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The pharmacology of selegiline ((-)deprenyl). New aspects

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ABSTRACT — Male rats were treated from the end of their 2nd year of life either with saline (1 ml/kg, s.c.) (n=66) or with deprenyl (0,25 mg/kg, s.c.) (n=66) three times a week until death. Whereas none of the two-year-old saline-treated rats displayed full scale sexual activity, this appeared in 64 out of 66 rats on deprenyl. The longest living rat in the saline-treated group lived 164 weeks. The average lifespan of the group was 147.05 ± 0.56 weeks. The shortest living animal in the (-)deprenyl-treated group lived 171 weeks and the longest living rat died during the 226th week of its life. The average lifespan was 191.91 ± 2.31 weeks. This is the first instance that a well-aimed medication prolonged lifespan of members of a species beyond their maximum age of death (182 weeks in the rat). A close relation between sexual activity and lifespan was detected.

Male rats (n=94) selected from an 8-month old population as sexually inactive ones were found to be miserable learners. This group was treated either with saline (1ml/kg, s.c.) (n=46) or with (-)deprenyl (0.25 mg/kg, s.c.) (n=48) three times a week for 36 weeks. Their performance in the shuttle box during 5 consecutive days was tested before and after treatment. The total number of conditioned avoidance responses (CAR) which remained unchanged in the saline-treated group (6.53 ± 1.41 before and 5.98 ± 1.15 after treatment) increased from 5.57 ± 0.65 to 20.73 ± 1.39 ($p < 0.001$) in the (-)deprenyl-treated group of rats. (-)Deprenyl-treatment (0.25-2 mg/kg, s.c., daily for 21 days) increased superoxide dismutase (SOD) activity in the striatum of CFY rats, whereas clorgyline-treatment (0.1—1 mg/kg) inhibited it.

Introduction

Parkinson's disease (PD) is still the only prevalent neurological illness the biological pathology of which seems to be firmly established by now: *the nigrostriatal dopaminergic machinery breaks down.*

PD is an age-related illness of unknown origin. Its onset is extremely rare in the first decades of life and about 0.1 % of the population develops the disease over 40 years. The prevalence increases sharply with age.

The dopamine substitution therapy of today (continuous administration of levodopa) supplemented with sophisticated adjuvants (peripheral decarboxylase inhibitors, selective inhibition of B-type MAO by (-)deprenyl) and enriched with postsynaptic dopamine receptor stimulants, makes life more tolerable for the patients, but because of the irreversible changes in the striatal dopaminergic system, the illness is still incurable. Prevention seems to remain the only solution.

To summarize new pharmacological data which further support the proposal that life-long administration of 2—3 tablets of (-)deprenyl weekly from the 5th decade of life may decrease the incidence of PD, is the aim of this paper.

The concept that the essence of PD is the premature rapid aging of the nigrostriatal dopaminergic neurons

The dopamine content of the human caudate nucleus decreases by 13 % per decade over 45 (1); dopamine itself is to a high degree of probability the culpable substance (2). The complex autooxidation of the high amounts of dopa and dopamine in the striatum, continuously generating substantial quantities of toxic free radicals and highly reactive quinones, creates a permanent danger for the nigrostriatal dopaminergic neurons, which have to mobilize their natural defensive measures to protect themselves from the deleterious effect of these toxic byproducts. Neuromelanin, which is generated via the polymerization of oxidative metabolites of dopamine with the evident aim of finally depositing waste products, is in the substantia nigra the visible sign of the successful self-defense of the neurons against the free radicals and quinones originating from dopamine metabolism. The sluggish depositing of neuromelanin in the human substantia nigra (3) is in excellent agreement with this view.

Table I illustrates the age-related changes in the physiological function of the human striatum. We know that parkinsonian symptoms appear if the dopamine content of the caudate sinks below 30 % of the normal level. Thus it is understandable that during the normal average life span the age-related decay of the striatal dopaminergic system does not lead to parkinsonian symptoms.

As in PD the dopamine content of the striatum decreases rapidly below the critical level, what essentially happens in this illness is a dramatic dissociation between the chronological and the physiological age of the striatum. A 65 year old parkinsonian is usually living with a striatum of a physiological age of 115 years. It is striking that the low level of dopamine (less than 10 %) characteristically found in the striatum of parkinsonian patients post mortem is theoretically reached in a normal aging brain at the maximum age of death of the human race (see Table I).

Starting from the assumption that PD is a premature rapid aging of the striatal dopaminergic system, of unknown origin, and considering that the natural aging process of the nigrostriatal dopaminergic neuron is in all probability due to specific endogenous neurotoxins originating from dopamine, it seems reasonable to develop drugs which will provide protection against the self-produced neurotoxins and slow down the age-related changes in the striatum. The understanding of the physiological aging process of the nigrostriatal dopaminergic neuron and an efficient, safe chemical strategy to counter this process, may be helpful to decrease the incidence of PD.

This paper is devoted to demonstrate, by the aid of a rat model, that long-term continuous administration of small doses of (-)deprenyl counters the age-related decay of the nigrostriatal dopaminergic neurons in a dramatic manner.

Table I. Illustration of the age-related changes in the physiological function of the human striatum

Chronological age	Physiological status of the striatal function in %
45	100
55	87
65	74
75	61
85	48
95	35 (Critical threshold)
105	22
115	9 TLS^h

The calculation is based on the fact that the average loss of dopamine per decade in the human caudate over age 45 amounts 13% (1).

Critical threshold: Parkinsonian symptoms appear if the dopamine content sinks below 30% of the normal level.

TLS^h: Technical life span, i.e. maximum age of death in humans (115 years).

(-)Deprenyl, the drug which protects the striatal dopaminergic system from aging with utmost selectivity

We developed (-)deprenyl in 1964—65 (4), and proved that in striking contrast to the known MAO inhibitors, which potentiate the effect of tyramine, this substance inhibits it; thus it is free of the main side effect ('cheese effect') of MAO inhibitors (5). We demonstrated in 1971 that this compound is a highly selective inhibitor of B-type monoamine oxidase (MAO) (6). This was the first described selective inhibitor of B-type MAO, still

serves as the reference substance for this purpose, and is the only drug of this type in clinical use.

(-)Deprenyl is a safe substance, which, when administered for long periods in very small doses, facilitates the activity of the nigrostriatal dopaminergic neurons with high selectivity (7, 8) and protects these neurons from the neurotoxicity of 6-hydroxydopamine (6-OHDA) (9) and l-methyl-4-phenyl-1, 2, 5, 6-tetrahydropyridine (MPTP) (10).

The hypothesis was put forward in 1981 (11, 12) that long-term (-)deprenyl treatment may counter the marked age-related decline of the nigrostriatal dopaminergic neurons. Sexual performance of male rats, a quantifiable striatadopamine dependent function decreasing with age, was selected as an experimental model to check the validity of this hypothesis. Using this model we were able to demonstrate that the continuous administration of low doses of (-)deprenyl increased the sexual vigour of aged male rats significantly (11—14). In a preliminary study on 16 rats, the extension of rats' lifespan by long-term (-)deprenyl treatment was also demonstrated (15).

(-)Deprenyl is at present the only known compound which may be used with a high likelihood of countering the age-related changes in the human striatum. The reasons for this are as follows:

a) It is now a widely used drug and there is general agreement about its safeness. The small dose administration of (-)deprenyl even for several years has been found to be free of significant side effects (for a review, see 16).
b) The supplementation of (-)deprenyl to Madopar (n=564) significantly prolonged the survival of parkinsonian patients as compared to those on Madopar alone (n=377), indicating that (-)deprenyl protected in some manner the nigrostriatal dopaminergic neurons in these patients (17).
c) (-)Deprenyl exerts its specific pharmacological effect in animals with an excellent safety margin (9). The subcutaneous administration of a very small dose, 0.25 mg/kg/day for 2—4 weeks, is usually sufficient to demonstrate the highly selective pharmacological spectrum in the rat. In long-term experiments (several months or years) 0.25 mg/kg three times a week is appropriate for maintaining the effect. The relation of the effective doses to the subcutaneous LD_{50} in the rat (205 mg/kg) and the pharmacological selectivity of the compound explain the safeness of the drug.
d) (-)Deprenyl is a highly selective inhibitor of B-type MAO (6, 18).
The role of the inhibition of glial MAO-B in the enhancement of the physiological function of the nigrostriatal dopaminergic neurons was analyzed in detail (11, 12, 19, 20). (-)Deprenyl was demonstrated to exert this effect in a low dose range (0.05—0.25 mg/kg), the long-term administration of which sustained the activity of MAO-A in the brain and in the periphery sufficient for the maintenance of its physiological role in metabolizing the biogenic amines (for reviews, see 7, 8, 18, 21, 22, 23).
e) (-)Deprenyl has been shown to be an efficient inhibitor of the uptake of dopamine in the striatum and this effect was found to play an important role in the facilitation of the activity of the nigrostriatal dopaminergic neurons in animals treated continuously with (-)deprenyl (7, 8, 9, 20).
f) In striking contrast to the MAO inhibitors earlier introduced in clinical practice, (-)deprenyl has been found to inhibit the noradrenaline releasing effect of indirectly acting amines (phenylethylamine, tyramine) in vascular smooth muscle (5). This peculiar effect of (-)deprenyl, which is not shared even with other known selective inhibitors of B-type MAO (20, 24) plays the leading role in the safeness of (-)deprenyl in man. This is the only MAO inhibitor free of the 'cheese effect' (for a review, see 23).
g) (-)Deprenyl protects the nigrostriatal dopaminergic neurons from the neuron toxic effects of 6-OHDA (8, 9, 25) and completely abolishes the dopamine receptor supersensitivity due to 6-OHDA pretreatment (26).
h) (-)Deprenyl protects the nigrostriatal dopaminergic neurons from the neurotoxic effect of MPTP in monkeys (10).
i) (-)Deprenyl enhances the activity of the nigrostriatal dopaminergic neurons in 0.25 mg/kg daily doses in the rat, whereas the activity of the limbic dopaminergic system is influenced by high doses (over 10 mg/kg) only (27).
j) (-)Deprenyl in a daily dose of 0.25 mg/kg inhibits the release of acetylcholine in the caudate nucleus, which is indirect evidence for the enhanced activity of the nigrostriatal dopaminergic neurons. This was demonstrated by measuring the release of ACh in the striatum (9,25). The turnover rate of ACh was

changed in (-)deprenyl-treated rats only in the striatum, but remained unchanged in the hippocampus, proving that the substance has no action on the cholinergic system (26).

k) The selectivity of (-)deprenyl in the small dose-range to the nigrostriatal dopaminergic neurons is also supported by our findings that whereas the turnover rate of dopamine was enhanced in the striatum, a significant decrease of the turnover rate of noradrenaline and unchanged level of this amine in the brain stem was found (28).

l) Repeated administration of 0.25 mg/kg/day (-)deprenyl left the activity of the serotonergic system in the brain practically unaffected (26, 29).

m) According to direct measurements by reverse phase high performance liquid chromatography with chemical detection, the release of dopamine from the striatum of rats treated with 0.25 mg/kg/day (-)deprenyl for 3 weeks increased 7-fold under stimulation (13, 30).

Increased superoxide dismutase (SOD) activity in the striatum of CFY rats treated with (-)deprenyl

Previous studies with (-)deprenyl showing the protection of the nigrostriatal dopaminergic neurons from the toxic effects of 6-OHDA led to the assumption that (-)depren may enhance the scavenger function in these neurons (8). To find direct evidence, measurements have been made of superoxide dismutase (SOD) activity in the rat striatum. This enzyme is known to play a key role in the detoxication of free radicals resulting from auto-oxidation of the endogenous metabolites of dopamine. It has been shown (Table II) that the daily administration of (-)deprenyl for three weeks enhanced the activity of SOD in the striatum of both male and female CFY rats in proportion to the dose given. The SOD activity in the cerebellum of (-)deprenyl-treated male and female CFY rats did not change in a statistically significant manner. It seems therefore that (-)deprenyl has no direct effect on SOD activity in general. We might look upon the remarkable changes in striatal SOD activity of the CFY rats, specifically as a consequence of the (-)deprenyl-induced activation of the nigrostriatal dopaminergic neurons.

The (-)deprenyl-induced enhancement of the SOD activity in the striatum of CFY rats is unrelated to the MAO inhibitory effect of the drug, as clorgyline, one of the most potent inhibitors of MAO, was found to inhibit rather than enhance striatal SOD activity in this strain of rats (Table III).

The basic striatal SOD activity and the (-)deprenyl-induced changes seem to be strain-dependent. In a series of experiments in progress, we found that SOD activity in the striatum of Wistar rats (19.84 ± 0.42 in females and 20.53 ± 0.75 in males) was much higher than in the members of the CFY strain (see Table 2). A 3-week treatment of the Wistar rats with 1 mg/kg (-)deprenyl increased SOD activity in the females to

Table II. The selective enhancement of superoxide dismutase (SOD) activity in the striatum of CFY rats treated with (-)deprenyl

(-)deprenyl mg/kg/day	SOD activity (mean activity: unit/mg protein ± SEM)			
	striatum		cerebellum	
	male	female	male	female
None (saline)	6.24 ± 0.27	6.42 ± 0.50	15.31 ± 0.68	11.16 ± 0.32
0.25	9.03 ± 1.00	9.76 ± 1.68	13.22 ± 0.52	12.75 ± 0.89
0.50	9.46 ± 1.30	17.43 ± 2.22*	—	—
1.00	40.62 ± 3.49**	17.96 ± 2.46**	19.66 ± 0.80	16.42 ± 1.08
2.00	67.60 ± 3.25**	26.50 ± 4.62**	—	—

Significances according to Student's t test for two means: * $p<0.001$ ** $p<0.0001$

Total SOD activity was determined by the adrenochrom method according to Misra and Fridovich (36). MAO inhibitors were injected subcutaneously daily for 21 days. A group of ten rats was used for each dose. Enzyme activity was measured 24 hours after the last injection.

Table. III. Diminished superoxide dismutase (SOD) activity in the striatum of CFY rats treated with clorgyline

Clorgyline mg/kg/day	SOD activity in the striatum (Mean activity: unit/mg protein ± SEM)	
	male	female
None (saline)	6.24 ± 0.27	6.42 ± 0.5
0.1	3.14 ± 0.17	3.06 ± 0.15
0.25	2.31 ± 0.15	3.09 ± 0.22
0.50	3.17 ± 0.13	3.47 ± 0.27
1.00	2.34 ± 0.24*	2.69 ± 0.37*

Significances according to Student's t test for two means: *$p<0.001$. For details see Table II.

23.70 ± 0.70 ($p>0.05$) and in the males to 24.86 ± 0.13 ($p<0.05$). Thus the nature and mechanism of (-)deprenyl-induced changes in the striatal SOD activity need careful analysis. The phenomenon is valuable as an additional indication of the complex nature of the effect of long-term (-)deprenyl treatment on the activity of the nigrostriatal dopaminergic neurons.

(-)Deprenyl-treatment extends the average lifespan of male rats beyond the maximum age of death of the species

A pilot study (15) has indicated that continuous administration of (-)deprenyl increased the life expectancy of male rats. A detailed study using 132 two-year-old sexually inexperienced male rats provided prima facie evidence that (-)deprenyl-treatment restores lost sexual activity and prolongs the lifespan of rats considerably. The age-related decline in sexual function was established by testing them once weekly during the 24th month of their lives, as described previously (14). At this age, none of the rats displayed full scale sexual activity (mounting, intromission and ejaculation), whereas over 60% of 8-month-old rats normally show ejaculation when tested. In this experiment, 44 rats were sexually sluggish (mounting and intromission but no ejaculation), 42 showed mounting only and 46 ("non-copulators") showed neither activity. Each of these three categories of rats was divided into equal groups, treated subcutaneously either with saline (0.1 ml/100 g) or (-)deprenyl (0.25 mg/kg), respectively, three times a week. Sexual activity was assessed once a week.

In the rats with saline, sexual activity decreased rapidly, the last intromission occurring in the 23rd week of treatment and the last mounting in the 33rd week. In the (-)deprenyl-treated groups sexual potency increased gradually, reaching a maximum between the 28th and 36th week of treatment. Table IV shows the large differences in sexual activity between the saline- and (-)deprenyl-treated groups of animals.

Fig. 1 shows the deaths of the male rats in the different groups treated with saline and

Table IV. Sexual activity of rats treated with saline (n = 66) or (-)deprenyl (n = 66), respectively

Classification of the groups according to sexual performance before treatment	No, of animals	Total number of mountings (M), intromissions (I) and ejaculations (E) of the groups during treatment					
		Saline-treated			Deprenyl-treated		
		M	I	E	M	I	E
Non-copulators	23	37	0	0	997	544	190
Mounting rats	21	425	54	0	1129	662	172
Sluggish rats	22	477	231	0	1696	1257	481

The rats were treated with saline (1 ml/kg) or (-)deprenyl (0.25 mg/kg) subcutaneously three times a week from the beginning of the third year of their life until death. For methodological details see (14).

Table V. Lifespan of rats treated with saline (n = 66) and (-)deprenyl (n = 66), respectively

Classification of the groups according to sexual performance before treatment	No. of animals	Average lifespan (weeks) saline-treated		(-)deprenyl-treated	
Non-copulators	23	142,74 ± 0.38	A	187.90 ± 3.27	D
Mounting rats	21	146.95 ± 0.42	B	191.95 ± 3.59	E
Sluggish rats	22	152.00 ± 0.92	C	214.05 ± 3.07	F
Total	66	147.05 ± 0.56	G	197.98 ± 2.36	H

Significances according to the Student's t test for two means:
A : B $p<0.001$; A : C $p<0.001$; B : C $p<0.001$; D : E $p>0.05$; D : F $p<0.001$;
E : F $p<0.001$; A : D $p<0.001$; B : E $p<0.001$; C : F $p<0.001$; G : H $p<0.001$

(-)deprenyl respectively, and selected according to their sexual activity before treatment. Table V gives the average lifespan of the six groups of rats shown in Fig, 1.

In the saline-treated groups, the shortest-lived animals died during the 140th week of age and the longest survived 164 weeks. In the (-)deprenyl-treated groups, the first rat died during the 171st week of its life and the longest living rat survived for 226 weeks. The data also reveal an important relationship between striatal dopamine-dependent activity and lifespan in the male rats. The sexually more active animals lived significantly longer than their less active peers. As Hayflick suggested (31), "It is probable that only by increasing lifespan, or maximum age of death, of members of a species, will important insights be made into the aging process".

In the case of the human race, the lifespan maximum most accurately established (the technical lifespan, TLS) according to the Guinness Book of Records is 115 years, although a single case completing 120 years is described in the 1988 edition of the book. Thus, 115—120 years is at present the longest properly documented range of age for the human race. According to the 1988 Guinness Book of Records 2, 1 billion die for every one person actually reaching this limit. However, the mere existence of this possibility is convincing proof that there are opportunities for science considerably to increase the average lifespan. With regard to the rat, the most commonly used experimental animal, the maximum age of death can only be estimated. Taking a combination of data in the literature and personal experience, three and a half years (182 weeks) would be a reasonable estimate of the maximum age.

The animals in the saline-treated group (n=66) had an aveerage lifespan of 147 ± 0.6 weeks. The deprenyl-treated rats (n=66), however, lived on an average 198 ± 2.5 weeks ($p<0.001$). In other words, they had an average lifespan beyond the TLS. The real extension of lifespan by (-)deprenyl-treatment is shown by the fact that even in the group of noncopulators, which was the shortest living group, 12 rats lived beyond the TLS and 4 rats lived longer than 4 years.

Out of the 21 deprenyl-treated rats belonging to the group which displayed mounting only before treatment, 7 rats lived more than 4 years. The sluggish rats, i.e. the most active ones at the start of the experiment, created the longest living group. Even the shortest living three members of the 22 deprenyl-treated rats belonging to this group died close to the limit estimated as the maximum age of death of the species and 19 rats lived longer than 4 years.

Thus we succeeded to transform a population of rats, by changing the status of striatal dopamine via the continuous administration of (-)deprenyl, to have an average lifespan beyond the TLS^r (rat technical lifespan). This is, to our knowledge, the first instance that a well-aimed medication has increased the lifespan of members of a species beyond the limit taken as lifespan maximum. Although the rat serves in the history of experimental pharmacology as a reliable and useful model for the elaboration of drug therapy in humans, however, the important differences between the two species are also obvious. The proof of the pudding is in its eating. To protect the nigrostriatal dopaminergic neurons in humans from natural aging by taking 2—3 tablets of (-)deprenyl weekly, from the 5th decade of life, is

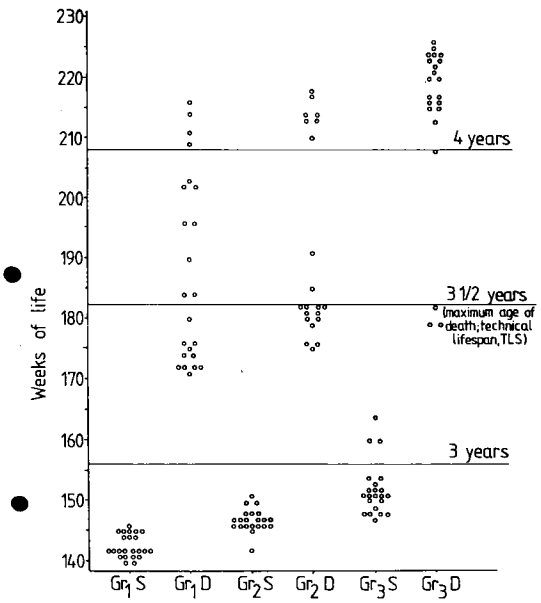

Fig. 1. *The close relationship between sexual activity and the duration of life in male rats and the extension of lifetime by treating 2-year-old male rats with (-)deprenyl until death.*

132 two-year-old male rats were classified according to their performance in four consecutive mating tests as 'non-copulators' (n = 46), showing mounting reaction only (n = 42) and presenting also intromissions (n = 44). Each of the three categories was divided into equal groups and injected subcutaneously with saline (0.1 ml/100 g) or (-)deprenyl (0.25 mg/kg), respectively, three times a week.

Gr_1S = Dying out of the saline-treated group of 'non-copulator' rats (n = 23)
Gr_1D = Dying out of the (-)deprenyl-treated group of 'non-copulator' rats (n = 23)
Gr_2S = Dying out of saline-treated group of 'mounting' rats (n = 21)
Gr_2D = Dying out of the (-)deprenyl-treated group of 'mounting' rats (n = 21)
Gr_3S = Dying out of the saline-treated group of 'sluggish' rats (n = 22)
Gr_3D = Dying out of the (-)deprenyl-treated group of 'sluggish' rats (n = 22)
TLS = Technical life span of rat i.e. maximum age at death

now open for clinical scrutiny. As a consequence of this safe and reasonable medication there is a hopeful possibility to extend the average human lifespan, improve the quality of life in senescence and lower the incidence of age-related CNS illnesses, like Parkinson's disease, Alzheimer's disease, senile dementia and involutional depression.

Long-lasting (-)deprenyl-treatment enhances learning in the shuttle-box in a selected low-performing rat population

The substantia nigra plays, a role of crucial importance in the maintenance of drive-motivated behavior. Unilateral lesioning of the substantia nigra in rats leads to severe learning deficits (32).

In randomly selected groups of young rats (3—8-month old) a single subcutaneous injection of (-)deprenyl in either small (0.25—1 mg/kg) or higher doses (2—10 mg/kg) left the acquisition of conditioned avoidance responses (CAR) in the shuttle box unchanged. The same was found in rats treated daily for 1—3 weeks with either the small dose (0.25 mg/kg) of (-)deprenyl which inhibits B-type MAO selectively or with high doses (2 and 5 mg/kg) which also block the A-type of MAO. We were able, however, to detect a remarkable deprenyl-induced enhancement of learning in the shuttle box in a specially selected population of rats treated three times a week with 0.25 mg/kg (-)deprenyl for several months.

We described in a previous paper that in a randomly selected young male rat population (n=387) 5,7% of the animals proved to be sexually inactive (for review see 33). Selecting 94 young

Table VI. The effect of longterm (-)deprenyl-treatment on the sexual performance of male rats selected as sexually inactive ones at their age of 8 months

	Total number of		
	Mountings	Intromissions (mean ± S.E.M.)	Ejaculations
Saline-treated rats (n=46)	24.76 ± 3.69	4.69 ● 1.92	ø
(-)Deprenyl-treated rats (n=48)	192.4 ± 8.43	23.5 ± 15.92	3.38± 0.43
Statistics: t-test for two means:	p<0.001	p<0.001	—

Male rats which proved to be sexually inactive in four consecutive mating tests, when tested for the first time after completing their 8th month of age, were selected (n = 94). The rats were treated subcutaneously either with 0.1 ml/100 mg saline or with 0.25 mg/kg (-)deprenyl, three times a week, for 36 weeks. Sexual activity was tested once a week. For methodological details see (14).

Table VII. The effect of longterm (-)deprenyl-treatment on the learning performance of male rats selected as sexually inactive ones at their age of 8 months

	Total number of conditioned avoidance responses (CAR) (mean ± S.E.M.)	
	before treatment	after
Saline-treated rats (n = 46)	6.53 ± 1.41	5.98 ± 1.15
(-)Deprenyl-treated rats (n = 48)	5.57 ± 0.56	20.73 ± 1.39
Statistics: t-test for two means	$p > 0.05$	$p < 0.001$

Performance in the shuttle box was tested before and 36 weeks after treatment. Each rat was trained at 20 trials daily for 5 days. Unconditioned stimulus (US) = electric shock via the grid of the floor; conditioned stimulus (CS) = buzzer + light. Unconditioned avoidance response: the rat escapes to US within 5 s; conditioned avoidance response (CAR): the rat escapes to CS within 10 s. The rat's performance was rated according to the total number of CARs produced during the 5 days of training. For other details see Table 6.

'non-copulator' rats from a huge 8-month old population (over 1400) we found that these rats proved to be miserable performers in the shuttle box. We started to treat 48 rats of this selected population with 0.25 mg/kg (-)deprenyl three times a week and the remaining 46 rats were treated similarly with saline. We tested once a week the sexual performance of the animals. The performance in the shuttle box was tested before and after a 36-week treatment. The administration of (-)deprenyl, as expected from previous studies, significantly improved the animals' performance in the mating tests (Table VI).

Table VII shows that the group of rats treated with (-)deprenyl for 36 weeks also learned in the shuttle box significantly better than their saline-treated peers.

The results in this experimental model may be helpful for the interpretation of the observed beneficial effect of (-)deprenyl-treatment in conditions with serious learning deficit (34, 35).

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