Pharmacology Biochemistry and Behavior, Vol. 47, pp. 41–45, 1994
Printed in the U.S.A.

0091-3057/94 $6.00 + .00

Chronic L-Deprenyl or L-Amphetamine: Equal Cognitive Enhancement, Unequal MAO Inhibition

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Received 11 February 1993

GELOWITZ, D. L., J. S. RICHARDSON, T. B. WISHART, P. H. YU AND C.-T. LAI. *Chronic L-deprenyl or L-amphetamine: Equal cognitive enhancement, unequal MAO inhibition.* PHARMACOL BIOCHEM BEHAV **47**(1) 41–45, 1994.—The effect of chronic (4 month), subcutaneous injections of saline, L-deprenyl (0.25 mg/kg), or L-amphetamine (0.25 mg/kg) on the acquisition of a learned spatial habit in a modified Morris Water Maze was investigated in middle aged rats. Injections, given three times weekly starting at 6 months of age, were continued during behavioral testing, which occurred at 10 months of age. The cognitive performance of the middle aged rats was compared to that of 2-month-old control rats. Twenty-four hours after the last behavioral test, the rats were sacrificed and their brains were removed, dissected, and frozen in liquid nitrogen. The activities of MAO-A and MAO-B in the lateral cortex were determined. Results indicate that rats in the L-deprenyl group, the L-amphetamine group, and the young control group all learned the water maze task equally rapidly and significantly faster than rats in the saline group. MAO-A did not differ among the saline, amphetamine, and young control rats, but MAO-B was significantly higher in the middle aged saline and L-amphetamine rats than in the young controls. Both MAO-A and MAO-B activities were significantly lower in the L-deprenyl group than in the other three groups. This indicates that low-dose L-deprenyl can also inhibit MAO-A following chronic SC administration. Moreover, the improved cognitive performance produced by L-deprenyl may not be due to its ability to inhibit MAO-B, but rather to some other effect such as the activation of growth factors. It remains to be determined whether this mechanism is produced by, shared with, or independent from deprenyl's amphetamine metabolites.

L-Deprenyl L-Amphetamine Water maze Rats MAO-A MAO-B Monoamine oxidase Cognitive Aging Alzheimer's disease Parkinson's disease

ALTHOUGH deprenyl was originally developed as an antidepressant drug (15), in recent years L-deprenyl (also known as selegiline) has generated considerable interest as a drug that improves cognitive activity, that reduces the impairments associated with aging and with neurodegenerative diseases, and that may even add years onto life. Several studies have suggested that L-deprenyl, a selective, irreversible inhibitor of MAO-B (11), might retard the cognitive decline normally associated with Alzheimer's disease (5,7,10,21,23,31,36,42). In addition to the classic plaques and tangles and deficits in acetylcholine, autopsy brains from patients with Alzheimer's disease show reduced monoamine neurotransmitter levels and increased cerebral MAO-B activity (8,29,40). When the effects of L-deprenyl in Alzheimer's disease were thoroughly evaluated using a complete neuropsychological test battery, it was found that 10 mg/day of L-deprenyl significantly improved the cognitive function and reduced the behavioral alterations of Alzheimer's patients (20). L-Deprenyl has also been reported to improve conditioned avoidance learning (15) and cognitive performance in the Morris Water Maze (3) in rats over two years old. In addition to these effects on cognitive functions, L-deprenyl appears to slow the progression of the symptoms of Parkinson's disease in people (30,37) and to extend the life span of rats (16,22). These effects of L-deprenyl have been attributed to the inhibition of MAO-B, but they may reflect other mechanisms such as the activation of growth factors and the maintenance of neuronal integrity as recently observed following the administration of L-deprenyl to rats pretreated with the neurotoxin MPTP (43,44).

Since L-deprenyl is metabolized to L-amphetamine and methamphetamine (13,32,50,51), and since low doses of amphetamine and other psychostimulant drugs enhance cognitive performance (9,34,45,46), it could be argued that the cognitive and locomotor effects of L-deprenyl reflect the action of its

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amphetamine metabolites rather than its own MAO-B inhibition (6,26). The purpose of the present study was to compare the effects of chronic L-deprenyl with those of L-amphetamine on brain MAO activity and on the cognitive performance of middle aged rats in the Morris Water Maze Task. The Morris Water Maze (24) is commonly considered to be a measure of spatial learning, and has been used in the assessment of cognitive impairment following brain damage, in determining changes in cognitive activity accompanying aging, and in the screening of the effects of pharmacological compounds on learning and memory (47,48,49).

METHOD

Subjects

Twenty-four naive male Wistar rats (Charles River Canada, St. Constant, Quebec) served as subjects. Eighteen of the subjects were obtained when 4 months old and were tested at 10 months of age (middle aged groups). Six subjects were obtained when 40 days old, and were tested at 2 months of age (young control group). The rats were individually housed in standard galvanized steel mesh rat cages with free access to food (Purina Rat Chow) and tap water. Subjects were maintained on a 12-h light/dark cycle, and testing was conducted during the light portion of the cycle.

Apparatus

The acquisition of spatial memory was assessed with a circular, plastic pool, 150 cm in diameter and 30 cm in depth, with various coloured decals on the walls. The pool was located near the wall of a large test room, elevated 1 m above the floor on a wooden platform, and surrounded by many cues external to but visible from the pool which could be used by the rats for spatial localization. The pool was filled to a height of 22 cm with 21°C tap water made opaque by the addition of powdered skim milk. The pool contained a hidden plastic platform (10 cm in diameter) mounted on a solid column 1 cm below the surface of the water, such that the platform could not be seen from water level. The top surface of the platform was covered with thin wire mesh to enable the rats to gain a foothold for climbing up on it. The platform was placed in the same position for all trials, 38 cm from one side of the pool wall and 25 cm from the other. A chronograph stopwatch was used to measure the time taken by subjects to swim to the platform.

Procedure

Drug injections. The 18 older rats were randomly divided into 3 treatment groups (n = 6). The first group received physiological saline SC, the second 0.25 mg/kg L-amphetamine SC, and the third 0.25 mg/kg L-deprenyl SC. The drugs were dissolved in saline and mixed fresh on Mondays. All injections were 1 ml/kg and were given three times per week (Monday-Wednesday-Friday) for 17 consecutive weeks prior to testing. Drug injections continued during testing but were given at the completion of the test session. The choice of drug dosage and route of administration of L-deprenyl were based upon previous studies with aged rats (16,22). The L-amphetamine dosage, route of administration, and isomer were chosen to remain consistent with the L-deprenyl group. The remaining six animals (young controls) were placed into individual cages at 40 days of age and handled daily until day 56 when testing commenced for this group. L-Deprenyl was purchased from Research Biochemicals Inc. (Natick, MA), and L-amphetamine was generously supplied by Smith, Kline and French (Mississauga, Ontario, Canada) following approval by the regulatory agency of the Government of Canada.

Water task. Each subject was evaluated on the ability to learn a modified Morris Water Maze Task during 120-s trials. To begin each trial, the subject was randomly placed in one of three start locations facing the pool wall. If the location of the platform is taken to be at three o'clock within the circular pool, the start locations would be approximately 7:30, 9:00, and 10:30. After finding the platform, the subjects were allowed 30 s of rest on the platform. If a subject failed to find the platform within the 120-s trial, it was removed from the water and immediately placed on the platform for 30 s. The subject was then removed from the platform, towel-dried, and returned to its home cage. The intertrial interval on each test day was approximately 10 min. Based on a pilot study, the criterion for having learned the water maze was defined as the ability to locate and climb upon the hidden platform with all four feet within 8 s on four trials in a row. Ten trials per day were given to all subjects for five consecutive days, regardless of whether they met criteria before all 50 trials were complete.

Neurochemical evaluation. Twenty-four hours after the last test trial all subjects were sacrificed by decapitation. For each subject the brain was rapidly removed from the skull, and the lateral cortex was dissected, frozen in liquid nitrogen, and stored for subsequent assessment of MAO activity. A radioenzymatic method for measuring MAO using ^{14}C-labelled substrates was followed as previously described (52). To determine MAO-A activity, the tissue preparations were preincubated with the MAO-B inhibitor L-deprenyl (1×10^{-6} M) at room temperature for 20 min, and then incubated at 37°C for 30 min in the presence of the MAO-A substrate 5-hydroxytryptamine (5×10^{-4} M, 0.1 μCi) in a final volume of 200 μl. MAO-B activity was measured by preincubating the tissue preparations with the MAO-A inhibitor clorgyline (1×10^{-8} M) at room temperature for 20 min followed by incubation at 37°C for 30 min in the presence of the MAO-B substrate 2-phenylethylamine (1×10^{-5} M, 0.05 μCi) in a final volume of 200 μl. The reactions were terminated by adding 250 μl of 2 M citric acid. The ^{14}C-labelled aldehyde products were extracted into 1 ml toluene : ethyl acetate (1 : 1, v/v), of which 600 μl was then transferred to a counting vial containing 10 ml of Omnifluor cocktail (New England Nuclear, Boston). Radioactivity was measured in a Beckman 7500 scintillation counter.

Statistical analysis. Cognitive performance and MAO activities were compared using a single-factor analysis of variance (ANOVA) (α = 0.05) involving the four test groups (saline, L-amphetamine, L-deprenyl, and young controls), and pairwise comparisons were performed between specific groups using the Student Newman-Keuls procedure.

RESULTS

Maze Performance

The average number of trials required by the rats in each group to reach criterion are shown in Table 1. The ANOVA revealed a significant main effect among the four groups, $F(3, 218) = 4.1355$, $p = 0.01$. Newman-Keuls comparisons showed that, relative to rats in the saline group, rats in the L-amphetamine, the L-deprenyl, and the young control groups learned the task more quickly. However, there were

TABLE 1

EFFECTS OF CHRONIC SUBCUTANEOUS INJECTIONS OF L-AMPHETAMINE (0.25 mg/kg) OR L-DEPRENYL (0.25 mg/kg) ON SPATIAL LEARNING AND ACTIVITY OF MAO ISOZYMES

	Trials to Criterion	MAO-A Activity	MAO-B Activity
Saline Controls	19 ± 2.0	2.22 ± 0.03	0.30 ± 0.01*
L-Amphetamine	12 ± 2.1†	2.18 ± 0.5	0.26 ± 0.03‡
L-Deprenyl	11 ± 1.5†	1.50 ± 0.02§	0.03 ± 0.001*§
Young Controls	13 ± 0.8†	2.18 ± 0.04	0.18 ± 0.003

Learning criterion defined as all four feet on platform within 8 s, four trials in a row. Enzyme activity is nmol/mg protein/min. $n = 6$ in all groups. Data are presented as means ± standard error of the mean. *$p < .001$ compared to young controls. †$p < .05$ compared to saline controls. ‡$p < .05$ compared to young controls. §$p < .001$ compared to saline controls.

no significant differences among the L-amphetamine, L-deprenyl, and young control animals. In addition, no differences were noted among the rats on swimming patterns, nor were signs of drug dependency or overt drug action (e.g., stereotypy, excessive grooming, hyperactivity) observed during any aspect of this study.

MAO-A Levels

The ANOVA indicated a significant main effect among the groups, $F(3, 20) = 77.55$, $p < 0.001$, and subsequent Newman-Keuls multiple comparisons indicated that the L-deprenyl group had significantly lower MAO-A activity as compared to the saline, the L-amphetamine, and the young control groups (Table 1). These latter three groups did not differ from one another on MAO-A activity. Compared to saline, L-deprenyl produced to a 32% inhibition of MAO-A.

MAO-B Levels

The ANOVA revealed a significant main effect among the four groups, $F(3, 20) = 45.37$, $p < 0.001$. Newman-Keuls comparisons showed that the MAO-B activity in the L-deprenyl group was significantly lower than that in the saline, the L-amphetamine, and the young control groups (Table 1). MAO-B activity was significantly higher in the saline group (65%) and the L-amphetamine group (45%) than in the young control group (Table 1). Compared to saline, L-deprenyl produced a 90% inhibition of MAO-B.

DISCUSSION

The continuous administration of L-deprenyl to male rats starting at age 24 months has been reported to prolong the rats' life span, to restore their physical vigor and sexual activity (14,16,22), and to improve their cognitive performance in maze-learning tasks (3). L-Deprenyl also appears to potentiate the therapeutic effects of L-DOPA in patients with Parkinson's disease (1,2), to retard the progression of the symptoms of Parkinson's disease in newly diagnosed patients (19,27, 30,33,37), and to slow the cognitive decline in patients with probable Alzheimer's disease (20,40,41,42). The mechanisms responsible for these actions of L-deprenyl have not been established, but since MAO-B increases with aging in rats (38,39 and the present study) and in humans (28,29,35), and since L-deprenyl is well known to be a selective MAO-B inhibitor, some consequence of reduced MAO-B activity is usually invoked to explain these observations. The most common explanation involves the inhibition of dopamine deamination by MAO-B that leads to both an increase in intracellular dopamine levels and a reduction in the levels of destructive free radicals, such as hydrogen peroxide formed by MAO during the metabolism of dopamine and other catecholamines. In this way, L-deprenyl is thought to augment the activity of intact dopamine neurons and at the same time to reduce further neuronal impairment due to oxidative damage [see Jesberger and Richardson (12) for a review of free radicals in brain disorders].

Our results demonstrate that the cognitive-enhancing ability of L-deprenyl is matched by the cognitive-enhancing ability of L-amphetamine. In addition, low dose L-deprenyl given chronically inhibits both MAO-A and MAO-B. However, since chronic L-amphetamine did not alter the activity of either form of MAO, it would appear that MAO inhibition is not necessary for the cognitive enhancement or the protection against the aging-related decline in cognitive function such as that seen after chronic L-deprenyl. Moreover, the beneficial effects of chronic L-deprenyl or L-amphetamine on cognitive performance are not restricted to elderly rats near the end of their two to three year life span (16,22) but are also expressed in middle aged rats approaching the halfway point of their laboratory life expectancy.

The plasma half-life of L-deprenyl is very brief, 10 to 15 min, and during this time it binds irreversibly to MAO. At low doses, acute injections of L-deprenyl are selective for MAO-B, but at higher doses MAO-A is also inhibited (15,25). Our data indicate that low dose L-deprenyl given three times a week for four months also inhibits both MAO-A and MAO-B. In samples of lateral cortex, the activity in the L-deprenyl group of MAO-A was 68% and of MAO-B 10% of that in the saline group. This indicates that, while the predominant effect of chronic L-deprenyl is on MAO-B, MAO-A is also significantly reduced when L-deprenyl is given in low doses for prolonged periods.

One of the main metabolites of L-deprenyl is L-amphetamine (15), a compound that is considerably less active than its + isomer D-amphetamine (25). D-Amphetamine has a plasma clearance half-life of 10 to 30 h (18). Acute injections of D-amphetamine release noradrenaline and dopamine from nerve terminals and block the synaptic clearance of noradrenaline and dopamine by inhibiting their active reuptake (17).

At low doses, D-amphetamine acts as a mental, motor, and sympathetic nervous system stimulant, but at comparable doses L-amphetamine is inactive. However, tolerance rapidly develops to the stimulant effect of D-amphetamine (4), and during chronic administration, physical dependence develops to D-amphetamine but not to L-amphetamine (25). The activities of MAO-A and MAO-B in the rats in the L-amphetamine group were the same as those in rats in the saline control group. However, the rats given L-amphetamine learned the water maze as rapidly as did the rats in the L-deprenyl group. This indicates that chronic low dose L-amphetamine is as effective as chronic low dose L-deprenyl in enhancing the cognitive performance of rats and suggests that the inhibition of either MAO-A or MAO-B is not necessary for the expression of the cognitive enhancement.

Moreover, the aging-related elevation of MAO-B activity may not be involved in the cognitive decline associated with aging. We found that, compared to the young controls, MAO-B activity is significantly higher in both the middle aged saline and L-amphetamine groups. However, unlike the saline rats, the L-amphetamine rats learned the water maze at the same rate as the young rats. Thus, even though they had higher MAO-B levels, the cognitive ability of the middle aged L-amphetamine-treated rats was the same as that of the young rats. This suggests that elevated MAO-B activity is not responsible for the aging-related cognitive impairment. The discovery of the mechanism (or mechanisms) of the cognitive enhancement produced by L-deprenyl and L-amphetamine would have wide-ranging implications not only for the treatment of neurodegeneration disorders, but also for the understanding of learning and memory.

ACKNOWLEDGEMENTS

Supported in part by grant IIRG-91-092 from the Alzheimer's Association (USA) to J.S.R. and by grants from the Parkinson's Foundation of Canada and from Deprenyl Research, Ltd. to P.H.Y. The authors would like to thank I. MacDonald and E. Habbick for their stenographic expertise.

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