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Further Proof That (−)Deprenyl Fails to Facilitate Mesolimbic Dopaminergic Activity

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TIMÁR, J., S. GYARMATI, K. TEKES, G. L. HÁRSING AND J. KNOLL. *Further proof that (−)deprenyl fails to facilitate mesolimbic dopaminergic activity.* PHARMACOL BIOCHEM BEHAV **46**(3) 709–714, 1993.—The selective monoaminooxidase (MAO)-B inhibitor (−)deprenyl facilitates the nigrostriatal dopamine (DA)-ergic system by a complex mechanism that includes inhibition of DA reuptake and increase of DA turnover. In this study, DA reuptake and DA turnover were measured in the olfactory tubercle of rats treated with O.25 mg/kg (−)deprenyl for 28 days. There was no difference between these rats and the saline-treated group. In another series of experiments, we analysed how (−)deprenyl influences the action of some indirectly acting DA agonists, such as amphetamine (AM) and phenylethylamine (PEA). The effect on different behavioural patterns related either to the nigrostriatal (stereotyped behaviour) or the mesolimbic (rearing, locomotion) DAergic system was investigated. As expected, the PEA-induced stereotyped behaviour was tremendously potentiated by (−)deprenyl and the AM-induced stereotypy was reduced. At the same time there was no change in locomotion and rearing. The results give futher biochemical and behavioural proof that (−)deprenyl enhances the function of the nigrostriatal DAergic system and leaves the mesolimbic DAergic neurons unaffected.

(−)Deprenyl Nigrostriatal and mesolimbic DAergic system Behavioural patterns DA turnover DA reuptake

(−)DEPRENYL (selegiline), the first and until now the only selective B-type monoaminooxidase (MAO) inhibitor used in clinical practice, is known to facilitate the activity of the nigrostriatal dopamine (DA)-ergic system when administered in small (0.25 mg/kg) daily doses for at least 2–3 weeks (16). As a consequence of this effect, rats maintained on (−)deprenyl lose their ejaculatory capacity later in life, retain their learning ability longer, and live longer than their saline-treated peers (17–19).

(−)Deprenyl has been found to retard the progress of Parkinson's disease. Parkinsonians on levodopa plus (−)deprenyl (10 mg daily) live significantly longer than those on levodopa alone (1). Newly diagnosed parkinsonians maintained on (−)deprenyl need levodopa significantly later than their placebo-treated peers (24,31). Maintenance on (−)deprenyl also improves significantly the performance of patients of Alzheimer's disease (7,20,21,26,29).

Presently, (−)deprenyl is the only known drug that acts on the striatal DAergic system with high selectivity. Small doses of (−)deprenyl fail to induce measurable changes in behaviour of rats; however, its effect on various DA agonist-induced behavioural patterns can be measured. Indirect evidence showing that (−)deprenyl leaves the mesolimbic DAergic function unchanged was indicated by the finding that (−)deprenyl failed to influence apomorphine-induced rearing (15), a behavioural pattern related to the mesolimbic DAergic system (12). This finding was recently corroborated by demonstrating that amphetamine (AM)-induced rearing remained uninfluenced, while AM-induced stereoptyped behaviour was inhibited by small doses of (−)deprenyl (34).

The aim of this paper is to give further experimental support and, for the first time, direct biochemical evidence that the daily administration of 0.25 mg/kg (−)deprenyl for 4 weeks, which changes striatal DAergic activity significantly (29,35,36), leaves the DAergic function unchanged in the olfactory tubercle, one of the mesolimbic structures.

METHOD

Subjects

Experiments were performed either on males (biochemical measurements) or on both sexes (behavioural tests) of Wistar

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rats aged 8 weeks, weighing 140–160 g at the beginning of the treatment. They were housed in groups of five under constant (20–21°C) temperature conditions and a standard 12L : 12D cycle (light on at 6:00 a.m.). Water and food were available ad lib, except during the behavioural tests.

All of the behavioural observations were made at comparable times of the day during the light period. The animals were used once only; the biochemical determinations were carried out on animals not used for behavioural observation.

Experiments 1A and 1B: Simultaneous Measurement of Phenylethylamine (PEA)-Induced Locomotion, Rearing, and Stereotyped Head Movements

Locomotion, rearing, and stereotyped head movements (STHMV) were measured simultaneously by an "Animal Activity Measurement System" (Research Institute of the Electrical Industry, Budapest, Hungary). It consisted of two testing boxes (both 50 × 50 × 30 cm), each provided with a TV camera and controlled by a common central unit based upon an Intel Z 80 microprocessor. The testing box was a black-painted open field area, set in an isolated dark room and illuminated by two standard laboratory lamps. The experimental animals were placed into the boxes individually; their movements were followed by the TV cameras, aided by a mirror inclined at an angle of 45°. The central unit separated the elements of activity, such as horizontal activity in any direction (locomotion), vertical activity (rearing), and stereotyped head movements (STHMV). The time spent on any of these activities during the whole observation period was recorded. All of the data were registered, processed, and statistically analysed by a Bondwell PC.

In Experiment 1A, the effect of single (−)deprenyl treatment on PEA-induced activity was investigated. The experimental animals were pretreated either with saline or with the selective MAO-B inhibitory dose of (−)deprenyl (0.25 mg/kg), 1 h prior to administration of different doses (2, 5, 10, 40, and 100 mg/kg) of PEA. There were a total of 10 groups with six animals per group. One group of six animals was treated only with saline; this group, however, was not included in the statistical analysis.

In Experiment 1B, the effect of repeated (−)deprenyl treatment on PEA-induced activity was checked. One group of the experimental animals was injected with (−)deprenyl, two groups were treated with saline daily between 9:00 and 10:00 a.m. These pretreatments were carried out for 1, 7, or 28 days. There were a total of nine groups with six animals in each group. Twenty-four hours after the last injection for each group, one group of the saline-pretreated rats was given saline again (control group) while the other saline-pretreated group and the deprenyl-pretreated group were injected with a standard dose of PEA (40 mg/kg).

Ten minutes following the administration of PEA or saline, the animals were placed into the testing box. The observation period started immediately and lasted 30 min.

Experiment 2: Amphetamine-Induced Stereotyped Behaviour

The AM-induced stereotypy was assessed according to the scoring system detailed in Costall et al. (4): 0—no apparent drug effect; 1—discontinuous sniffing, constant exploratory activity; 2—continuous sniffing and periodic exploratory activity; 3—continuous sniffing, discontinuous licking and/or biting, very brief periods of locomotor activity; 4—continuous licking and/or biting, no exploratory activity.

The animals were pretreated either with different doses (0.25, 1, 2, and 5 mg/kg) of (−)deprenyl or with saline, and 30 min later they were placed individually into rectangular wire mesh cages (20 × 20 × 20 cm each). Following a 30-min adaptation to the cages, both the deprenyl and the saline-treated animals were injected with AM (2.5 or 5 mg/kg) and observed for stereotyped behaviour for a 60-s period every 10 min until the behaviour ceased. The intensity of the stereotypy was estimated on the basis of the highest score value measured during this period. There were a total of 10 groups with six animals in each group.

Experiment 3: Determination of DA Turnover in Olfactory Tubercle

Fifty animals were used in Experiment 3. Twenty-five of them were treated daily with (−)deprenyl (0.25 mg/kg) and 25 with saline for 28 days. DA turnover was determined 24 h following the last injection. The rats were decapitated, the brain was removed and placed on an ice-chilled plate, and the olfactory tubercle was dissected according to the method detailed in Glowinski and Iverson (6). The tissue was sonicated in 0.4 mol/l perchloric acid containing 0.1% $Na_2S_2O_5$ (antioxidant), 0.05% EDTA (chelator), and dibenzylamine (DBZA) as internal standard. Following a purification by batch alumina, DA was detected electrochemically according to the method detailed elsewhere (10). A sample of 100 μl was injected into a Biotronik high performance liquid chromatography–electrochemical detection (HPLC-ED) system. The analytical column was 140 × 4.6 mm, prepacked with Nucleosil C18 reversed-phase resin, particle size 5 μm, and it was protected by a guard column, 30 × 4.6 mm. The values were corrected for recovery of internal standard. DA turnover rate was measured by the decline of DA content following IP administration of alfa-MT (320 mg/kg) at different time intervals (0, 30, 60, 90, and 120 min) on five animals at each time point. Fractional rate constant and turnover rate were calculated as described in Brodie et al. (2).

Experiment 4: [^{3}H]Dopamine Uptake in Cell-Free Homogenate of Olfactory Tubercle

The effect of (−)deprenyl on DA uptake was checked in four groups of rats. Group I (n = 13) was treated with a single dose of (−)deprenyl (0.25 mg/kg) 1 h prior to decapitation. Group II (n = 13) was injected daily with 0.25 mg/kg (−)deprenyl for 28 days and the animals were decapitated 24 h after the last injection. Control animals received saline either once (group III, n = 12) or for 28 days daily (group IV, n = 12).

Following decapitation, the brain was removed immediately and the olfactory tubercle was dissected over an ice-cold aluminium surface. The tissues were individually homogenized in 20 vol. of 0.32 mol/l saccharose and spun down at 1000 × g for 10 min at 0°C. The cell-free supernatant was used for the uptake studies according to the method detailed elsewhere (28).

In short, 100-μl aliquots of the homogenates were equilibrated at 37°C for 5 min in 800 μl of Krebs-Henseleit buffer containing ascorbic acid (0.2 mg/ml), Na_2EDTA (0.05 mg/ml), and pargyline HCl (1.25×10^{-4} mol/l), saturated with carbogen (CO_2/O_2 5%/95%), and adjusted to pH 7.4. Then 100 μl of [^{3}H]dopamine (Amersham, spec.act. 1.5 TBq/mmol) was added (final concentration 0.1 μmol/l). Following a 5-min incubation, reaction was stopped by diluting with 3.0 ml of ice-cold buffer, and samples were quickly filtered (Whatman GF/C) under vacuum, washed (3 × 3.0 ml of ice-cold

buffer), and dried at room temperature. Radioactivity was determined by liquid scintillation in toluene (0.5% PPO, 0.01% POPOP) using a Beckman LS 9000 type apparatus. Active uptake was corrected by the blank value (0°C) and was given as nmol/min × mg protein. Protein determinations were made as described in Peterson (25).

Drugs

The drugs used were (−)deprenyl HCl (Chinoin, Hungary), beta-phenylethylamine HCl (PEA, Chinoin), *dl*-amphetamine sulfate (AM, Chinoin), alfa-methylparatyrosine methylester HCl (alfa-MT, Sigma), and dibenzylamine HCl (DBZA, Sigma). The dose of AM refers to the free base.

All the drugs were dissolved in 0.9% saline and were given SC, except alfa-methylparatyrosine, which was given IP. In the course of daily treatment, fresh deprenyl solution was prepared every day.

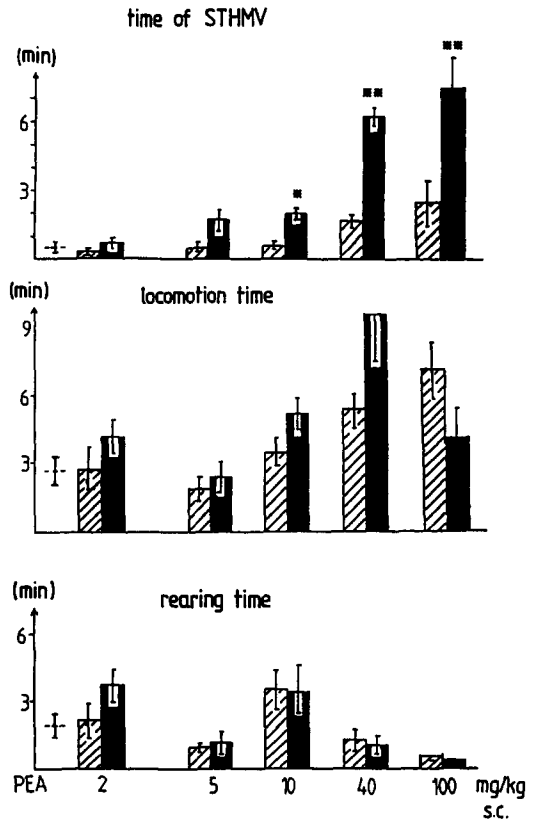

FIG. 1. Effect of single (−)deprenyl pretreatment on phenylethylamine (PEA)-induced activity. Five different doses of PEA SC were given 1 h after saline (striped columns) or 0.25 mg/kg (−)deprenyl (black columns) SC injection. Behavioural observations started 10 min later and lasted 30 min. The heights of columns indicate the time (in min) spent displaying the respective behavioural patterns. The numbers below the columns refer to the dose of PEA. The dotted horizontal lines show the results for the animals treated only with saline. STHMV = stereotyped head movement. $*p < 0.05$, $**p < 0.001$ compared to saline-pretreated + PEA-treated group (Newman-Keuls comparison performed after two-way ANOVA). $n = 6$ per group.

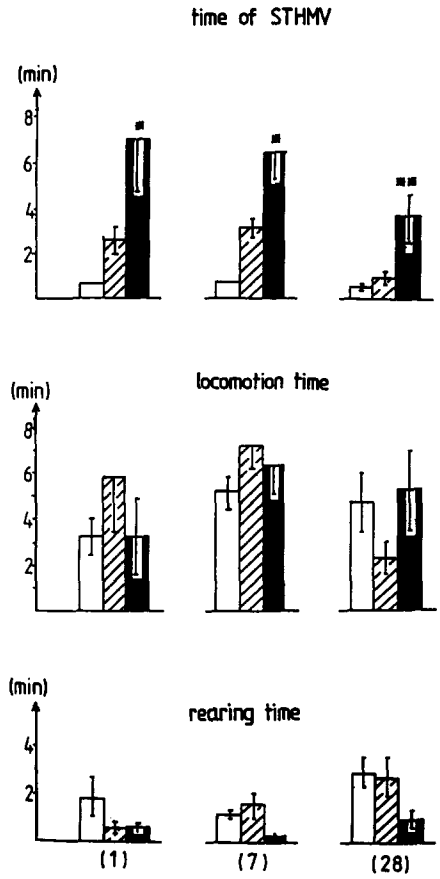

FIG. 2. Effect of repeated (−)deprenyl pretreatment on the phenylethylamine (PEA)-induced activity. Animals were pretreated with saline or (−)deprenyl (0.25 mg/kg) once daily SC for 1, 7, or 28 days. Saline-pretreated animals were injected either with saline (open columns) or with PEA 40 mg/kg SC (striped columns) 24 h after the last pretreatment. All of the (−)deprenyl-pretreated animals were injected with PEA 40 mg/kg SC (black columns). The numbers below the columns refer to the pretreatment in days. See other details as in Fig. 1 legend. $*p < 0.05$, $**p < 0.001$ compared to saline-pretreated + PEA-treated group (Newman-Keuls comparison performed after one-way ANOVA). $n = 6$ per group.

Statistical Analysis

Through the text the data are presented as mean values, with standard errors of the mean (mean ± SEM). Statistical significance of difference between mean values was evaluated by two-way ANOVA in Experiment 1A, by one-way ANOVA in Experiment 1B (both followed by Newman-Keuls multiple comparison), and by nonparametric two-way ANOVA (Friedman test) in Experiment 2. In Experiment 3, fractional rate constants and turnover rates were determined from analysis of the data using the SAS General Linear Models procedure (27). The data of Experiment 4 were statistically analysed by two-tailed Student's *t*-test. A p value of less than 0.05 was considered to be significant.

RESULTS

Experiment 1A

Single (−)deprenyl pretreatment (0.25 mg/kg) given 1 h prior to PEA enhanced the length of time spent displaying

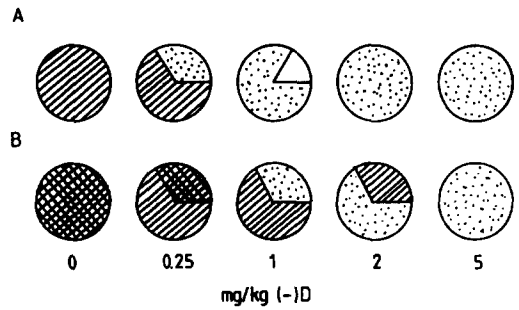

FIG. 3. Effect of single (−)deprenyl pretreatment on amphetamine (AM)-induced stereotyped behaviour. Animals were pretreated with five different doses of (−)deprenyl (including vehicle) 1 h prior to AM. (A) 2.5 mg/kg AM SC; (B) 5 mg/kg AM SC. Observation of stereotyped behaviour started immediately after injection of AM and was measured in score values (see details in text). Open segment—score 0; dotted segments—score 1; striped segments—score 2; cross-striped segments—score 3. $n = 6$ per group.

stereotyped head movment (STHMV). A two-way ANOVA analysis (saline + PEA vs. deprenyl + PEA) revealed a significant difference, $F(1, 10) = 63.44$, $p < 0.001$, and the multiple comparison (Newman-Keuls test) showed a good dose-response relationship for PEA in the deprenyl-pretreated groups; the higher doses (40 and 100 mg/kg) differed significantly from the lower ones (2, 5, and 10 mg/kg). The difference between deprenyl- and saline-pretreated animals proved to be significant at doses of 10, 40, and 100 mg/kg PEA (Fig. 1).

Concerning the amount of time displaying locomotion and rearing after PEA challenge, the deprenyl-pretreated groups failed to differ significantly from the saline-pretreated ones [Fig. 1; two-way ANOVA, $F(1, 10) = 2.47$ and 1.04, $p > 0.1$ and $p > 0.3$, respectively].

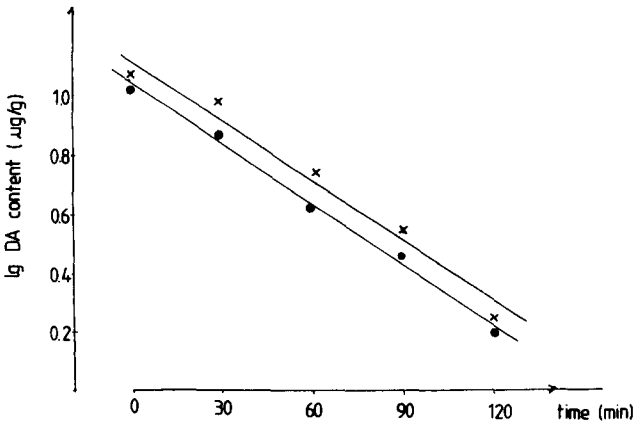

FIG. 4. Ineffectiveness of repeated (−)deprenyl pretreatment on alfa-MT-induced DA content decline in the olfactory tubercle. Animals were pretreated with saline (x) or with (−)deprenyl (●) (0.25 mg/kg) SC daily for 28 days; alfa-MT (320 mg/kg) IP was given 24 h after the last pretreatment. Each point represents the mean of five determinations at different time intervals (0, 30, 60, 90, and 120 min) following alfa-MT administration.

Experiment 1B

The influence of repeated (−)deprenyl pretreatment on the PEA-induced activity was similar to that of the single pretreatment.

One-way ANOVAs performed for each time point (1-day, 7-day, and 28-day pretreatment) failed to show significant differences in the length of time the animals exhibited locomotion [$F(2, 10) = 0.62$, 2.68, and 1.99, $p > 0.5$, $p > 0.5$, $p > 0.2$, respectively] and rearing [$F(2, 10) = 2.68$, 2.51, and 2.46, respectively; $p > 0.1$ in each cases].

Significant differences, however, were demonstrated for the length of time the animals displayed STHMV at all three time points [$F(2, 10) = 5.78$, 11.69, and 20.51, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively]. This was attributable, as Newman-Keuls comparison revealed, to the increase of time in the deprenyl-pretreated groups (Fig. 2).

Experiment 2

In saline-pretreated animals, AM induced a stereotyped behaviour with a dose-dependent increase in intensity; 2.5 mg/kg provoked continuous sniffing (score 2) and 5 mg/kg induced both sniffing (score 2) and discontinuous licking and/or biting (score 3).

(−)Deprenyl pretreatment decreased the intensity of the AM-induced stereotypy (Fig. 3). Evaluation of data by nonparametric two-way ANOVA revealed a significant difference both in the 2.5 mg/kg [Friedman test statistic (4) = 15.63, $p < 0.01$] and in the 5 mg/kg AM-treated [Friedman test statistic (4) = 19.3, $p < 0.001$] groups.

The detailed analysis of the respective stereotyped components expressed by score values revealed that (−)deprenyl pretreatment, depending on the dose, reduced or abolished stereotyped oral movements (score 3) and sniffing (score 2) without influencing the appearance of rearing (score 1), even with as high a dose of (−)deprenyl as 5 mg/kg (Fig. 3).

Experiment 3

As expected, alfa-MT induced a reduction in the DA concentration of the olfactory tubercle in both the (−)deprenyl-treated and the control groups. The slopes of the two curves were practically parallel, showing that repeated (−)deprenyl did not influence the DA content measured at different time intervals (0, 30, 60, 90, and 120 min) following alfa-MT treatment (Fig. 4). The results calculated from the above data show that repeated (−)deprenyl treatment failed to induce any significant change in DA turnover rate, DA efflux, or turnover time of the olfactory tubercle (Table 1).

TABLE 1

INEFFECTIVENESS OF REPEATED (−)DEPRENYL PRETREATMENT ON DA TURNOVER OF THE OLFACTORY TUBERCLE

Treatment	TR_{DA} (µg/g/h)	K_b (h)	Turnover Time (h)
Saline	7.85 ± 0.46	0.73	1.37
(−)Deprenyl	7.39 ± 0.26 NS	0.62	1.61

(−)Deprenyl was administered 0.25 mg/kg SC daily for 28 days. $n = 5$ at each time point. TR_{DA}, DA turnover rate; K_b, DA efflux.

Experiment 4

There was no significant change in the DA uptake of the olfactory tubercle following both single [group I vs. III, $t(25) = 0.51$, $p > 0.5$], and repeated [group II vs. IV, $t(23) = 0.42$, $p > 0.6$] (−)deprenyl pretreatment (Table 2).

DISCUSSION

(−)Deprenyl has proven to possess a remarkable pharmacological spectrum. A single dose of 0.25 mg/kg (−)deprenyl blocks MAO-B completely and irreversibly, and inhibits the reuptake of catecholamines and indirectly acting amines. The most important effects of (−)deprenyl on the striatal dopaminergic machinery of the brain, however, need the repeated administration of 0.25 mg/kg (−)deprenyl for at least a couple of weeks (16).

Repeated administration of small doses of (−)deprenyl saves the striatal dopaminergic neurons from the toxic effect of 6-OHDA (9,16) and MPTP (3), and by countering the age-related decay of the nigrostriatal DAergic neurons, prolongs the life span of rats (17,22). As a consequence of repeated (−)deprenyl treatment, the scavenger function in the striatum (but not in the cerebellum) is enhanced (18) and dopamine release in response to stimulation is significantly facilitated (14). These effects are independent from the MAO and the uptake inhibitory effects of the drug (17–19).

The nigrostriatal DAergic system differs from the mesolimbic one both in its physiological and pathological significance. The former one is thought to be involved first of all in the coordination of movement; its stimulation in rats induces stereotyped behaviour. The mesolimbic tract is considered to be involved in arousal, locomotor activity, and motivational and affective states. Its stimulation induces increased locomotion (5).

Our previous data have already shown that small doses of (−)deprenyl fail to induce any amphetamine-like hyperactivity (33), but they influence the stereotyped behaviour induced by different types of DA agonists. The effect of PEA, the main substrate of MAO-B enzyme, is tremendously enhanced by single or repeated (−)deprenyl treatment (32), while the stereotypy-inducing effect of AM is reduced by small (1–2 mg/kg) doses of (−)deprenyl (34). As these doses of (−)deprenyl fail to influence the sensitivity of postsynaptic DA receptors to apomorphine (33,34), this reduction cannot be the consequence of postsynaptic inhibition. It seems very likely that (−)deprenyl, similar to the inhibition of tyramine or DA uptake, may reduce the uptake of AM, thereby decreasing its stereotypy-inducing effect.

The present data revealed, however, that those types of DA agonist-induced activities that are related to the mesolimbic system (locomotion and rearing) are not influenced by (−)deprenyl. In (−)deprenyl-pretreated animals (both in the case of single and repeated pretreatment), the time spent displaying PEA-induced STHMV significantly increased, but there was no significant change in the time spent exhibiting PEA-induced locomotion or rearing (Figs. 1 and 2).

A similar conclusion can be drawn by detailed analysis of changes in the individual stereotyped components of AM-induced stereotypy. (−)Deprenyl pretreatment reduced or abolished the AM-induced stereotyped oral movements and sniffing (score 3 and 2), while AM-induced vertical activity (rearing) was not changed (Fig. 3).

Many data indicate that the mechanisms involved in the regulation of DA uptake in the corpus striatum and nucleus accumbens are different. Recently, several DA uptake inhibitors (cocaine, nomifensine, etc.) have been reported to bind to the Na^+-dependent DA reuptake transporter in the striatum (11). However, Na^+-dependent cocaine binding was not detectable in the nucleus accumbens, and a single cocaine injection influenced DA uptake in the corpus striatum and nucleus accumbens in the opposite direction (23). Nomifensine, which displaces [^{3}H]cocaine binding (13), inhibits DA uptake with high and low affinity in corpus striatum, but only with low affinity in the nucleus accumbens (23).

Our results show that the repeated (−)deprenyl injection schedule, which inhibits DA reuptake in the striatum (30,36), failed to influence DA reuptake in the olfactory tubercle. A similar discrepancy between the effect on the striatum and on the olfactory tubercle was obtained following a single administration of (−)deprenyl. This result might explain why (−)deprenyl is able to decrease the nigrostriatal effect of AM (stereotypy) but fails to change the mesolimbic one (rearing).

As for PEA, the situation is not so simple. (−)Deprenyl can potentiate the effect of PEA partly by blocking its metabolism and partly by inhibiting the reuptake of the released DA. The results presented show that inhibition of DA reuptake fails to take place in the mesolimbic system (at least in the olfactory tubercle). In connection with influencing the metabolism of PEA, interesting data were published recently about (−)deprenyl causing higher increase of endogenous PEA in the striatum than in other parts of the brain (8).

Knoll concluded that (−)deprenyl acts via a hitherto unknown mechanism, selectively influencing the striatal system (19). The data concerning DA turnover give further support to this conclusion. The daily administration of 0.25 mg/kg (−)deprenyl for 4 weeks enhances DA turnover in the striatum (35), but fails to change DA turnover in the olfactory tubercle.

Both the behavioural and biochemical results presented show that (−)deprenyl has no effect in the olfactory tubercle, one of the mesolimbic DAergic structures. It is, of course, possible that (−)deprenyl may influence DA turnover in the nucleus accumbens, but in the light of our present findings it appears unlikely. Our data give further evidence to Knoll's proposal (18) that the mechanism through which the function of the nigrostriatal DAergic neurons is enhanced by (−)deprenyl is selective to the striatal machinery and is not operating elsewhere, e.g., in the mesolimbic DAergic system.

TABLE 2

INEFFECTIVENESS OF (−)DEPRENYL ADMINISTRATION ON DA UPTAKE OF THE OLFACTORY TUBERCLE

	DA Uptake (nmol/minxmg protein)
Single administration*	
Saline	1.51 ± 0.06
(−)Deprenyl (0.25 mg/kg)	1.64 ± 0.24 NS
Repeated administration†	(daily for 28 days)
Saline	1.51 ± 0.09
(−)Deprenyl (0.25 mg/kg)	1.52 ± 0.08 NS

*Injection 1 h prior to decapitation.
†Last injection 24 h prior to decapitation.
n = 12–14 per group.

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