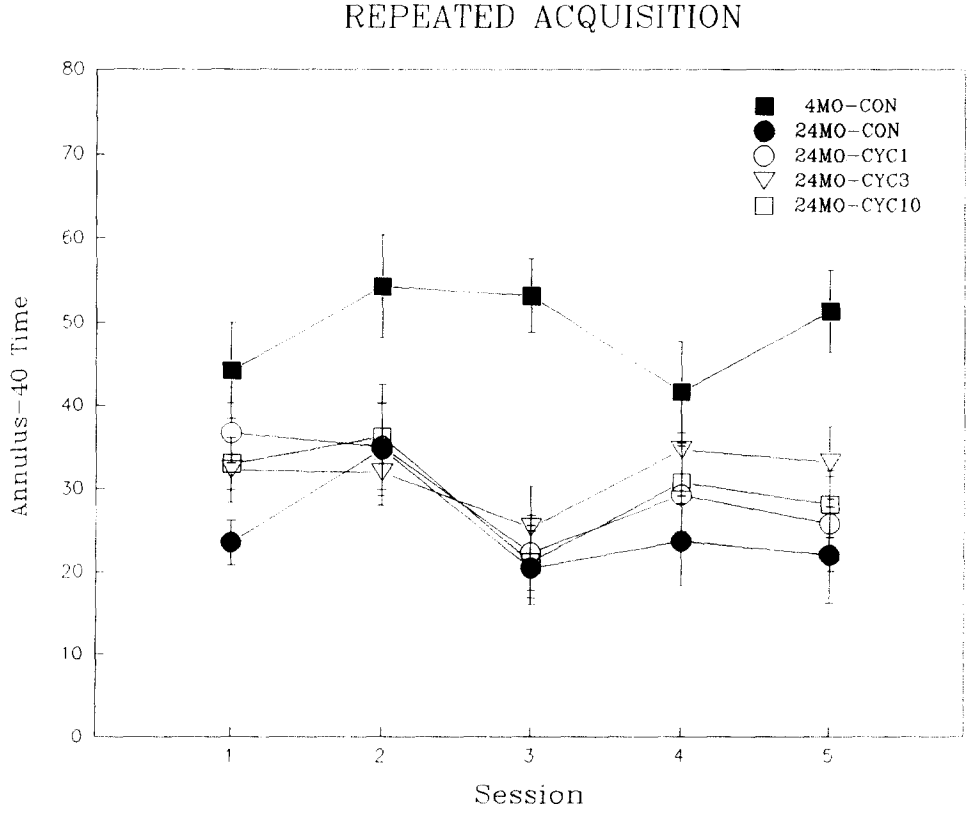

FIG. 4. Repeated acquisition, annulus-40 time. The symbols represent the mean value; the vertical bars represent 1 SEM.

TABLE 5

SENSORIMOTOR SKILLS, AGE EFFECTS: MEAN ± SEM SCORES OF 4MO–CON AND 24MO–CON-RATS

Measure	4MO–CON	24MO–CON
Time in seconds to:		
Turn in alley	8.6 ± 1.3	25.6 ± 7.9
Fall from 6 cm bridge	120.0 ± 0.0	90.5 ± 11.8
Fall from 4 cm bridge	120.0 ± 0.0	86.4 ± 10.7
Escape from 2 cm bridge	83.1 ± 9.8	113.7 ± 3.5
Fall from 2 cm bridge	110.9 ± 5.0	30.6 ± 4.6
Fall from round bridge	25.0 ± 7.0	2.5 ± 0.5

All age differences are statistically significant ($p < 0.05$). D-cycloserine did not significantly affect sensorimotor performance at any dose ($p > 0.05$).

ability that D-cycloserine produces gross changes in age-related deficits in sensorimotor function that could affect water maze performance. Taken together, these data suggest that D-cycloserine acts to enhance performance through a mnemonic mechanism, but do not conclusively show that D-cycloserine has no beneficial noncognitive effects.

The dose producing the preponderance of significant results was 3.0 mg/kg for place discrimination and both 3.0 mg/kg and 10.0 mg/kg for repeated acquisition. A U-shaped dose-response curve characterizes D-cycloserine. The "best" dose has varied from study to study, from 1.0 mg/kg (other doses were 0.3 mg/kg and 3.0 mg/kg) in reversing scopolamine-induced deficits in water maze performance (16) to 20 mg/kg (doses ranged from 2.5 mg/kg to 50 mg/kg) in facilitating retention of passive avoidance in young mice (2). The common shape of the dose-response curve suggests a common pharmacological mechanism for D-cycloserine, even though the dosage required to enhance cognition may be specific to the type of deficit.

In summary, D-cycloserine reduced the magnitude of age-related memory deficits. These results are consistent with those of other studies indicating that glycine agonists such as D-cycloserine may be effective therapeutic agents to treat age-related cognitive impairments.

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