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Oral Versus Transdermal Selegiline: Antidepressant-Like Activity in Rats

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GORDON, M. N., C. D. MULLER, K. A. SHERMAN, D. G. MORGAN, A. J. AZZARO AND L. WECKER. *Oral versus transdermal selegiline: Antidepressant-like activity in rats.* PHARMACOL BIOCHEM BEHAV **63**(3) 501–506, 1999.—These studies compared the dose–response effects of oral vs. transdermal selegiline on antidepressant-like activity and brain monoamine oxidase (MAO) activities in rats. Rats received selegiline by gavage (0–100 mg/kg) or via transdermal patches (0–4.8 cm^2, 0–8.7 mg/kg) daily for 7 days; antidepressant-like activity was determined using the forced-swim test. Following behavioral testing, cerebral cortices were assayed for MAO-A and MAO-B activities. Doses of selegiline that selectively inhibited MAO-B (3 and 10 mg/kg/day by gavage and 0.4 mg/kg/day via patch) did not alter either immobility or latency time. However, the oral administration of 30 or 100 mg/kg/day or the transdermal administration of 8.7 mg/kg/day, doses that led to greater than 70% inhibition of MAO-A, decreased immobility time significantly. The IC_{50}s for inhibition of MAO-A following oral and transdermal administration for 7 days were 19.8 and 1.1 mg/kg, respectively. Results indicate that both oral and transdermal selegiline have antidepressant-like activity as assessed by the forced-swim test, and that transdermal administration, which bypasses first-pass metabolism, allows for using lower doses than oral administration. © 1999 Elsevier Science Inc.

Selegiline l-deprenyl Forced-swim test Antidepressant-like activity Monoamine oxidases Transdermal drug administration

SELEGILINE hydrochloride, [(R)-(−)-N,2-dimethyl-N-2-propynyl-phenethylamine hydrochloride, l-deprenyl], is a preferential inhibitor of mitochondrial monoamine oxidase type B (MAO-B) that has been reported to have numerous neurochemical and behavioral effects. Early studies suggested that oral selegiline was effective as an antidepressant in a dose range that preserved the selectivity of MAO-B inhibition (17–20). However, further open-trial studies (16) demonstrated that doses of oral selegiline required for clinical antidepressant-like activity in most patients are relatively high (⩾30 mg/day) and nonselective, producing inhibition of MAO-A [for reviews, see (3,14,15)].

Studies have shown that selegiline is metabolized by the hepatic mono-oxygenase system to methamphetamine and amphetamine, and that oral doses of ⩽10 mg/day given to patients with Parkinson's or Alzheimer's diseases do not produce sufficient amounts of these active metabolites to contribute significantly to the clinical efficacy of the parent compound (11,12,29). However, it is possible that antidepressant doses of selegiline, which are three to six times higher than those used for Parkinson's or Alzheimer's diseases, may lead to the accumulation of significant amounts of these metabolites, perhaps contributing to the effects of the parent compound (3). Indeed, animal studies have suggested that these metabolites may have some antidepressant-like activity and contribute to the central actions of selegiline (5,7,10). Thus, it is unclear whether the antidepressant-like effects of selegiline can be attributed to MAO-A inhibition or the actions of methamphetamine and amphetamine as a consequence of selegiline metabolism [for reviews, see (3,15)].

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Although the oral administration of selegiline provides for extensive first-pass metabolism, leading to the production of methamphetamine and amphetamine (13,25), transdermal drug administration bypasses first-pass metabolism; consequently, sustained and higher plasma levels of selegiline are achieved and metabolite production is decreased as compared to oral administration (2,25). Thus, the objective of this study was to compare the dose–response effects of oral vs. transdermal selegiline in rats on behavior in the forced-swim test (23) and on brain MAO-B and MAO-A activities.

METHOD

Subjects

Male Fischer 344 (F344) rats (300 g, 4 months of age, Charles River Laboratories, Wilmington, MA) were group housed in a restricted access, temperature-controlled vivarium on a 12 L:12 D cycle with food and water available ad lib. Animals were assigned randomly to experimental groups. To acclimatize the animals to human exposure, all rats were handled daily for 2 weeks prior to initiation of the experiments. Rats were weighed at least 2 days prior to initiation of drug treatment, and daily thereafter. Procedures involving animals and their care were conducted in conformity with the NIH Guide for the Care and Use of Laboratory Animals and approved by the University of South Florida Animal Care and Use Committee.

Procedure

Drug administration. Selegiline was administered either orally by gavage or via transdermal patch delivery. Based on extensive dose–response studies, doses of selegiline were chosen that produced: 1) complete inhibition of MAO-B without significant inhibition of MAO-A; 2) complete inhibition of MAO-B with moderate inhibition of MAO-A; and 3) complete inhibition of both MAO subtypes (high dose). For gavage, the doses chosen were 3, 10, 30, and 100 mg/kg selegiline HCl (dissolved in 5% sucrose) delivered daily for 7 days; control rats received 5% sucrose vehicle. For transdermal delivery, selegiline "minipatches" sized 0.09 cm^2, 1.2 cm^2, and 4.8 cm^2 were cut from 10 cm^2 transdermal patches (double-disk overlay configuration) containing 2.2 mg selegiline-HCl/cm^2 [Selegiline Transdermal System (STS); Somerset Pharmaceuticals, Inc., Tampa, FL]; the doses of selegiline delivered by these patches, calculated from analysis of residual drug in patches following 24-h application and removal, were 0.4, 2.3, and 8.7 mg/kg/day, respectively. Control rats received placebo patches. On the first day of STS delivery, rats were anesthetized with isoflurane, grossly shaved with animal clippers, followed by fine shaving with a disposable razor and shaving cream. The skin was cleaned with water and alcohol to remove cut hair, and with Betagen surgical scrub to preclude infection of minor shaving nicks or abrasions. Patches cut to the desired size were affixed to the skin and covered with a piece of Elastikon™ (Johnson & Johnson Medical, Inc., Canada) slightly larger than the minipatches (4–5 mm on all sides). Both of these procedures were instituted to assure tight adhesion of the patch to the skin. Patches were replaced daily, and affixed to a skin area not covered previously with a patch. Close shaving was repeated as necessary without additional anesthesia. Rats received drug daily for 7 days, and behavior, was assessed daily.

Forced swim test. Behavioral testing was performed as described by Sortwell and Sagan (26) by an investigator unaware of the drug condition. The Plexiglas apparatus used was 40 cm high × 18 cm diameter, filled to a depth of approximately 20 cm with 25°C water. Sensitization to the forced-swim apparatus was conducted approximately 24 h after the first drug administration. Immobility and latency times in a 5-min forced-swim test were measured daily from day 2 to day 7 of drug administration. The latency time measured the duration of swimming from the beginning of a given trial until the onset of immobility, the latter defined when the rat remained motionless for 2 s; antidepressants delay the onset of immobility, increasing latency time (23,26).

MAO activities. Following completion of the behavioral testing on day 7, rats were anesthetized with isoflurane and decapitated. Cerebral cortices were isolated, homogenized (glass: Teflon, 10 strokes by hand followed by 10 strokes at 890 rpm) in 2 ml 0.32 M sucrose/5 mM EDTA (buffered to pH 7.4 with 10 mM HEPES), diluted (30× volume), and centrifuged at 1,000 × *g* for 10 min at 4°C to remove nuclei and cellular debris. The supernatants were decanted and recentrifuged at 17,000 × *g* for 20 min at 4°C to obtain the crude mitochondrial fraction (P_2). The resultant pellets were lysed in 10 vol water buffered with 5 mM HEPES, and samples were stored at −80°C. MAO-B and MAO-A activities were determined by standard protocols using [^{14}C]phenethylamine and [^{14}C]serotonin (New England Nuclear, Boston, MA) as substrates, respectively (1). Triplicate 40 μl tissue samples were preincubated for 10 min at 37°C in phosphate buffer (100 mM, pH 7.4). For measures of MAO-B activity, reactions were initiated by the addition of 10 μM [^{14}C]phenethylamine and allowed to proceed for 4 min. For measures of MAO-A activity, reactions were initiated by the addition of 200 μM [^{14}C]serotonin, and allowed to proceed for 15 min. The reactions were stopped by the addition of 2.5 mM citrate on ice; ascorbic acid/EDTA was added as an antioxidant. Reaction products were extracted by the addition of octane for MAO-B assays or ethylacetate for MAO-A assays, followed by shaking and centrifugation. The organic phases containing the deaminated products were transferred to scintillation vials, scintillation cocktail was added, and radioactivity was determined on a Beckman 3801 Scintillation Counter (Beckman Inst., Houston, TX). Enzyme activities were calculated taking both blanks (determined in the presence of boiled tissue) and quench correction into account; enzyme activities are expressed as μmol product formed/g wet weight/h.

Statistical analyses. Data were analyzed on a Macintosh computer using SuperANOVA (Abacus Concepts, Inc., Berkeley, CA). A two-way ANOVA (analysis of variance) was used for evaluations (drug dose × day). In those instances where significant ($p < 0.05$) main effects were noted, individual group differences were determined using Newman–Keuls test. For analysis of immobility times, because the duration of the sensitization trial was longer than the subsequent tests, the maximum theoretical immobility time that could be attained was larger for the first day of testing than for the remaining days of testing. Consequently, ANOVA was performed utilizing the data obtained on days 2–7 of testing. A level of $p < 0.05$ was accepted as evidence of a statistically significant effect.

IC_{50}s for dose–response data were calculated using PRISM (GraphPad Software, Inc., San Diego, CA), and were determined by fitting the data to sigmoidal dose–response curve analysis consistent with the law of mass action.

RESULTS

General Health of Animals

The effects of selegiline on body weight of rats during the experimental period is shown in Fig. 1. Control animals main-

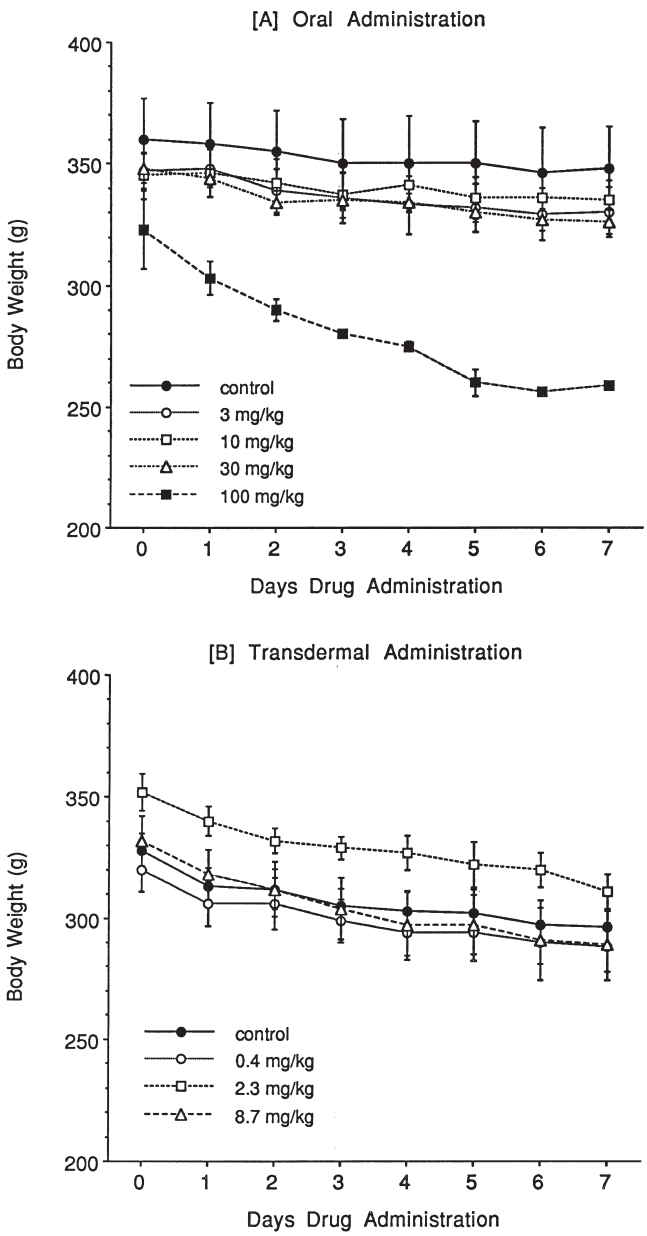

FIG. 1. Effects of selegiline on maintenance of body weight during a 7-day treatment regimen. Rats received selegiline via gavage (A) or transdermal patch (B), and body weight was measured daily. Control animals received vehicle or placebo patches. Each point is the mean ± SEM of five to six rats with the exception of the oral 100 mg/kg dose, which represents the mean of two rats on days 0–5, and one rat on days 6–7.

tained their body weight over the time course of this study, and the oral administration of selegiline at doses of 3–30 mg/kg/day did not significantly alter weight maintenance (Fig. 1A). In contrast, the highest oral dose used, 100 mg/kg, led to a significant loss of body weight and the manifestation of toxicity. One of the two rats receiving this dose expired on day 6 following drug administration. Necropsy revealed that the rat had self-mutilated the digits of both forelimbs, with loss of significant quantities of blood; there were no remarkable internal abnormalities. Consequently, administration of this dose was discontinued.

The effects of transdermal administration of selegiline on body weight of rats is shown in Fig. 1B. Over the 7-day testing period, control animals lost approximately 32 g or 10% of their body weight. The change in weight of animals receiving the lowest transdermal dose of selegiline (0.4 mg/kg) was identical to the controls. However, animals receiving 2.3 and 8.7 mg/kg/day lost approximately 42 g throughout the 7 days, representing 25–30% of their body weight. This weight loss was the only apparent difference between the test and control

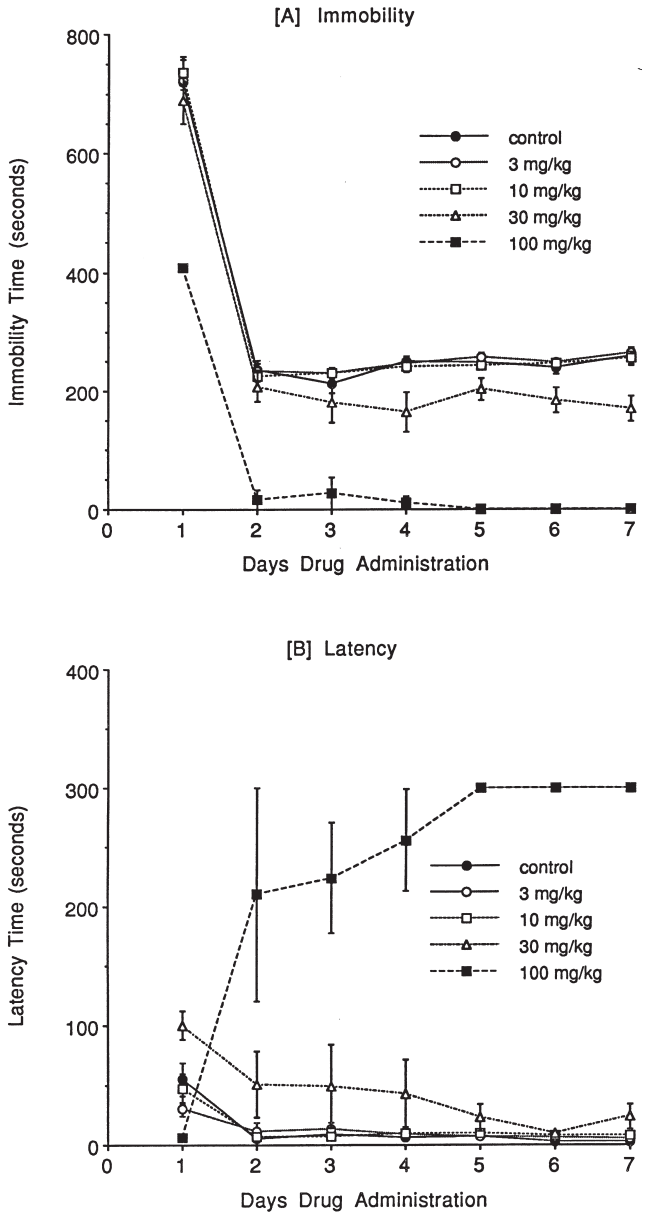

FIG. 2. Effects of oral selegiline daily on behavior in the forced swim test. Rats received selegiline via gavage (0–100 mg/kg) daily for 7 days and immobility time (A) and latency time (B) in the forced swim test was determined. Control animals received vehicle. Each point is the mean ± SEM of five to six rats, with the exception of the oral 100 mg/kg dose, which represents the mean of two rats on days 0–5, and one rat on days 6–7.

groups; no signs of toxicity were apparent. It is possible that the stress associated with the daily testing and experimental manipulations may have contributed to the weight loss.

Behavior

The effects of oral selegiline administration on immobility and latency times in the forced-swim test are presented in Fig. 2. The administration of 3 or 10 mg/kg/day did not affect either immobility (A) or latency (B). In contrast, 30 mg/kg/day significantly ($p < 0.05$) decreased immobility time by 20–30% on days 4–7, while it did not alter latency time. Thus, the oral administration of 30 mg/kg/day was associated with antidepressant-like activity. Although the administration of 100 mg/kg/day decreased immobility time to 0 on all days of testing, and increased latency time to the maximal allotted time of 300 s in both rats by day 5 of testing, this dose was associated with significant toxicity.

The effects of transdermal administration of selegiline on immobility and latency times are shown in Fig. 3. Patches delivering 0.4 or 2.3 mg/kg/day did not alter either immobility (A) or latency (B) times. In contrast, the largest patch (delivering 8.7 mg/kg/day) significantly ($p < 0.05$) decreased immobility time by 50–80% on days 4–7, and significantly ($p < 0.05$) increased latency time five- to sevenfold on days 5–7.

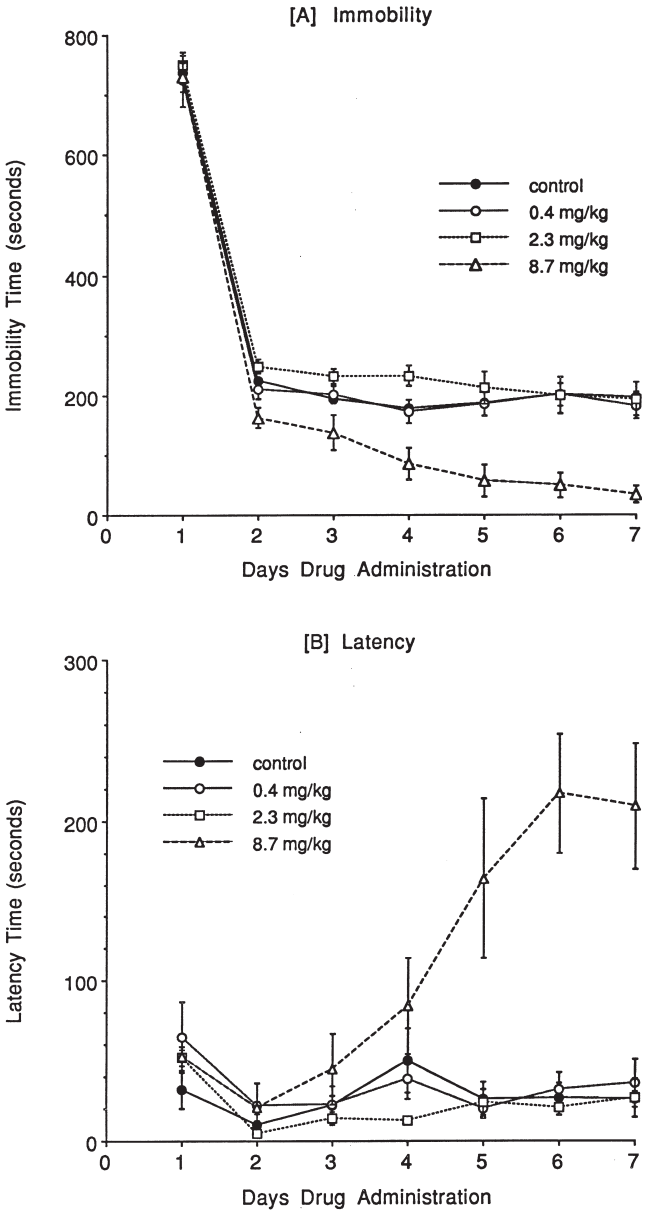

FIG. 3. Effects of transdermal selegiline daily on behavior in the forced swim test. Rats received selegiline via patch application (0–8.7 mg/kg) daily for 7 days and immobility time (A) and latency time (B) in the forced swim test was determined. Control animals received placebo patches. Each point is the mean ± SEM of five to six rats.

Enzyme Activities

MAO-B and MAO-A activities in cerebral cortices from rats following 7 days drug administration and behavioral testing are shown in Fig. 4. Results indicate that all oral doses of selegiline produced virtually complete inhibition of MAO-B, whereas inhibition of MAO-A was dose related with an IC_{50} of 19.8 ± 1.27 mg/kg/day (A). The effects of transdermal selegiline on MAO-B and MAO-A activities in cerebral cortices are shown in (B). Similar to the results obtained from oral administration, all transdermal doses of selegiline totally inhibited MAO-B, whereas MAO-A inhibition was dose-dependent, with an IC_{50} of 1.1 ± 2.27 mg/kg/day.

DISCUSSION

The objective of these experiments was to determine whether the administration of selegiline via the transdermal route, which bypasses hepatic metabolism, was effective as an antidepressant as assessed by the forced-swim test. Results demonstrate that (a) selegiline is effective as an antidepressant in the forced-swim test after both oral and transdermal delivery; (b) the antidepressant-like effect of selegiline requires greater than 70% inhibition of MAO-A activity, and inhibition of MAO-B in the absence of MAO-A inhibition was ineffective; and (c) the transdermal delivery of selegiline is 10–20 times more potent (on a mg/kg basis) than oral selegiline in producing both its antidepressant-like effect and inhibiting cortical MAO-A compared to the oral administration of selegiline.

It is now widely accepted that MAO-A inhibition is required for clinical improvement in depressed patients following the administration of selegiline (3,14–16,27,30), but the contribution of metabolites to this effect is equivocal. First-pass metabolism of selegiline is substantial, is mediated by the hepatic cytochrome P450 system, and does not result in racemization; major metabolites include desmethylselegiline, methamphetamine, and amphetamine (11). In addition, MAO-B inhibition leads to a decreased metabolism and increased accumulation of phenylethylamine (PEA), an amphetamine-like compound (4,6,10,22,24,28,30). Several reports suggest that oral, intraperitoneal, and subcutaneous administration of selegiline can result in sufficient circulating levels of amphetamine and PEA to influence general locomotor activity in open-field tests and cognition in the water maze. Engberg et al. (7) demonstrated that general locomotion increased significantly in a dose-dependent manner by selegiline, an effect that was completely blocked by prior administration of proadifen hydrochloride, an inhibitor of microsomal liver enzymes. Similarly, Okuda et al. (21) demonstrated that the effects of selegiline on both locomotor activity and brain dopamine levels resembled those of amphetamine, and could not be attrib-

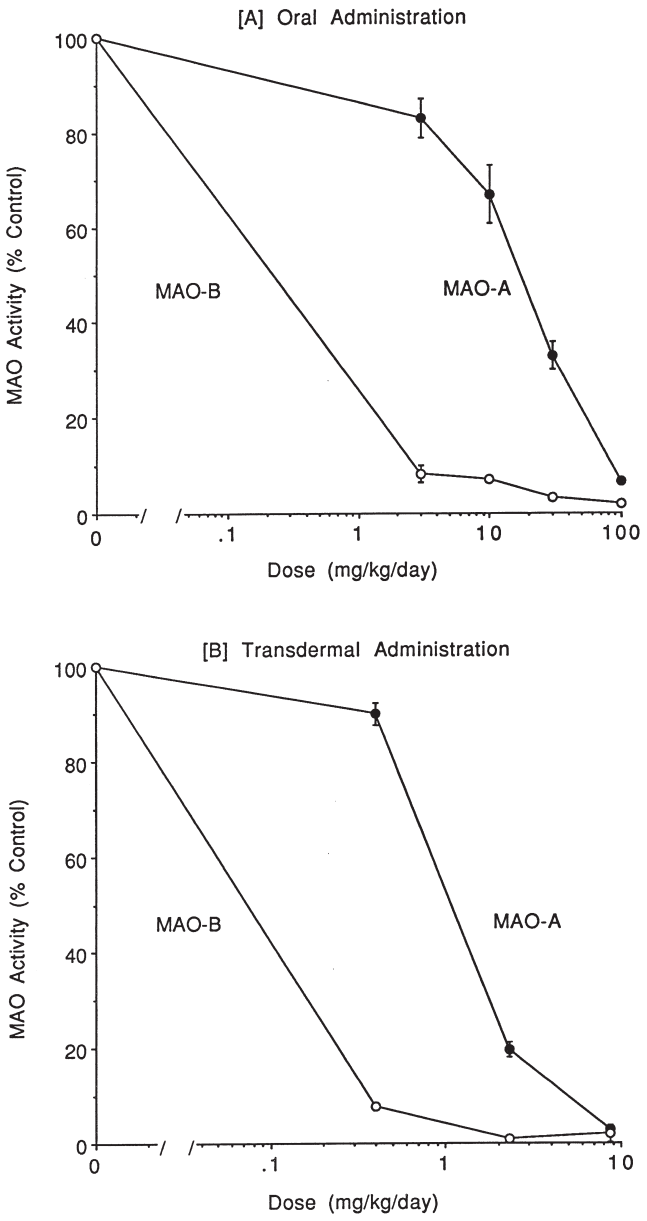

FIG. 4. Effects of selegiline on MAO-B and MAO-A activities in cerebral cortices. Rats received selegiline via gavage (A) or transdermal patch (B) and were monitored in the forced swim test daily for 7 days. Following that time, animals were killed, and the cerebral cortices were removed and analyzed for enzyme activities. Control animals received vehicle or placebo patches. Each point is the mean ± SEM of five to six rats, with the exception of the oral 100 mg/kg dose, which represents the determination from one rat. Control values for MAO-B activity were 2.37 ± 0.10 μmol/g wet weight/hr (n = 12); control values for MAO-A activity were 7.05 ± 0.18 μmol/g wet weight/h (n = 12).

uted to MAO-A inhibition, while Head and Milgram (10) attributed the effects of selegiline on stereotypic and exploratory behavior to the production of amphetamines or accumulation of PEA. In addition, Gelowitz et al. (9) demonstrated that both selegiline and amphetamine enhanced learning the Morris water maze, and that the improvement in cognitive performance was unrelated to MAO inhibition.

Although evidence suggests that the locomotor and cognitive effects of selegiline may be attributed to its metabolites or to the accumulation of PEA, few studies have investigated the relationship among selegiline metabolism, MAO inhibition, and the antidepressant-like effects of this compound. Both amphetamine and PEA have been shown to produce mood elevation, although it is unlikely that the latter reaches sufficiently high levels to produce this effect following MAO-B inhibition (3,22). Fozard et al. (8) compared the effects of selegiline with another MAO-B inhibitor [(E)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine HCl, MDL 72145] in the forced-swim test and demonstrated that although both compounds produced equivalent inhibition of MAO-B, only selegiline decreased immobilization times. In addition, this behavioral effect was manifest following a dose of selegiline that did not alter MAO-A activity, suggesting that the antidepressant-like action of selegiline was unrelated to enzyme inhibition. Interestingly, based on the ability of selegiline, but not the other MAO-B inhibitor, to reverse reserpine hypothermia and stimulate blood pressure and heart rate, effects that could be mimicked by the administration of amphetamine, these authors suggested that the antidepressant-like effects of selegiline may be attributed to its sympathomimetic metabolites (8). Results from the present experiments do not support this idea. Rather, results suggest that the antidepressant-like effects of selegiline are a consequence of MAO-A inhibition and do not involve actions of the metabolites. Studies have shown that the STS provides consistent plasma levels of selegiline (minimal peak-trough fluctuations), increases the amount of drug in plasma delivered to the brain, and decreases metabolite production compared to oral administration (2,25). Indeed, plasma levels of amphetamine and methamphetamine, determined 24 h following a single oral dose of 30 mg/kg selegiline to rats, were 15.4 ± 3.87 and 12.2 ± 2.72 ng/ml (mean ± SEM, n = 3), respectively, whereas there were undetectable levels of amphetamine and methamphetamine in plasma from rats who had received a single patch application, even at doses twice that used in the present study (unpublished results). Thus, transdermal application of selegiline bypassed first-pass metabolism.

In conclusion, results indicate that both oral and transdermal selegiline have antidepressant-like activity as assessed by the forced-swim test, and that transdermal administration allows for using lower doses than oral administration, thereby decreasing the likelihood of adverse reactions.

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