Psychopharmacology (1993) 110:421–426

Psychopharmacology

Effects of acute doses of oxiracetam in the scopolamine model of human amnesia

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Received August 7, 1992 / Final version September 16, 1992

Abstract. The scopolamine model of amnesia has been used to test the pharmacodynamic efficacy of oxiracetam in 12 healthy volunteers. The subjects were divided into four experimental groups, according to a double-blind cross over incomplete randomized block design. After a baseline neuropsychological examination, each subject received in two separate sessions one of the following treatments, as acute oral doses: oxiracetam 800, 1600, 2400 mg or placebo. One hour after treatment scopolamine hydrobromide (0.5 mg) was given subcutaneously. The cognitive performance was tested before and 1, 2, 3 and 25 h after scopolamine administration. Scopolamine caused a deterioration of performance of verbal episodic memory, semantic memory and attention tests. In comparison to placebo, oxiracetam improved the overall test performance, with a statistically significant difference at the dose of 1600 mg on delayed recall of word lists, and showed dose-related antagonism of scopolamine-induced effects also on semantic memory and attention. The efficacy of an acute dose of oxiracetam in reducing scopolamine-induced cognitive impairment supports the potential usefulness of this pharmacological model of amnesia for studying the effects of cognition enhancers in humans.

Key words: Oxiracetam – Scopolamine – Nootropic drugs – Memory and learning

Scopolamine is a cholinergic muscarinic receptor antagonist, able to cross the blood-brain barrier and to induce transient memory impairment. Many previous reports support the hypothesis that scopolamine affects mainly secondary memory and the ability to learn new information while leaving primary memory unaffected (Drachman and Leavitt 1974; Beatty et al. 1986; Kopelman and Corn 1988) This pattern of cognitive impairment is similar to that associated with normal ageing (Wesnes et al. 1988; Flicker et al. 1990) and, under some aspects, also to that found in Alzheimer's disease (AD), especially for long-term and working memory impairment (Ober et al. 1985; Baddeley et al. 1991). However, many features of memory impairment found in AD, such as primary, remote and semantic memory impairment, are not induced by scopolamine, suggesting that other neurotransmitter or neuromodulator systems, beside acetylcholine, are involved in the genesis of these deficits (Kopelman and Corn 1988). Further interest in the model of scopolamine-induced amnesia stems both from the hypothesis of association between cognitive decline in the elderly and deficit in cholinergic neurotransmission (Bartus et al. 1982), and from the observation of a severe dysfunction of the cholinergic neurotransmitter system in AD (Perry et al. 1978; Whitehouse et al. 1981).

Scopolamine has since been extensively used as a pharmacological model of amnesia in animals and has proved a useful test drug for evaluating the pharmacodynamic efficacy of new cognition enhancers in healthy volunteers, prior to their use in long-term trials on elderly populations (Wesnes et al. 1987, 1990).

Oxiracetam is a nootropic drug structurally related to piracetam, 2–5 times more active than piracetam in improving learning and memory in healthy animals as well as in animals with cerebral impairment related to ageing or to acute and chronic noxious stimuli (Banfi and Dorigotti 1984).

Controlled clinical trials on AD and vascular dementia have indicated that the drug is well tolerated and it is superior both to placebo (Saletu et al. 1985; Villardita et al. 1992) and to piracetam (Ferrero 1984) in improving objective measurement of cognitive function, logical performance and attention.

Oxiracetam has been previously tested against scopolamine-induced amnesia in animals (Ponzio et al. 1988; Pozzi et al. 1988; Magnani et al. 1992). The aim of this study was to investigate whether the effects of scopolamine on memory and attention could be antagonized by acute doses of oxiracetam, thus supporting the hypothesis of an action of the drug on cholinergic central modulation.

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Materials and methods

Subjects

Twelve healthy volunteers (eight males and four females) entered the study. Their mean age was 25 years (SEM = 0.8; range 21–30 years) and mean weight was 66 ± 8 kg (range 49–82). The healthy condition of each subject was defined through a detailed clinical interview, a physical examination including ECG, and results of routine laboratory examinations.

They had a medium-high education degree (13–17 years) and scored in the normal range in intelligence and memory tests. Their Memory Quotient on the Wechsler Memory Scale (Wechsler 1945) had to be higher than 90 and IQ on the Wechsler Adult Intelligence Scale (Wechsler 1955) higher than 100. Exclusion criteria were as follows: pregnancy for women; hematological values outside the normal range; increased intraocular tension and/or ECG alterations; chronic intake of central nervous system active drugs.

A written informed consent for participation in the study was obtained from each subject, in accordance with the Declaration of Helsinki and its subsequent amendments.

Design and treatments

The 12 subjects were tested twice, in double blind conditions, and received at each session acute oral doses of one of the following treatments: oxiracetam 800 mg, 1600 mg, 2400 mg and placebo, according to an incomplete randomized cross over block design (six subjects per dose). Scopolamine hydrobromide (0.5 mg) was given subcutaneously 1 h after tablets intake. There was a wash-out period of at least 7 days between the two sessions.

Baseline clinical and laboratory examinations were carried out in the pre-trial screening period, together with a neuropsychological test training session in order to familiarize the subjects with the experimental tasks and to reduce practice effects.

Alcohol, smoke and coffee were not allowed starting from the evening before the testing session.

Neuropsychological assessment

Neuropsychological tests were performed just before drug intake (T0), and 2(T1), 3(T2), 4(T3) and 26(T4) h after drug intake (respectively 1, 2, 3 and 25 h after scopolamine administration). Each neuropsychological session lasted about 20 min. On each presentation of the battery of tests, different items or stimulus sequences balanced for level of difficulty were used. The test sequence was kept constant in both sessions.

The testing procedure included 5 neuropsychological tests:

Word lists free recall (immediate and delayed). A list of 20 bisyllabic words, equated for frequency (Bortolini et al. 1972) and for degree of imaginability (Paivio et al. 1968), was read three times to the subjects, at a rate of approximately one word every 2 s. At the end of each presentation, the subjects were instructed to write all the words they could remember, regardless of their order of presentation. Time allowed for written recall was 90 s. A score of 1 was assigned to each word correctly recalled. Range of scores: 0–20 for each presentation (0–60 for the comprehensive three presentations of each list).

Number of intrusions and false alarms (previous list and extralist errors) were also calculated.

After an interval, involving a cancellation task, the subjects were asked to write all the words they recalled of the previous list (delayed recall).

Cancellation task. Subjects were given a matrix of 36 rows and 20 columns of randomly generated digits, printed in 4 mm height on a white 30 × 42 cm sheet of paper. Three digits were designed as targets of a given session. The subjects had to cancel, as rapidly and accurately as possible, all the targets they could detect within 2 min. A score of 1 was assigned to the correct detection of each target digit. Range of scores: 0–210.

Semantic memory test. Subjects were given a matrix of 120 words, subdivided in 12 rows and 10 columns, printed in 4 mm height on a white 30 × 42 cm sheet of paper. The subject had to cancel each word belonging to a given semantic category. The 30 target words were intermingled with 90 distractors, 30 of which belonged to a semantically linked category (i.e. target: flowers; distractors: trees). A score of 1 was assigned to each correct detection of a target word. Range of scores: 0–30. Time allowed for the task was 60 s.

Reading tasks. The subjects were instructed to cancel a target word, presented in a matrix similar to that utilized for the semantic memory test. The 30 target words were intermingled with 90 distractors. In a first condition (phonological distractor) 30 of the distractors were phonologically similar to the target word (i.e. target: quaderno; distractor: quadrante, quartiere). A score of 1 was assigned to each correct detection of the target word. Range of scores: 0–30. Time allowed for each reading test: 30 s. In the second condition (non-phonological distractor) the distractors were selected in order to be different both semantically and phonologically from the target word [i.e. target: orologio (clock); distractor: fattoria (farm), cappotto (over-coat)].

Statistics

Demographic characteristics (age, education) of the four treatment subgroups were compared by unpaired t tests.

In order to examine the effect of scopolamine on neuropsychological performance, Wilcoxon tests for small groups were performed between baseline neuropsychological performance (T0), and T1, T2, T3 and T4 neuropsychological test results of the two experimental groups (placebo versus treatment).

In order to reduce intersubject baseline performance variability, results of neuropsychological examinations of each subject were transformed into delta scores subtracting results at T1, T2, T3 and T4 from those at baseline (T0). The existence of an effect of treatment factor (four level: placebo and oxiracetam at 800, 1600, 2400 mg) on scopolamine-induced effect, was explored with a non parametric analysis of variance (Kruskall Wallis H test); planned contrasts between placebo and different doses of oxiracetam were performed with Mann-Whitney U test.

Results

The groups were not significantly different for age, education and laboratory examinations results. No adverse events related to oxiracetam or placebo were reported. Scopolamine caused midriasis and mild drowsiness in all the subjects, dry fauces in 11 subjects, mild ataxia in 8 subjects, nausea and vertigo in 3 subjects, flush and dysmetria in 1 subject. Raw scores of neuropsychological tests are reported in Table 1. Distribution of the delta scores of the four experimental groups and results of linear contrasts are presented in Figs 1–3.

Scopolamine caused a deterioration of performance in almost all neuropsychological tests, in both oxiracetam and placebo groups.

Word list free recall

Scopolamine caused a significant decrement of performance at different times of evaluation on immediate recall ($P < 0.0001$ at T1, T2 and T3; P = NS at T4) and

Table 1. Mean raw scores of neuropsychological tests (SD in brackets) in the four experimental groups at different times (T0–T4)

Placebo					Oxiracetam 800 mg					Oxiracetam 1600 mg					Oxiracetam 2400 mg				
T0	T1	T2	T3	T4	T0	T1	T2	T3	T4	T0	T1	T2	T3	T4	T0	T1	T2	T3	T4
Immediate free recall																			
31.2	19.5	20.7	17.7	33.8	30.0	17.2	18.8	18.3	31.7	31.0	21.8	20.2	20.2	34.5	31.8	18.3	22.7	20.8	37.5
(4.5)	(5.0)	(1.5)	(2.1)	(4.3)	(3.6)	(3.4)	(4.3)	(5.2)	(3.5)	(3.1)	(4.2)	(5.8)	(4.1)	(5.7)	(4.9)	(1.5)	(5.6)	(3.5)	(3.8)
Delayed recall																			
13.5	4.5	5.0	5.7	11.8	11.0	4.2	5.0	5.7	11.8	11.2	7.2	6.8	8.2	11.8	11.8	4.5	6.8	5.3	13.8
(1.2)	(1.5)	(1.8)	(1.0)	(2.3)	(2.4)	(2.8)	(2.1)	(1.4)	(2.8)	(1.9)	(2.0)	(1.2)	(2.6)	(2.3)	(3.1)	(1.0)	(2.3)	(2.6)	(2.4)
Cancellation task																			
131.5	89.0	88.8	110.0	148.8	111.5	81.0	84.5	98.0	137.7	123.3	98.5	96.3	106.3	143.8	125.7	98.5	101.7	106.3	143.5
(23.1)	(30.8)	(24.6)	(18.8)	(30.9)	(24.2)	(15.2)	(19.9)	(19.6)	(18.4)	(21.5)	(19.7)	(24.6)	(25.4)	(12.5)	(14.9)	(11.3)	(20.5)	(24.2)	(16.5)
Semantic memory																			
21.5	15.8	19.8	23.2	22.0	22.3	19.0	21.7	23.2	22.8	23.0	23.2	23.6	24.8	24.3	21.2	21.0	24.2	22.5	21.1
(5.7)	(5.4)	(6.5)	(2.1)	(3.7)	(6.9)	(5.7)	(4.4)	(3.6)	(3.8)	(4.3)	(2.8)	(4.1)	(3.4)	(4.3)	(3.0)	(4.3)	(2.1)	(5.1)	(4.4)
Random reading																			
27.8	23.5	24.1	24.1	24.5	26.2	22.2	24.5	23.2	24.8	26.3	24.2	25.2	23.5	25.7	25.8	26.8	26.7	25.7	26.0
(1.7)	(6.7)	(4.6)	(3.8)	(4.3)	(2.8)	(4.8)	(3.2)	(5.0)	(3.2)	(2.7)	(2.6)	(3.8)	(3.4)	(4.2)	(3.1)	(2.6)	(2.6)	(4.2)	(2.1)
Phonological reading																			
25.3	21.2	20.3	21.5	25.7	23.2	19.7	17.0	24.0	23.0	24.7	21.5	20.0	22.7	24.5	24.2	20.8	21.0	22.7	25.0
(3.1)	(4.2)	(4.9)	(6.6)	(2.7)	(2.6)	(4.6)	(3.5)	(2.7)	(3.9)	(2.9)	(3.9)	(4.3)	(2.2)	(3.5)	(1.9)	(2.6)	(4.4)	(5.7)	(3.2)

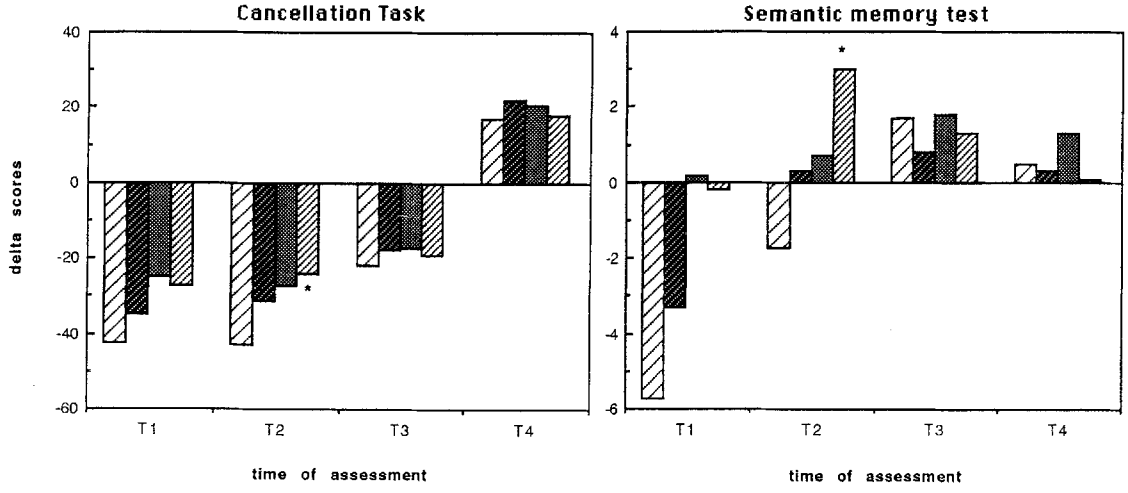

Fig. 1. Histograms of mean delta scores in the four experimental groups for cancellation task and semantic memory test. $*P < 0.05$ in comparison with placebo (▨). (▩) Ox 800; (■) Ox 1600; (▨) Ox 2400

delayed recall tests ($P < 0.0001$ at T1, T2, T3; P = NS at T4) in both groups of subjects. No statistically significant difference emerged in number of intrusion errors both in immediate and delayed recall conditions. Treatment factor had no statistically significant effect on immediate free recall, while it yielded a significant effect on delayed recall performance at T1, T2, T3 ($H = 10.06$, $P < 0.02$; $H = 10.04$, $P < 0.02$; $H = 8.042$, $P < 0.04$, respectively).

Analysis of different doses revealed a positive effect versus placebo of 800 mg on T3 delayed recall performance ($U_{prime} = 30.5$, $P < 0.05$) and of 2400 mg on T2 delayed performance ($U_{prime} = 30.5$; $P < 0.05$). Oxiracetam 1600 mg showed a statistically significant effect on delayed recall at T1 ($U_{prime} = 36$, $P < 0.004$), T2 ($U_{prime} = 35$; $P < 0.006$), T3 ($U_{prime} = 32.5$, $P < 0.02$) and a trend in the same direction at T4 ($U_{prime} = 29.5$, $P < 0.06$).

Cancellation task

Scopolamine caused a significant decrease of performance at T1 ($P < 0.001$) and T2 ($P < 0.004$). The decrease was still evident also at T3 ($P < 0.03$) while it disappeared after 25 h (P = NS) in both groups. Treatment factor yielded a positive effect on performance at T1 ($H = 8.040$, $P < 0.05$) and T2 ($H = 8.26$, $P < 0.04$) Analysis of single doses revealed a statistically significant effect of 2400 mg on T2

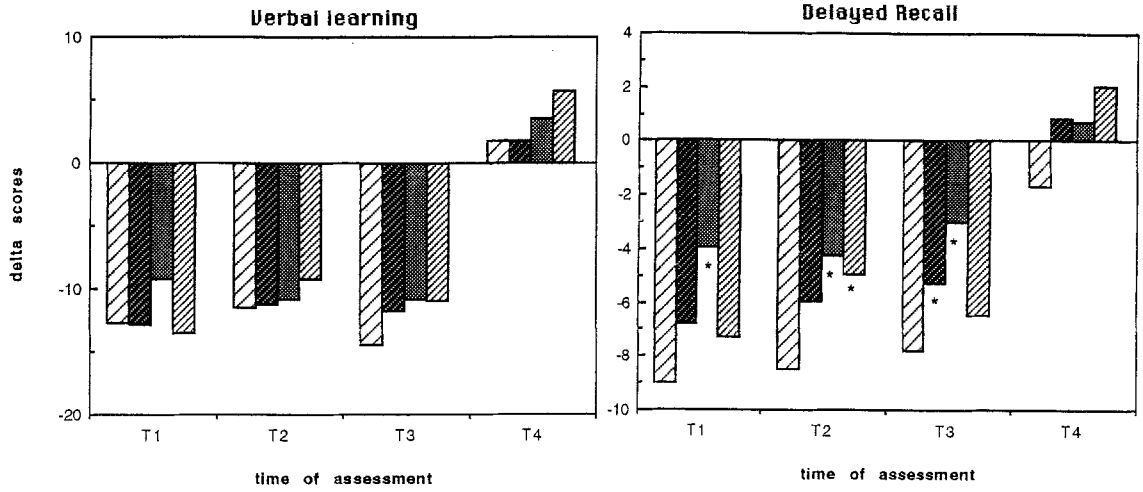

Fig. 2. Histograms of mean delta scores in the four experimental groups for verbal learning and delayed recall. *$P < 0.05$ in the comparison with placebo. For symbols see legend of Fig. 1

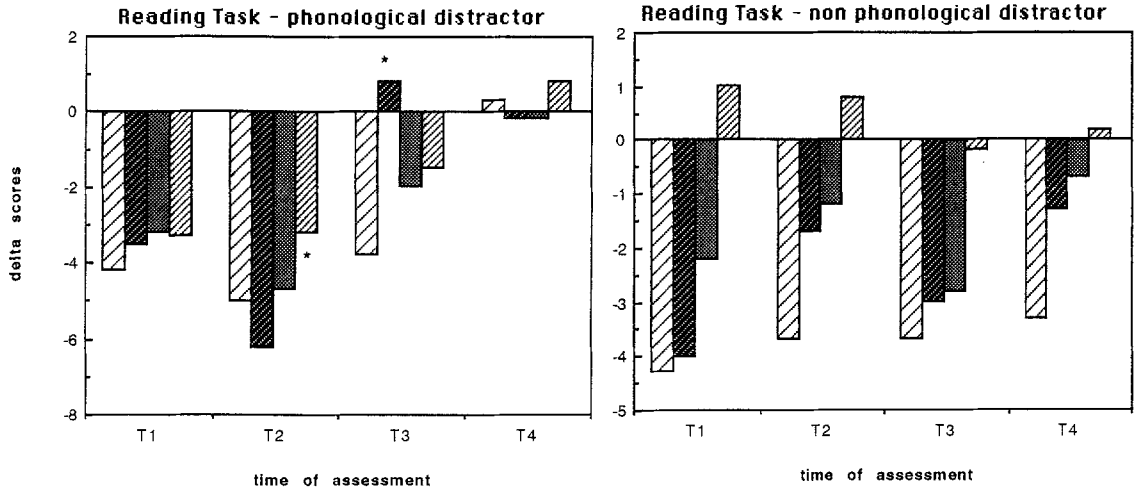

Fig. 3. Histograms of mean delta scores in the four experimental groups for reading tasks with phonological and non-phonological disturbers. *$P < 0.05$ in the comparison with placebo. For symbols see legend of Fig. 1

performance ($U_{prime} = 32$, $P < 0.03$) and a positive trend of 1600 mg on T1 ($U_{prime} = 29.5$, $P = 0.06$).

Semantic memory

Scopolamine caused a significant decrease of performance at T1 session ($P < 0.02$) only in the placebo group. Treatment factor had a positive effect on performance at T1 ($H = 10.00$; $P < 0.02$). Analysis of different doses showed no efficacy of oxiracetam 800 mg; 1600 mg had a significant effect on T1 performance ($U_{prime} = 31.5$, $P < 0.03$); 2400 mg a positive trend at T1 ($U_{prime} = 30$, $P < 0.06$) and a statistically significant positive effect at T2 ($U_{prime} = 33$, $P < 0.02$).

Reading tasks

Scopolamine did not significantly affect the non-phonological distractor reading task, while it yielded a significant impairment in the phonological distractor condition at T1 ($P < 0.001$) and T2 ($P < 0.03$). Analysis of oxiracetam (all doses) versus placebo conditions did not reveal any significant difference on the two tasks at any time of assessment, a part from the efficacy of oxiracetam 2400 on T2 performance ($U_{prime} = 33$, $P < 0.02$).

Discussion

In accordance with the results of previous studies, in our experiment scopolamine induced a marked anterograde memory deficit; this impairment was partially antagonized by acute doses of oxiracetam, as already shown in animals (Ponzio et al. 1988; Pozzi et al. 1988; Magnani et al. 1992).

Most published studies support that scopolamine specifically impairs the learning of new information, without affecting the retention of data (Petersen 1977). Scopolamine would interfere with memory trace acquisition (encoding and consolidation), affecting the transfer of

information from short to long-term storage and the formation of stable memory traces (Drachman 1977; Ghoneim and Mewaldt 1977; Beatty et al. 1986), or alternatively, it would disrupt the organization of material at input, so that items which have achieved durable storage are not accessible to recall (Rusted and Warburton 1989).

Oxiracetam treatment did not influence learning ability but significantly improved delayed recall performance of the treated subjects, suggesting its action would be essentially exerted on mechanisms of memory trace acquisition and consolidation. Oxiracetam induced an improvement, not a reversal of scopolamine effects: the effectiveness was at its most for 1600 mg treatment, but some effects could be detected also with 800 and 2400 mg.

At variance with Wesnes et al. (1988) and Broks et al. (1988), but in accordance with the majority of studies (Beatty et al. 1986; Kopelman and Corn 1988; Flicker et al. 1990), we did not detect significant increases in number of intrusion errors in immediate or delayed recall after scopolamine administration.

Scopolamine is known not to impair the recall of information learnt immediately before drug treatment (Petersen 1977; Rusted and Warburton 1989). Furthermore, it would not affect semantic memory performance (Beatty et al. 1986; Kopelman and Corn 1988; Rusted and Warburton 1989), even if some studies report a decrease in spontaneous retrieval of previously well rehearsed semantic information (Drachman and Leavitt 1974).

In our trial we could detect only a transient significant decrease in the semantic memory test performance one hour after scopolamine administration. The impairment of semantic memory test performance was paralleled by a significant impairment of the phonological disturber reading test, which poses the same demands on reading speed and accuracy, as well as on attentional resources. The semantic memory impairment could then be accounted for by the central attentional processing speed decrease induced by scopolamine, complex cognitive computations requiring longer time to be accomplished and resulting thereafter affected.

In some authors' view the central attentional processing impairment could represent the key disturbance of scopolamine-induced cognitive impairment: the memory disturbance could be related to a non-specific decrease in alertness (Mewaldt and Ghoneim 1979; Parrott 1986; Wesnes et al. 1988), or to a scopolamine-induced impairment of the central executive component of the working memory system (Rusted and Warburton 1989). The issue is still rather controversial because others (Petersen 1977, Kopelman 1986; Kopelman and Corn 1988) report that memory and attentional impairment would be independent.

Aim of our study was to assess the efficacy of oxiracetam on scopolamine-induced memory cognitive impairment and our study design does not allow us to draw strong inferences about the interdependence of the two phenomena. To assess arousal, as sedation is an usual side-effect of scopolamine, we choosed not to use a visual analogue scale which may be influenced by several factors (psychological, environmental, drug side-effects other than sedation) that can bias it as a measure of attention, and preferred an objective measure of attentional performance, with a high degree of consistency and validity to assess clinical sedation (Lezak 1983).

In our trial scopolamine had a disruptive effect on the cancellation task performance, which paralleled memory disturbance and lasted at least 6 h after scopolamine administration. Lack of evidence of an impairment in attentional performance in some of the previous published studies might depend on the selection of relatively unsensitive measures: our results show a persistent decrease in the cancellation task performance, while the decrease was of far lesser amplitude and less long-lasting in the two reading tasks, which require abilities not dissimilar from those implied in the cancellation task. The main difference between the two tasks stems from the time allowed to complete the tests: in the cancellation task the subjects have to endure the selective attention effort for 2 min, while in the reading task the time allowed was 30 s. These data are in accordance with the conclusion that sustained attention would represent a more sensitive measure of scopolamine sedation rather than selective attention (Broks et al. 1988)

Oxiracetam exerted a positive effect on the decrease in attentional performance induced by scopolamine: oxiracetam 2400 mg significantly improved the performance in different attention loaded tasks (cancellation task, reading tasks), with 1600 mg showing just a trend in the same direction. As in the case of memory, we did not observe a reversal of scopolamine effects, but only an improvement of performance.

The observation that scopolamine-induced cognitive effects are antagonized by cholinergic agonists (e.g. physostigmine) but not by other drugs known to increase arousal (e.g. amphetamine) (Drachman and Leavitt 1974; Ghoneim and Mewaldt 1977; Preston et al. 1989), supports the hypothesis of an action of oxiracetam on cholinergic transmission, which would mediate its effects both on memory and on attention. Since oxiracetam has no pharmacologically identifiable cholinergic activity (Pepeu et al. 1989), one may argue that its nootropic and scopolamine-antagonizing properties might be mediated by an indirect modulation of cholinergic mechanisms.

The effect of oxiracetam might be exerted at an aspecific and rather global level of action, increasing the level of arousal. An alternative explanation stems from the observation of an effectiveness of 1600 mg on scopolamine-induced memory impairment and of 2400 mg on scopolamine-induced attention impairment, thus accounting for a possible dissociation of the two phenomena, as an increase of arousal would not per se bring to an amelioration of memory performance. Our data could indicate that an increase in cholinergic modulation would act initially on possibly more sensitive neural cholinergic circuits involved in long term memory learning (i.e. amygdalo-hyppocampal areas). A further increase in cholinergic level could exert a more diffuse non-specific effect on arousal, possibly through diffuse cholinergic cortical pathways. This global action could in some measure interfere with learning mechanisms, possibly through an increase of the noise-to-sound ratio.

Limitations in the nature of the experimental design (multiple dose, cross-over design) and the relatively restricted number of subjects studied, have to be considered. More research is needed to explore this issue: results of the

present research may be considered only as a preliminary contribution in this field.

References

Baddeley D, Bressi S, Della Sala S, Logie R, Spinnler H (1991) The decline of working memory in Alzheimer's Disease. Brain 114:2521–2542

Banfi S, Dorigotti L (1984) Experimental behavioural studies with oxiracetam on different types of chronic cerebral impairment. Clin Neurophys 7:768–769

Bartus R, Dean R, Beer B, Lippa A (1982) The cholinergic hypothesis of geriatric memory dysfunction: a critical review. Science 217:408–417

Beatty W, Butters N, Janowsky D (1986) Patterns of memory failure after scopolamine treatment: implications for cholinergic hypothesis of dementia. Behav Neural Biol 45:196–211

Bortolini U, Tagliavini C, Zampolli A (1972) Lessico di frequenza della lingua italiana contemporanea. Garzanti, Milan

Broks P, Preston G, Traub M, Poppleton P, Ward C, Stahl S (1988) Modelling dementia: effects of scopolamine on memory and attention. Neuropsychologia 26:685–700

Drachman D, Leavitt J (1974) Human memory and the cholinergic system. Arch Neurol 30:113–121

Ferrero E (1984) Controlled clinical trial of oxiracetam in the treatment of chronic cerebrovascular insufficiency in the elderly. Curr Ther Res 36:298–308

Flicker C, Serby M, Ferris S (1990) Scopolamine effects on memory, language, visuospatial praxis and psychomotor speed. Psychopharmacology 100:243–250

Ghoneim M, Mewaldt S (1977) Studies of human memory: the interactions of diazepam, scopolamine and physostigmine. Psychopharmacol 52:1–6.

Kopelman M (1986) The cholinergic neurotransmitter system in human memory and dementia: a review. Q J Exp Psychol 38A:535–573

Kopelman M, Corn T (1988) Cholinergic 'blockade' as a model for cholinergic depletion. A comparison of memory deficits with those of Alzheimer-type dementia and the alcoholic Korsakoff syndrome. Brain 111:1079–1110

Lezak MD (1983) Neuropsychological assessment. Oxford University Press, New York

Magnani M, Pozzi O, Banfi S, Biagetti R, Dorigotti L (1992) Oxiracetam antagonizes the disruptive effects of scopolamine on memory in the radial maze. Psychopharmacology 106:175–178

Mewaldt S, Ghoneim M (1979) The effects and interactions of scopolamine, physostigmine and metamphetamine on human memory. Pharmacol Biochem Behav 10:205–210

Ober B, Koss E, Friedlan R (1985) Processes of verbal memory failure in Alzheimer type dementia. Brain Cogn 4:90–103

Paivio A, Yuille J, Madigan S (1968) Concreteness, imagery and meaningfulness values for 925 nouns. J Exp Psychol 76:1–25

Parrott A (1986) The effects of transdermal scopolamine and four doses of oral scopolamine (0.15, 0.30, 0.6, 1.2 mg) upon psychological performance. Psychopharmacology 29:347–354

Pepeu G, Spignoli G, Magnani M (1989) The relationship between the behavioural effects of cognitive-enhancer's drugs and brain acetylcholine. Pharmacopsychiatry 22:116–118

Perry E, Tomlinson B, Blessed G, Bergmann K, Gibson P, Perry R (1978) Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. BMJ 2:1457–1459

Petersen R (1977) Scopolamine-induced learning failures in man. Psychopharmacology 52:283–289

Ponzio F, Pozzi O, Banfi S, Dorigotti L (1988) Experimental evidence of oxiracetam direct activity on memory mechanisms. Psychopharmacology 96:71

Pozzi O, Allievi E, Biagetti R, Banfi S, Dorigotti L (1988) Behavioural screening for potential nootropic drugs. Pharmacol Res Common 20:315

Preston G, Ward C, Lines P, Poppleton P, Haigh J, Traub M (1989) Scopolamine and benzodiazepine models of dementia: cross-reversals by RO 15-1788 and physostigmine. Psychopharmacology 98:487–494

Rusted J, Warburton D (1989) Effects of scopolamine on verbal memory: a retrieval or acquisition deficit? Neuropsychobiology 21:76–83

Saletu B, Linzmayer L, Gruenberger J, Pietschwan H (1985) Double-blind, placebo controlled, clinical, psychometric and neuropsychological investigations with oxiracetam in the organic brain syndrome of late life. Neuropsychobiology 13:44–52

Villardita C, Grioli S, Lomeo C, Cattaneo C, Parini J (1992) Clinical studies with oxiracetam in patients with senile dementia of Alzheimer's type and multi-infarctual dementia of mild to moderate degree. Neuropsychobiology 25:24–28

Wechsler D (1945) A standardized memory scale for clinical use. J Psychol 18:87–95

Wechsler D (1955) The measurement of adult intelligence. Psychological Corporation, New York

Wesnes K, Simpson P, Kidd A (1987) The use of scopolamine model to study the nootropic effects of tenilsetam (CAS97). Med Sci Res 15:1063–1064

Wesnes K, Simpson P, Kidd A (1988) An investigation of the range of cognitive impairments induced by scopolamine 0.6 mg. Hum Psychopharmacol 3:27–43

Wesnes K, Anand R, Simpson P, Christmas L (1990) The use of a scopolamine model to study the potential nootropic effects of aniracetam and piracetam in healthy volunteers. J Psychopharmacol 4:246–254

Whitehouse P, Price D, Clark A, Coyle J, DeLong M (1981) Alzheimer's disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol 10:122–126