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Deprenyl Alters Behavior and Caudate Dopamine Through an Amphetamine-Like Action

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OKUDA, C., D. S. SEGAL AND R. KUCZENSKI. *Deprenyl alters behavior and caudate dopamine through an amphetamine-like action.* PHARMACOL BIOCHEM BEHAV **43**(4) 1075–1080, 1992.—In vivo microdialysis was used to concurrently measure the behavioral and caudate dopamine (DA) responses to the alleged irreversible type B monoamine oxidase inhibitor deprenyl. The effects were contrasted to those of the type A monoamine oxidase inhibitor, clorgyline. Consistent with its effects as an irreversible monoamine oxidase inhibitor, clorgyline produced an increase in DA concentration that remained elevated for at least 6 h. In contrast, the deprenyl-induced elevation in DA concentration occurred more rapidly, achieved a higher peak response, and then returned to baseline within 2 h following drug administration. The two drugs also produced distinctive changes in DA metabolite levels. Whereas the pattern of clorgyline-induced effects were consistent with irreversible monoamine oxidase inhibition, deprenyl produced an amphetamine-like response profile. Further, deprenyl but not clorgyline significantly increased locomotor activity. These results suggest that deprenyl does not augment caudate DA levels through monoamine oxidase inhibition. Rather, the pattern of its effects on caudate DA dynamics and behavior supports previous evidence that deprenyl produces its effects through its metabolism to amphetamine-like substances.

Dopamine Caudate Deprenyl Clorgyline Amphetamine Monoamine oxidase

DEPRENYL, an irreversible type B monoamine oxidase (MAO-B) inhibitor (11,18,19,37,39) appears to be useful in the treatment of Parkinson's disease (4). Because MAO-B is effective in deaminating dopamine (DA) in vitro (10,37), deprenyl's anti-Parkinson effects might derive from an elevation of DA consequent to inhibition of this enzyme. However, evidence suggests that caudate DA neurons contain only type A MAO (MAO-A) (1,6,7,24,35). Thus, deprenyl, at doses purportedly selective for MAO-B, might not be expected to alter the availability of functional DA by inhibition of MAO. In fact, Demarest and Moore (6) reported that systemic administration of deprenyl did not alter caudate levels of DA or 3.4-dihydroxyphenylacetic acid (DOPAC), and more recent studies using in vivo microdialysis failed to detect a deprenyl-induced increase in extracellular DA (5,17).

It has also been suggested that the efficacy of deprenyl as an anti-Parkinson drug may result from its conversion to amphetamine (AMPH) (8,34). Clinical observations indicate that deprenyl can produce AMPH-like behavioral effects such as insomnia and elevated mood (8,34) and that the onset of these effects are rapid (4,23,27). AMPH and meth-AMPH have also been detected in the urine and brain of Parkinson patients treated with deprenyl (12,16,26), and recent animal studies indicate that the locomotor-stimulant effects of deprenyl can be blocked by inhibition of deprenyl metabolism (9). However, although these results implicate AMPH-like actions in the effects of deprenyl, such an interpretation is not consistent with the reported failure of deprenyl to elevate caudate extracellular DA because even low doses of AMPH markedly increase extracellular concentrations of this transmitter (20).

The present study examined the behavioral and caudate extracellular DA responses of a locomotor stimulant dose of deprenyl (9) that should maximally inhibit MAO-B with little effect on MAO-A (25). In preliminary studies, we found that deprenyl (0,5–15 mg/kg) produced a dose-dependent locomotor activation with a threshold increase between 5 and 10 mg/kg. The locomotor and DA response profiles produced by a dose of 10 mg/kg were compared to the effects of clorgyline, a relatively selective MAO-A inhibitor (13). Our results are consistent with the suggestion that deprenyl induces behavioral activation and increased extracellular DA via its conversion to AMPH-like substances.

METHOD

Male Sprague-Dawley rats (Simonsen Lab) (300–350 g) were housed four per cage with food and water available ad

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lib in an animal colony maintained at constant temperature and humidity on a 14 white : 10 red light cycle (white lights on 5:00 a.m.-7:00 p.m.). Following at least 1 week of habituation to the animal colony, a guide cannula was stereotaxically implanted in each animal according to procedures previously described in detail (20). Following surgery, animals were housed individually and allowed at least 1 week to recover before receiving any treatment. Concentric-design microdialysis probes were constructed (20) of Spectra/Por hollow fiber (MW cut-off 6000, o.d. 250 μm) with an active surface of 2.0 mm. Probes were placed in the caudate (1.0 mm anterior to bregma and $\pm$2.8 mm lateral, 6.2 mm below dura). Probes were perfused with artificial cerebrospinal fluid (in mM: NaCl 147, $CaCl_2$ 2.3, $MgCl_2$ 0.9, KCl 4.0) delivered by a microinfusion pump (2 μl/min) an samples were collected through glass capillary tubing outside the experimental chamber. Individual probe recoveries, which ranged from 2.5-3.5%, were estimated by sampling a standard DA/DOPAC solution in vitro.

Dialysate samples were assayed for DA, DOPAC, homovanillic acid (HVA), and 3-methoxytyramine (3-MT) in 40μl aliquots by high-performance liquid chromatography with electrochemical detection (HPLC-EC). The HPLC-EC consisted of a 80 $\times$ 4.6-mm ODS-C18 3 μm column (Regis, Morton Grove, IL) maintained at 40°C. Mobile phase (0.06 M citric acid, 7% methanol, 0.1 mM Na_2 EDTA and 0.8 mM octane sulfonate adjusted to pH 3.7-4.2) was delivered at 0.6 ml/min by a Waters model 510 pump (Waters Assoc., Milford, MA). Amines were detected with a Waters 460 detector with glassy carbon electrode maintained at +0.65 V relative to an Ag/AgCl reference electrode. Concentrations of extracellular substances, corrected for individual probe recoveries, were estimated from peak areas using a Waters Maxima 820 data station. Although the exact relationship between dialysate concentration and extracellular transmitter content is not clear (2,3,36), substances in the dialysates were corrected for individual probe recoveries and are presented as concentration to allow for meaningful comparisons to other data in the literature.

Experiments were conducted in 12 $\times$ 12 $\times$ 15-in. sound-attenuated, temperature- and humidity-controlled chambers, previously described in detail (20). Automated behavioral data were collected continuously by computer. Animals were also videotaped to allow direct observational rating of behavior (31).

L-Deprenyl (Research Biochemicals, Inc., Natick, MA) (10 mg/kg) and clorgyline (May & Baker Ltd., Manchester, UK) (4 mg/kg), dissolved in saline, were injected intraperitoneally in a volume of 1 ml/kg body weight.

Each rat was placed in a testing chamber on the day prior to treatment (3:00-4:00 p.m.) to allow for acclimation to the test environment and for adequate equilibration of the dialysis probe. At about 9:00 a.m. the following morning, animals were injected with deprenyl, clorgyline, or saline. Baseline DA and its metabolites were defined as the median of the three 20-min dialysis samples prior to injection. Following drug administration, 20-min samples were collected for 2 h followed by 40-min samples for the next 4 h. At the end of the experiment, each animal was sacrificed and the brain was removed and fixed in 3% formalin for histological verification of probe placement.

Behavior and amine data were tested for significance with an analysis of variance (ANOVA). For each analysis that yielded a significant F ratio, t-tests with Bonferroni adjustment were applied for posthoc comparisons within or between groups. Where only one comparison was assessed, a paired or unpaired Student's t-test was utilized.

RESULTS

Extracellular concentrations of DA and its metabolites remained constant during the 6 h following injection of saline (Fig. 1). By contrast, both clorgyline and deprenyl produced pronounced effects on all these measures. However, although the effects of clorgyline and deprenyl were in the same direction the time course and magnitude of the two response profiles were markedly different (Fig. 1).

After clorgyline DA levels gradually increased to about 350% of baseline within 1-2 h after injection and did not further change over the next 4 h [Fig. 1A; 100-360 min: $F(6, 24) = 0.91$, $p = 0.51$]. Concomitantly, both DOPAC (Fig. 1B) and HVA (Fig. 1C) decreased to below 15% of baseline. Clorgyline also elevated 3-MT (Fig. 1D), but, in contrast to DA, the concentration of 3-MT continued to increase throughout the 6 h [100-360 min: $F(6, 24) = 4.85$, $p = 0.002$].

Clorgyline had no significant effect on locomotor activity (crossover and rearing) (Fig. 2B). Further, observations of animals revealed no obvious behavioral differences between the saline and clorgyline groups during the more than 5-h period of clorgyline-induced elevation in dialysate DA.

Deprenyl produced a rapid increase in DA (greater than sevenfold within 40 min after injection) that, in contrast to the lesser effects of clorgyline, recovered to control levels within 2.5 h (Fig. 1A). Further, the reductions in DOPAC and HVA were markedly less than those produced by clorgyline (Figs. 1B and 1C), and, in contrast to the DOPAC response to clorgyline, after deprenyl administration the level of DOPAC was not significantly different from controls by 6 h. However, HVA did not recover from peak inhibition and remained at about 80% of baseline levels for at least 6 h after injection (saline vs. deprenyl, 320-360 min; $p < 0.05$). Deprenyl also produced a relatively small, transient (20-80 min) increase in 3-MT to a maximum of 300% baseline during the 40- to 60-min interval ($p = 0.031$).

Also in contrast to clorgyline, deprenyl produced a pronounced increase in locomotor activity that paralleled the DA response (Fig. 2C). Observational ratings of these animals (data not shown) revealed that the qualitative features of the deprenyl response resembled the behavioral profile associated with low doses of AMPH (29,30,33).

DISCUSSION

The effects of clorgyline on striatal DA dynamics are consistent with its alleged action as a relatively specific irreversible MAO-A inhibitor (13). As reported previously (5,17), this drug produced a prolonged decrease in extracellular DOPAC and HVA concentrations that appears to be directly attributable to the reduction in metabolism of cytoplasmic DA by MAO. The elevation in extracellular DA may therefore reflect leakage of cytoplasmic DA into the synapse. However, it is also likely that vesicular concentrations of DA are increased after MAO inhibition and therefore that impulse-mediated DA release also contributes to the enhanced extracellular DA levels. The prolonged elevation of 3-MT may further reflect increased extracellular levels of DA because catechol-*O*-methyl transferase is localized outside of DA neurons (14,15,28). However, the accumulation of 3-MT may also result from a reduction in 3-MT metabolism to HVA, at least to the extent that the MAO that mediates this conversion is inhibited by clorgyline.

Despite the approximately threefold increase in extracellular DA, no obvious changes in behavior were detected after clorgyline administration (Fig. 2B). The absence of behavioral

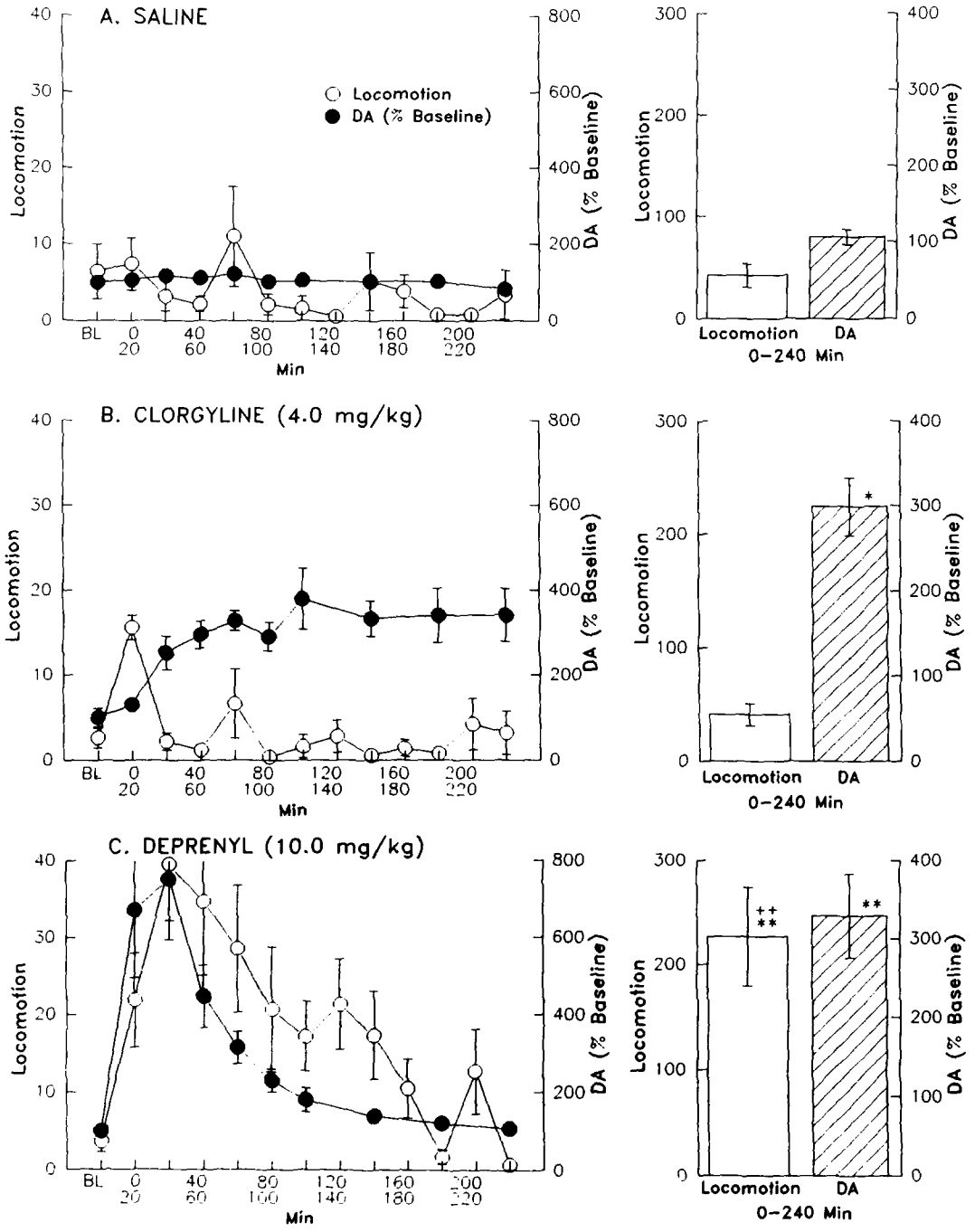

FIG. 1. Left: Temporal profile of caudate dopaminergic response to administration of saline (n = 7), deprenyl (10 mg/kg) (n = 6), or clorgyline (4 mg/kg) (n = 5). Each data point represents the mean dialysate concentration for each substance ± SEM, expressed as percent of each animal's preinjection baseline (BL). Baseline values for dopamine (DA) and its metabolites—dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 3-methoxytyramine (3-MT)—did not differ among the three groups and, combined, were 24.2 ± 2.6, 6,725 ± 540, 3,339 ± 295, and 5.7 ± 0.9, respectively. Right: Histograms represent the dopaminergic response cumulated over the 0- to 360-min interval, expressed as percent of baseline. t-Tests revealed significant differences between saline and drug-treated groups (*$p < 0.05$, **$p < 0.01$) and between drug-treated groups ($^{++}p < 0.01$).

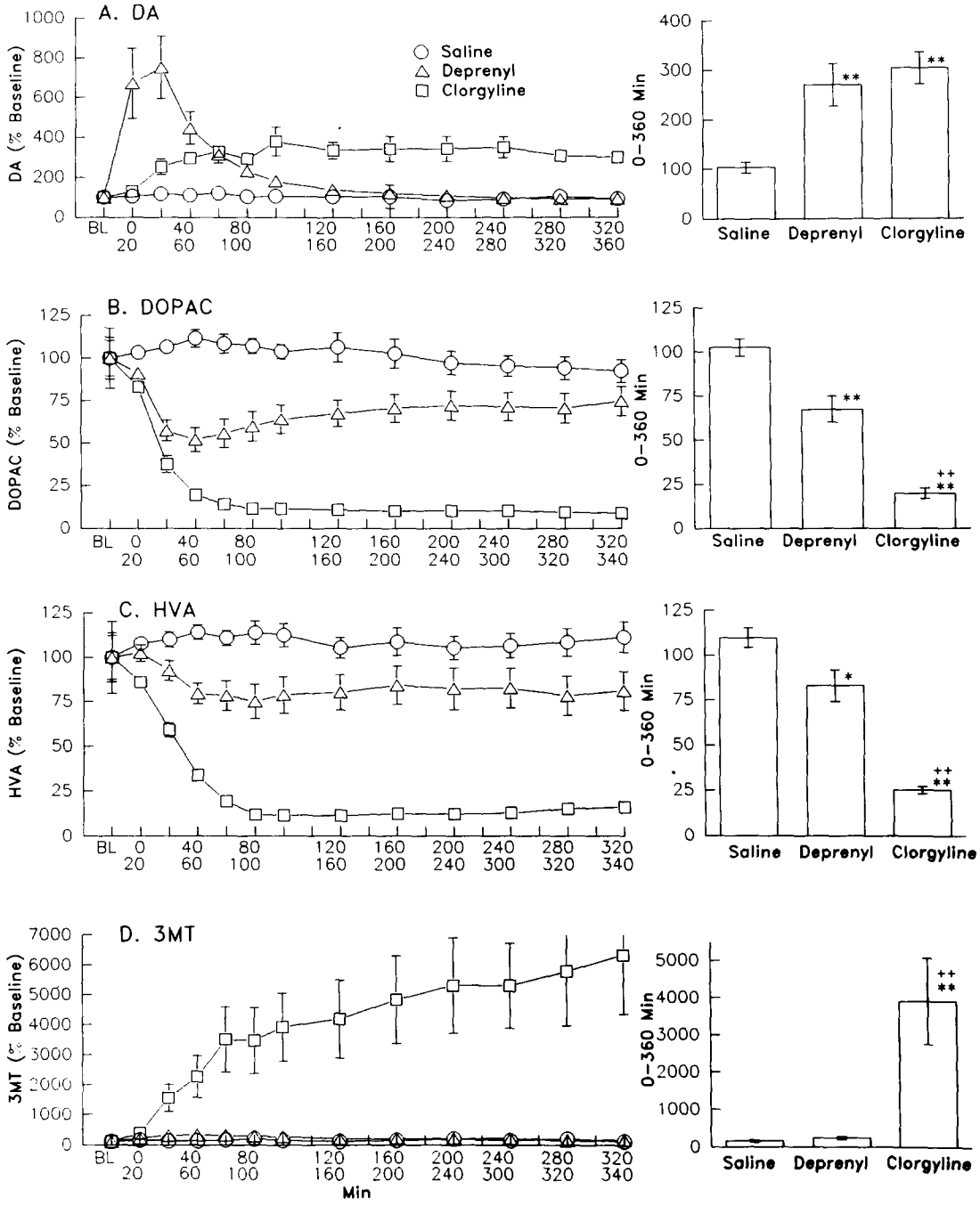

FIG. 2. Left: Temporal pattern of locomotion and extracellular dopamine (DA) in response to administration of saline (n = 7), clorgyline (4 mg/kg) (n = 5), or deprenyl (10 mg/kg) (n = 6). Values are means ± SEM. Locomotor activity represents cage crossings plus rearings, and DA, reproduced from Fig. 1, is expressed as percent of preinjection baseline values (see legend to Fig. 1 for additional details). Right: Histograms represent the locomotor (mean ± SEM crossovers plus rearings) and DA (percent baseline) responses cumulated over the 4-h interval following experimental treatment. Comparisons to saline: $^{*}p < 0.05$, $^{**}p < 0.01$; comparisons between drug treatments: $^{++}p < 0.01$.

change may be due to the relatively slow rate of extracellular DA accumulation (as compared to AMPH or cocaine, e.g.), that is, the gradual emergence of compensatory adjustments (e.g., receptor desensitization) may counteract the increase in DA. It is also possible, as we suggested previously (20–22), that DA increases alone cannot fully account for stimulant-like behavioral activation and that MAO inhibition alone may not produce other neurochemical changes that are critical components for the expression of this behavioral profile. It could also be argued that an evaluation of the dopaminergic

contribution to stimulant-induced behaviors should include terminal fields of the mesocorticolimbic DA pathway. However, our preliminary studies indicate that the effects of clorgyline on DA metabolism in the nucleus accumbens are not distinguishable from the caudate.

Deprenyl produced a pattern of effects on DA dynamics and behavior distinctly different from clorgyline, that is, the effects of deprenyl on DA, 3-MT, and DOPAC, while rapid and in the same direction as those produced by clorgyline, were transient and were no longer evident by 6 h after drug administration. Because DOPAC appears to arise predominantly from the intraneuronal metabolism of DA through MAO-A, it could be argued that the deprenyl-induced decrease in DOPAC reflects partial inhibition of MAO-A. However, this possibility seems unlikely because, in contrast to the persistent effects of clorgyline, the deprenyl-induced changes in DOPAC, like DA and 3-MT, were transient. Thus, the short-term changes in DA dynamics cannot readily be attributed to irreversible inhibition of MAO-A. However, in contrast to DOPAC HVA remained somewhat depressed for at least 6 h after deprenyl injection. The persistent depression of HVA along with a recovery of DOPAC might reflect a deprenyl-induced inhibition of MAO-B outside of DA neurons, but such an interpretation would predict that 3-MT concentrations after deprenyl would exhibit a more persistent elevation than was observed. In fact, our clorgyline data seem to indicate that MAO-A is primarily responsible for the metabolism of 3-MT. Therefore, while the mechanism underlying the persistent HVA decrease after deprenyl remains to be determined it is unlikely that inhibition of MAO is responsible for the deprenyl-induced changes in DA dynamics. Rather, the effects of deprenyl on DA dynamics are more like AMPH and likely reflect the metabolism of this MAO-B type inhibitor (11,18,37,39) to AMPH-like compounds (12,16,26,38). Thus, as with AMPH, deprenyl induced a relatively large and rapid, but transient, increase in DA and a correspondingly brief 3-MT elevation. The transient DOPAC decrease also closely resembles the response pattern associated with low doses of AMPH.

These results differ somewhat from other data in the literature. Kato et al. (17) failed to observe any changes in extracellular DA following 10 mg/kg deprenyl, but their assays were not sufficiently sensitive to quantitate extracellular DA. Butcher et al. (5) also failed to observe any changes in DA or 3-MT although they did report decreases in DOPAC and HVA like those we observed following this dose of deprenyl. Those studies were performed in anesthetized animals, and it is conceivable that the use of anesthetics and/or other methodological factors may account for the failure to observe a deprenyl-induced increase in extracellular DA.

The behavioral profile in response to deprenyl is also similar to that produced by AMPH. This similarity is apparent both with respect to the time course and in the qualitative features of the deprenyl effect, which are not distinguishable from a low-dose AMPH profile. In addition, our preliminary results indicate that repeated administration of 10 mg/kg deprenyl results in a progressively enhanced locomotor activation similar to the augmented behavioral response associated with repeated AMPH administration (31–33). That these deprenyl effects may at least in part be due to the conversion of this drug to AMPH-like compounds is consistent with the recent observation that the locomotor stimulant effects of 10 mg/kg deprenyl could be blocked by inhibition of microsomal metabolism (9). Together, these results suggest that deprenyl-induced inhibition of MAO-B has little effect on caudate DA dynamics or behavior and that the neurochemical and locomotor-stimulant effects of this drug are mediated by its metabolism to AMPH-like compounds. Thus, deprenyl's rapid initial effectiveness in the treatment of Parkinson's disease may be derived from the DA-releasing effects of its AMPH-like metabolites, although other actions of deprenyl may be implicated in its apparent ability to retard the progression of the disease (9).

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