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ORIGINAL INVESTIGATION

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Psychomotor stimulant effects of β-phenylethylamine in monkeys treated with MAO-B inhibitors

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Abstract *Rationale and objective:* Sufficiently high doses of β-phenylethylamine (β-PEA), a trace amine that is rapidly metabolized by monoamine oxidase-type B (MAO-B), can produce effects comparable to those of cocaine or methamphetamine (MA). The present experiments were conducted to study how the discriminative-stimulus (S^D) and reinforcing-stimulus (S^R) effects of β-PEA in monkeys are modified by treatment with inhibitors of MAO-B [R-(–)-deprenyl and MDL 72974]. *Methods and results:* In studies of its S^D effects, doses of β-PEA up to 30 mg/kg engendered only sporadic responding on the drug-associated lever in squirrel monkeys that discriminated intramuscular injections of 0.3 mg/kg MA from vehicle whereas lower doses of 0.3–1.0 mg/kg β-PEA produced full substitution when administered after either R-(–)-deprenyl or MDL 72974 (0.3 mg/kg). The MA-like S^D effects of β-PEA were attenuated by either dopamine D_1 or D_2 receptor blockers. In studies of its S^R effects, high doses of β-PEA maintained responding in two of three monkeys under a second-order fixed-interval schedule (3.0 or 10 mg/kg per injection) and two of three monkeys under a simple fixed ratio (FR) schedule (0.3–1.0 mg/kg per injection) of intravenous (i.v.) self-administration. MAO-B inhibition by R-(–)-deprenyl or MDL 72974 enhanced the S^R effects of β-PEA in all monkeys and, under the FR schedule, induced a 30-fold or greater leftward shift in the dose-response function for its i.v. self-administration. Based on time-course determinations, the enhanced S^R effects of β-PEA under the FR schedule were long-lasting and dissipated gradually over 3–7 days. *Conclusions:* These results show that inhibition of MAO-B enhances S^D and S^R effects of β-PEA in monkeys, presumably by delaying its inactivation. MAO-B inhibition leading to increased levels of β-PEA may be useful, alone or in combination with other therapeutic agents, in the pharmacological management of selected aspects of drug dependence.

Keywords MAO-B inhibition · β-PEA · Drug discrimination · Drug self-administration · Psychomotor stimulant · Drug abuse

Abbreviations SCH 39166: (–)-*trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho[2,1-*b*]azepine · MDL 72974: (E)-2-(4-fluoro-phenethyl)-3-fluoroallylamine

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Introduction

β-Phenylethylamine (β-PEA) is a monoamine product of the decarboxylation of the amino acid L-phenylalanine. It is heterogeneously distributed throughout mammalian brain in trace concentrations (generally about 2 nM) and it is extensively and rapidly metabolized by monoamine oxidase-type B (MAO-B; Johnston 1968; Henry et al. 1988; Paterson et al. 1990). Treatment with clinically relevant doses of R-(–)-deprenyl (up to 10 mg) that selectively inhibit MAO-B can result in a nearly 100-fold increase in the urinary excretion of β-PEA. Such doses of R-(–)-deprenyl also have been shown to produce a 1,000- to 3,000-fold increase in levels of the monoamine in postmortem brains taken from patients treated with R-(–)-deprenyl for Parkinsonism when compared with control levels (Elsworth et al. 1978; Riederer and Youdim 1986).

A functional role for β-PEA has been extensively investigated. It is thought to enhance dopaminergic trans-

mission, yet its particular mechanism of action remains uncertain (Paterson et al. 1990). β-PEA has been reported to bind to a specific recognition site in brain (Antelman et al. 1977; Jackson 1978; Hauger et al. 1982). However, the suggestion that such binding sites might be receptors that mediate β-PEA's actions has not been confirmed and, more recently, those data have been alternatively proposed to reflect interactions between β-PEA and endogenous MAO (Li et al. 1992). In studies employing in vitro (synaptosomal or striatal brain slice) or in vivo preparations, β-PEA additionally has been found to inhibit the uptake and promote the release of the monoamines dopamine, norepinephrine, and, to a lesser extent, serotonin (Raiteri et al. 1977; Dyck 1983, 1989; Philips and Robson 1983; Bailey et al. 1987; Parker and Cubeddu 1988). The potency with which β-PEA induces changes in the activity of these neurotransmitters is comparable to the potency with which amphetamines produce similar actions (Nakamura et al. 1998). However, concentrations of β-PEA necessary for such actions are at least 100-fold higher than those measured in the CNS under basal conditions. They generally occur only following exogenous administration of large doses of β-PEA or, alternatively, blockade by MAO-B inhibitors of its oxidative deamination. Similarly high concentrations of β-PEA also are thought to interact directly with postsynaptic monoaminergic receptors to facilitate dopaminergic transmission (see Paterson et al. 1990; Barroso and Rodriguez 1996). However, it is presently unknown whether such interactions occur under physiologically normative conditions.

The behavioral effects of β-PEA that occur following administration of large doses likely result from its effects on monoamine turnover and are comparable to those of sympathomimetic psychomotor stimulant drugs such as d-amphetamine. For example, β-PEA has been reported to induce increases in locomotor activity and stereotypic behavior in rats, mice, and monkeys (Tinklenberg et al. 1978, 1979; Jackson 1988; Paterson et al. 1990). β-PEA also has been reported to increase behavior maintained by intracranial self-stimulation (Stein 1964; Greenshaw et al. 1985) and, like d-amphetamine or cocaine, to maintain intravenous (i.v.) self-administration in non-primate species under varying parameters and schedules of reinforcement (Risner and Jones 1977; Shannon and DeGregorio 1982; Shannon and Thompson 1984). These last findings, though based on the effects of exogenously administered β-PEA, have led to the suggestion that endogenous β-PEA may play a role in reinforcement processes in the CNS (Greenshaw et al. 1985).

Although relatively large doses of β-PEA are required to produce behavioral effects, its potency and effectiveness are enhanced by MAO-B inhibition. For example, treatment with the irreversible MAO-B inhibitor R-(–)-deprenyl (selegiline), which may be used in the treatment of Parkinson's disease, has been shown to potentiate β-PEA-induced behavioral effects, e.g., stereotypies in rodents (Ortmann et al. 1984; Timar and Knoll 1986). It is noteworthy that R-(–)-deprenyl recently has been forwarded as a candidate medication for the treatment of cocaine and, possibly opioid, dependence (Grasing and Ghosh 1998; Bartzokis et al. 1999). Pharmacologically, the actions of R-(–)-deprenyl are complex, and involve its conversion to amphetamine metabolites, its inhibition of both MAO-A and MAO-B leading to increased levels of dopamine and β-PEA, and, at relatively large doses, its inhibition of dopamine uptake (Knoll 1978, 1987; Heinonen and Lammintausta 1991; Fang and Yu 1994). The contribution of these different actions, independently or interdependently, to the potential utility of R-(–)-deprenyl as a pharmacotherapeutic for cocaine (or opioid) dependence is currently ambiguous.

The present experiments were conducted, first, to examine the enhancement of stimulant-like discriminative-stimulus and reinforcing effects of β-PEA by treatment with R-(–)-deprenyl in monkeys and, second, to compare alteration in the behavioral effects of β-PEA produced by the structurally dissimilar MAO-B inhibitors R-(–)-deprenyl and MDL 72974. Initially, the effects of β-PEA and their antagonism by dopamine D_1 and D_2 receptor blockers were studied in squirrel monkeys trained to discriminate intramuscular (i.m.) injections of 0.3 mg/kg methamphetamine (MA) from vehicle. Subsequently, β-PEA was evaluated in squirrel monkeys and rhesus monkeys trained to self-administer cocaine under different self-administration procedures previously used to assess the reinforcing effects of drugs. Results of the present experiments indicate that inhibition of MAO-B by either R-(–)-deprenyl or MDL 72974 increases the potency of β-PEA for producing MA-like discriminative-stimulus effects and for maintaining i.v. drug self-administration behavior. Such actions presumably result from the delayed inactivation of β-PEA and may be useful in the pharmacological treatment of selected aspects of drug dependence.

Materials and methods

Subjects

Nine adult male squirrel monkeys (*Saimiri sciureus*), weighing 750–1,000 g, and three adult rhesus monkeys (*Macaca mulatta*; two males and one female), weighing 4.9–6.4 kg were individually housed in stainless steel cages in climate-controlled vivaria with regular access to Purina Monkey Chow (Ralston-Purina, St. Louis, Mo., USA) and water. Each monkey's diet also was supplemented with fresh fruit and vegetables. Six squirrel monkeys were studied under the drug discrimination procedure described below. The remaining six monkeys were used in i.v. drug self-administration studies. For i.v. self-administration studies, both squirrel monkeys and rhesus monkeys were surgically prepared with indwelling i.v. catheters under general anesthesia and using sterile procedures. Squirrel monkeys wore vests to protect the catheter in the home cage and were studied in separate sound-attenuated chambers, whereas rhesus monkeys wore tubular stainless steel harness/spring arm assemblies (Mackal, Chicago, Ill., USA), and were studied in the home cage. All rhesus monkeys (except V64) previously were trained under the procedures described below and had previous exposure to behaviorally active drugs including psychomotor stimulants. Monkey V64 was experimentally na at the outset of experiments.

The animals used in this study were maintained in accordance with guidelines described in the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare publication number (NIH)85–23, revised 1985. Research protocols were approved by the Institutional Animal Care and Use Committees of the Harvard Medical School, University of Michigan Medical School, and the Intramural Research Program of the National Institute on Drug Abuse.

Drug discrimination

Apparatus

During experimental sessions in a sound-attenuating experimental chamber, squirrel monkeys sat in a Plexiglas chair equipped with stimulus lights, two response levers, and a tailstock-electrode assembly for drug-discrimination studies as described elsewhere (Kelleher and Morse 1968; Tidey and Bergman 1998). Monkeys were trained to discriminate i.m. injections of MA from saline under a ten-response fixed-ratio (FR10) schedule of stimulus-termination. Completion of ten lever-press responses or delivery of four electric stimuli turned off the lights and terminated the program, initiating a 40-s time-out (TO) period. Once responding was stable, monkeys were trained to discriminate i.m. injections of 0.3 mg/kg MA (1.0 mg/kg MA in S-173) from saline in daily sessions comprising one to four components. The left lever was associated with MA injection in four monkeys and the right lever was associated with MA in the other two monkeys. During training sessions, presses on the incorrect lever reset the response requirement.

Drug testing

Drug testing was conducted once or twice per week, and training sessions were conducted on intervening days. Test sessions were conducted if >90% of all responses were made on the injection-appropriate lever during the preceding training session and four of the last five training sessions. Test sessions consisted of four components, each preceded by a 10-min TO. During test components, ten consecutive responses on either lever terminated stimulus lights and the programmed delivery of electric stimuli. Prior to beginning experiments with drugs, the effects of saline injections (0.3 ml i.m.) were determined several times in all monkeys.

Experiments began with determination of the effects of cumulative doses of β-PEA (1.0–30.0 mg/kg), the selective MAO-A inhibitor clorgyline (Johnston 1968; 0.1–3.0 mg/kg), and the selective irreversible MAO-B inhibitors R-(–)-deprenyl (0.03–1.0 mg/kg) and MDL 72974 (Zreika et al. 1989; 1.0–17.8 mg/kg) in four monkeys (S-75, S-125, S-173, and S-491). Dose-effect data were obtained for up to four cumulative doses during a single test session or, by studying overlapping ranges of cumulative doses, five or more drug doses across separate test sessions (Spealman 1985; Bergman and Spealman 1988). Next, the effects of β-PEA following pretreatment with the MAO-A inhibitor clorgyline or the MAO-B inhibitors R-(–)-deprenyl or MDL 72974 were examined in the same monkeys by administering these drugs 10 min before the first component of the session and, subsequently, administering cumulative doses of β-PEA during sequential components of the test session. Finally, modification of the effects of β-PEA after treatment with MDL 72974 by either the dopamine D_1 receptor blocker SCH 39166 (0.03 or 0.1 mg/kg, i.m.) or the dopamine D_2 receptor blocker nemonapride (0.003 or 0.006 mg/kg, i.m.) was examined in four monkeys (S-91, S-92, S-125, and S-173). After establishing the effects of the MDL 72974/β-PEA combination in all monkeys, subjects received single doses of the dopamine receptor blockers 5 min (SCH 39166) and 60 min (nemonapride) prior to injection with MDL 72974 (i.e., 15 and 75 min, respectively, prior to the test session). Doses of the dopamine receptor blockers and pretreatment times were selected on the basis of results from previous studies of their effects on schedule-controlled behavior in squirrel monkeys (Bergman et al. 1990) and were administered no more often than twice weekly in individual monkeys.

Data analysis

Response rate was calculated by dividing the total number of lever-press responses in each component by the total component duration. Percent drug-lever responding was calculated by dividing the number of responses on the MA-associated lever by the total number of responses on both levers. Components in which the average response rates were less than 0.2 responses/s were excluded from analysis. Full substitution with β-PEA alone or following administration of R-(–)-deprenyl or MDL 72974 in the individual subject was defined as ≥90% responding on the MA-associated lever following at least one dose of test drug(s). Data for the group of monkeys are expressed in terms of averaged results (± SEM). In antagonism studies, a difference of >2 SD between averaged ED_{50} values for β-PEA alone and following pretreatment with a dopamine receptor blocker was considered statistically significant.

Drug self-administration

Apparatus

During daily sessions (Monday to Friday), squirrel monkeys sat in a customized Plexiglas chair equipped with a response lever and stimulus lights. The external portion of the i.v. catheter connected to an automatic infusion pump (Harvard Apparatus, Braintree, Mass., USA) outside the sound-attenuating chamber; each operation of the pump delivered 0.2 ml fluid in a 0.2-s infusion. At the end of the daily session, the catheter was flushed through with saline and obturated.

The experimental apparatus and conditions for experiments with rhesus monkeys were comparable to those previously described (Winger et al. 1989). Briefly, a panel equipped with stimulus lights and two response levers was fastened to the home-cage. The external portion of the catheter passed through a protective spring arm, exited the cage, and connected to an infusion pump (model MHRK 55; Watson-Marlow, Falmouth, UK) through an in-line 0.2-µm sterilizing filter (Gelman Sciences, Ann Arbor, Mich., USA) and one port of a three-way valve. The other ports of the valve connected to syringes for saline or drug delivery.

Behavioral procedures

Experimental procedures differed in studies with squirrel monkeys and rhesus monkeys. For squirrel monkeys, i.v. cocaine self-administration behavior was established under a second-order 5-min fixed-interval (FI) schedule with 10-response FR units [FI 5′ (FR10:S)]. Under this schedule, the completion of every tenth lever-press response produced a brief 2-s flash of colored stimulus lights (FR10:S). Completion of the first FR unit after the passage of a 5-min interval of time (FI 5′) produced both the 2-s flash and a 200-ms i.v. infusion of 56 µg/kg cocaine. A 60-s TO during which all lights were extinguished and responses had no programmed consequences followed each infusion. Daily sessions ended after eight presentations of the second-order schedule or after 90 min.

After cocaine-maintained performance was stable, the effects of saline or β-PEA were studied in each squirrel monkey by replacing cocaine for three consecutive sessions with saline or different unit doses of β-PEA (0.1–10.0 or, in S-391, 17.8 mg/kg per infusion). After each substitution, baseline cocaine conditions were restored for several sessions to re-establish control performance. When initial dose-effect determinations for β-PEA were completed, its effects were re-determined in the presence of 1.0 mg/kg R-(–)-deprenyl, given i.m. 60 min before test sessions. Periods of substitution were separated by a week or more of base-

line self-administration to permit effects of R-(–)-deprenyl treatment to dissipate.

For rhesus monkeys, i.v. cocaine self-administration behavior was maintained under a 30-response FR schedule, with a 45-s TO following each completion of the response requirement (FR30; TO 45-s). Under this schedule, every 30th response on the lever during the illumination of red stimulus lights operated the infusion pump, turned off the red stimulus lights, and turned on green stimulus lights (see below). When the TO 45-s ended, the green lights turned off, the red lights turned on again, and the self-administration schedule was again in effect.

Two 130-min sessions of drug self-administration were scheduled each day (10:00 a.m. and 4:00 p.m.) Each session was divided into four 25-min components, with a 10-min blackout period between components. Infusion duration was varied from component to component to allow self-administration of a two log unit range of i.v. doses. During training and under baseline conditions, i.v. doses of cocaine that were available for self-administration ranged from 0.001 to 0.03 mg/kg per infusion, corresponding to pump durations of 0.5, 1.7, 5.0, or 16.7 s. Dose order varied among subjects; however each monkey was exposed to an ascending, descending, or mixed order of doses on a random basis. During the availability of cocaine or β-PEA for i.v. self-administration, saline was substituted approximately every third session and until response rates were below 0.5 responses/s in all four components of the session.

In experiments with β-PEA, substitution for cocaine occurred no more frequently than once every fourth session. Initially, self-administration of β-PEA was studied with unit doses ranging from 0.001 to 0.32 mg/kg (monkey RC 239) or 1.0 mg/kg (monkeys 168F and V64). For all monkeys, the order of dose availability (ascending, descending, mixed) varied randomly from session to session. A full range of unit doses was studied by evaluating the effects of overlapping sets of four unit doses in individual test sessions. Following experiments with self-administration of β-PEA alone, its effects after i.v. pretreatment with 1.0 mg/kg of the MAO-B inhibitor R-(–)-deprenyl (30 min prior to morning test sessions) were determined in all monkeys. Next, the effects of β-PEA were determined again at 24 and 72 h in monkey RC 239, at 30, 54, and 120 h in monkey 168F, or at 48 h in monkey V64. During intervening sessions, either cocaine or saline were available for self-administration.

More than 7 days following the completion of experiments with R-(–)-deprenyl, a final set of studies was conducted to determine how β-PEA self-administration was modified by the MAO-B inhibitor MDL 72974 (0.3 mg/kg i.m., 10 min before the morning test session). As with R-(–)-deprenyl, self-administration of β-PEA was evaluated again at varying time points after MDL 72974 (48 and 102 h in 168F, and 30, 72, 120, and 174 h in RC 239). Catheter-related problems prevented further determinations in the third monkey, V64.

Data analysis

Response rate for individual subjects was calculated by dividing the number of lever-press responses during the session (squirrel monkeys) or component of the session (rhesus monkeys) by the time the session or component was in effect, excluding the brief 2-s stimulus presentations and the TO periods that followed infusions. Self-administration under the second-order FI schedule is expressed as the average of response rates from the last two test sessions in which that dose was studied. Self-administration under the FR30 schedule is given as the response rates during components of the test session when different doses of β-PEA were available. Response rates that differed by at least two standard deviations of the mean from mean values obtained during substitution with saline were considered to be statistically significant.

Drugs

Clorgyline, MA HCl, and β-PEA HCl were obtained from Sigma Pharmaceuticals, St. Louis, Mo., USA. R-(–)-deprenyl and MDL 72974 were kindly supplied by Chinoin, Budapest, Hungary and Merrell-Dow Research Institute, Strasbourg, France, respectively. Drugs were dissolved and diluted to concentration with sterile water or 0.9% saline. Excepting for i.v. self-administration or i.v. pretreatment with R-(–)-deprenyl in rhesus monkeys, drug solutions were administered i.m. in calf or thigh muscle in volumes of 0.3 ml/kg body weight or less. Control infusions were equivalent volumes of saline.

Results

Methamphetamine discrimination

Control performance

All monkeys consistently discriminated injections of MA from saline; injections of the training dose of MA (0.3 or, for S-173, 1.0 mg/kg) produced >99% responding on the MA-associated lever, and injection of saline produced an average of <1% MA-lever responding. Control response rates (responses/s) were consistent across the course of experiments and, for the group of six monkeys, averaged 1.91±0.31 and 1.41±0.18 (mean ± SEM) after injection of, respectively, the training dose of MA and saline.

Substitution with β-PEA

β-PEA produced varying degrees of responding on the MA-associated lever in individual monkeys (up to 55% at 17.8 mg/kg in S-125) but failed to substitute fully for MA in any subject (Table 1; dashed lines in Fig. 1). The greatest responding on the MA-associated lever occurred at doses of 17.8 or 30.0 mg/kg and averaged 39% among monkeys (Table 1). At these doses of β-PEA, response rates did not differ appreciably from control values and, for the group, averaged 1.95±0.24 responses/s. Cumulative doses above 30.0 mg/kg were not studied to avoid potential adverse effects of high tissue concentrations of β-PEA.

Cumulative doses of clorgyline (0.1–3.0 mg/kg), R-(–)-deprenyl (0.03–1.0 mg/kg), and MDL 72974 (1.0–17.8 mg/kg) did not substitute for MA and did not

Table 1 Effects of β-phenylethylamine (β-PEA) in squirrel monkeys trained to discriminate injections of methamphetamine (MA) from vehicle. Data are shown for the group of four monkeys for which data are shown in Fig. 1. Results are expressed as the percentage of responses on the MA-associated lever during the component following intramuscular (*i.m.*) administration of the cumulative dose of β-PEA. Data were obtained by administering graded doses of β-PEA during sequential components of single test sessions

Monkey	Dose (mg/kg, i.m.)				
	1.0	3.0	10.0	17.8	30.0
S-75	3	16	15	29	7
S-491	0	0	14	15	25
S-125	1	2	47	55	20
S-173	35	17	25	4	44

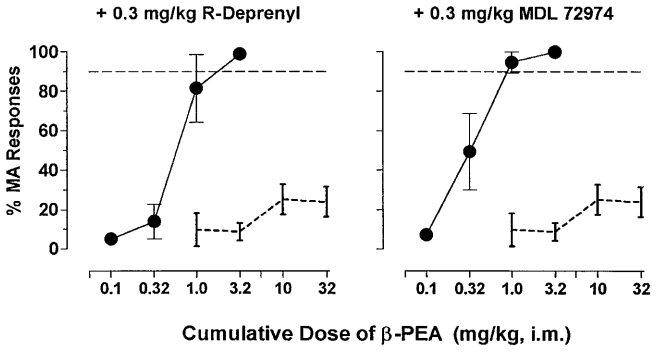

Fig. 1 Substitution for 0.3 mg/kg methamphetamine (MA) by cumulative intramuscular (i.m.) doses of β-phenylethylamine (β-PEA) after treatment with 0.3 mg/kg R-(–)-deprenyl (*left panel*) or 0.3 mg/kg MDL 72974 (*right panel*) for the group of four monkeys for which individual data are shown in Table 1. Pretreatment drugs were administered i.m. 10 min prior to the experimental session. *Abscissae:* cumulative i.m. dose of β-PEA in mg/kg; *ordinates:* percent responding on the lever associated with i.m. injection of 0.3 mg/kg MA. *Dashed lines* connecting the function showing *standard error bars* show effects of β-PEA alone averaged across monkeys. *Dashed lines* at 90% on the ordinate shows criterion for full substitution, i.e., 90% responding on the MA-associated lever

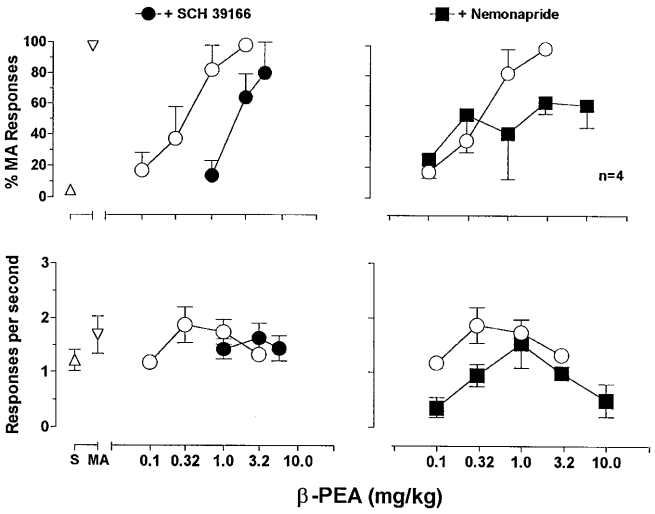

Fig. 2 Antagonism of the effects of β-PEA after treatment with 0.3 mg/kg MDL 72974 by SCH 39166 (*left panels*) or nemonapride (*right panels*) averaged for a group of four monkeys. Pretreatment doses of SCH 39166 were given i.m. 10 min prior to the experimental session and were 0.03 mg/kg in monkeys S-91, S-173, and S-98, and 0.1 mg/kg in monkey S-125. Pretreatment doses of nemonapride were given i.m. 60 min prior to the session and were 0.003 mg/kg in all monkeys. *Abscissae:* cumulative i.m. dose of β-PEA in mg/kg; *ordinates* (*top panels*): percent responding on the lever associated with i.m. injection of 0.3 mg/kg MA; *ordinates* (*bottom panels*): response rate in responses/s. Points above *S* and *MA* show mean (± SD) effects of treatment with saline and 0.3 mg/kg MA during training sessions over the course of the present studies

generally alter rates of responding (data not shown). Emesis was observed in one monkey following a cumulative dose of 17.8 mg/kg MDL 72974, and larger doses of this MAO-B inhibitor were not administered. Larger doses of clorgyline, which would inhibit both MAO-A and MAO-B, or of R-(–)-deprenyl, which might yield behaviorally active concentrations of metabolites including l-amphetamine and l-methamphetamine during the test session (Yasar and Bergman 1994), also were not studied.

Pretreatment with 0.3 mg/kg of the MAO-B inhibitors R-(–)-deprenyl or MDL 72974 markedly altered the effects of β-PEA; dose-related increases in responding on the MA-associated lever and full substitution now were observed in all monkeys (Fig. 1). The potency of β-PEA differed among monkeys but was generally comparable in the presence of the two MAO-B inhibitors; full substitution was observed at doses of 1.0–3.0 mg/kg β-PEA following treatment with R-(–)-deprenyl, and 0.3–3.0 mg/kg β-PEA following treatment with MDL 72974. ED_{50} values (mean ± SEM) for β-PEA in the presence of R-(–)-deprenyl and MDL 72974 also were comparable and averaged 0.73±0.58 and 0.59±0.30 mg/kg, respectively. Response rates were not noticeably affected by the combination of MAO inhibitors and β-PEA (data not shown). In contrast to R-(–)-deprenyl and MDL 72974, the MAO-A inhibitor clorgyline (0.3 mg/kg) did not alter the effects of β-PEA in any monkey (data not shown).

Pretreatment with the dopamine D_1 blocker SCH 39166 did not greatly disrupt responding but surmountably antagonized the effects of β-PEA in the presence of MDL 72974 in all monkeys (Fig. 2 left panels). Doses of 0.03 mg/kg or, for one monkey, 0.1 mg/kg SCH 39166 produced rightward shifts in dose-effect functions for drug discrimination, resulting in an approximately sixfold increase in the ED_{50} value for β-PEA averaged for the group of monkeys (3.52±1.99 mg/kg).

The D_2 receptor blocker nemonapride, like SCH 39166, generally attenuated the effects of β-PEA (Fig. 2 right panels). However, the effects of nemonapride were not consistent across monkeys. Thus, 0.003 mg/kg nemonapride produced an approximately twofold increase in the averaged ED_{50} value for the MDL 72974/β-PEA combination but displaced the position of its dose response function slightly leftward (one monkey), approximately threefold rightward (one monkey), or downward (two monkeys). Response rates also were somewhat decreased initially by 0.003 mg/kg nemonapride; however, these effects appeared to diminish following increasing doses of β-PEA (see Fig. 2). A higher dose of nemonapride, 0.006 mg/kg, decreased responding in all monkeys below 0.2 responses/s throughout the session, despite the administration of cumulative doses of β-PEA up to 3.0 mg/kg in the presence of MDL 72974. Consequently, drug discrimination data from those test sessions were not analyzed further.

Drug self-administration

Control performance

Cocaine (0.03 mg/kg per injection) maintained high rates of responding in squirrel monkeys under the second-

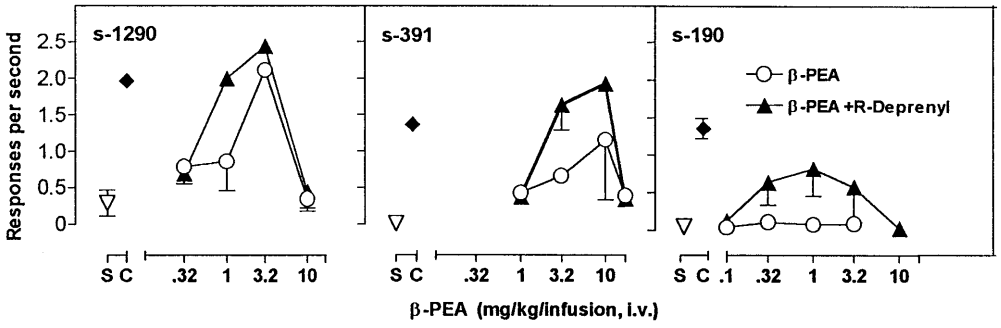

Fig. 3 Response rates maintained by β-PEA alone (*open circles*) and after i.m. treatment with R-(–)-deprenyl (*filled triangles*) under the second-order fixed-interval schedule of intravenous (i.v.) self-administration in squirrel monkeys. Panels show data for individual monkeys under the two conditions. *Abscissae:* unit dose of β-PEA available for i.v. self-administration; *ordinates:* response rates maintained by i.v. infusions of β-PEA. Each point represents the mean (± SD) response rate obtained over 3 consecutive days during which the dose was studied. *Error bars* within the symbols are not shown. Points above *S* and *C* show response rates maintained when saline and cocaine (0.03 mg/kg per infusion), respectively, were available for self-administration

order FI schedule (1.36–1.97 responses/s; Fig. 3) and rhesus monkeys under the FR30 schedule (2.47–3.08 responses/s; Figs. 4, 5). When saline was substituted for cocaine, response rates decreased to below 0.5 responses/s in both squirrel and rhesus monkeys.

Substitution with β-PEA

β-PEA produced dose-related increases in i.v. self-administration behavior in two of three squirrel monkeys (S-1290 and S-391; Fig. 3) and two of three rhesus monkeys (168F and V64; shown in Figs. 4, 5). In the remaining monkeys, doses of β-PEA up to 3.0 mg/kg (under the second-order FI schedule in squirrel monkey S-190) or 0.3 mg/kg (under the FR schedule in rhesus monkey RC 239) did not maintain rates of self-administration behavior above values obtained during substitution with saline.

Prior administration of 1.0 mg/kg R-(–)-deprenyl modified the potency or effectiveness with which β-PEA served as a reinforcer in all monkeys (Figs. 3, 4). For example, in the two monkeys (S-190 and RC 239) for which it alone failed to maintain self-administration, β-PEA produced high rates of responding and inverted U-shaped dose-effect functions characteristic for drug-maintained behavior following pretreatment with R-(–)-deprenyl. In the remaining monkeys for which β-PEA alone had served as a reinforcer, its potency or effectiveness were enhanced by R-(–)-deprenyl. These changes were especially noteworthy in rhesus monkeys responding under the FR self-administration schedule. In these subjects (168F and V64; Fig. 4), peak rates of responding after pretreatment were maintained by doses of β-PEA that were 30- to 100-fold lower than previously determined (0.01 vs 0.3–1.0 mg/kg per infusion).

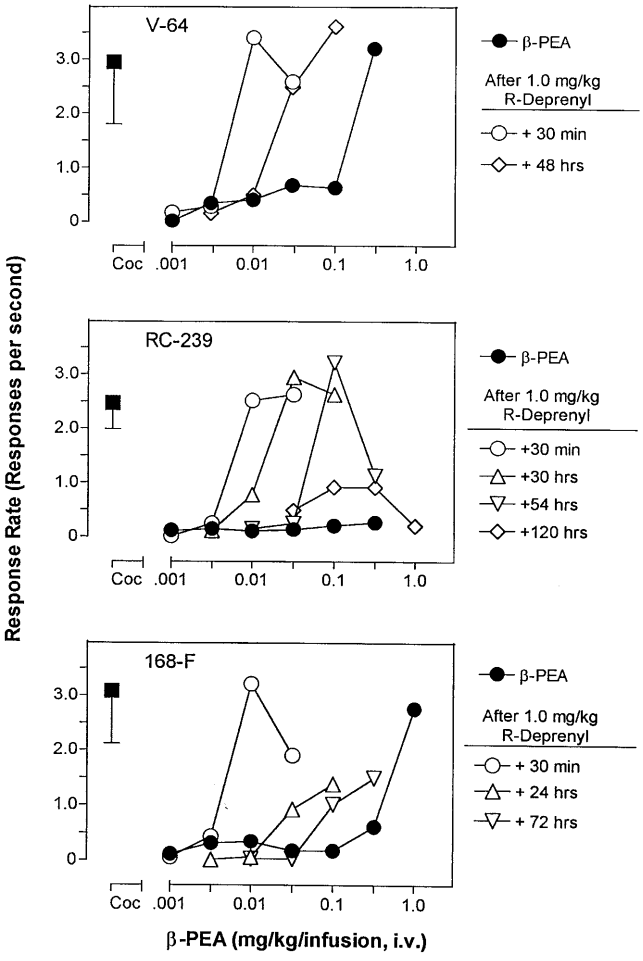

Fig. 4 Response rates maintained by β-PEA alone (*filled circles*) and at differing times following i.v. treatment with 1.0 mg/kg R-(–)-deprenyl (*open symbols*) under the fixed-ratio schedule of i.v. self-administration in rhesus monkeys. Panels show data for individual monkeys under the two conditions. *Abscissae:* unit dose of β-PEA available for i.v. self-administration; *ordinates:* response rates maintained by i.v. infusions of β-PEA. Data for self-administration of β-PEA alone were obtained over the course of at least three sessions during which overlapping ranges of doses were studied. Data for self-administration of β-PEA after treatment with R-(–)-deprenyl represent single determinations at differing time points. Data above *Coc* show average response rates (± SD) maintained by 0.03 mg/kg per infusion of i.v. cocaine in each monkey

Alteration of the reinforcing effects of β-PEA in rhesus monkeys by the selective MAO-B inhibitor MDL 72974 was highly comparable to the effects of R-(–)-deprenyl (Fig. 5). Thus, MDL 72974 engendered

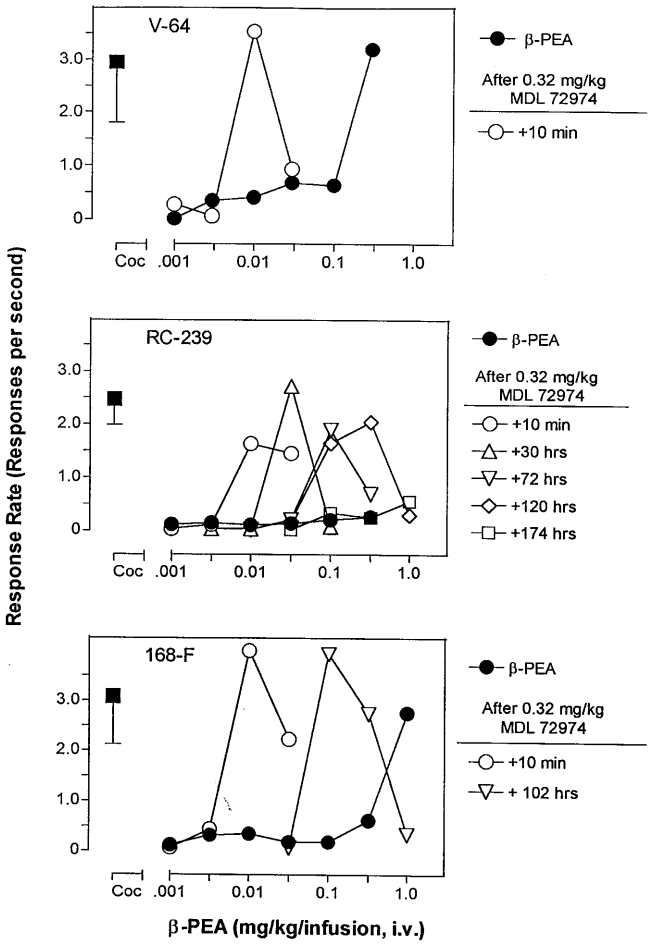

Fig. 5 Response rates maintained by β-PEA alone (*filled circles*) and at differing times following i.v. treatment with 0.3 mg/kg MDL 72974 (*open symbols*) under the fixed-ratio schedule of i.v. self-administration in rhesus monkeys. Other details as in Fig. 4

self-administration of β-PEA in RC 239 and increased the potency of β-PEA; maximal rates of drug-maintained behavior maintained by low doses of 0.01 or 0.03 mg/kg per infusion of β-PEA generally were similar to those previously maintained by higher doses of β-PEA alone or by the unit dose of 0.03 mg/kg cocaine.

Periodic inspection of the position of the β-PEA dose-effect function at differing time points in individual rhesus monkeys suggested that the effects of a single injection of R-(–)-deprenyl or MDL 72974 waned steadily but endured for at least 2 days and, in monkey RC 239, as long as 5 days. This apparent time course of action was evident in the consistent stepwise movement of the β-PEA dose-effect function toward its original position. The dissipation of the effects of MAO-B inhibition was most striking in monkey RC 239 (Figs. 4, 5 middle panel). Following sessions in which doses of 0.01 or 0.03 mg/kg per infusion of β-PEA maintained high rates of self-administration behavior, its potency gradually diminished to the point at which doses of β-PEA up to 1.0 mg/kg per infusion no longer maintained self-administration (Fig. 5).

Discussion

The present results show that β-PEA may mimic the discriminative-stimulus effects of MA and, like cocaine, maintain i.v. self-administration behavior in monkeys under differing schedules of reinforcement. β-PEA previously has been shown to increase motoric activity in rodents and monkeys (Tinklenberg 1978, 1979; Dourish and Jones 1982; Jackson 1988; Paterson et al. 1990) and to maintain i.v. self-administration behavior in dogs (Risner and Jones 1977; Shannon and DeGregorio 1982; Shannon and Thompson 1984). The present data are consistent with these previous findings in other species and support the view that the effects of exogenously administered β-PEA are highly similar to those of psychomotor stimulant drugs such as MA or cocaine in monkeys.

The similarity in behavioral effects of β-PEA and abused psychomotor stimulant drugs has been previously noted and has led to the occasional labeling of β-PEA as an "endogenous amphetamine" (Sandler and Reynolds 1976). However, such effects are not easily observed, even when circulating levels of β-PEA are increased by inhibition of MAO-B, the enzyme responsible for its degradation. For example, the MAO-B inhibitor R-(–)-deprenyl which is used clinically to retard the development of Parkinson's Disease generally does not produce psychomotor-stimulant effects at therapeutic doses nor does it possess psychomotor stimulant-like abuse liability (see, for example, O'Regan et al. 1987; The Parkinson Study Group 1989; Yasar et al. 1993). In the present studies, even following treatment with doses of R-(–)-deprenyl or MDL 72974 sufficient to completely block MAO-B activity in monkeys (Paterson et al. 1995), further administration of β-PEA was necessary to produce MA-like discriminative-stimulus effects and to engender or enhance self-administration behavior maintained by i.v. β-PEA. These findings are consistent with previous reports that MAO-B inhibition alone produces few noticeable behavioral effects in laboratory studies but can serve to exacerbate stereotypies induced by exogenously administered β-PEA in rodents (Mantegazza and Riva 1963; Ortman et al. 1984; Timar and Knoll 1986). As in the present studies, the prolonged time course of such behavioral effects of β-PEA appears to mirror the time course of MAO-B inhibition (see, for example, Turkish et al. 1988). The present findings also confirm preliminary observations that i.v. self-administration of β-PEA may be potentiated by R-(–)-deprenyl (Yasar et al. 1993) and extend those results to include the potentiation of the reinforcing effects of β-PEA by differing types of MAO-B inhibitors in both squirrel and rhesus monkeys responding under differing schedules of self-administration.

Previous studies showing that clinically relevant doses of R-(–)-deprenyl have little, if any, psychomotor stimulant effect also indicate that higher doses (≥1.0 mg/kg) may produce cocaine-, amphetamine-, or MA-like discriminative-stimulus effects in rats and monkeys (Yasar et al. 1993, 1994; Yasar and Bergman 1994).

Such effects of large doses of R-(–)-deprenyl have been attributed, at least partly, to the psychomotor stimulant effects of its metabolites, l-amphetamine and l-methylamphetamine. It is possible that actions of amphetamine metabolites of R-(–)-deprenyl also contributed to the present results by enhancing the effects of exogenously administered β-PEA. However, the effects of β-PEA were highly similar following treatment with either R-(–)-deprenyl or MDL 72974. Inasmuch as MDL 72974 is not converted to amphetamine metabolites, it seems unlikely that the present results can be attributed primarily to effects of metabolites. More likely, the increased potency or effectiveness of β-PEA in the present studies result from the common MAO-B inhibitory actions of R-(–)-deprenyl and MDL 72974 that retard the metabolic degradation of exogenously administered β-PEA (Zreika et al. 1989).

β-PEA may have differing neurochemical actions depending on its concentration in CNS. At steady-state concentrations such as might be achieved following MAO-B inhibition, β-PEA has been proposed to play a modulatory role in monoaminergic transmission (see Paterson et al. 1990, 1991). In electrophysiological studies of neuronal firing patterns in rat striatal neurons, for example, the inhibition of firing by dopamine or dopamine agonists is heightened by treatment with MAO-B inhibitors such as R-(–)-deprenyl. This effect may be reversed by the l-amino acid decarboxylase inhibitor NSD 1015, which selectively inhibits synthesis of β-PEA (Boulton et al. 1990; Paterson et al. 1990, 1991; Berry et al. 1994). However, the expression of MA-like or cocaine-like behavioral effects only following the administration of additional β-PEA suggests that ongoing modulation of monoaminergic transmission may not be the single neurochemical action that contributes to the psychomotor-stimulant effects of β-PEA. In this regard, high concentrations of β-PEA such as those that are achieved following its exogenous administration have been reported to also act presynaptically to stimulate the release and inhibit the uptake of dopamine, noradrenaline, and serotonin (Horn and Snyder 1973; Raiteri et al. 1977; Philips and Robson 1983; Bailey et al. 1987). The behavioral effects of psychomotor stimulants such as MA or cocaine are thought to result from such presynaptic actions in monoaminergic systems, and it seems reasonable that psychomotor stimulant-like effects of β-PEA may be similarly mediated (see Paterson et al. 1990; Izenwasser 1998).

Previous studies have shown that the discriminative-stimulus effects of indirect dopamine agonists including GBR 12909, amphetamine, MA, and cocaine may be surmountably antagonized by dopamine D_1 receptor blockers in monkeys (Kamien and Woolverton 1989; Kleven et al. 1990; Melia and Spealman 1991; Spealman et al. 1991; Tidey and Bergman 1998). In conjunction with those findings, the surmountable antagonism of the MA-like discriminative-stimulus effects of β-PEA by the D_1 receptor blocker SCH 39166 in the present experiments further support the view that behavioral effects of psychomotor stimulant drugs with dopamine-related actions are mediated at least partly by dopamine D_1-related mechanisms.

The discriminative-stimulus effects of psychomotor stimulant drugs such as cocaine or MA in monkeys also may be surmountably antagonized by dopamine D_2 receptor blockers, suggesting an additional involvement of dopamine D_2 mechanisms (Kleven et al. 1990; Melia and Spealman 1991; Spealman et al. 1991; Tidey and Bergman 1998). However, the antagonistic actions of D_2 receptor blockers are not consistently observed across studies or even across subjects within a single study. For example, the discriminative-stimulus effects of amphetamine in rhesus monkeys were antagonized by the D_1 receptor blocker SCH 23390 but not by D_2 receptor blockers including pimozide and raclopride (Kamien and Woolverton 1989). In other studies in which the D_1 receptor blocker SCH 39166 consistently produced rightward shifts in dose-response curves for the discriminative-stimulus effects of GBR 12909 or MA in squirrel monkeys, D_2 receptor blockers including eticlopride, haloperidol, or remoxipride were less consistent antagonists and even enhanced those effects in individual subjects (Melia and Spealman 1991; Tidey and Bergman 1998). In the present experiments, the D_2 receptor blocker nemonapride similarly produced varying effects among monkeys and surmountably antagonized the MA-like effects of β-PEA in only one subject. The factors that contribute to the apparently more consistent antagonism of the discriminative-stimulus effects of psychomotor stimulant drugs by dopamine D_1 receptor blockers than by dopamine D_2 receptor blockers are not currently well understood. Observational studies in monkeys have suggested that D_2 receptor blockers produce a more severe disruption of ongoing behavior than noted with dopamine D_1 receptor blockers (see, for example, Coffin et al. 1989). Possibly, the disruption of ongoing behavior by D_2 receptor blockers is sufficiently profound in individual monkeys to limit the extent to which antagonism can be measured in studies involving schedule-controlled performance.

The effects of treatment with the MAO-B inhibitors R-(–)-deprenyl and MDL 72974 in the present study may be relevant to the development of medications for the treatment of drug addiction. As with methadone in the treatment of heroin addiction, rational strategies for the treatment of psychomotor stimulant abuse and dependence have included the development of candidate medications with behavioral effects that overlap those of the abused drugs. Conceivably, such replacement therapeutics may lessen the attraction of illegal psychomotor stimulants such as cocaine or MA and, thereby, help to reduce ongoing drug abuse. It is noteworthy that doses of R-(–)-deprenyl or MDL 72974 sufficient to fully inhibit MAO-B do not engender behavioral effects that overlap those of psychomotor stimulant drugs such as cocaine or MA. Following the logic of replacement therapeutics, then, these or similar MAO-B inhibitors may not be effective medications with which to combat ongoing abuse

of psychomotor stimulant drugs (present results; Colpaert et al. 1980; Porsolt et al. 1984; Moser 1990; Winger et al. 1994). However, it is reasonable to presume that different types of medications will be appropriate for differing target populations. For example, medications used to reduce ongoing drug abuse may differ substantially from those used to forestall relapse in abstinent individuals (see Mendelson and Mello 1996). In this regard, MAO-B inhibitors such as R-(–)-deprenyl previously have been reported to improve mood or affect (see Fang and Yu 1994; Schneider et al. 1994), effects that may result from enhanced monoaminergic transmission consequent to increased circulating levels of β-PEA. Conceivably, MAO-B inhibitors, by indirectly enhancing monoaminergic transmission, also may prove to be clinically useful medications with which to reduce the probability of relapse in the abstinent individual. Alternatively, these actions of MAO-B inhibitors might serve to augment the salutary effects of replacement therapeutics. Such a prophylactic or auxiliary role for MAO-B inhibitors, while speculative at this point, deserves to be further investigated.

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References

Antelman SM, Edwards DJ, Lin M (1977) Phenylethylamine: evidence for a direct, postsynaptic dopamine-receptor stimulatory action. Brain Res 127:317–322

Bailey BA, Philips SR, Boulton AA (1987) In vivo release of endogenous dopamine, 5-hydroxytryptamine and some of their metabolites from rat caudate nucleus by phenylethylamine. Neurochem Res 12:173–178

Barroso N, Rodriguez M (1996) Action of β-phenylethylamine and related amines on nigrostriatal dopamine neurotransmission. Eur J Pharmacol 297:195–203

Bartzokis G, Beckson M, Newton T, Mandelkern M, Mintz J, Foster JA, Ling W, Bridge TP (1999) Selegiline effects on cocaine-induced changes in medial temporal lobe metabolism and subjective ratings of euphoria. Neuropsychopharmacology 20:582–590

Bergman J, Spealman RD (1988) Behavioral effects of histamine H_1 antagonists: comparison with other drugs and modification by haloperidol. J Pharmacol Exp Ther 245:471–478

Bergman J, Kamien JB, Spealman RD (1990) Antagonism of cocaine self-administration by selective dopamine D_1 and D_2 antagonists. Behav Pharmacol 1:355–363

Berry MD, Juorio AV, Paterson IA (1994) The functional role of monoamine oxidases A and B in the mammalian central nervous system. Prog Neurobiol 42:375–391

Boulton AA, Juorio AV, Paterson IA (1990) Phenylethylamine in the CNS: effects of monoamine oxidase inhibiting drugs, deuterium substitution and lesions and its role in the neuromodulation of catecholaminergic neurotransmission. J Neural Transm 29:119–129

Coffin VL, Latranyi MB, Chipkin RE (1989) Acute extrapyramidal syndrome in cebus monkeys: development mediated by dopamine D_2 but not D_1 receptors. J Pharmacol Exp Ther 249:769–774

Colpaert FC, Niemegeers CJE, Janssen PAJ (1980) Evidence that a preferred substrate for type B monoamine oxidase mediates stimulus properties of MAO inhibitors: a possible role for β-phenylethylamine in the cocaine cue. Pharmacol Biochem Behav 13:513–517

Dourish CT, Jones RS (1982) Dopamine agonist-induced restoration of drinking in response to hypertonic saline in adipsic dopamine denervated rats. Brain Res Bull 8:375–379

Dyck LE (1983) Release of monoamines from striatal slices by phenelzine and β-phenylethylamine. Prog Neuropsychopharmacol Biol Psychiatry 7:799–800

Dyck LE (1989) Release of some endogenous trace amines from rat striatal slices in the presence and absence of a monoamine oxidase inhibitor. Life Sci 44:1149–1156

Elsworth JD, Glover V, Reynolds GP (1978) Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the "cheese effect". Psychopharmacology 57:33–38

Fang J, Yu PH (1994) Effect of l-deprenyl, its structural analogues and some monoamine oxidase inhibitors on dopamine uptake. Neuropharmacology 33:763–768

Grasing K, Ghosh S (1998) Selegiline prevents long-term changes in dopamine efflux and stress immobility during the second and third weeks of abstinence following opiate withdrawal. Neuropharmacology 37:1007–1017

Greenshaw AJ, Sanger DJ, Blackman DE (1985) Effects of d-amphetamine and of β-phenylethylamine on fixed interval responding maintained by self-regulated lateral hypothalamic stimulation in rats. Pharmacol Biochem Behav 23:519–523

Hauger RL, Skolnick P, Paul SM (1982) Specific [^{3}H]β-phenylethylamine binding sites in rat brain. Eur J Pharmacol 83: 147–148

Heinonen EH, Lammintausta R (1991) A review of the pharmacology of selegiline. Acta Neurol Scand Suppl 136:44–59

Henry DP, Russell WL, Clemens JA, Plebus LA (1988) Phenylethylamine and *p*-tyramine in the extracellular space of the rat brain: quantification using a new radioenzymatic assay and in situ microdialysis. In: Boulton AA, Juorio AV, Downer RGH (eds) Trace amines: comparative and clinical neurobiology. Humana Press, Clifton, NJ, pp 239–250

Horn AS, Snyder SH (1973) Steric requirements for catecholamine uptake by rat brain synaptosomes: studies with rigid analogs of amphetamine. J Pharmacol Exp Ther 180:523–530

Izenwasser S (1998) Basic pharmacological mechanisms of cocaine. In: Higgins ST, Katz JL (eds) Cocaine abuse: behavior, pharmacology, and clinical applications. Academic Press, New York, pp 1–20

Jackson DM (1978) β-Phenylethylamine: studies on the mechanism of its stimulant effects. In: Mosnaim AD, Wolf ME (eds) Noncatecholic phenylethylamines, part 1. Phenylethylamine: biological mechanisms and clinical aspects. Dekker, New York, pp 289–313

Jackson DM (1988) 2-Phenylethylamine, dopamine and behaviour. In: Sandler M, Dahlstrom A, Belmaker RH (eds) Progress in catecholamine research, part B. Central aspects. Liss, New York, pp 429–432

Johnston JP (1968) Some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol 17:1285–1297

Kamien JB, Woolverton WL (1989) A pharmacological analysis of the discriminative stimulus properties of *d*-amphetamine in rhesus monkeys. J Pharmacol Exp Ther 248:938–946

Kelleher RT, Morse WH (1968) Determinants of the specificity of behavioral effects of drugs. Ergeb Physiol 60:1–56

Kleven MS, Anthony EW, Woolverton WL (1990) Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J Pharmacol Exp Ther 254:312–317

Knoll J (1978) The possible mechanisms of action of (–)deprenyl in Parkinson's disease. J Neural Transm 43:177–198

Knoll J (1987) R-(–)-deprenyl (selegiline, Movergan) facilitates the activity of the nigrostriatal dopaminergic neuron. J Neural Transm Suppl 25:45–66

Li XM, Juorio AV, Paterson IA, Boulton AA (1992) Absence of 2-phenylethylamine binding after monoamine oxidase inhibition in rat brain. Eur J Pharmacol 210:189–193

Mantegazza P, Riva M (1963) Amphetamine-like activity of β-phenethylamine after a monoamine oxidase inhibitor in vivo. J Pharm Pharmacol 15:472–478

Melia KF, Spealman RD (1991) Pharmacological characterization of the discriminative-stimulus effects of GBR 12909. J Pharmacol Exp Ther 258:626–632

Mendelson JH, Mello NK (1996) Management of cocaine abuse and dependence. N Engl J Med 334:965–972

Moser PC (1990) Generalization of *l*-deprenyl, but not MDL-72974, to the d-amphetamine stimulus in rats. Psychopharmacology 101:S40

Nakamura M, Ishii A, Nakahara D (1998) Characterization of β-phenylethylamine-induced monoamine release in rat nucleus accumbens: a microdialysis study. Eur J Pharmacol 349:163–169

O'Regan D, Kwok RP, Yu PH, Bailey BA, Greenshaw AJ, Boulton AA (1987) A behavioural and neurochemical analysis of chronic and selective monoamine oxidase inhibition. Psychopharmacology 92:42–47

Ortmann R, Schaub M, Felner A, Lauber J, Christen P, Waldmeier PC (1984) Phenylethylamine-induced stereotypies in the rat: a behavioral test system for assessment of MAO-B inhibitors. Psychopharmacology 84:22–27

Parker EM, Cubeddu LX (1988) Comparative effects of amphetamine, phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding. J Pharmacol Exp Ther 245:199–210

Paterson IA, Juorio AV, Boulton AA (1990) 2-Phenylethylamine: a modulator of catecholamine transmission in the mammalian central nervous system? J Neurochem 55:1827–1837

Paterson IA, Juorio AV, Berry MD, Zhu MY (1991) Inhibition of monoamine oxidase-B by (–)-deprenyl potentiates neuronal responses to dopamine agonists but does not inhibit dopamine catabolism in the rat striatum. J Pharmacol Exp Ther 258: 1019–1026

Paterson IA, Davis BA, Durden DA, Juorio AV, Yu PH, Ivy G, Milgram W, Mendonca A, Wu P, Boulton AA (1995) Inhibition of MAO-B by (–)-deprenyl alters dopamine metabolism in the macaque (*Macaca fascicularis*) brain. Neurochem Res 20:1503–1510

Philips SR, Robson AM (1983) In vivo release of endogenous dopamine from the rat caudate nucleus by phenylethylamine. Neuropharmacology 22:1297–1301

Porsolt RD, Pawelec C, Jalfre M (1984) Discrimination of the amphetamine cue: effects of A, B and mixed type inhibitors of monoamine oxidase. Neuropharmacology 23:569–573

Raiteri M, Del Carmine R, Bertollini A, Levi G (1977) Effect of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine, and 5-hydroxytryptamine. Eur J Pharmacol 41:133–143

Riederer P, Youdim MBH (1986) Monoamine oxidase activity and monoamine metabolism in brains of Parkinsonian patients treated with *l*-deprenyl. J Neurochem 46:1359–1365

Risner ME, Jones BE (1977) Characteristics of β-phenethylamine self-administration by dog. Pharmacol Biochem Behav 6:689–696

Sandler N, Reynolds GP (1976) Does phenethylamine cause schizophrenia? Lancet 1:70–71

Schneider LS, Tariot PN, Goldstein B (1994) Therapy with *l*-deprenyl (selegiline) and relation to abuse liability. Clin Pharmacol Ther 56:750–756

Shannon HE, DeGregorio CM (1982) Self-administration of the endogenous trace amines β-phenylethylamine, *N*-methylphenylethylamine and phenylethanolamine in dogs. J Pharmacol Exp Ther 222:52–60

Shannon HE, Thompson WA (1984) Behavior maintained under fixed-interval and second-order schedules by intravenous injections of endogenous noncatecholic phenylethylamines in dogs. J Pharmacol Exp Ther 228:691–695

Spealman RD (1985) Discriminative-stimulus effects of midazolam in squirrel monkeys: comparison with other drugs and antagonism by Ro 15-1788. J Pharmacol Exp Ther 235:456–462

Spealman RD, Bergman J, Madras BK, Melia KF (1991) Discriminative-stimulus effects of cocaine in squirrel monkeys: involvement of dopamine receptor subtypes. J Pharmacol Exp Ther 258:945–953

Stein L (1964) Self-stimulation of the brain and the central stimulant action of amphetamine. Fed Proc 23:837–850

The Parkinson Study Group (1989) Effect of deprenyl on the progression of disability in early Parkinson's disease. Science 245:519–522

Tidey JW, Bergman J (1998) Drug discrimination in methamphetamine-trained monkeys: agonist and antagonist effects of dopaminergic drugs. J Pharmacol Exp Ther 285:1163–1174

Timar J, Knoll B (1986) The effect of repeated administration of (–) deprenyl on the phenylethylamine-induced stereotypy in rats. Arch Int Pharmacodyn 279:50–60

Tinklenberg JR, Gillin JC, Murphy GM, Staub R, Wyatt RJ (1978) The effects of phenylethylamine in rhesus monkeys. Am J Psychiatry 135:576–578

Tinklenberg JR, Gillin JC, Murphy GM, Staub R, Wyatt RJ (1979) Phenylethylamine in rhesus monkeys: interactions with alpha-methyl-para-tyrosine and l-dopa. Am J Psychiatry 136:311–313

Turkish S, Yu PH, Greenshaw AJ (1988) Monoamine oxidase-B inhibition: a comparison of in vivo and ex vivo measures of reversible effects. J Neural Transm 74:141–148

Winger GD, Palmer RK, Woods JH (1989) Drug-reinforced responding: rapid determination of dose-response functions. Drug Alcohol Depend 24:135–142

Winger GD, Yasar S, Negus SS, Goldberg SR (1994) Intravenous self-administration studies with l-deprenyl (selegeline) in monkeys. Clin Pharmacol Ther 56:774–780

Yasar S, Bergman J (1994) Amphetamine-like effect of l-deprenyl (selegiline) in drug discrimination studies. Clin Pharmacol Ther 56:768–773

Yasar S, Winger G, Nickel B, Schulze G, Goldberg SR (1993) Preclinical evaluation of l-deprenyl: lack of amphetamine-like abuse potential. In: Szelenyi I (ed) Inhibitors of monoamine oxidase B. Birkhauser, Basel, pp 215–233

Yasar S, Schindler CW, Thorndike EB, Goldberg SR (1994) Evaluation of deprenyl for cocaine-like discriminative stimulus effects in rats. Eur J Pharmacol 259:243–250

Zreika M, Fozard JR, Dudley MW, Bey PH, McDonald IA, Palfreyman MG (1989) MDL 72,974: a potent and selective enzyme-activated irreversible inhibitor of monoamine oxidase type B with potential for use in Parkinson's disease. J Neural Transm 1:243–254