Intravenous self-administration studies with *l*-deprenyl (selegiline) in monkeys*

l-Deprenyl and its stereoisomer *d*-deprenyl did not maintain intravenous self-administration behavior in rhesus monkeys. In contrast, *l*-methamphetamine, the major metabolite of *l*-deprenyl, as well as the baseline drug, cocaine, maintained high rates of intravenous self-administration behavior. Treatment with *l*-deprenyl doses up to 1.0 mg/kg before self-administration sessions failed to alter self-administration of either cocaine or *l*-methamphetamine. Thus *l*-deprenyl did not appear to have cocaine- or methamphetamine-like reinforcing properties in monkeys and was ineffective in altering established patterns of psychomotor-stimulant self-administration behavior. These results support clinical findings that despite long-term use of *l*-deprenyl for the treatment of Parkinson's disease by large numbers of patients, no instances of abuse have been documented. *l*-Deprenyl has recently been suggested as a potential medication for the treatment of various types of drug abuse, including cocaine abuse, but its failure to produce selective effects in decreasing cocaine or methamphetamine self-administration behavior in the present experiments makes such an application seem unlikely. (CLIN PHARMACOL THER 1994;56:774-80.)

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*The drug names *d*- and *l*-methamphetamine used in this article have been commonly employed in the experimental literature and are used herein. It should be noted, however, that methamphetamine does not exist in racemic form but *d*-methamphetamine instead refers to the *d*-isomer of N-methylamphetamine and that *l*-methamphetamine is more correctly named *l*-N-methylamphetamine.

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l-Deprenyl (selegiline) has been known for several years to increase and prolong the effectiveness of *l*-dihydroxyphenylalanine (L-dopa) in the treatment of the symptoms of Parkinson's disease.[1-5] More recently, *l*-deprenyl alone has been found to slow the progression of Parkinson's disease and to delay the need for L-dopa therapy.[5,6] However, the mechanism by which it produces these therapeutic benefits is not clearly understood.[7]

l-Deprenyl is a selective and irreversible antagonist of monoamine oxidase B (MAO-B),[8,9] an enzyme that primarily has an extraneuronal location in the human brain[10,11] and that deaminates synaptic accumulations of cathecolamines and β-phenylethylamine (β-PEA).[12,13] *l*-Deprenyl inhibits deamination of dopamine in vitro, and its mechanism of therapeutic action was thought to be by increasing brain levels of dopamine in vivo. However, MAO-B is not present within dopaminergic nerve terminals in human brain and does not appear to be a primary contributor to dopamine's inactivation in vivo in humans. However, the administration of *l*-deprenyl to intact rats, which show a greater distribution of MAO-B in brain than in humans, can produce increased dopamine levels.[14]

Recent studies in rats have suggested that *l*-deprenyl's mechanism of therapeutic effect might be from its metabolic conversion to *l*-methamphetamine[15,16] or that its inhibition of MAO-B might lead to increases

in striatal levels of β-PEA, which in turn might potentiate the responses of striatal neurons to dopamine.[17] Both of these mechanisms of action of *l*-deprenyl suggest the possibility that this drug might be abused by susceptible individuals. *d*-Methamphetamine has acknowledged abuse potential in humans, and *l*-methamphetamine is an effective reinforcer of intravenous self-administration behavior in the rat.[18] Phenylethylamine is a naturally occurring amine that is structurally similar to amphetamine. The administration of large doses of β-PEA to rhesus monkeys can produce an amphetamine-like stereotypy.[19] This compound has been shown to maintain intravenous self-administration behavior in dogs.[20,21] Thus medications that increase levels of β-PEA may have potential for abuse by humans.

Indications that *l*-deprenyl itself might have abuse liability come primarily from preclinical studies in which it has been found to have effects in common with amphetamine or cocaine. Several investigators have reported that *l*-deprenyl has cocaine-like discriminative stimulus properties in rats[22,23] and pigeons.[24] The racemic form of deprenyl but not other MAO-B inhibitors have discriminative stimulus effects in common with *d*-amphetamine.[25] Yasar et al.[26] and Yasar and Bergman[27] found that in animals trained to discriminate the stimulus effects of *d*-amphetamine or *d*-methamphetamine from saline solution, large doses of *l*-deprenyl had discriminative stimulus effects in common with the *d* - and *l*-isomers of amphetamine in rats and the *d* - and *l*-isomers of methamphetamine in squirrel monkeys.

The abuse liability of *l*-deprenyl can be assessed more directly by evaluation of its ability to maintain drug-seeking and drug-taking behavior, that is, its effectiveness as a reinforcer of self-administration behavior.[28] Studies in which intravenous drug injection is contingent on behavioral responses made by experimental animals have shown that many of the drugs that are subject to abuse by humans are self-administered by experimental animals.[29] In the current study the reinforcing effects of both the *l*- and the *d*-stereoisomers of deprenyl were evaluated in rhesus monkeys that were experienced with self-administration of cocaine. In addition, the reinforcing effects of *l*-methamphetamine, the major metabolite of *l*-deprenyl, were evaluated in these monkeys, and the ability of *l*-deprenyl to modify responding maintained by either cocaine or *l*-methamphetamine was determined. Finally, the effects of *l*-deprenyl on food-maintained behavior were evaluated in an additional group of monkeys.

METHODS

The reinforcing effects of *l*-deprenyl, *d*-deprenyl, and *l*-methamphetamine were evaluated with operant procedures in rhesus monkeys *(Macaca mulatta)* by making specified doses of each drug available for intravenous self-administration. Results with *l*-deprenyl have been reported previously.[1] Using apparatus first described by Deneau et al.[29] and modified as described by Winger et al.,[30] each monkey was surgically prepared with a long-term venous catheter and individually housed 24 hours a day in a stainless-steel cage containing a side panel with two response levers and three stimulus lights. Each monkey wore a harness that was connected to a flexible steel spring arm, which was designed to allow the animal free movement within the cage but to protect the venous catheter. The catheter was led through the arm to an injection pump (model MHRK 55 Watson and Marlow Co.) that was located behind the cage.

A procedure for rapidly evaluating the reinforcing effects of intravenously delivered drugs in rhesus monkeys was used.[30] Silicone rubber catheters (Max-Med. Inc., Portage, Wis.) were surgically implanted in a jugular, femoral, or brachial vein with ketamine (10 mg/kg) and xylamine (2 mg/kg) anesthetic. During twice-daily experimental sessions, one of the stimulus lights was illuminated red, which signaled drug availability. In the presence of the red light, 30 responses (fixed ratio 30) on the lever beneath the light resulted in the intravenous delivery of drug or saline solution. A center, green, stimulus light was on during pump activation. Each injection was followed by a 45-second blackout period, when all lights were extinguished and lever presses had no programmed consequences. Experimental sessions were limited to 130 minutes, and two sessions were scheduled each day, separated by at least 4 hours. Each session was divided into four components; each component was signaled by illumination of the red stimulus light and was separated from the following component by a 10-minute intercomponent interval. During the intercomponent interval, no lights were illuminated, and responses on the lever had no programmed consequences.

With this rapid-evaluation procedure, a unique dose per injection of drug was available during each of the four components of a session. A component ended after 20 injections of that particular dose were earned or 25 minutes had elapsed, whichever occurred first. Drug concentration was kept constant throughout a session and doses were altered by adjusting the dura-

tion of activation of the injection pump. Doses were evaluated in one-half logarithm unit steps. Monkeys were initially trained with *l*-cocaine in doses of 0.0003 (0.5 second), 0.001 (1.7 seconds), 0.003 (5 seconds), and 0.01 (16.7 seconds) mg/kg per injection. Four dose orders were used: ascending, descending, and two mixed orders. Selection of dose order was made randomly.

When saline solution was substituted, injection durations continued to be different in each component, as they were with drug injections. If rates of saline-maintained responding were higher than 0.5 response per second at any injection duration, saline solution was substituted again until rates were consistently below 0.5 response per second. Different doses of *l*-deprenyl, *d*-deprenyl, *l*-methamphetamine, or *l*-cocaine were substituted during single sessions after rates of saline-maintained responding were low. Full dose-response curves were obtained by testing overlapping ranges of cumulative doses during different test sessions. When higher or lower dose ranges were tested, drug concentration was altered: injection durations were always 0.5, 1.7, 5 or 16.7 seconds. Before some sessions, an intravenous dose of *l*-deprenyl was given through the catheter 30 minutes before the start of the session (pretreatment), with different doses of *l*-cocaine, *l*-methamphetamine, or saline available for self-administration during the session.

Nine rhesus monkeys (six males and three females) served as subjects in the self-administration studies. Three monkeys were used to evaluate the reinforcing effects of *d*-deprenyl. Five monkeys (including the three used to evaluate the reinforcing effects of *d*-deprenyl) were used as subjects for evaluation of the effects of *l*-deprenyl on the reinforcing effects of cocaine. Three monkeys (two of which participated in one or more of the other studies) were used for evaluation of the effects of *l*-deprenyl on the reinforcing effects of *l*-methamphetamine.

The reinforcing effects of *d* - and *l*-deprenyl were evaluated between one and six times in each monkey; a different dose range was typically used when more than one evaluation was made. The effects of pretreatment with *l*-deprenyl (1.0 and 3.2 mg/kg, intravenously) were usually evaluated only once in monkeys self-administering cocaine; *l*-deprenyl (1.0 mg/kg, intravenously) was administered between two and four times to monkeys self-administering *l*-methamphetamine.

An additional three male rhesus monkeys served as subjects to evaluate the effects of *l*-deprenyl on food-reinforced behavior. These animals were on a schedule of limited feeding, receiving 20 to 25 Purina high-protein monkey chows each day. The apparatus used in this portion of the experiment has been described by Negus et al.[31] Subjects remained in their home cages during testing. An experimental panel containing two levers (model PRL-001, BRS/LVE, Laurel, Md.), on either side of a food receptacle, with colored stimulus lights above each of the levers, was mounted on one wall of each cage. The reinforcer was a 300 mg, banana-flavored pellet (formula G/T, P.J. Noyes Co., Lancaster, N.H.), delivered by an externally mounted pellet dispenser (model G5210, Gerbrands Co., Arlington, Mass.).

Sessions were carried out five to six days per week. A session was initiated with a timeout period during which no stimulus lights were illuminated and responses on the levers had no programmed consequences. After 10 minutes, the stimulus lights were turned on; in the presence of the lights 30 responses on either lever (fixed ratio 30) resulted in the delivery of a food pellet. The lights were extinguished again for 10 minutes after 10 pellets had been delivered or 5 minutes had passed, whichever occurred first, which initiated another 15-minute cycle (10-minute timeout followed by a 5-minute response period). A daily session consisted of five of these cycles; sterile water or a sham injection was given at the beginning of each time-out period on baseline sessions. For a drug test to be given, the monkeys were required to respond at a rate of 1.0 response per second or higher on all five cycles of the session immediately preceding the test session.

During the test session, increasing doses of *l*-deprenyl were given subcutaneously on subsequent cycles. Administration was cumulative in that each injection contained sufficient drug so that this plus the amount administered in previous injections was a half log-unit increment in total dose. In this fashion the drug was administered until 3.2 mg/kg *l*-deprenyl had been administered. Because this was completed in four cycles, the monkeys were exposed to a fifth 15-minute cycle that was preceded by an injection of saline solution.

RESULTS AND DISCUSSION

Cocaine was an effective reinforcer of self-administration behavior in the present experiments (Fig. 1) as it has been in previous studies with similar schedules and access conditions.[30] As the injection dose of cocaine was increased, a dose-dependent increase occurred in rates of responding, with maximum overall rates of lever pressing exceeding 2 responses per second at an injection dose of 0.01 mg/kg. In marked contrast, neither *l*-deprenyl nor its enantiomer *d*-

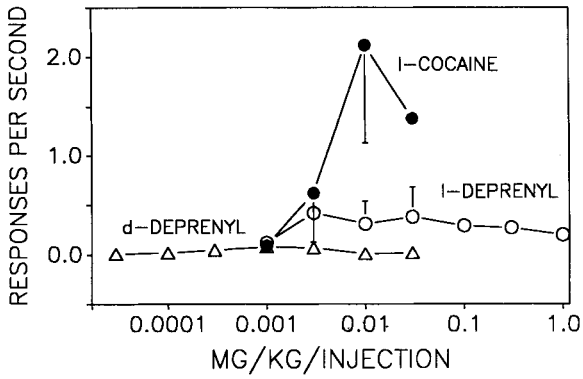

Fig. 1. Rates of responding maintained by different doses of *l*-cocaine *(closed circles)*, *d*-deprenyl *(open triangles)*, or *l*-deprenyl *(open circles)* when delivered intravenously to rhesus monkeys. *Abscissa* is drug dose in mg/kg per injection. *Ordinate* is rate of responding generated when responses produced intravenous administration of indicated doses; *vertical lines* are standard errors of mean. Where no SEMs are apparent, they are either within size of symbol or fewer than three monkeys were studied at that particular dose.

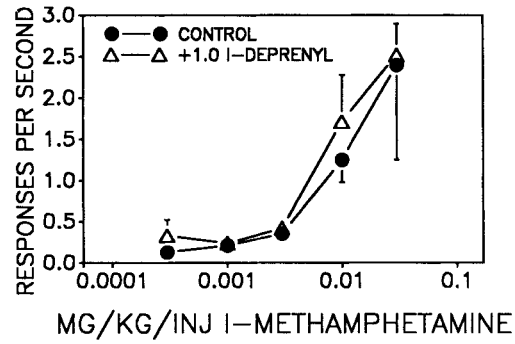

Fig. 2. Effects of 1.0 mg/kg *l*-deprenyl *(open triangles)* on rates of responding maintained by intravenous delivery of *l*-methamphetamine. Rate-maintaining effects of *l*-methamphetamine in absence of *l*-deprenyl are indicated by *closed circles*. *Abscissa* is dose of *l*-methamphetamine in mg/kg per injection; *ordinate* is response rate generated by intravenous administration of indicated doses; *vertical lines* are standard errors of mean. Where no SEMs are apparent, they are within size of symbol.

deprenyl maintained the self-administration behavior of rhesus monkeys above saline levels (Fig. 1). An injection dose of *l*-deprenyl as high as 1.0 mg/kg was studied, which would have allowed monkeys to self-administer as much as 20.0 mg/kg *l*-deprenyl intravenously within a 25-minute session. Because a cumulative subcutaneous dose of *l*-deprenyl of 3.2 mg/kg markedly depressed food-maintained responding (Table I), the dose range of *l*-deprenyl selected for evaluation was clearly large enough. *d*-Deprenyl at doses up to 0.03 mg/kg per injection was also ineffective in maintaining self-administration. Because of a tendency for monkeys to show reduced rates of cocaine-maintained responding for several sessions after evaluation of the reinforcing effects of 0.001 to 0.03 mg/kg per injection of *d*-deprenyl, a higher dose range was not evaluated. In other studies that compared behavioral effects of *l* - and *d*-deprenyl in rats[32] or monkeys,[27] *d*-deprenyl was more potent than *l*-deprenyl, although it is less potent as an MAO-B inhibitor. Perhaps this is attributable to the fact that the metabolism of *d*-deprenyl results in the metabolites *d*-methamphetamine and *d*-amphetamine, which are more potent than the metabolites of *l*-deprenyl, *l*-methamphetamine and *l*-amphetamine, in behavioral measures.[33-35]

The major metabolite of *l*-deprenyl in humans is *l*-methamphetamine, which accounts for approximately 50% of the initial metabolism of the parent compound.[36] For example, after an oral dose of 10.0 mg *l*-deprenyl to human subjects, 4.0 mg *l*-methamphetamine and somewhat less than 1.0 mg of *l*-amphetamine can be recovered from urine.[36,37] The metabolism of deprenyl is stereospecific, with only *l*- or *d*-isomers of methamphetamine, amphetamine, and desmethyldeprenyl resulting from metabolism of *l*-deprenyl or *d*-deprenyl, respectively; there is no racemic transformation.[36]

Table I. Effects of cumulative doses of *l*-deprenyl on food-maintained responding

	Monkey		
	E108	*PA*	*407*
Control rate (responses/sec)	2.54	2.74	3.52
+ 0.1 mg/kg *l*-deprenyl	1.96	2.52	3.82
+0.32 mg/kg *l*-deprenyl	1.96	3.06	3.75
+ 1.0 mg/kg *l*-deprenyl	2.28	2.61	3.69
+ 3.2 mg/kg *l*-deprenyl	1.32	1.46	2.89
30 after 3.2 *l*-deprenyl	0	0	

In the present experiments, *l*-methamphetamine in doses of 0.01 and 0.03 mg/kg per injection was an effective reinforcer of intravenous self-administration behavior by the rhesus monkeys (Fig. 2). Response rates of more than 2 per second were maintained by 0.03 mg/kg per injection of *l*-methamphetamine. These rates of responding were similar to the maximal rates of responding maintained by intravenous injections of cocaine (Fig. 1). Because *l*-deprenyl is pri-

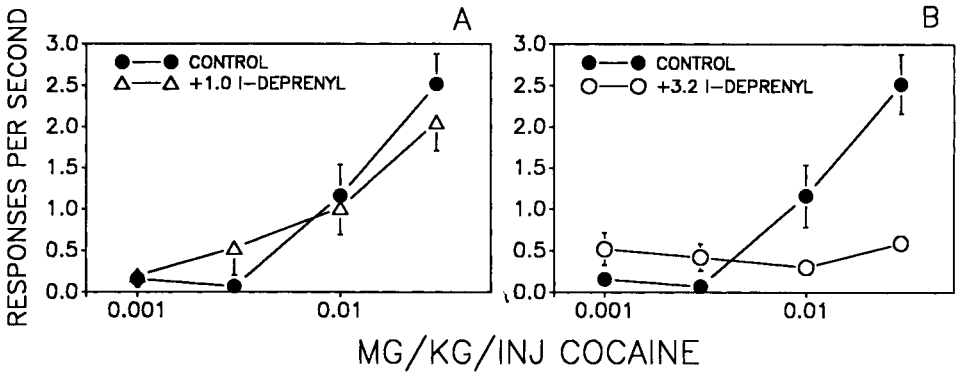

Fig. 3. Effects of 1.0 mg/kg *l*-deprenyl (**A**, *open triangles*) or 3.2 mg/kg *l*-deprenyl (**B**, *open circles*) on behavior maintained by intravenous administration of *l*-cocaine. Rates of cocaine-maintained responding are indicated by *closed circles* in both graphs. *Abscissae* are doses of cocaine in mg/kg/injection; *ordinates* are rates of responding maintained by these doses of cocaine in presence and absence of *l*-deprenyl given intravenously 30 minutes before beginning of session; *vertical lines* are standard errors of mean. Where no SEMs are apparent, they are within size of symbol.

marily metabolized to *l*-methamphetamine, at the 30- to 100-fold higher injection dose levels of *l*-deprenyl studied, any self-administered injections of *l*-deprenyl should have eventually led to blood levels of *l*-methamphetamine similar to those generated by *l*-methamphetamine self-administration. However, *l*-deprenyl injection doses as high as 1.0 mg/kg did not maintain rates of responding above saline levels, suggesting that the increase in *l*-methamphetamine blood levels that resulted from the metabolism of self-administered *l*-deprenyl was not rapid enough to allow *l*-deprenyl to serve as an effective reinforcer of self-administration behavior under the present schedule and access conditions. It is also possible that residual *l*-deprenyl could counteract any reinforcing effects of the *l*-methamphetamine and *l*-amphetamine metabolites. However, this is unlikely because pretreatment with 1.0 mg/kg *l*-deprenyl before self-administration sessions failed to alter behavior maintained by *l*-methamphetamine during the session (Fig. 2). This dose of *l*-deprenyl is sufficient to modify self-administration of β-PEA.[1] A dose of 0.3 mg/kg *l*-methamphetamine, given to a single monkey, failed to modify behavior maintained by *l*-methamphetamine (data not shown).

The lack of effect of *l*-deprenyl on *l*-methamphetamine self-administration is surprising, because presession intravenous treatment with *l*-deprenyl should have resulted in appreciable blood levels of *l*-methamphetamine during self-administration sessions. This failure to see altered *l*-methamphetamine self-administration behavior after presession treatment with 1.0 mg/kg *l*-deprenyl suggests that the simple presence of drug at the critical receptor is not responsible for the reinforcing effects. Rather, a drug must have a rapid onset of action after each injection for it to maintain self-administration behavior under the conditions described here.

Treatment with 1.0 mg/kg *l*-deprenyl in the present experiments also failed to produce any changes in the dose-response curve for *l*-cocaine self-administration, although such treatment should have resulted in appreciable metabolite levels of *l*-methamphetamine and perhaps *l*-amphetamine during the self-administration session (Fig. 3, *A*). After a dose of 3.2 mg/kg *l*-deprenyl, the monkeys responded at nearly the same rate in each of the four components of cocaine availability. For three of the four tested monkeys, this stabilized rate was higher than that maintained by the smaller two doses of cocaine and considerably lower than rates maintained by the larger two doses of cocaine. The data for these three monkeys are shown in Fig. 3, *B*. The fourth monkey, whose data were not included in the figure, showed the same general effect of consistent response rates throughout the session. However, on both occasions on which this monkey was given 3.2 mg/kg *l*-deprenyl, the rates of cocaine-maintained responding were very high and ranged from 3 to 5 responses per second, independent of the dose of cocaine delivered as a consequence of responding. A fifth monkey showed a similar effect of 3.2 mg/kg *l*-deprenyl in an earlier pilot study of this dose. The high rates of cocaine-maintained responding in these

two monkeys after a high dose of *l*-deprenyl are consistent with the concept that *l*-deprenyl or its metabolites prevent the monkeys from discriminating the rapid onset of effects of self-administered injections of *l*-cocaine. Thus *l*-cocaine may lose the dose-dependent nature of its reinforcing effects in the presence of elevated levels of *l*-methamphetamine and *l*-amphetamine.

A dose of 3.2 mg/kg *l*-deprenyl reduced slightly rates of food-maintained responding 15 minutes after cumulative subcutaneous administration and completely suppressed this behavior 30 minutes after administration in each of the three monkeys studied (Table I). This delayed effect indicates that slowly appearing amphetamine metabolites of *l*-deprenyl are responsible for its rate-suppressing effects. It is interesting that the dose of *l*-deprenyl that, given subcutaneously, completely suppressed food-maintained responding, when given intravenously did not completely suppress similar rates of cocaine-maintained responding in any monkey and produced stimulation in a few subjects. It is not clear whether this difference is related to the different routes of administration of *l*-deprenyl, and consequently a potentially different metabolic rate, or to a difference in the reinforcer maintaining behavior, perhaps reflecting an anorectic effect of the amphetamine metabolites of *l*-deprenyl.

l-Deprenyl has recently been suggested as a medication for the treatment of various types of drug abuse. Such a use is postulated on the basis of its ability at certain doses to facilitate dopaminergic functions either by directly blocking reuptake of dopamine[38,39] or by elevating β-PEA levels[12] and thus stimulating dopamine release and/or potentiating postsynaptic actions of dopamine. Although the present results do not indicate that *l*-deprenyl would be of use in selectively modifying ongoing use of cocaine or other stimulants, it is possible that it might have effects in preventing relapse to drug use after drug use is terminated by other treatments. Such an effect could perhaps be mediated by amelioration of certain symptoms of drug withdrawal that might otherwise serve to trigger return to use of drugs.

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