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Citicoline Improves Memory Performance in Elderly Subjects

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SUMMARY

Citicoline is a choline donor involved in the biosynthesis of brain phospholipids and acetylcholine extensively used in the treatment of neurodegenerative diseases. In this study we investigated the effects of the oral administration of citicoline alone (C1000: 1000 mg/day; C500: 500 mg/day) or in combination with nimodipine (C+Ni: 300 + 90 mg/day) during 4 weeks on memory performance in elderly subjects with memory deficits and without dementia (N = 24; age = 66.12 ± 10.78 years; MMS score = 31.69 ± 2.76). Results indicated that citicoline in comparison with placebo improves memory in free recall tasks, but not in recognition tests. A significant improvement in word recall (5.17 ± 1.1 vs. 3.95 ± 1.2 omissions; p < 0.005), immediate object recall (6.5 ± 1.6 vs. 5.5 ± 1.2 omission; p < 0.05) and delayed object recall (8.5 ± 2.1 vs. 6.7 ± 2.4 omissions; p < 0.005) was observed after citicoline treatment. Similar results were found in the three subgroups of treatment (8 subjects per group), suggesting that citicoline possesses memory-enhancing activity at doses of 300-1000 mg/day. A decrease in systolic blood pressure and minor changes in lymphocyte cell counting were also observed in old subjects after receiving citicoline. These effects are consistent with the vasoregulatory and neuroimmune actions of citicoline and suggest that this compound may improve memory by acting on mechanisms of brain neurotropism and cerebrovascular regulation. According to the present results, showing that citicoline improves memory performance in elderly subjects, we concluded that this molecule is suitable for the treatment of memory deficits in old people.

Key words: Citicoline - Memory - Recall - Recognition - Elderly - Humans

INTRODUCTION

Citicoline is a choline donor acting as an endogenous intermediate in the biosynthesis of membrane phospholipids (1-4). It has been found that citicoline protects against neurodegeneration induced by hypoxia, ischemia and β-amyloid deposition in laboratory animals (5-8). In these experimental conditions citicoline increases brain phospholipid synthesis and glucose metabolism, reduces free fatty acid release and exerts neuroimmunotrophic actions that might account for its neuroprotective effect (5-8). Furthermore, citicoline improves learning and memory in rodents, reverses amnesia induced by scopolamine, neurotoxic lesions of the nucleus basalis of Meynert and bromazepam and attenuates behavioral deficits in aged animals (9-11). Significant clinical improvements after treatment with citicoline have been reported in patients with brain trauma, stroke, cerebrovascular disorders, vascular dementia and Alzheimer's disease (12-16).

Age-associated memory impairments are prevalent in elderly nondemented subjects and have been related to alterations in brain neurotransmission systems, mainly cholinergic deficits (17-21). According to the cholinergic hypothesis of memory, citicoline has been proposed for the treatment of memory deficits in elderly people, in which it improves memory performance in some tasks (forward and backward digit span, logical story test and Bali picture memory test) and reduces memory and physical complaints (21).

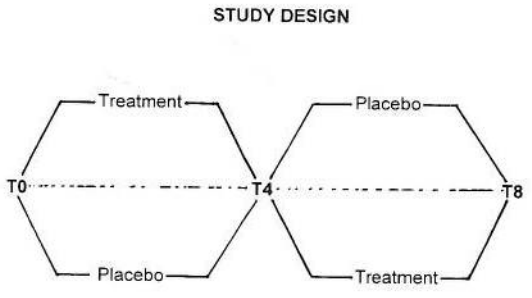

FIG. 1. Study design. T0: baseline evaluation; T4: evaluation at week 4; T8: assessment at week 8. Half of the subjects received active treatment the first 4 weeks and no treatment the next 4 (placebo); the other half of subjects were without active treatment for the first 4 weeks (placebo) and then on treatment for the next 4 weeks.

In this study we investigated the effects of treatment with citicoline (1000 or 500 mg/day) or with citicoline plus nimodipine (300 + 90 mg/day) during 4 weeks on memory performance in elderly individuals. Subjects were treated according to a cross-design (Fig. 1) open clinical trial in which half of the subjects received active treatment during 4 weeks (treatment period) and did not receive it the next 4 weeks (no treatment period); the other half of the subjects were treated in the reverse order (first no treatment and then treatment). Before and after each treatment period, memory assessment and evaluation of physiological, biochemical and hematological parameters were done.

SUBJECTS AND METHODS

Subjects

Twenty-four elderly subjects (18 women/6 men; age = 66.12 ± 10.78 years; mean MMS score = 31.69 ± 2.76) were included in the present study. Medical and neurological examination, psychometric evaluation, EKG and laboratory analysis were performed in all subjects before inclusion. None of the subjects met DSM-IV and/or NINCDS-ADRDA criteria for senile dementia (22, 23). Eight subjects were completely drug-free and had only minor memory complaints. Sixteen subjects were receiving treatment for different medical conditions (cardiopathy, arterial hypertension, depression, thrombocytosis, fibromyalgic syndrome, hypercholesterolemia, osteoporosis, varicose veins, cerebrovascular disorder, Parkinson's disease and gastric ulcers). To demonstrate memory impairment in elderly subjects, neuropsychological assessment was conducted in 24 young controls (15 women/9 men; age = 29.20 ± 5.74 years; mean MMS score = 34.41 ± 0.67) and scores obtained in memory tasks by the two groups of subjects were compared.

Study design and treatment regimen

In this open clinical trial, elderly subjects were randomly distributed into three groups of treatment: (a) Citicoline 1000 mg/day, single p.o. dose (C1000); (b) citicoline 500 mg/day, single p.o. dose (C500); and (c) citicoline 300 mg/day plus nimodi pine 90 mg/day, divided in three p.o. doses (C + Ni). All subjects were involved in treatment and no treatment four-week periods in a cross-design manner; half of the subjects in each group received active treatment the first 4 weeks and no treatment during the next 4 weeks, while the other half received no treatment for the first 4 weeks and received treatment during the next 4 weeks (Fig. 1). All participants were tested before and after each treatment period. With this type of study design the potential influence of retest on memory performance was similar in both experimental phases. The effect of active treatment on memory scores was evaluated in two ways, first by comparing pre- and posttreatment scores and second by studying differences in memory changes observed during treatment and no treatment periods in the same subjects.

Memory assessment

Neuropsychological evaluation was conducted in basal conditions, and 4 and 8 weeks later by using the Mini-Mental State Examination of Folstein (MMS) (24), the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS) (25) and the Syndrome-Kurztest (SKT) (26, 27). Memory tasks included for analysis were word recall and word recognition items of the ADAS, immediate and delayed recall of objects (12 object representations), and recognition of objects (12 target objects and 12 distractor objects) of the SKT. Memory performance is expressed as mean error score in all tasks, the highest scores indicating the worst memory functioning and *vice versa*.

Testing procedures

Word recall task of the ADAS

Subjects read 10 words, exposed for 2 seconds each, and then recalled them aloud. Three trials of reading and recall were given. The score equals the mean number of words not recalled on three trials (maximum = 10).

Word recognition task of the ADAS

Subjects read aloud 12 words. These words were then randomly mixed with 12 words not presented before. The subject indicated whether or not the word was shown previously. Then two more trials of reading the original words and recognition were given. The score equals the mean number of incorrect responses for three trials (maximum = 12).

Immediate object recall item of the SKT

The subject named 12 objects represented in an illustrated cardboard and then recalled them aloud. The number of omissions (objects not recalled) is scored. Immediately after recall the illustrated cardboard was presented again to the subject during 5 seconds.

Delayed object recall item of the SKT

Ten minutes after the second presentation of the illustrated cardboard the subject had 60 seconds to recall objects. The number of omissions (objects not recalled) is scored.

Object recognition task of the SKT

Immediately after delayed recall, a cardboard containing 24 illustrations (12 target objects shown before and 12 distractor pictures of objects the subject had not seen) was presented. Subjects indicated during a 60-second interval whether or not the object picture had been shown previously. The number of objects not recognized (omissions) is scored.

Physiological, biochemical and hematological parameters evaluated

Systolic and diastolic blood pressure, mean heart rate, body temperature and body weight were recorded at baseline, 4 weeks and 8 weeks. The biochemical parameters analyzed in serum were glucose, cholesterol, triglycerides, proteins, albumin, uric acid, urea, CK, GOT, GPT, GGT, calcium, sodium, potassium and chloride. Hematologic study included red cells, hematocrit, hemoglobin, MCV, MCH, MCHC, platelets, leukocytes, lymphocytes, monocytes and granulocytes.

Statistics

Data are presented as means ($\pm$ standard deviation of the mean). The nonparametric Wilcoxon test was used to compare paired data obtained before and after treatment and no treatment periods. Memory improvement was analyzed by using split-plot analyses of variance with treatment (yes and no) as the independent factor and testing day (day 1 and day 28) as the repeated measure. Any memory improvement due to treatment is reflected by a significant treatment x day interaction. Statistical analysis was conducted in the whole sample (24 subjects) and in particular treatment subgroups (C1000, C500 and C + Ni), in order to evaluate the efficacy of active treatment as well as of each treatment regimen.

RESULTS

Memory performance

Elderly subjects showed significantly higher mean error scores than young controls in word recall, word recognition, immediate object recall, delayed object recall and object recognition tasks (Table 1).

When all subjects where analyzed together, a significant treatment by day interaction was observed for word recall ($F(46,1) = 5.95$; $p < 0.02$) and delayed object recall tasks ($F(46,1) = 20.04$; $p < 0.001$), these interactions reflecting that active treatment significantly improves memory performance with respect to the no treatment period. No significant changes in memory scores were observed during the no treatment period (Table 2, Fig. 2). Active treatment induced a significant improvement in memory performance, reducing mean error scores from day 1 to day 28 of treatment in word recall ($z = -3.22$, $p < 0.005$), immediate object recall ($z = -2.19$, $p < 0.05$) and delayed object recall tests ($z = -3.42$, $p < 0.005$), but not in word and object recognition tasks (Table 2, Fig. 2).

TABLE 1. Memory performance in young and elderly subjects.

Memory task	Young subjects (X ± SD)	Elderly subjects (X ± SD)
Word recall	2.14 ± 1.01	5.22 ± 1.24**
Word recognition	1.40 ± 0.88	2.95 ± 1.98*
Immediate object recall	4.00 ± 1.53	6.54 ± 1.44**
Delayed object recall	4.91 ± 1.66	7.70 ± 2.23**
Object recognition	0.87 ± 1.15	2.54 ± 1.71**

*$p < 0.005$ and **$p < 0.001$ *vs.* young subjects (Student's *t* test). Results: omissions (mean ± SD)

TABLE 2. Effects of citicoline on memory performance in elderly subjects.

Group	N	Memory task	Treatment (No/Yes)	Day 1 (X ± SD)	Day 28 (X ± SD)	Treatment x day interaction
Whole sample	24	Word recall	N	4.83 ± 1.24	4.74 ± 1.34	F(46,1) = 5.95
			Y	5.17 ± 1.18	3.95 ± 1.24**	$p < 0.02$
	24	Word recognition	N	2.69 ± 2.02	2.40 ± 1.70	F(46,1) = 1.65
			Y	2.44 ± 1.64	3.05 ± 2.46	NS
	24	Immediate object recall	N	6.04 ± 1.23	5.96 ± 1.33	F(46,1) = 2.76
			Y	6.50 ± 1.62	5.50 ± 1.25*	NS
	24	Delayed object recall	N	7.00 ± 2.27	7.96 ± 2.61	F(46,1)= 20.04
			Y	8.46 ± 2.19	6.75 ± 2.40**	$p < 0.001$
	24	Object recognition	N	2.42 ± 1.79	2.29 ± 2.10	F(46,1) = 0.01
			Y	2.63 ± 1.86	2.46 ± 1.9	NS

*$p < 0.05$ and **$p < 0.005$ *vs.* day 1 scores (Wilcoxon test). Results: omissions (mean ± SD).

Daily treatment with a single 1000 mg dose of citicoline (C1000) significantly improved memory performance in the delayed object recall test as compared with the no treatment period ($F(14,1) = 7.44$; $p < 0.02$) (Table 3, Fig. 3). Memory improvement in this task was evident when scores obtained before and after citicoline treatment were compared (Table 3, Fig. 3). After treatment with 1000 mg of citicoline, a nonsignificant improvement was also observed in immediate word recall, but not in recognition tasks (Table 3).

Citicoline (500 mg/day; C500) induced significant improvements in delayed object recall and object recognition tests, improved immediate word and object recall in a nonsignificant manner, and did not alter word recognition scores (Table 3, Fig. 4).

Subjects of the C + Ni group, receiving daily treatment with citicoline plus nimodipine (300 + 90 mg/kg), showed a significant improvement in word recall and delayed object recall tasks, a nearly significant improvement in immediate object recall and no change in word and object recognition tests (Table 3, Fig. 5).

Physiological, biochemical and hematological parameters

A significant decrease in systolic blood pressure scores was found during the treatment period in the whole sample ($z = -.265$; $p < 0.01$), and the same tendency was observed in all treatment subgroups (Table 4). No significant changes in body weight, diastolic blood pressure, mean heart rate and body temperature were observed during yes and no treatment periods in the total group or in any particular subgroup of subjects.

No significant modifications in biochemical parameters were found during treatment and no treatment periods.

Active treatment induced a slight reduction in lymphocyte cell counting ($z = -2.35$; $p < 0.05$),

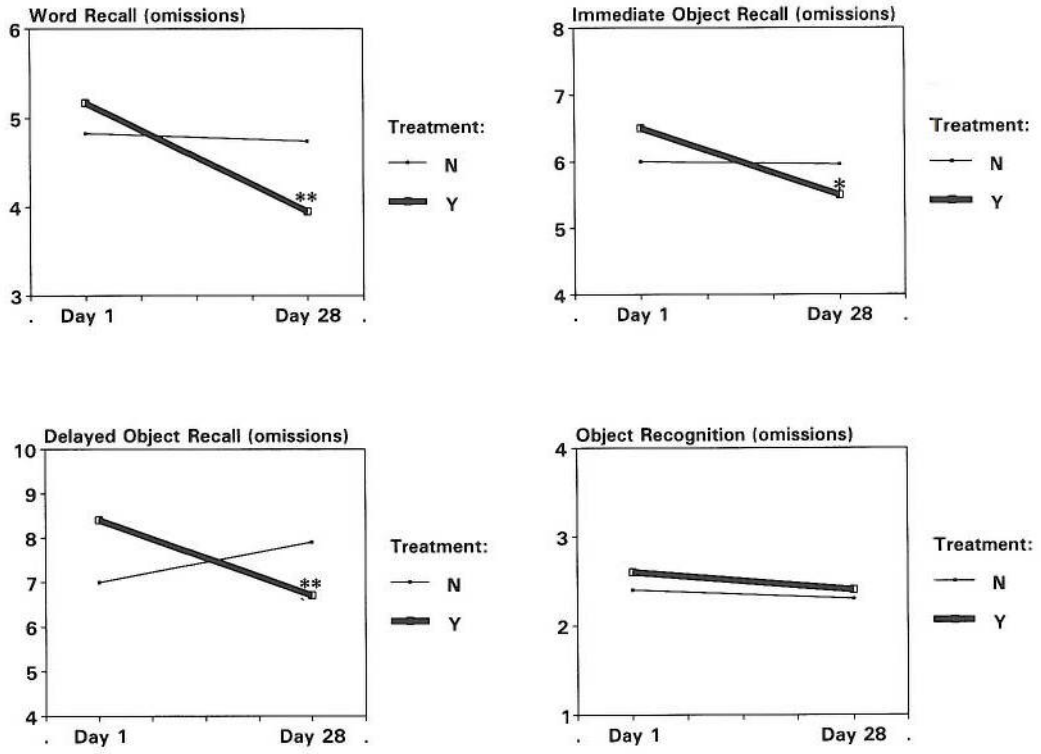

FIG. 2. Effects of citicoline on memory performance in elderly subjects. Mean results before (day 1) and after (day 28) placebo (N) and treatment (Y) periods are represented. $^{*}p < 0.05$ and $^{**}p < 0.005$ *vs.* day 1.

being the number of lymphocytes into the normal range (1.2-3.2 x $10^3/mm^3$) in all cases and had no effect on the other hematological parameters tested.

DISCUSSION

According to the present results, old subjects performed worse than young people in all memory tasks evaluated. These data confirm the presence of a generalized decline in memory functioning in elderly subjects included in this study, which is in agreement with the episodic memory deficit reported in old age (18). Apart from the influence of age, differences in educational status might also contribute to enhance differences between young and elderly subjects in memory functioning. However, mean error score for the memory subtest of the ADAS was also higher in our sample (8.17 omissions) than that reported for normal elderly subjects (3.4 omissions) in a previous study (25). Therefore, elderly individuals are susceptible to improving performance in the memory tasks tested.

Analysis of the whole sample (24 elderly subjects) shows that active treatment is effective in improving word and object recall, but not in ameliorating recognition deficits in aged individuals indicating that the memory-enhancing activity of citicoline is not the result of a nonspecific generalized action. The most striking effect of citicoline treatment on memory was found in the delayed object recall task, with improved performance in all treatment subgroups. From these results showing that citicoline potentiates immediate and short-term memory, it is suggested that this compound acts on brain mechanisms underlying processes of memory retrieval and storage. Encoding and retrieval are similar in both types of memory tasks, whereas the process of storage consolidation is important in delayed recall but not for the immediate retrieval of information. Our data also indicate that citicoline is most efficient in improving free recall than cued recall in elderly people. As a difference with free

TABLE 3. Effects of different doses of citicoline on memory performance in elderly subjects.

Group	N	Treatment period	Inmmediate Word recall		Word recognition		Immediate object recall	
			Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
C1000	8	No	4.7 ± 1.2	4.4 ± 1.7	2.2 ± 1.4	2.4 ± 1.0	6.2 ± 1.5	5.4 ± 1.2
		Yes	5.0 ± 1.1	4.2 ± 0.7	1.9 ± 1.2	2.6 ± 2.6	5.9 ± 1.1	5.4 ± 1.4
C500	8	No	5.0 ± 1.2	5.0 ± 1.2	2.9 ± 1.8	2.8 ± 2.5	5.5 ± 0.9	5.7 ± 1.0
		Yes	5.0 ± 1.3	3.8 ± 1.6	2.6 ± 2.0	3.4 ± 2.4	6.2 ± 1.9	5.4 ± 1.3
C + Ni	8	No	4.7 ± 1.3	4.7 ± 1.0	2.9 ± 2.8	2.0 ± 1.4	6.4 ± 1.2	6.7 ± 1.5
		Yes	5.4 ± 1.1	3.7 ± 1.2*	2.8 ± 1.6	3.1 ± 2.6	7.4 ± 1.5	5.7 ± 1.1
Group	N	Treatment period	Delayed object recall		Object recognition			
			Day 1	Day 28	Day 1	Day 28		
C1000	8	No	6.7 ± 2.9	7.7 ± 3.4	2.8 ± 2.7	1.6 ± 2.2		
		Yes	8.4 ± 2.7	6.1 ± 2.9*	2.1 ± 2.0	2.1 ± 2.2		
C500	8	No	7.5 ± 2.1	8.7 ± 2.5	2.2 ± 0.9	2.7 ± 2.3		
		Yes	9.0 ± 2.3	7.1 ± 2.3*	3.4 ± 1.8	1.9 ± 0.3*		
C + Ni	8	No	6.7 ± 1.9	7.3 ± 1.7	2.1 ± 1.3	2.5 ± 1.8		
		Yes	8.0 ± 1.6	7.0 ± 2.1*	2.4 ± 1.7	3.3 ± 2.3		

C1000: citicoline (1000 mg/day); C500; citicoline (500 mg/day); C + Ni: citicoline plus nimodipine (300 mg/day + 90 mg/day). *$p < 0.05$ *vs.* day 1 score (Wilcoxon test). Results: omissions (mean ± SD).

recall tests (immediate and delayed), recognition tasks involve cued retrieval, in which words and figures of objects previously seen are presented again to subjects in combination with distractors. In accordance with authors reporting that memory deficits in elderly subjects are less evident in cued conditions (18), we found lower mean error scores in recognition than in recall tasks (Table 1). Thus, it is possible that a ceiling effect might account for the lack of effect of citicoline on performance in recognition tasks. In fact, citicoline improves object recognition only in C500 subjects, the subgroup with the highest pretreatment impairment (Table 3).

Similar memory-enhancing effects of citicoline were found in the three subgroups of treatment, delayed object recall being the most significantly

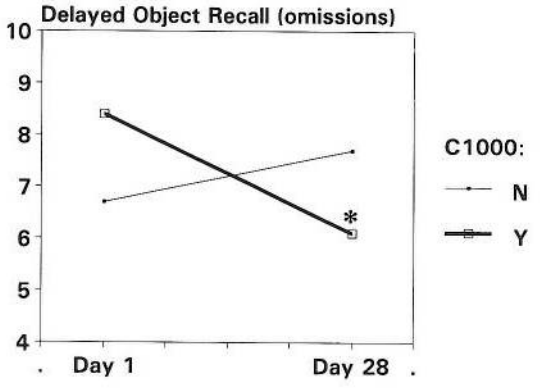

FIG. 3. Effects of citicoline (1000 mg/day) on delayed object recall in elderly subjects. Mean results before (day 1) and after (day 28) placebo (N) and treatment (Y) periods are represented. *$p < 0.05$ *vs.* day 1.

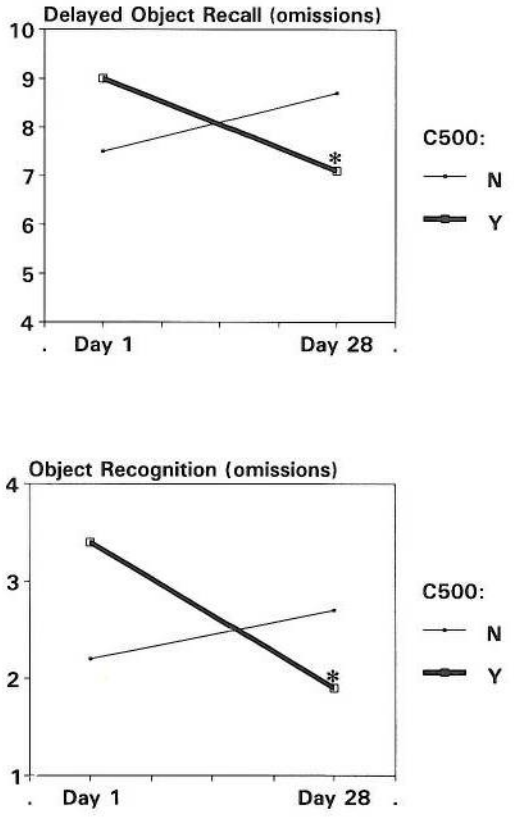

FIG. 4. Effects of citicoline (500 mg/day) on delayed object recall and on object recognition in elderly subjects. Mean results before (day 1) and after (day 28) placebo (N) and treatment (Y) periods are represented. $^{*}p < 0.05$ *vs.* day 1.

improved in all cases. Improvement in word recall and immediate object recall in the different subgroups does not reach significant values owing to the low number of subjects included in each one. In subjects treated with citicoline plus nimodipine it is difficult to know if the positive effect on memory is induced by citicoline or by a combined action of the two compounds. On the other hand, although the 500 mg dose of citicoline appears to be the most effective in improving recall and recognition functions, we have not found differences among treatment subgroups, indicating that citicoline in the 300-1000 mg/day dose range is able to improve memory performance in elderly subjects. A more extensive study is needed to establish the optimum promnesic dose of citicoline.

Our results are in agreement with the memory improvement reported in elderly demented subjects treated with citicoline for 2-3 weeks (21). It has also been found that citicoline increases cognitive performance in the MMS test in patients with early-onset Alzheimer's disease (16) or vascular dementia (14). In the Suryani *et al.* study (21), however, the different effect of citicoline on immediate recall, delayed recall and recognition tasks was not evaluated. Furthermore, these authors did not include a placebo period and retested subjects every week, making it not possible to exclude the effect of retesting on memory scores. Results of the open clinical trial reported here are hence relevant in demonstrating the promnesic activity of citicoline in non-demented elderly subjects. In addition, all the

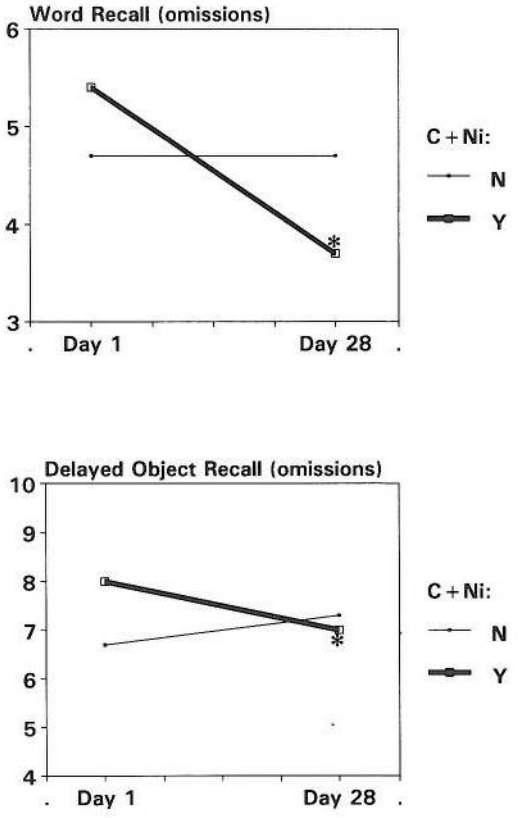

FIG. 5. Effects of citicoline plus nimodipine (300 + 90 mg/day) on word recall and on delayed object recall in elderly subjects. Mean results before (day 1) and after (day 28) placebo (N) and treatment (Y) periods are represented. $^{*}p < 0.05$ *vs.* day 1.

TABLE 4. Effects of citicoline on systolic blood pressure in elderly subjects.

Group	N	Treatment	Systolic blood pressure		Treatment x day interaction
			Day 1	Day 28	
Total	24	No	139.6 ± 22.2	141.1 ± 23.7	F(46,1) = 5.93
		Yes	144.0 ± 21.8	133.0 ± 15.3**	$p < 0.02$
C1000	8	No	132.5 ± 23.0	135.0 ± 27.7	F(14,1) = 5.38
		Yes	139.7 ± 25.3	129.8 ± 18.7*	$p < 0.05$
C500	8	No	135.6 ± 15.2	135.7 ± 16.5	NS
		Yes	140.0 ± 14.0	129.8 ± 10.6	
C + Ni	8	No	150.7 ± 25.2	152.6 ± 24.1	NS
		Yes	152.2 ± 24.8	139.3 ± 15.4	

C1000: citicoline (1000 mg/day); C500: citicoline (500 mg/day); C + Ni: citicoline plus nimodipine (300 mg/day + 90 mg/day). *$p < 0.05$ and **$p < 0.01$ *vs.* day 1 score (Wilcoxon test). Results: mmHg (mean ± SD).

mentioned studies are consistent with a memory-enhancing effect of citicoline in elderly people with cognitive deficits.

Although the specific goal of the present study was not to investigate the mechanisms responsible for the positive effects of citicoline on memory, we can speculate about such mechanisms by reviewing the actions of citicoline on brain neurochemical, bioelectrical and hemodynamic functions. Citicoline increases the biosynthesis of acetylcholine, phosphatidylcholine and lecithin, reduces phospholipase A_2 activation and the inhibition of ATPase activities in brain injury, improves cerebral glucose uptake and inhibits free fatty acid release and lactic acid accumulation in the brain (1-4, 8, 12, 13, 28, 29). All these neurochemical actions of citicoline may be beneficial in alleviating memory deficits in elderly subjects with a general decline in brain functioning. In fact, most compounds used for the treatment of Alzheimer's disease act on one or some of the mentioned brain mechanisms (1). It has also been demonstrated that citicoline improves cerebrovascular perfusion by increasing blood flow velocities and decreasing vascular resistance in the mean cerebral artery (14, 16). This vasoregulatory effect of citicoline is consistent with the decrease in systolic blood pressure observed in the present study and may potentiate memory performance by facilitating tissular perfusion and oxygenation in brain areas like the hippocampus.

In addition, it was found that citicoline reduces θ activity in fronto-temporal areas and increases relative α power in occipital regions in patients with Alzheimer's disease evaluated by brain mapping (16). This effect of citicoline on brain bioelectrical activity might reflect an activation of arousal/attentional mechanisms contributing to a better cognitive functioning. In this regard, significant correlations between bioelectrical activity values and MMS scores were reported (16).

On the other hand, citicoline reduces the increased circulating levels of histamine and interleukin-1β in Alzheimer's disease (16, 30) and hippocampal interleukin-1β content in an animal model of neurodegeneration induced by β-amyloid implants into the brain (5).

The reduction in lymphocyte cell counts observed in aged subjects is consistent with these neuroimmune effects of citicoline. Since the immunomodulatory actions of citicoline are accompanied by cognitive improvements and reduced neuronal death, it is suggested that changes in neuroimmune factors, as the result of a direct influence of the compound on immune responses or as an event secondary to its neuroprotective action, reflect a neurotrophic activity of citicoline. Therefore, it is possible that citicoline may improve mental performance by reducing immune activation and potentiating neurotrophic mechanisms into the brain. In line with this possibility, it has been found that citicoline is able to stimulate growth hormone release in elderly people in basal conditions and under stimulation with growth hormone releasing factor (31), and several studies have demonstrated the influence of the somatotropinergic system on cognitive functions in animals and humans (32-35). However,

investigation of the effects of citicoline on growth hormone, somatomedins and other trophic factors in subjects tested for memory performance has never been done and could be relevant in order to clarify the specific involvement of such biological parameters on the promnesic activity of citicoline.

In summary, we conclude that citicoline improves memory performance in elderly subjects, mainly in free recall tasks, at doses ranging from 300 to 1000 mg/day, probably by influencing brain neurotrophic mechanisms and processes of cerebrovascular regulation. According to these results, and taking into account the lack of relevant side effects, citicoline seems to be a useful and safe drug for the treatment of memory deficits in elderly people.

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