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The Effects of Exifone, a New Agent for Senile Memory Disorder, on Two Models of Memory in the Mouse

R. D. PORSOLT,* A. LENÈGRE,* I. AVRIL,*
L. STÉRU* AND G. DOUMONT†[1]

*I.T.E.M.-LABO, 201 rue d'Alésia, 75014 Paris, France
†Laboratoires Pharmascience, 73 bd de la Mission Marchand, 92400 Courbevoie, France

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PORSOLT, R. D., A. LENÈGRE, I. AVRIL, L. STÉRU AND G. DOUMONT. *The effects of exifone, a new agent for senile memory disorder, on two models of memory in the mouse.* PHARMACOL BIOCHEM BEHAV **27**(2) 253–256, 1987.—The effects of exifone (ADLONE®), hexahydro-2,3,4,3',4',5'-benzophenone, were tested in two models of memory in the mouse: habituation of exploratory activity and antagonism of amnesia induced by scopolamine in a passive avoidance task. In the first model, mice which had received exifone (128 and 256 mg/kg IP) 30 minutes before a 3 minute exposure to a staircase exploratory test showed a more marked decrease in exploratory activity in the same apparatus 24 hours later (habituation) than a control group indicating improved memory. Similar results were obtained with piracetam (512 mg/kg, IP). In the second model exifone (512 mg/kg PO), administered 60 minutes before both the learning and retention trials of a standard step-through passive avoidance, task partially antagonized the amnesia induced by 10 mg/kg scopolamine IP administered immediately after the learning trial. Similar results were obtained with piracetam (800 mg/kg PO). Taken together these results suggest that exifone facilitates memory function in simple rodent models in a manner consistent with its supposed therapeutic effects in man.

Exifone Piracetam Rodent memory models Habituation of exploratory activity
Scopolamine-induced amnesia Passive avoidance

EXIFONE (ADLONE®), hexahydro-2,3,4,3',4',5'-benzophenone, is a novel compound which has recently been proposed for the treatment of senile cognitive disorder. Several clinical studies, both open and double blind placebo-controlled, have indicated that the compound is effective in reducing various forms of cognitive disturbance, particularly memory deficits, in geriatric and Parkinsonian patients [1,6].

The present experiments were undertaken to test the effects of exifone on two simple models of memory and memory dysfunction in the mouse, the habituation of exploratory activity and the antagonism of amnesia induced by scopolamine in a passive avoidance task.

METHOD

Experimental Animals

The animals used in these studies were male NMRI-CERJ mice, 20–25 g, obtained from the Centre d'Elevage Roger Janvier, Le Genest Saint Isle, France. They were delivered to the laboratory at least 3 days before being used and were housed in groups of 10 in macrolon cages (25.5×19.5×13.5 cm) with free access to food (UAR 113) and water. The housing facility was maintained on a non-inverted 12 hr/12 hr light cycle with the lights turned on at 8:00. The ambient temperature within the animal house and the laboratories was maintained between 20° and 22°C.

Drugs

Exifone (Batch No. 4R4540), in yellow powder form, was obtained from Pharmascience (France). The following reference compounds in powder form were used: piracetam (UCB, Batch No. 5439); scopolamine hydrobromide (Sigma, Batch No. B0462).

Exifone, which is insoluble, was dispersed in an acqueous suspension of Arabic gum (5%) diluted to the required concentration with distilled water and maintained in suspension with a magnetic agitator. Piracetam and scopolamine were dissolved in distilled water. Compounds were administered in a volume of 0.25 ml/20 g body weight. Doses are expressed as base or salt where appropriate. Drugs were administered IP in the habituation test and PO in the passive avoidance test to ensure that effects could be observed by both routes of administration (see below).

Procedure

Habituation of exploratory activity. The principle of this

[1]Requests for reprints should be addressed to Dr. G. Doumont.

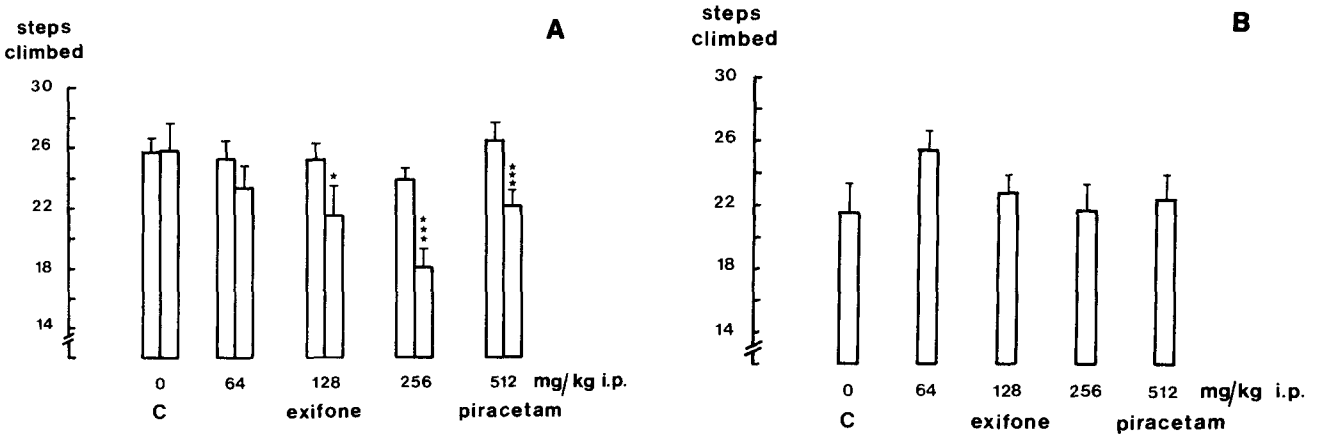

FIG. 1. Habituation test: (a) The effects of exifone and piracetam, administered IP 30 minutes before the first session (S1), on the number of steps climbed during a 3 minute test in the staircase apparatus at S1 (left columns) and S2 (right columns). Twenty mice were used per group. Results are expressed as means and standard errors (S.E.M.). *=$p<0.05$; **=$p<0.01$ (unpaired Student t-test on the S1-S2 difference scores). ***=$p<0.001$.7 (b) The effects of exifone and piracetam administered 24 hours before a single test on the number of steps climbed during a 3 minute test in the staircase apparatus. Ten mice were used per group. Results are expressed as means and standard errors (S.E.M.).

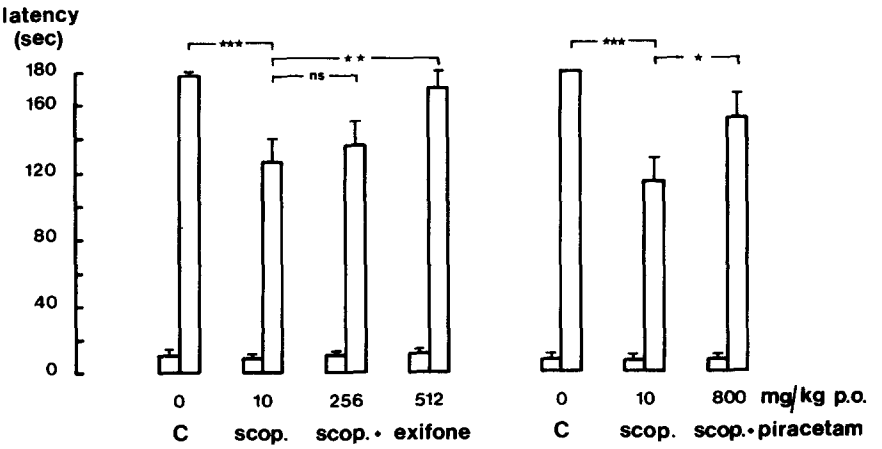

FIG. 2. Scopolamine-induced amnesia: The effects of exifone and piracetam, administered PO 60 minutes before both the first (S1) and second (S2) sessions, on the S1 (left columns) and S2 (right columns) step-through latencies (sec) in a passive avoidance task. Twenty mice were used per group. All animals, except the non-amnesic control groups, received an IP injection of scopolamine (10 mg/kg) immediately after S1. Results are expressed as means and standard errors (S.E.M.). *=$p<0.05$; ***=$p<0.001$ (unpaired Student's t-test on the S2 latencies).

test is that animals which show a decrease in exploratory activity on a second exposure to the same exploratory situation (habituation) indicate that they remember having been there before [8]. Mice were individually placed in a white enclosure containing a staircase with 5 steps [13]. The number of steps climbed during a 3 minute test was counted (S1). Twenty-four hours later the animals were replaced in the same situation and the 3 minute test was repeated (S2). Twenty mice were studied per group. Drug injections were given IP 30 minutes before S1.

Exifone was studied at 3 doses (64, 128 and 256 mg/kg IP) with piracetam (512 mg/kg IP) being used as a reference compound. Control animals received the vehicle. To control for eventual long-term effects which might confuse the interpretation of the findings, both exifone and piracetam, in a separate experiment, were administered by the same route (IP) and tested for the first time in the staircase apparatus 24 hours later.

Results were analysed for statistical significance using unpaired t-tests either on the exploration scores (number of steps climbed) at S1 or on the difference scores between S1 and S2 (habituation effect).

Scopolamine-induced amnesia in a passive avoidance task. The principle of this test is that animals exposed to aversive stimulation (mild electric shock) in a particular place will avoid going there on a second occasion (passive avoidance). An injection of scopolamine immediately after the exposure to shock causes a deficit in the acquisition of the passive avoidance response which can be antagonized by agents which facilitate memory [11].

Mice were individually placed in the smaller, but brightly lit, compartment of a two compartment box. When they crossed into the larger darker compartment they received a mild electric foot-shock (0.3 mA) until they returned to the lighted compartment (S1). They were immediately removed and received an IP injection of scopolamine (10 mg/kg) or distilled water (non-amnesic control group) and were replaced in their home cages. Twenty-four hours later they were replaced in the lighted compartment and their latency before crossing to the dark compartment was measured with a cut-off time of 180 seconds (S2). Twenty mice were studied per group.

Exifone was tested at two doses (256 and 512 mg/kg) administered orally twice, 60 minutes before S1 and 60 minutes before S2, to animals which received scopolamine immediately after S1. Piracetam (800 mg/kg, PO), administered in the same conditions as exifone, was used as a reference compound. Two control groups were used: a non-amnesic control group which received only distilled water (before and after S1 and before S2) and an amnesic control group which received distilled water before S1 and S2 and an IP injection of scopolamine (10 mg/kg) immediately after S1.

Results were analysed for statistical significance using unpaired *t*-tests on either S1 or S2 latencies to cross from the lighted to the dark compartment.

RESULTS

Habituation of Exploratory Activity

Neither exifone (64, 128, 256 mg/kg IP) nor piracetam (512 mg/kg IP) exerted any direct effect on the number of steps climbed measured either 30 minutes (Fig. 1a) or 24 hours (Fig. 1b) after injection. In contrast, a clear and dose-dependent decrease in the number of steps climbed at S2 was observed in groups which had received exifone 30 minutes before S1. This difference from the control group was statistically significant (unpaired *t*-test on the S1-S2 difference scores) at 128 and 256 mg/kg. A similarly statistically significant decrease in the number of steps climbed at S2 was observed in the groups which had received piracetam (512 mg/kg IP) before S1. These results suggest therefore that both exifone and piracetam facilitated the habituation of exploratory activity as measured in this situation.

Scopolamine-Induced Amnesia in a Passive Avoidance Task

All animals showed a marked increase in S2 latencies indicating memory (Fig. 2). Control animals which received an IP injection of scopolamine (10 mg/kg) immediately after S1 (amnesic controls) showed a statistically significant decrease in S2 latencies compared with the non-amnesic controls indicating amnesia. Both exifone (512 mg/kg PO) and piracetam (800 mg/kg PO) significantly increased S2 latencies as compared with the amnesic control group indicating that both compounds at least partially antagonized the amnesia induced in these experimental conditions by scopolamine.

DISCUSSION

The results obtained with these two simple behavioral procedures suggest that both exifone and piracetam improve memory and attenuate experimental amnesia in a manner which could be expected with drugs proposed for improving cognitive function in senile patients. In the habituation task both compounds caused a greater decrease in exploratory activity between the first and second trials than was observed in the control group. In the passive avoidance task both compounds at least partially antagonized the amnesia-inducing effects of an injection of scopolamine administered immediately after the acquisition trial (S1). These effects occurred at doses which were without apparent effect on spontaneous activity as measured at S1 either by the number of steps climbed in the staircase apparatus or the step-through latencies in the passive avoidance task. As concerns the staircase test, the decreases in exploratory activity at S2 do not appear to be due to any long-term effects of the drugs either because no effects were observed when the compounds were administered 24 hours before placing the animals for the first time in the test situation. Furthermore, the partial antagonism of scopolamine-induced amnesia would not appear to be due to a simple pharmacological antagonism as neither compound appears to exert classical cholinergic activity [4,9], although piracetam has been reported to act synergistically with the acetylcholine precursor, choline, in facilitating memory function in rodents [7].

Like piracetam, exifone does not possess a marked profile in a standard battery of psychopharmacological tests [9]; it has no effects on spontaneous behaviour at doses well in excess of those employed in the present experiments and is devoid of activity in classical tests for neuroleptic, antidepressant, anxiolytic, anticonvulsant or anticholinergic activity. On the other hand it causes moderate decreases in the duration of immobility in the tail suspension test [12] and like some atypical antidepressants antagonizes the hypothermia induced by a low but not a high dose of apomorphine [10]. It exerts protective effects in several models of cerebral dysfunction [5,14] and antagonizes some of the central neurotransmitter changes induced in rats by intoxication with triethyl tin or transient global ischemia [13,15]. Other findings [2] suggest that exifone can act as a scavenger of free radicals which have been suggested to be an etiological factor in pathological aging. In general, however, the available findings do not as yet provide a clear indication of exifone's possible mechanism of action.

Nonetheless, the results obtained in the present experiments provide suggestive evidence that exifone can indeed facilitate memory function in simple rodent models in a manner consistent with its supposed effects in man.

REFERENCES

1. Allain, H., D. Milon, D. Pape, J. M. Reymann, D. Bentué-Ferrer, P. Bignol and J. Denmat. Assessment of exifone on Parkinsonian cognitive disorders. Proc Int Congr: Senile Dementia: Early Detection, Paris, October, 1986.

2. Bentué-Ferrer, D., V. Philouze, D. Pape, J. M. Reymann, H. Allain and J. van den Driessche. Comparative study of scavenger properties of exifone. Proc. NATO Congr.: Modification of Cell to Cell Signals During Normal and Pathological Aging, Salo, September, 1986.

3. Bentué-Ferrer, D., J. M. Reymann, H. Bagot, H. Allain and J. van den Driessche. Action de l'exifone sur les perturbations neurobiologiques induite par une ischémie cérébrale globale transitoire chez le rat. Proc Congr Pharmacol Franç, Rouen, May, 1986.
4. Gobert, J. G. Génèse d'un médicament: le piracétam, métabolisme et recherche biochimique. *J Pharmacol (Belg)* **27:** 281–304, 1972.
5. Hérold, M. Etudes pharmacologiques du PPP-17. Investigator's Report to Pharmascience, October, 1981.
6. Piette, F., S. Siboni, M. Favre-Berrone, C. Rainsard, V. Poulain, P. Rosen, C. Lapeyre and P. Berthaux. Effets de l'exifone sur les troubles mnésiques, le comportement et la dépendance de malades atteints de démence sénile de type Alzheimer. *Gériatrie,* in press, 1986.
7. Platel, A., M. Jalfre, C. Pawelec, S. Roux and R. D. Porsolt. Habituation of exploratory activity in mice: Effects of combinations of piracetam and choline on memory processes. *Pharmacol Biochem Behav* **21:** 209–212, 1984.
8. Platel, A. and R. D. Porsolt. Habituation of exploratory activity in mice: a screening test for memory enhancing drugs. *Psychopharmacology (Berlin)* **78:** 346–352, 1982.
9. Porsolt, R. D., A. Lenègre, I. Avril, L. Stéru and G. Doumont. Psychopharmacological profile of exifone (Adlone°), a new agent for the treatment of the cognitive deficiencies of old age. *Arzneimittelforsch,* in press, 1987.
10. Puech, A. J., R. Chermat, M. Poncelet, L. Doaré and P. Simon. Antagonism of hypothermia and behavioural response to apomorphine: a simple, rapid and discriminating test for screening antidepressants and neuroleptics. *Psychopharmacology (Berlin)* **75:** 84–91, 1981.
11. Schindler, U., D. K. Rush and S. Fielding. Nootropic drugs: animal models for studying effects on cognition. *Drug Dev Res* **4:** 567–576, 1984.
12. Stéru, L., R. Chermat, B. Thierry and P. Simon. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berlin)* **85:** 367–370, 1985.
13. Stéru, L., B. Thierry, R. Chermat, B. Millet, P. Simon and R. D. Porsolt. Comparing benzodiazepines using the staircase test in mice. *Psychopharmacology (Berlin),* in press, 1987.
14. Truchaud, M. PPP-17: étude comparative du pouvoir anti-anoxique. Investigator's Report to Pharmascience, April, 1979.
15. van den Driessche, J. Action de l'exifone sur les concentrations cérébrales en neurotransmetteurs aminergiques dans le cerveau de rats normaux ou de rats intoxiqués au chlorure de triethylétain. Investigator's report to Pharmascience, November, 1985.