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Improvement of Cognitive Function by MAO-B Inhibitor L-Deprenyl in Aged Rats

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BRANDEIS, R., M. SAPIR, Y. KAPON, G. BORELLI, S. CADEL AND B. VALSECCHI. *Improvement of cognitive function by MAO-B inhibitor L-deprenyl in aged rats.* PHARMACOL BIOCHEM BEHAV **39**(2) 297–304, 1991.—This study evaluated the ability of the selective MAO-B inhibitor, L-deprenyl, to reverse cognitive impairments appearing in aged rats, using the reference memory, Morris Water Maze paradigm. L-Deprenyl significantly improved learning and memory deficits associated with old age in doses of 1.25 and 5 mg/kg PO (escape latency measure) and doses of 1.25, 2.5 and 5 mg/kg PO (path length measure). L-Deprenyl also improved reversal learning impairments in doses of 1.25, 2.5 and 5 mg/kg PO, as expressed by the escape latency measure. The data suggest that L-deprenyl possesses potential cognitive enhancement abilities probably due to an increase in dopaminergic activity.

Aging MAO-B inhibitor L-Deprenyl Morris Water Maze

THE decline in cognitive functions is a fundamental aspect of cerebral aging (40). Furthermore, at present, it is very difficult to distinguish between the deterioration of mental functions, especially memory disorders, due to normal aging and mental impairment due to dementia-type illnesses (20).

Brain aging is caused and/or accompanied by a loss of neurones, with concomitant gliosis (23). The temporal lobe and the hippocampus are the areas most strongly affected by increased plaques and tangle formation in Alzheimer's disease (AD) and in senile dementia of the Alzheimer type (SDAT), but considerable senile changes in the hippocampus are also found in elderly nondemented subjects (56).

It has been proposed that the background of impaired adaptability associated with aging involves functional changes in neurotransmission both in humans and animals. In general, a reduction in the levels of cholinergic (6) and catecholaminergic (2) markers had been found. These changes might affect other neuronal processes, inducing a decrease in dopamine turnover and dopamine uptake (24), as well as an imbalance between unchanged monoamine oxidase type A (MAO-A) and increased monoamine oxidase type B (MAO-B) activity (14).

Brain MAO-B activity increases with age in humans and in rats (19). This seems to be a general phenomenon in all brain regions (nigrostriatal and limbic regions with comparatively rapid rates of increase) with the possible exception of the brainstem (14,50). In contrast, MAO-A activity seems to be independent of age (25). A greater increase in MAO-B activity than expected from age has been found in brains from patients with AD (with an especially significant increase in the hippocampus and cortex gyrus cinguli) (1, 39, 42).

It has been suggested that an elevation of MAO-B levels per se might account for some symptoms of senescence (28) as well as for AD (54). A vast body of animal data suggests a role for noradrenaline and dopamine in cognitive functions (4, 43, 47, 48, 58). The results of treatment of cognitive deficits in humans using L-dopa (12,33) or memantine (a neurotropic drug with indirect dopaminergic effect) (3) also support this idea. However, there is still a need for evidence concerning the relationship between central MAO-B activity and cognitive deficits in aging and AD.

Deprenyl (L-deprenyl, Selegiline) selectively and irreversibly inhibits MAO-B (17). Being relatively free from side effects, the compound has enjoyed widespread clinical use for several years as an adjunct to L-dopa in the treatment of Parkinson's disease (37), and it has also been proposed as prophylactic therapy in this disease (17). Deprenyl has been known for many years as a MAO-I antidepressant (17), although its clinical antidepressant efficacy is disputed and may also vary as a function of dose (31, 37, 45).

Recently, preliminary data have suggested that deprenyl may have some beneficial effects in AD (55). The behavioral changes were associated with improvement in performance on an episodic memory and learning task requiring complex information processing and sustained conscious effort. In animals, a short treatment with L-deprenyl caused positive effects in the "Behavioral Despair" test in mice (15), while a longer deprenyl treatment restored full-scale sexual activity in old rats as well as significantly increasing their lifespans (29). However, there is a lack of evidence about the possible cognitive effects of L-deprenyl in old as well as in young animals and humans.

In view of the above data, the present study examined the effects of deprenyl by oral route, at dose levels in the range of those that selectively inhibit MAO-B (15), on cognitive functions, specifically spatial learning. Old and young rats had been tested in the Morris Water Maze (MWM) task, which is considered a useful behavioral test for detecting lesions, age- and drug-related cognitive changes (7–11, 16, 21, 30, 32, 36, 41, 52, 53, 58, 60). The paradigm used in our study assesses spatial

learning abilities in a reference memory (RM) regimen (21, 22, 34, 35).

METHOD

Subjects

Old male Sprague-Dawley rats (24–25 months old, weighing about 520 g), obtained from Charles River Breeding Laboratories, UK, were housed two per cage, in a temperature-controlled environment (22 ± 21°C) with a 12-h normal light/dark cycle. Young male Sprague-Dawley rats (3 months old, weighing about 260 g) were housed under the same conditions. The rats had ad lib access to food and drinking water. Behavioral testing was carried out between 0800 and 1300 h, five days a week.

Behavioral Test

Drug administration. Each of the young and old groups of rats were randomly subdivided into 5 treatment subgroups (n = 9). Subgroups 1–4 were treated with L-deprenyl (Selegiline, supplied by Chiesi Farmaceutici s.p.a.) in doses of 1.25, 2.5, 5 and 10 mg/kg PO in a volume of 10 ml/kg, while subgroup 5 (control group) was treated with the solvent, double distilled water (DDW).

L-Deprenyl and DDW were administered once a day for 5 days before starting the behavioral testing, and then for the duration of the 5-day experiment, 60 minutes before testing.

Apparatus. Rats were tested in a circular metal water maze (diameter: 1.4 m, height 50 cm), which was painted white and was filled to a height of 25 cm with water (26 ± 1°C) in which powdered milk was dissolved. A white metal platform (12 × 12 cm) covered by wire mesh was present inside the pool; its top surface was 20 mm below the surface of the water; thus the platform was invisible to a viewer inside the pool.

The pool surface was divided into 4 quadrants of equal area, NE, NW, SE and SW. The platform was placed midway between the center and rim of the pool in any of the 4 quadrants. The maze was brightly lit and surrounded by well-lit, salient objects, which were held constant throughout training. Performance in the maze was monitored by a tracking system consisting of an overhead video camera linked to a TV monitor and an image analyzer (CIS-2) coupled to a microcomputer (8-MZHz IBM AT) (system designed and produced by Galai Laboratories, Ltd., Migdal Ha-Emek).

Procedure

Habituation. Rats were placed in the pool with no platform for a one-minute habituation trial 72 h prior to the start of training.

Training. Each rat was trained for four consecutive days, four trials (one block) per day, in which the platform position remained constant and was located in the center of the southeast quadrant of the pool. Within each block of four trials, each rat started at each of the starting locations, but the sequence of locations was randomly selected. A trial consisted of placing a rat by hand into the water facing the wall of the pool at one of four starting locations, north, south, east or west, around the pool's perimeter. Prior to training, the rat was placed on the platform for 60 s. If, on a particular trial, a rat found the platform, it was permitted to remain on it for 60 s. A trial was terminated after 120 s if a rat failed to find the platform, and the rat was placed on the platform for 60 more s before starting the next trial. Escape latency (the time to find the platform), path length (the distance travelled by the rat) and speed (the swimming rate of the rat) were recorded on each trial by the monitoring system.

Transfer test. During trial No. 17, on the fifth day, the platform was entirely removed from the pool (a probe trial). In this trial, the rat was placed into the water for a limited period (60 s), and its spatial bias was measured by recording the relative distribution of escape latency and path length over the four quadrants of the pool.

Reversal test. During trials 18–21, on the fifth day, the platform position was changed to the northwest quadrant, opposite to the training quadrant. Thus, during reversal learning, the platform location was moved relative to the configuration of objects within the room, but the pool occupied the same place within the room throughout the entire experiment. Testing of the rats and measures taken were the same as in training.

Side effects. During the 10 days of drug administration, the animals were observed for diarrhea (degrees ranging from slight to moderate or severe) and altered motor activity.

RESULTS

Training

For each rat, the escape latency, path length and swimming speed of the 4 trials in each of the 4 training days were grouped into blocks (one block for each day).

The escape latency, path length and swimming speed scores were analyzed by a 3-way ANOVA ($2 \times 5 \times 4$) with one repeated variable (days) and two nonrepeated variables (age—old/young, and treatment—various doses of L-deprenyl). Specific comparisons were performed, using the simple main effects contrasts analysis (59), which is specifically suited for testing significant interactions when some of the variables involved are of repeated measurement type.

Escape latency. Old rats showed significantly longer escape latencies (indicating a worse RM performance) than young rats, $F(1,80) = 54.72$, $p < 0.001$. L-Deprenyl treatment positively affected old rats' training performance, $F(4,80) = 5.26$, $p < 0.005$. Specifically, the doses of 1.25 and 5 mg/kg improved the old rats' escape latencies ($p < 0.02$ and $p < 0.01$, respectively, by a simple main effects contrasts analysis), while the dose of 10 mg/kg had no significant effect on this measure. The 2.5-mg/kg dose had a slightly improving effect on the old rats' performance, albeit statistically nonsignificant. L-Deprenyl did not significantly affect the young rats' escape latencies during training. Figure 1 presents the dose-response curve of the escape latencies of old and young rats across days.

The results also indicated a significant general effect of training, $F(3,240) = 44.97$, $p < 0.001$; the escape latencies of all groups significantly decreased between the first and the second days as well as between the third and the fourth days of training. Furthermore, the escape latencies of old rats treated with 1.25 and 5 mg/kg were significantly shorter than those of old rats treated with water, beginning from the second day of training. Old rats treated with 2.5 mg/kg showed a similar decrease on the second and fourth days of training only, $F(12,240) = 2.80$, $p < 0.005$. Old rats treated with the dose of 10 mg/kg did not show a different training curve compared with old rats treated with water. There were no significant differences between the training curves of the various groups of young rats.

In part of the trials, some of the rats were not able to locate the platform within the allotted time period and therefore had to be manually placed on the platform. The number of these "non-

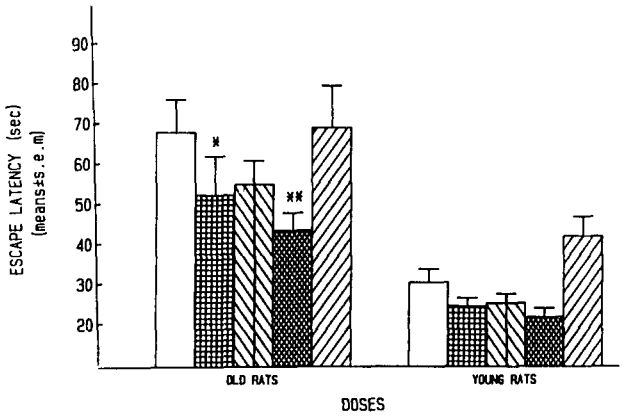

FIG. 1. Dose-response curve of old and young rats treated with L-deprenyl—Escape latency during training. Open bars: DDW; checked bars: 1.25 mg/kg; hatched bars with solid line: 2.5 mg/kg; cross-hatched bars: 5 mg/kg; hatched bars: 10 mg/kg. *$p<0.02$, **$p<0.01$ compared to DDW treatment.

arrivals" was computed for each rat and transformed into percentages (out of 20 trials during training and reversal learning). These scores were analyzed by a 2-way ANOVA (2×5) with two variables (age—old/young, and treatment—various doses of L-deprenyl). Specific comparisons were performed using the simple main effects contrasts analysis (59).

The percent of "nonarrivals" was significantly greater for old rats ($24.88\pm7.82\%$) than for young rats ($4.11\pm2.12\%$), $F(1,80)=41.37$, $p<0.001$. Furthermore, an interaction between age and treatment was found, $F(4,80)=3.65$, $p<0.01$. The percentages of "nonarrivals" for old rats treated with 1.25 mg/kg ($17.22\pm7.29\%$), 2.5 mg ($18\pm4.70\%$) and 5 mg/kg ($14.44\pm3.06\%$) of L-deprenyl were significantly smaller ($p<0.001$) than that of old rats treated with water ($36.11\pm7.17\%$) or old rats treated with the dose of 10 mg/kg ($37.77\pm10.49\%$). The last two groups did not differ from each other. No significant differences were found between the percentages of "nonarrivals" in any of the groups of young rats.

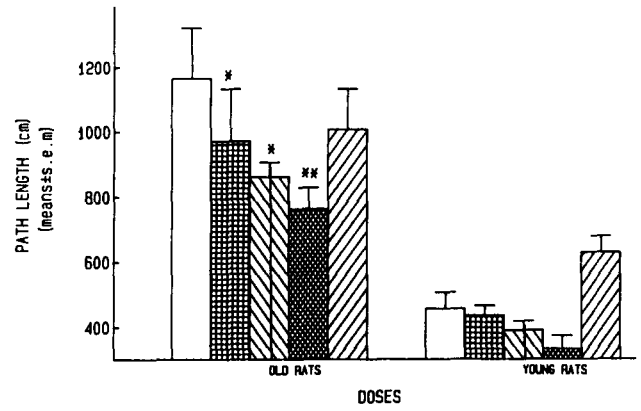

FIG. 2. Dose-response curve of old and young rats treated with L-deprenyl—Path length during training. Open bars: DDW; checked bars: 1.25 mg/kg; hatched bars with solid line: 2.5 mg/kg; cross-hatched bars: 5 mg/kg; hatched bars: 10 mg/kg. *$p<0.02$, **$p<0.01$ compared to DDW treatment.

Path length. Old rats showed significantly longer path lengths (indicating a worse RM performance) than young rats, $F(1,80)=79.94$, $p<0.001$. L-Deprenyl treatment positively affected old rats' training performance, $F(4,80)=3.81$, $p<0.01$. Specifically, the doses of 1.25, 2.5 and 5 mg/kg improved the old rats' path lengths ($p<0.02$, $p<0.02$ and $p<0.01$, respectively, by a simple main effects contrasts analysis), while the dose of 10 mg/kg had no significant effect on this measure. L-Deprenyl did not significantly affect the young rats' path lengths during training. Figure 2 presents the dose-response curve of the path lengths of old and young rats across days.

The results also indicate a significant general effect of training, $F(3,240)=30.44$, $p<0.001$; the path lengths of all groups significantly decreased between the first and the second days as well as between the third and the fourth days of training. Furthermore, the path lengths of old rats treated with 1.25, 2.5 and 5 mg/kg were significantly shorter than those of old rats treated with water, beginning from the second day of training, $F(12,240)=2.55$, $p<0.005$. Old rats treated with the dose of 10 mg/kg did not show different training curves compared to old rats treated with water. There were no significant differences between the training curves of the various groups of young rats.

A characteristic computer depiction of the paths travelled by old and young rats treated with L-deprenyl or DDW is illustrated in Fig. 3.

Swimming speed. Old rats showed significantly higher swimming speeds than young rats, $F(1,80)=44.51$, $p<0.001$. L-Deprenyl treatment had no significant effect on the old rats' swimming speeds. However, the drug affected the young rats' motor activity, $F(4,80)=5.34$, $p<0.001$. Specifically, only the dose of 1.25 mg/kg enhanced the young rats' swimming speeds ($p<0.001$, by a simple main effects contrasts analysis). Figure 4 presents the dose-response curve of the swimming speeds of old and young rats across days.

The results also indicate a significant general effect of training, $F(3,240)=7.96$, $p<0.001$; the swimming speeds of all groups significantly increased between the first and the second days of training and remained stable thereon. No significant differences between the training curves of the various groups were found, except for the young rats treated with the dose of 1.25 mg/kg whose swimming speeds were higher than those of the other young groups during all days of training.

Transfer Trial

The escape latency and path length measures for the transfer trial (trial No. 17) were analyzed by a 3-way ANOVA ($2\times5\times4$) with one repeated variable (quadrant in the pool) and two nonrepeated variables (age—old/young, and treatment—various doses of L-deprenyl).

Neither age nor the administration of L-deprenyl had any consistent effect on the relative distribution of escape latency or path length over the four quadrants of the pool.

Reversal Test

For each rat, the escape latency, path length and swimming speed of the reversal test (trials No. 18–21) were grouped into one block. All three measures were analyzed by a 2-way ANOVA (2×5) with two variables (age—old/young, and treatment—various doses of L-deprenyl). Specific comparisons were performed using the simple main effects contrasts analysis (59).

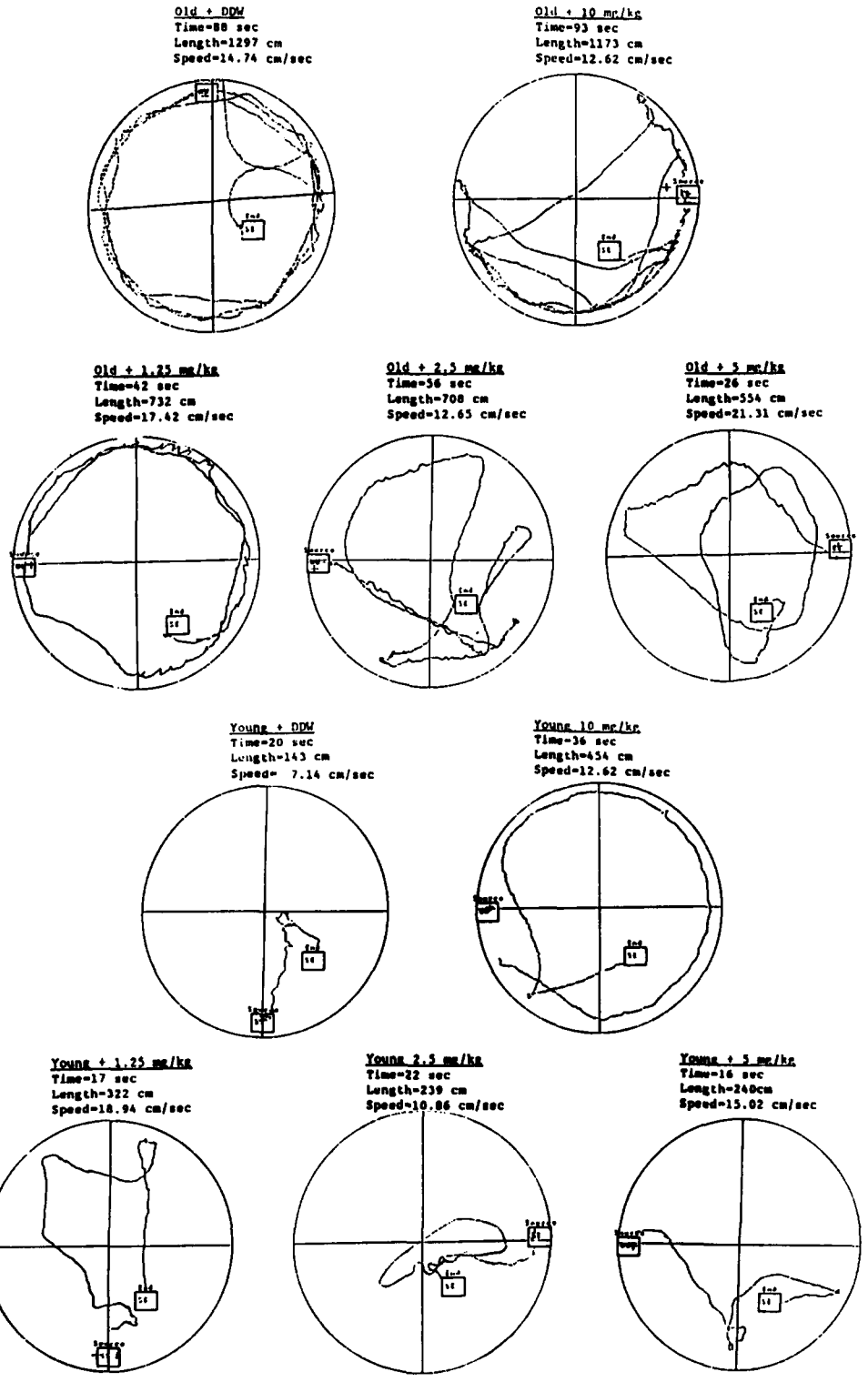

FIG. 3. A characteristic computer depiction of the path travelled by old and young rats treated with L-deprenyl or DDW.

Escape latency. Old rats showed significantly longer escape latencies during reversal learning than young rats, $F(1,80) = 20.68$, $p<0.001$ (Fig. 5).

L-Deprenyl treatment positively affected the old rats' reversal learning, $F(4,80) = 2.67$, $p<0.05$. Specifically, the doses of 1.25, 2.5 and 5 mg/kg improved the old rats' escape latencies

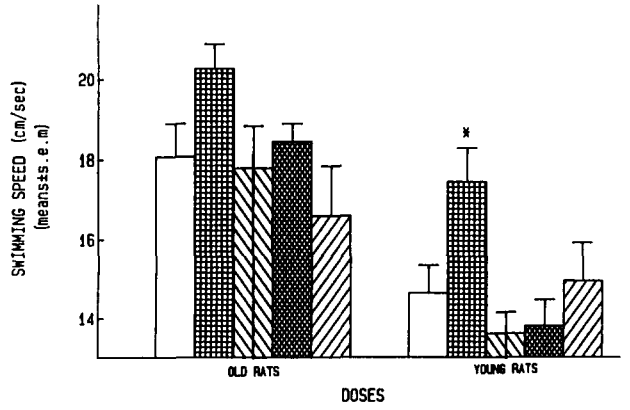

FIG. 4. Dose-response curve of old and young rats treated with L-deprenyl—Swimming speed during training. Open bars: DDW; checked bars: 1.25 mg/kg; hatched bars with solid line: 2.5 mg/kg; cross-hatched bars; 5 mg/kg; hatched bars: 10 mg/kg. *$p<0.001$ compared to DDW treatment.

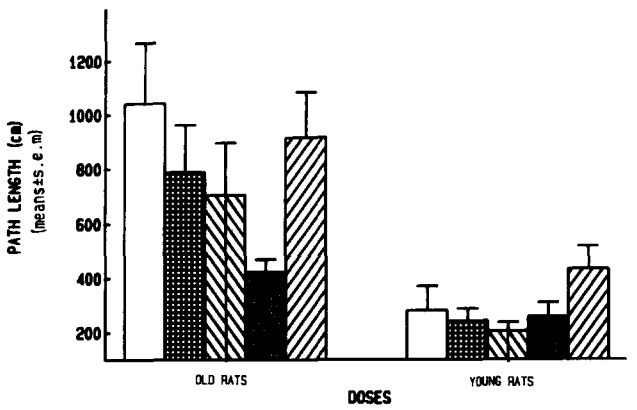

FIG. 6. Dose-response curve of old and young rats treated by L-deprenyl—Path length during reversal test. Open bars: DDW; hatched bars with solid line: 1.25 mg/kg; checked bars: 2.5 mg/kg; cross-hatched bars: 5 mg/kg; hatched bars: 10 mg/kg.

($p<0.01$, $p<0.01$ and $p<0.001$, respectively, by a simple main effects contrasts analysis), while the dose of 10 mg/kg had no significant effect on this measure. L-Deprenyl had no significant effect on the young rats' escape latencies during reversal learning.

Path length. Old rats showed significantly longer paths during reversal learning than young rats, $F(1,80)=35.91$, $p<0.001$ (Fig. 6). L-Deprenyl had no significant effect on the rats' path lengths except for a nonsignificant improvement obtained by the old rats treated with a dose of 5 mg/kg.

Swimming speed. Old rats showed significantly higher swimming speeds than young rats, $F(1,80)=104.93$, $p<0.001$ (Fig. 7). L-Deprenyl had no significant effect on the rats' motor activity during reversal learning.

Side Effects

Old rats. Only two of the 5-mg/kg-treated old rats exhibited moderate diarrhea, which started following the seventh day of drug administration. Nine of the 10-mg/kg-treated old rats exhibited severe diarrhea, which started following the eighth day of drug administration. These animals showed considerable hyperactivity and restlessness.

On the whole, old rats significantly lost weight during the treatment period. The weight loss was on the third day of drug administration, marginally greater with the doses of 2.5, 5 and 10 mg/kg as compared to DDW-treated animals (3.5–4 vs. 2%; $p<0.05$). On day 5 of treatment, significant differences in comparison with DDW-treated rats were observed only at the dose of 10 mg/kg (5.5 vs. 4%, respectively; $p<0.05$). Later on, no significant changes in weight were observed compared to DDW-treated old rats.

Young rats. Most of the young rats treated with the dose of 10 mg/kg exhibited severe diarrhea, which started following the sixth day of drug administration, together with considerable hyperactivity, which was observed following the eighth day of drug administration.

Young rats gained weight during the treatment period. The weight gain was on the fifth day of treatment, with the dose of 2.5 mg/kg marginally greater than that in DDW-treated animals

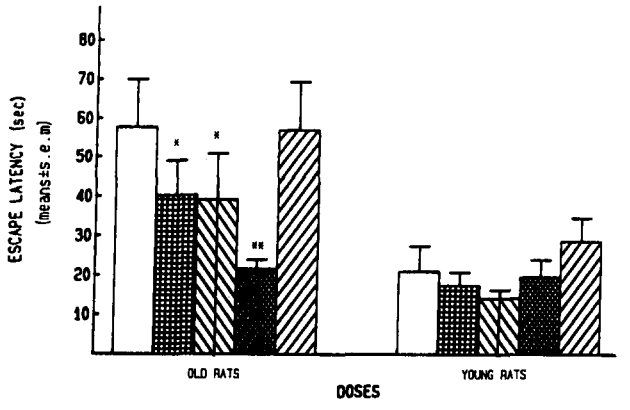

FIG. 5. Dose-response curve of old and young rats treated with L-deprenyl—Escape latency during reversal test. Open bars: DDW; checked bars: 1.25 mg/kg; hatched bars with solid line: 2.5 mg/kg; cross-hatched bars: 5 mg/kg; hatched bars: 10 mg/kg. *$p<0.01$; **$p<0.001$ compared to DDW treatment.

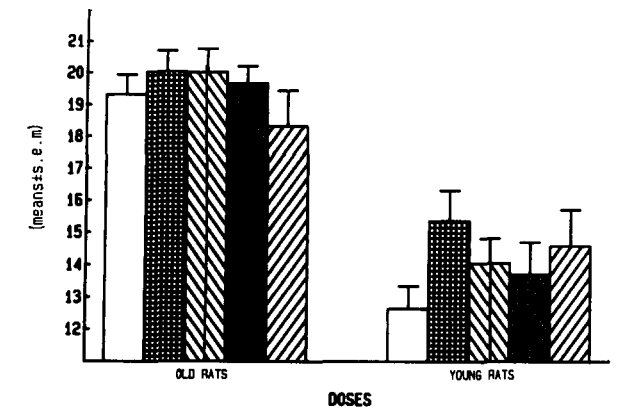

FIG. 7. Dose-response curve of old and young rats treated with L-deprenyl—Swimming speed during reversal test. Open bars: DDW; hatched bars with solid line: 1.25 mg/kg; checked bars: 2.5 mg/kg; cross-hatched bars: 5 mg/kg; hatched bars: 10 mg/kg.

(about 13 vs. 10.5%; $p<0.01$). Later on, the doses of 2.5 and 10 mg/kg caused a gain in weight of about 5.5–6.5% compared to 3% observed in the DDW-treated young rats.

DISCUSSION

Aging often produces impairments in cognitive functions (57). Memory is the function that suffers most both in animals and humans (5, 6, 40). These impaired populations are obviously in quest of therapeutic interventions.

Old rats demonstrated in our study a clear impairment in learning and memory abilities. L-Deprenyl significantly reversed these impairments, both during acquisition and reversal learning periods, as shown by both measures of the MWM task: escape latency and path length.

A significant improvement of the age-induced cognitive deficits during training was demonstrated equally well using doses of 1.25 and 5 mg/kg (escape latency measure) and doses of 1.25, 2.5 and 5 mg/kg (path length measure). The higher dose of 10 mg/kg had no significant effect on learning and memory ability of old rats. The measure of percentage of "nonarrivals" showed a similar picture. A significant improvement of the age-induced cognitive impairments was demonstrated for the three lower doses of L-deprenyl. No such effect was demonstrated for the higher dose.

The deterioration in reversal learning, associated with old age, was also improved significantly by the administration of L-deprenyl. Reversal learning is an expression of the ability to shift strategies to task demands (49). The effect of L-deprenyl was, however, expressed only in the escape latency measure, following treatment by doses of 1.25, 2.5 and 5 mg/kg. Since the path length measure did not clearly reflect this result, the potential effect of L-deprenyl on this ability, a function that is impaired both in aged rats and in AD, should be considered cautiously.

L-Deprenyl had no significant effect on the old rats' swimming ability both during acquisition and reversal learning; therefore, the beneficial effects of this drug on learning and memory could not be attributed to nonspecific, motor coordination effects.

One of our findings that needs to be explained is that old rats showed surprisingly significantly higher swimming speeds than young rats, both during training and the reversal test. Nevertheless, old rats were still deficient compared to young rats in their cognitive ability, as was illustrated by their longer escape latencies and swimming paths. A possible explanation is that old rats were more stressed than young rats thus engaged in redundant swimming movements, although the MWM task is relatively untraumatic when compared with other means that have been adopted to motivate learning in aged rats, such as food deprivation or foot shocks (7, 16, 35).

Many cognitive enhancers have been investigated for their potential use in aged and AD patients. Recent research has centered on the cholinergic neurotransmitter system which is probably most closely related to learning and memory. However, it has been shown that other important neurotransmitters also degenerate with aging (2, 19, 46, 56), among them, the dopaminergic system. The nigrostriatal dopaminergic neurones were recently even claimed to be the most rapidly aging neurones in the brain (29). Moreover, structural and functional disturbances of catecholamine and indoleamine systems have been reported to occur also in AD (19,44).

Since cholinergic agonists have shown only partial behavioral and cognitive improvement, in AD patients, pharmacologic strategies designed to improve the impaired function of other neurotransmitter systems in aging and AD are in order.

As far as we now know, cognitive effects have hardly been reported in detail with L-deprenyl administration in both animals and humans (54). It seems that, in addition to improving mood and motor symptoms in Parkinson's disease (13), inducing "psychic energizing effect" in mixed psychiatric populations (54), and restoring lost sexual vigour of aged male rats and extending their lifespans (29), L-deprenyl might be seriously considered as a cognitive enhancer as well. Our results support the idea that the catecholaminergic system plays a decisive role in the activation of the CNS and that it seems to be reasonable to develop new compounds that activate, in the long run, the limbic dopaminergic system, thus protecting it from aging (29).

Aging entails a complex variety of biological changes, including some at the neuronal level involving impairment of intra- and interneuronal functions. An age-dependent increase in MAO-B activity, compared to MAO-A's, has been shown in many studies (14, 19, 39, 50, 51, 54). It has been suggested that an increased population of nonneuronal mitochondrial cells may account for this increase (42) because: 1) aging is accompanied by a loss of neurons, with a possible increase in the amount of glial tissue; and 2) it has been shown that, in rats, MAO-B is predominantly localized extraneuronally (25, 42, 51). Therefore, deprenyl, a selective blocker of MAO-B, might act by inhibiting glial MAO-B (27,29). This hypothesis was strengthened by data that show that there is an increase of DA level when deprenyl is given to animals, whereas DOPAC, the assumed main metabolite of DA within DA neurons, remains unchanged (27). This increase in DA level might account for the improvement of the age-induced cognitive deficits shown in our study. However, the situation has been claimed to be different in the human brain; there are several strands of evidence suggesting that MAO-B is localized both intraneuronally and extraneuronally in the human brain (38, 42, 45). On the basis of this finding, it has been assumed (42) that deprenyl blocks intraneuronal MAO-B, in this way improving DA neurotransmission, and that the extraneuronal blockade facilitates the hormonal action of DA. Whether acting extra- or intraneuronally, MAO-B has been hypothesized to serve a modulatory function in monoamine neurotransmission. In this case of L-deprenyl administration, MAO-B inhibition might selectively result in improved modulation of residual monoaminergic neurotransmission, leading to amelioration of those symptoms related to the reversible impairment of monoaminergic function, including cognitive changes. It could be expected that the effects of deprenyl will be much more pronounced in human patients, since in the human brain MAO-B is responsible for the oxidation of a higher percentage of DA than in the rat brain (38).

To summarize, L-deprenyl, a selective MAO-B inhibitor, has been shown to improve performance of aged rats in a spatial reference memory task. Its neuropsychological effects have varied in a generally dose-dependent fashion, with enhancing effects at the lower doses and an absence of any effect at the higher dose tested. The drug did not induce any drastic changes in the animals' weights nor did it cause any observed side effects at the doses which were found to enhance cognitive processes. These results, concerning the safeness of the drug, are in agreement with other studies (17, 26, 29) which emphasize that a cardinal virtue of deprenyl is its relative freedom from side effects. The structural and functional disturbances of the catecholamine system, together with the elevated levels of MAO-B in the brains of older subjects and particularly in AD patients, suggest that a MAO-B inhibitor be considered for treating symptoms of senescence. The unique activity of L-deprenyl in reversing learning and memory loss associated with aging along a fairly wide therapeutic range, together with a good safety margin, support this approach.

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