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Short communication

Tetrahydroaminoacridine and D-cycloserine stimulate acquisition of water maze spatial navigation in aged rats

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Abstract

We investigated the effect of tetrahydroaminoacridine, a cholinesterase inhibitor and D-cycloserine (a partial glycine-B agonist of the NMDA receptor complex) on the defect of water maze spatial navigation in rats induced by aging. Tetrahydroaminoacridine (3 mg/kg, i.p.) or D-cycloserine (10 mg/kg, i.p.) enhanced acquisition of the water maze task. A combination of subthreshold doses of tetrahydroaminoacridine (1 mg/kg) and D-cycloserine (3 mg/kg) improved water maze acquisition, but a combination of lower subthreshold doses (tetrahydroaminoacridine 0.3 mg/kg + D-cycloserine 1 mg/kg) was ineffective. Consolidation in water maze test was not improved by tetrahydroaminoacridine (3 mg/kg) and/or D-cycloserine (10 mg/kg). The results suggest that tetrahydroaminoacridine and D-cycloserine synergistically enhance acquisition of spatial navigation in aged rats. © 1998 Elsevier Science B.V.

Keywords: Tetrahydroaminoacridine; D-Cycloserine; Water maze; Combined therapy; Acquisition; Consolidation; Alzheimer's disease

1. Introduction

The cholinergic cells of the basal forebrain are adversely affected during the development of Alzheimer's disease and the loss of cholinergic cells may be related to the development of dementia (Whitehouse et al., 1982). Indeed, recent evidence indicates that treatment with cholinesterase inhibitors, such as tetrahydroaminoacridine, can enhance cholinergic activity in Alzheimer disease patients and alleviate the severity of their dementia (Sahakian et al., 1993; Knapp et al., 1994). However, the treatment response to cholinesterase inhibitors is likely to be modest at best (Sahakian et al., 1993; Knapp et al., 1994). For example, tetrahydroaminoacridine does not alleviate memory dysfunction in Alzheimer's disease (Sahakian et al., 1993). This defect may result from severe neuronal atrophy in the hippocampus (Riekkinen et al., 1997b). Therefore, it is important to develop treatment strategies that could have positive additive or synergistic effects on cognitive functioning when combined with cholinesterase inhibitors.

The degeneration of glutamate-containing pyramidal projection neurons in brain regions important for memory formation, such as the hippocampus and surrounding medial temporal lobe cortical structures, is also an ubiquitous finding in Alzheimer disease (Francis et al., 1994; Aigner, 1995). Indeed, combined atrophy of cholinergic and glutamatergic projections in those brain regions involved in memory formation may play a role in the memory loss associated with Alzheimer disease (Francis et al., 1994; Aigner, 1995).

Pharmacological studies corroborate this concept, since acetylcholine and glutamate receptors jointly regulate synaptic plasticity and modulate the performance of animals in tests used to assess learning and memory. First, administration of the muscarinic antagonist, scopolamine, disrupts escape performance to a hidden platform in the water maze swim pool test and D-cycloserine, a partial agonist of the strychnine insensitive glycine-B binding site, alleviates the performance defect produced by scopolamine treatment (Sirviö et al., 1992). Importantly, D-cycloserine can enhance the function of the NMDA receptor complex via the strychnine insensitive glycine-B binding site (Huettner, 1991).

Aged rats have been used a model for the evaluation of Alzheimer disease-related spatial learning defect and for investigation of the efficacy of drugs in improving memory function (Barnes, 1994). For example, the number of cell bodies that contain the acetylcholine synthesizing enzyme, choline acetyltransferase, may decrease during ag-

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ing (Riekkinen et al., 1992). Furthermore, electrophysiological experiments have revealed that the impaired spatial learning in aged rats is linked to dysfunction of connections between the entorhinal cortex and hippocampus and within the hippocampus, all of which are mediated via glutamate containing synapses (Barnes, 1994).

Also pharmacological evidence favors the importance of cholinergic and NMDA receptor dysfunction in the cognitive decline in aged rats. Administration of tetrahydroaminoacridine and D-cycloserine dose-dependently alleviated the failures in water maze spatial navigation induced by aging in rats (Baxter et al., 1994; Riekkinen et al., 1996). Furthermore, we observed recently that subthreshold doses of nicotine and D-cycloserine stimulated spatial navigation in aged rats (Riekkinen and Riekkinen, 1997). We also found that D-cycloserine alleviated the water maze acquisition defect induced by a nicotinic antagonist (Riekkinen and Riekkinen, 1997). In contrast, nicotine could not alleviate water maze dysfunction induced by an NMDA antagonist (Riekkinen and Riekkinen, 1997). Therefore, it is possible that nicotine may stimulate water maze acquisition performance in aged rats via increased activity of NMDA receptors (Riekkinen and Riekkinen, 1997).

Importantly, it has not been investigated if combined treatment with a cholinesterase inhibitor, such as tetrahydroaminoacridine, and D-cycloserine can have additive effects in alleviating the water maze acquisition failure in aged rats. We designed this study to elucidate whether combined treatment with tetrahydroaminoacridine and D-cycloserine is more effective than treatment with either drug on it's own in stimulating spatial navigation in aged rats. Therefore, we evaluated the effects of single and combined treatment with tetrahydroaminoacridine and D-cycloserine on water maze behavior in aged rats.

2. Materials and methods

2.1. Animals

Young (4 months old) and aged (22–26 months) male Han:Wistar rats were used in the present study. The rats were obtained from the National Laboratory Animal Cen-

Table 1
Effects of tetrahydroaminoacridine (0.3, 1 and 3 mg/kg, i.p.) and D-cycloserine (1, 3 and 10 mg/kg, i.p.) on the number of rats that escaped to the platform during the first trial of platform training (part A) and spatial bias (number of annulus crossings, part B) performance in water maze. The spatial bias was measured on day 5 immediately after the daily platform trainings had been finished. All the groups and drug treatments used in this study are shown here

Part A: Drug treatments did not affect the number of aged rats that escaped to the platform during the first trial
Drugs were injected before training, days 1–5

Groups	Escape +/−	Groups	Escape +/−	Groups	Escape +/−
YC	1/7	YC	2/7		
C	2/7	C	1/8	C	2/7
THA 3	0/7	THA 1	0/9	THA 0.3	0/9
DCS10	1/7	DCS3	0/9	DCS 1	1/8
THA 3 + DCS 10	0/8	THA 1 + DCS 3	1/8	THA 0.3 + DCS 1	4/5

Part B: Single DCS and combined DCS and THA increased annulus crossings in aged rats
Drugs were injected before training, days 1–5

Groups	Crossings	Groups	Crossings	Groups	Crossings
YC	6.1 ± 1.1	YC	6.0 ± 0.6		
C	3.3 ± 0.8**	C	3.6 ± 0.5**	C	3.0 ± 0.9
THA 3	2.9 ± 1.4**	THA 1	4.0 ± 1.0**	THA 0.3	4.0 ± 1.0
DCS10	6.2 ± 1.0*	DCS3	3.9 ± 1.0**	DCS 1	4.0 ± 0.8
THA 3 + DCS 10	6.0 ± 0.8*	THA 1 + DCS 3	6.4 ± 0.7*	THA 0.3 + DCS 1	4.6 ± 1.5

Drugs were injected after training, days 1–4

Groups	Crossings
YC	6.3 ± 1.1
C	3.4 ± 1.0**
THA 3	4.2 ± 1.1**
DCS10	4.1 ± 1.0**
THA 3 + DCS10	3.4 ± 0.6**

Abbreviations; crossings = annulus crossings, C = aged controls, DCS 1, 3 or 10 = D-cycloserine 1, 3 or 10 mg/kg, escape +/− = number of rats that were able to escape or were not able to escape to the platform during the first trial, THA 0.3, 1 and 3 = tetrahydroaminoacridine 0.3, 1 and 3 mg/kg, YC = young controls. The group mean ± S.D. of annulus crossings is shown.
* $p < 0.05$ versus aged controls.
** $p < 0.05$ versus young controls, Duncan's post hoc multiple group comparison.

ter, Kuopio, Finland. The rats were housed in a controlled environment with food and water available ad lib (temperature 22 ± 2°C, lights on: 07.00–19.00 h, humidity 60%). We have the permission of municipal government of Kuopio to perform these studies.

2.2. Drugs

Tetrahydroaminoacridine (0.3, 1 and 3 mg/kg, i.p. 2 ml/kg, 40 min before daily testing) and D-cycloserine (1, 3 and 10 mg/kg, i.p. 2 ml/kg, 30 min before daily testing) doses were selected based on previous experience (Riekkinen et al., 1996; Riekkinen and Riekkinen, 1997) and injected before or after (only in one study) the daily platform training. Controls received NaCl 0.9% injections. Table 1 details the treatment groups used.

2.3. Water maze

The swimming patterns of the rats to the hidden platform were monitored with a computerized video tracking system. The computer calculated the means of daily swim speed (m/s), distance (cm) to the hidden platform and the crossing over the previous location of the escape platform. The daily escape distance values were stored for statistical analysis of the effects of drug treatment on water maze acquisition.

The starting locations (labeled North, South, East and West) were located arbitrarily on the pool rim. The pool was divided into 4 quadrants (Southwest, Southeast, Northwest, and Northeast) and 3 annuli of equal surface area. Rats were placed in the water, with their nose pointing towards the wall, at one of the starting points. The platform was located in the middle annulus of the Southwest quadrant. The reference memory training consisted of 5 consecutive days of training (three trials per day, maximum duration 70 s). The first daily trial was started always from the North or East. The starting point of second and third trial was selected in a semi-random manner (never from the same place during the second and third daily trial). Those rats that did not find the platform during the maximum duration of a trial, were placed on the platform by the experimenter. The rats were allowed to stay on the platform for 5 s. An intertrial interval of 30 s was used between trials.

After the last platform training session was finished on the 5th day, the platform was removed and spatial bias was analyzed (crossings over the previous platform location) during a single 50 s trial. The trial was started from the North.

2.4. Statistics

A oneway-analysis of variance followed by Duncan's post hoc multiple group comparison was used to measure the effects of drug treatments on water maze acquisition (escape distance) and retrieval (spatial bias) performance. A twoway-analysis of variance was used to assess the interactions of (independent variables) tetrahydroaminoacridine and D-cycloserine treatments on water maze escape distance values in aged rats (dependent variable). The proportion of the rats that found/failed to find the escape platform on the first trial was analyzed with a chi-square test.

3. Results

Five groups of eight rats were used in the first study: young and aged controls, aged tetrahydroaminoacridine 3 mg/kg, D-cycloserine 10 mg/kg and tetrahydroaminoacridine 3 mg/kg + D-cycloserine 10 mg/kg. The proportion of the rats that found the platform during the first trial of the first day did not vary between the groups ($P > 0.05$; Table 1A). Tetrahydroaminoacridine 3 mg/kg or D-cycloserine 10 mg/kg were equally effective in decreasing the escape distance values (Fig. 1A) of aged rats (overall group effect: $F(4, 35) = 6.12$, $p < 0.001$, $P < 0.05$ for comparison with the young and control aged rats). Tetrahydroaminoacridine 3 mg/kg and D-cycloserine 10 mg/kg alone decreased the escape distance values of aged rats ($P < 0.05$). A combination of tetrahydroaminoacridine 3 mg/kg and D-cycloserine 10 mg/kg was no more effective in decreasing the escape distance ($P > 0.05$) than single treatments alone. Furthermore, no interaction was found between the two treatments (D-cycloserine 10 mg/kg * tetrahydroaminoacridine 3 mg/kg twoway-interaction on escape distance: ($F(1, 28) = 1.2$, $P = 0.27$)). The aged rats that were treated with D-cycloserine 10 mg/kg and D-cycloserine 10 mg/kg + tetrahydroaminoacridine 3 mg/kg during the training made more correct annulus crossings than the other groups of aged rats during the spatial bias trial (overall group effect: $F(4, 35) = 6.0$, $P < 0.001$; $P < 0.05$ versus single tetrahydroaminoacridine 3 mg/kg or control aged rats) (Table 1B). Aged rats treated with either D-cycloserine 10 mg/kg alone or the combination of D-cycloserine 10 mg/kg and tetrahydroaminoacridine 3 mg/kg had as accurate spatial bias as the young control group ($P > 0.05$). In contrast, tetrahydroaminoacridine 3 mg/kg alone had no effect on the spatial bias of aged rats ($P > 0.05$).

Five groups of 9 rats were used in the second study: young controls, aged controls, tetrahydroaminoacridine 1 mg/kg D-cycloserine 3 mg/kg or tetrahydroaminoacridine 1 mg/kg + D-cycloserine 3 mg/kg. Again, we found that the proportion of the rats that found the platform during the first trial of the first day did not vary between the groups ($P > 0.05$; Table 1A). Tetrahydroaminoacridine 1 mg/kg or D-cycloserine 3 mg/kg on their own had no effect on escape distance (overall group effect: $F(4, 40) = 0.37$, $P > 0.1$; $P > 0.05$ versus aged controls) (Fig. 1B) or spatial bias values (overall group effect: $F(4, 40) = 0.8$,

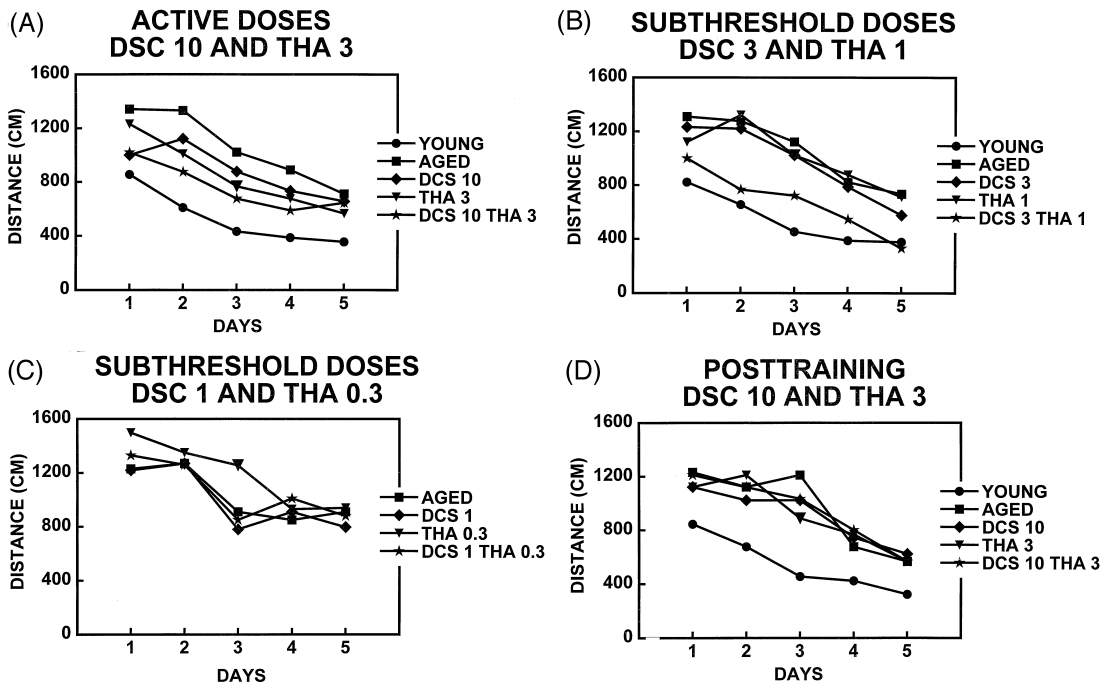

Fig. 1. Effects of tetrahydroaminoacridine (0.3, 1 and 3 mg/kg, i.p.) and D-cycloserine (1, 3 and 10 mg/kg, i.p.) on the acquisition of water maze navigation in aged rats during the hidden platform training (days 1–5). Single or combined tetrahydroaminoacridine (3 mg/kg) and D-cycloserine (10 mg/kg) doses produced a marked effect on escape distance values in aged rats (part A). A combination of subthreshold doses (tetrahydroaminoacridine, 1 mg/kg, and D-cycloserine, 3 mg/kg) decreased escape distance values effectively (part B). However, lower subthreshold doses did not decrease escape distance values (tetrahydroaminoacridine, 0.3 mg/kg, and D-cycloserine, 1 mg/kg) (part C). Drug treatments failed to affect memory consolidation (part D). Drugs were injected before daily training sessions (parts A–C) or immediately after training (part D). Abbreviations: AGED = aged rats, DCS 1, 3 or 10 = D-cycloserine 1, 3 or 10 mg/kg, THA 0.3, 1 and 3 = tetrahydroaminoacridine 0.3, 1 and 3 mg/kg, YOUNG = young controls. *X*-axis: training days 1–5, *Y*-axis: escape distance in cm, group mean of daily training trials.

$P > 0.1$; $P > 0.05$ versus aged controls) (Table 1B) in aged rats. However, those aged rats treated with the combination of tetrahydroaminoacridine 1 mg/kg and D-cycloserine 3 mg/kg had the shortest escape distance values and a significant twoway-interaction between these treatments on escape distance was observed ($F(1, 28) = 5.2$, $P = 0.03$). Tetrahydroaminoacridine 1 mg/kg + D-cycloserine 3 mg/kg also interacted to increase the spatial bias of aged rats ($F(1, 28) = 5.1$, $P = 0.03$).

Four groups of 9 aged rats were used in the third study: aged controls, tetrahydroaminoacridine 0.3 mg/kg D-cycloserine 1 mg/kg or tetrahydroaminoacridine 0.3 mg/kg + D-cycloserine 1 mg/kg. The proportion of the rats that found the platform during the first trial of the first day did not vary between the groups ($P > 0.05$; Table 1A). Tetrahydroaminoacridine 0.3 mg/kg or D-cycloserine 1 mg/kg plus their combination had no effect on escape distance or spatial bias (overall group effect: $F(3, 32) < 0.4$, $P > 0.1$ for both comparisons, $P > 0.05$ for all group comparisons) (Fig. 1C and Table 1B).

Five groups of eight rats were used in the fourth study that examined the effect of drug treatments delivered after daily training sessions: young controls, aged controls, tetrahydroaminoacridine 3 mg/kg or D-cycloserine 10 mg/kg tetrahydroaminoacridine 3 mg/kg + D-cycloserine 10 mg/kg. The proportion of the rats that found the platform during the first trial of the first day did not vary between the groups ($P > 0.05$; Table 1A). The results revealed again that all of the aged rats were impaired in comparison with the young rats during the platform training days 1–5 (overall group effect: $F(4, 35) < 7.3$, $P < 0.001$). Administration of single or combined D-cycloserine 10 mg/kg or tetrahydroaminoacridine 3 mg/kg after daily training trails failed to decrease escape distance or increase spatial bias of aged rats ($P > 0.05$ control versus drug-treated aged rats) (Fig. 1D; Table 1B).

4. Discussion

Our results support previous evidence that administration of tetrahydroaminoacridine and D-cycloserine before daily training sessions can improve acquisition of spatial navigation in aged rats (Riekkinen et al., 1996; Riekkinen and Riekkinen, 1997). Importantly, a combination of subthreshold doses of tetrahydroaminoacridine and D-cycloserine produced a greater effect on water maze acquisition speed than either of the treatments on their own.

However, tetrahydroaminoacridine and D-cycloserine had no effect on memory consolidation, as treatment with the study drugs immediately after daily training did not stimulate spatial escape behavior.

The beneficial action of tetrahydroaminoacridine and D-cycloserine on water maze escape performance during the hidden platform trials cannot be interpreted solely in terms of enhanced spatial memory. The number of rats that found the platform on the first trial of the first day was not affected by the drug treatments. This suggests that the compounds do not change the spontaneous exploration patterns of rats, and may rule out effects on anxiety also. However, changes in arousal and attention may affect water maze acquisition performance if the drugs are administered before daily training sessions. For example, the learning curves of tetrahydroaminoacridine and D-cycloserine treated rats were parallel which may be a reflection of some non-mnemonic improvement in performance. Furthermore, tetrahydroaminoacridine alone had no effect on the spatial bias measure, suggesting that the encoding of spatial cues was not improved by tetrahydroaminoacridine. Thus, it is likely that tetrahydroaminoacridine treatment stimulates acquisition of spatial navigation performance by modulating some process other than spatial memory per se. The nucleus basalis cholinergic system controls the functioning of the frontal cortex and plays an important role in attention (Jäkälä et al., 1992; Muir et al., 1994, 1995). Lesions of the nucleus basalis induced by infusion of excitatory amino acid analogues or treatment with a muscarinic acetylcholine receptor antagonist impair behavior in young rats in tests measuring attentional functioning (Jäkälä et al., 1992; Muir et al., 1994, 1995). Therefore, it is possible that improvement in the alertness of the aged rats induced by tetrahydroaminoacridine treatment may be the reason for the facilitated water maze acquisition performance. In contrast, we observed that D-cycloserine enhanced spatial bias during the memory retrieval trial, suggesting that the drug may stimulate spatial memory functioning. However, a recent study by Bannerman et al. (1995) suggests that NMDA receptors mediate functions other than spatial memory, such as development of an escape strategy, that are important for water maze spatial navigation performance (Bannerman et al., 1995). Furthermore, we observed that the learning curves of aged rats treated with D-cycloserine or placebo before daily training sessions were parallel and D-cycloserine failed to stimulate memory consolidation. Therefore, it is possible that D-cycloserine does not stimulate spatial memory per se in aged rats, but modulates other cognitive processes needed for effective water maze spatial navigation (Bannerman et al., 1995).

Our present finding showed that a cholinesterase inhibitor and a NMDA modulator jointly stimulated water maze spatial navigation, since we found that a combination of tetrahydroaminoacridine and D-cycloserine at subthreshold doses enhanced acquisition and spatial bias. On the contrary, a combination of active tetrahydroaminoacridine and D-cycloserine doses did not produce any greater effect on acquisition or retention of water maze behavior than either of the treatments alone. These results indicate that tetrahydroaminoacridine and D-cycloserine may act synergistically to enhance functioning of the brain systems necessary for water maze acquisition performance, but only D-cycloserine stimulated those mechanisms important for retrieval of spatial memories. Importantly, a recent study found that treatment with a cholinesterase inhibitor, physostigmine, can increase functioning of glutamate containing projection neurons (Dijk et al., 1995). These workers used 'in vivo' microdialysis to show that glutamate release from corticostriatal fibers was enhanced by cholinesterase inhibition. Thus, it is possible that the increase in acetylcholine activity occurring after tetrahydroaminoacridine treatment can stimulate water maze navigation performance by enhancing glutamate (Dijk et al., 1995) mediated functions. Therefore, subthreshold doses of tetrahydroaminoacridine and D-cycloserine may produce a measurable effect on water maze navigation by stimulating glutamate release (Dijk et al., 1995) and NMDA receptor activity (Huettner, 1991), respectively. However, combinations of other doses of tetrahydroaminoacridine and D-cycloserine and other cholinesterase inhibitors and D-cycloserine will need to be tested before one may argue that the maximum therapeutic effect can be increased by combining a cholinesterase inhibitor and a NMDA modulator.

The present results may have some relevance for the development of pharmacological treatments for cognitive defects observed in Alzheimer disease that are associated with impaired functioning of NMDA and basal forebrain cholinergic systems (Whitehouse et al., 1982; Francis et al., 1994; Aigner, 1995). It is possible that combined treatment with an anticholinesterase and a positive NMDA modulator may produce a clinical response with lower doses than either treatment alone and this may decrease dose-dependent side-effects. Furthermore, drugs acting via different neurochemical systems may enhance separate cognitive domains, such as memory or attention. Our results suggest that combined treatment with a cholinesterase inhibitor, such as tetrahydroaminoacridine, and a positive allosteric modulator of NMDA receptors should be tested to alleviate cognitive deficits and clinical dementia in Alzheimer disease. Previous studies have indicated that tetrahydroaminoacridine alleviates the attentional dysfunction in Alzheimer disease (Riekkinen et al., 1997a,b), but has no effect on memory functioning (Sahakian et al., 1993). In contrast, treatment with positive allosteric NMDA receptor modulators may enhance memory function by stimulating synaptic plasticity (Barnes, 1994; Aigner, 1995). Therefore, it is theoretically possible that a combination of a cholinesterase inhibitor and a positive allosteric NMDA modulator may stimulate attention and memory in Alzheimer disease patients.

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