ELSEVIER

European Journal of Pharmacology 364 (1999) 1–6

ejp

The amphetamine-like reinforcing effect and mechanism of L-deprenyl on conditioned place preference in mice

Wei-Ran Wu, Xing-Zu Zhu *

Department of Pharmacology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 294 Tai-Yuan Road, Shanghai 200031, China

Received 2 April 1998; revised 4 November 1998; accepted 10 November 1998

Abstract

The present study investigated the reinforcing effect of L-deprenyl on conditioned place preference in mice and its mechanism. Conditioned place preference was induced by 10 and 25 mg/kg L-deprenyl in a dose-dependent fashion during five consecutive conditioning days, and its reinforcing property was about five-fold less potent than that of L-amphetamine. Pretreatment with the dopamine antagonist, haloperidol (1 mg/kg i.p.), effectively blocked the place preference produced by L-deprenyl (10 and 25 mg/kg i.p.) and L-amphetamine (2 and 5 mg/kg i.p.), but haloperidol itself produced no place aversion. The neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 30 mg/kg did not modify the place preference induced by both L-deprenyl and L-amphetamine, though the dopamine concentration in striata assayed by high performance liquid chromatography with electrochemical detection (HPLC-EC) was significantly reduced. These results suggest that L-deprenyl has amphetamine-like reinforcing properties. The reinforcing effect of L-deprenyl may be mediated by central dopaminergic neuronal systems, while the nigrostriatal dopaminergic pathway is not involved.

Keywords: L-Deprenyl; L-Amphetamine; Reinforcement; Haloperidol; MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); Dopamine

1. Introduction

L-Deprenyl (selegiline), a selective irreversible inhibitor of monoamine oxidase B, has been used as an important adjuvant to L-DOPA in the treatment of Parkinson's disease (Birkmayer et al., 1975; Knoll, 1983; The Parkinson Study Group, 1993) for more than 20 years. L-Deprenyl has also been used alone as a primary treatment in the early phase of Parkinson's disease (Myllyla et al., 1989; The Parkinson Study Group, 1989), as an antidepressant (Mendlenicz and Youdim, 1983; Mann et al., 1989), an anti-Alzheimer's disease agent (Monteverde et al., 1990; Tariot et al., 1993), a smart drug (Knoll, 1988; Morgenthaler, 1992) and as medication for drug abuse (Winger et al., 1994; Zheng et al., 1995).

Although there are few reports about the physical dependence and abuse potential of L-deprenyl in clinical application, including no evidence for the development of tolerance during the continuation and abstinence syndromes after the discontinuation of L-deprenyl therapy (Yasar et al., 1993b; Schneider et al., 1994), the abuse liability of L-deprenyl still needs attention. There are several reasons for this. Firstly, L-deprenyl is mainly metabolized into L-methamphetamine and L-amphetamine, both of which have definite abuse potential and can produce physical dependence (Salonen, 1990; Heinonen et al., 1994). Secondly, L-deprenyl can augment the effects of phenylethylamine and other sympathomimetic agents (Ortmann et al., 1984; Timar and Knoll, 1986), which means it can induce abuse potential for humans (Risner and Jones, 1977; Shannon and De Georgio, 1982). Thirdly, some preclinical studies demonstrate that L-deprenyl has amphetamine- and cocaine-like discriminative stimulus properties in experimental animals (Johanson and Barrett, 1993; Yasar et al., 1994; Yasar and Bergman, 1994). Further, L-deprenyl has become attractive to the general population as a potent enhancer of cognition, concentration, intellectual activity and longevity, even as an aphrodisiac, all of which appear to be forms of drug abuse (Knoll, 1988; Morgenthaler, 1992; Schneider et al., 1994). Finally, trials to evaluate the abuse of L-deprenyl in clinical application

* Corresponding author. Tel.: +86-21-6431-1833, ext. 309; Fax: +86-21-6437-0269; E-mail: xzzhu@server.shcnc.ac.cn

0014-2999/99/$ - see front matter
PII: S0014-2999(98)00831-0

have not been designed systematically (Schneider et al., 1994).

In preclinical research, several studies have been designed to evaluate the physical dependence potential of L-deprenyl. Such studies involve watching behavior, recording cortical electrical activity, and analyzing the electroencephalogram of experimental animals (Nickel et al., 1994). The abuse potential of L-deprenyl was evaluated both in a drug discrimination procedure, which showed that L-deprenyl fully substituted for both amphetamine in rats and methamphetamine in monkeys (Yasar and Bergman, 1994), and with an intravenous self-administration method, which indicated that high doses of L-deprenyl could maintain cocaine-induced self-administration behavior of monkeys (Winger et al., 1994).

We now applied a modified model (Carr and White, 1986; Bals-Kubik et al., 1993) of conditioned place preference to assess the reinforcing property of L-deprenyl in mice, and used pretreatment with a dopamine receptor antagonist, haloperidol, and a dopaminergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), to investigate the possible involvement of central dopaminergic neuronal pathways.

2. Materials and methods

2.1. Animals

Female C57BL/6 mice (18–22 g) from the Animal Center of the Shanghai Institute of Materia Medica (Shanghai, China) were housed with constant temperature (22–24°C) and humidity (50–60%) for 1 week before the experiments. The animals were kept on a 12-h light and dark cycle with free access to food and water.

2.2. Drugs

L-Deprenyl and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were purchased from RBI (Natick, MA, USA). L-Amphetamine and dopamine were obtained from Sigma (St. Louis, MO, USA). Haloperidol was produced by Puhai Pharmaceutical Factory (Shanghai, China). The drugs were dissolved in saline just before use.

2.3. Apparatus for conditioned place preference

The testing apparatus was a rectangular plastic box ($60 \times 20 \times 20$ cm^3), consisting of two distinct interconnected chambers of equal volume. One chamber with white walls and a glossy floor was illuminated by a 15-W bulb (white chamber), and the other chamber with black walls and a grid floor had no illumination (black chamber). The chambers were separated by a guillotine door. The apparatus was placed in a sound-insulated room.

2.4. Procedure for conditioned place preference

Each mouse was allowed to freely explore the two chambers for 15 min on three consecutive days before any drug treatment. The time spent by each animal in the black and white chambers was respectively recorded by visual observation and a manually operated timer. The chamber in which the animal spent most time was considered to be the preferred side, and almost all the animals preferred the black chamber. From the 4th day on, each animal of different groups injected intraperitoneally with saline, L-deprenyl (2, 10 or 25 mg/kg), L-amphetamine (2 or 5 mg/kg), haloperidol (1 mg/kg) or MPTP (30 mg/kg) was immediately placed in the non-preferred side (white chamber) for 30 min with the guillotine door closed. Animals from other groups were pretreated with haloperidol (1 mg/kg i.p.) or MPTP (30 mg/kg i.p.), and then injected with L-deprenyl (2, 10 or 25 mg/kg i.p.) or L-amphetamine (2 or 5 mg/kg i.p.) 30 min later. Immediately after the later injection the animals were also placed in the white chamber for 30 min. This conditioning phase was run for five consecutive days. On the 9th day, the mice received no drug and were allowed to explore two chambers with the door opened again for 15 min, and the time spent in the chambers was recorded.

2.5. Preparation of samples for HPLC

Immediately after the time spent in the chambers was recorded on the 9th day, the mice were decapitated. The paired striata were dissected out, weighed and homogenized in ice-cold 0.1 M $HClO_4$ containing 1% Na_2EDTA and 0.5% $Na_2S_2O_5$. After centrifugation ($20\,000 \times g$, 15 min, 4°C), the supernatants were collected for chromatographic assay.

2.6. HPLC conditions

A modified method of Antkiewicz-Michaluk et al. (1997) was used to measure dopamine by liquid chromatography (CC-5, Bioanalytical Systems, West Lafayette, IN, USA) with electrochemical detection (LC-44, BAS). A phase-2 ODS-3 μm column (100×3.2 mm, BAS) was used for all separations with flow rate maintained at 1.0 ml/min (PM-80, BAS). The full scale on the detector (LC-4C, BAS) was set to 10 nA, the operating potential was 750 mV, and the temperature was controlled at 25°C (LC-22C). The mobile phase consisted of 0.15 M monochloroacetate, 0.117 M NaOH, 1 mM sodium octyl sulfate, 0.1 mM Na_2EDTA and 6% methanol. Dopamine

was quantified from the peak area (DA-5, BAS) compared with that for a standard run on the same day.

2.7. Statistical analysis

Data are expressed as means ± S.E.M. Statistical analyses were performed using an analysis of variance followed by the Student–Newman–Keuls test to identify significant differences between experimental groups. $P < 0.05$ was considered significant.

3. Result

3.1. Effects of L-deprenyl on conditioned place preference

Three groups of mice ($n = 10$) received different doses of L-deprenyl (2, 10 and 25 mg/kg i.p.). After five consecutive conditioning days, these mice spent more time in the drug-paired side (white chamber) than before. Fig. 1 showed that L-deprenyl induced place preference in a dose-dependent fashion.

3.2. Amphetamine-like reinforcing property of L-deprenyl

L-Amphetamine is one of main metabolites of L-deprenyl, thus the reinforcing property of L-amphetamine was compared with that of L-deprenyl. Groups of mice received different doses of L-amphetamine to determine the optimal doses at which place preference was achieved. L-Amphetamine at doses of 2 and 5 mg/kg i.p. significantly induced place preference in the mice, and its reinforcement potency was approximately equal to that of L-deprenyl at doses of 10 and 25 mg/kg i.p., respectively (Fig. 1).

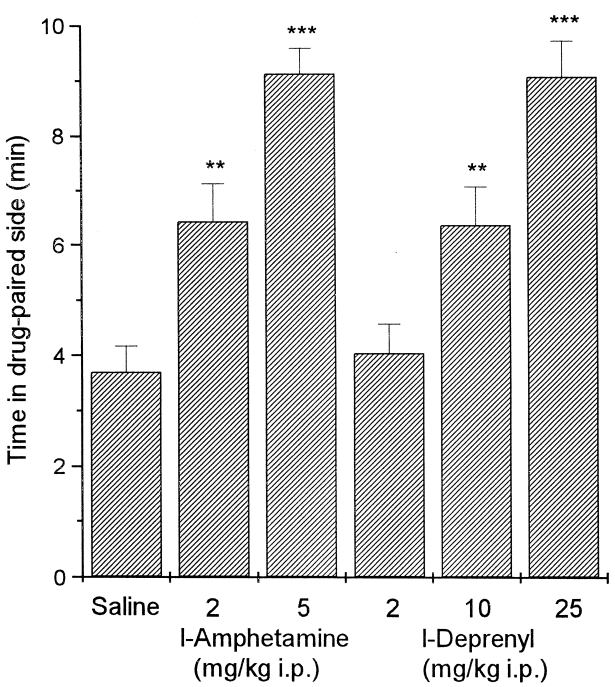

Fig. 1. The amphetamine-like reinforcing property of L-deprenyl on place preference in mice. The bars represent the mean ± S.E.M., $n = 10$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with saline group.

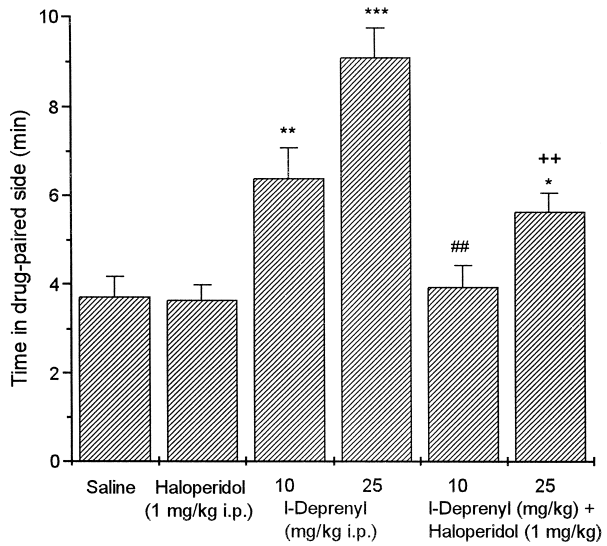

Fig. 2. Effects of haloperidol on the reinforcing effects of L-deprenyl in mice. The bars represent the mean ± S.E.M., $n = 8$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with saline group; $^{\#\#}P < 0.01$ compared with L-deprenyl (10 mg/kg i.p.) group; $^{++}P < 0.01$ compared with L-deprenyl (25 mg/kg i.p.) group.

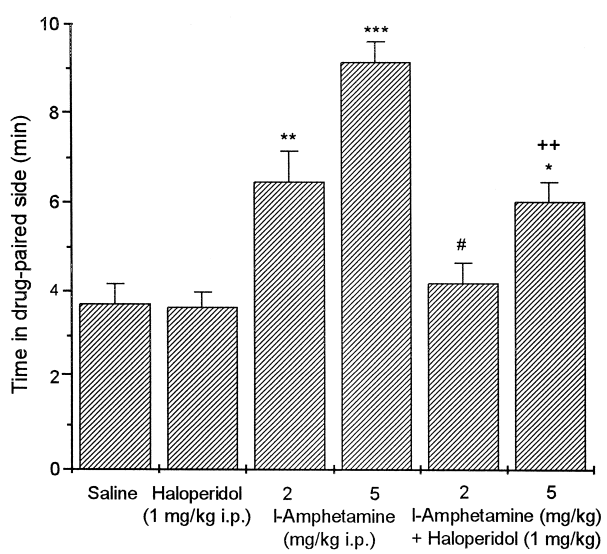

Fig. 3. Effects of haloperidol on the reinforcing effects of L-amphetamine in mice. The bars represent the mean ± S.E.M., $n = 8$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with saline group; $^{\#}P < 0.05$ compared with L-amphetamine (2 mg/kg i.p.) group; $^{++}P < 0.01$ compared with L-amphetamine (5 mg/kg i.p.) group.

3.3. Effects of haloperidol on reinforcing property of L-deprenyl

Haloperidol (1 mg/kg i.p.) was given as pretreatment to additional groups of mice ($n = 8$), and 30 min later these mice were injected with L-deprenyl (10 or 25 mg/kg i.p.) or L-amphetamine (2 or 5 mg/kg i.p.), respectively. Haloperidol effectively antagonized the L-deprenyl- and L-amphetamine-induced place preference (Figs. 2 and 3).

3.4. Effects of MPTP on reinforcing property of L-deprenyl

MPTP (30 mg/kg i.p.) was given as pretreatment to additional groups of mice ($n = 10$) injected with different doses of L-deprenyl (2, 10 and 25 mg/kg i.p.). MPTP did not modify the effects of L-deprenyl (Fig. 4) and L-amphetamine (data not shown) on conditioned place preference, and MPTP itself had no reinforcing property.

3.5. Effects of MPTP and L-deprenyl on dopamine levels of striata

MPTP, whose effects are mediated by 1-methyl-4-phenylpyridinium (MPP^+), has a selective neurotoxic effect on the dopamine-containing nerve terminals of the nigrostriatal system to lead to nerve degeneration (Heikkila et al., 1984; Anne Johnson et al., 1989), which can be antagonized by L-deprenyl, an irreversible inhibitor of monoamine oxidase B (Gerlach et al., 1996; Wu et al., 1999). MPTP (30 mg/kg i.p.) significantly induced dopaminergic neurotoxicity, depleting the striatal dopamine level by 72.9%, an effect which was partially antagonized by L-deprenyl (2 and 10 mg/kg i.p.) and completely blocked by L-deprenyl (25 mg/kg i.p.) (Fig. 5).

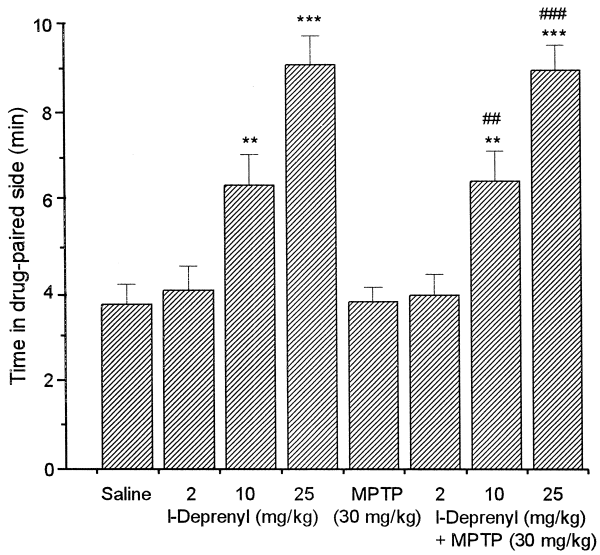

Fig. 4. Effects of MPTP on the reinforcing property of L-deprenyl in mice. The bars represent the mean ± S.E.M., $n = 10$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with saline group; $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ compared with MPTP group.

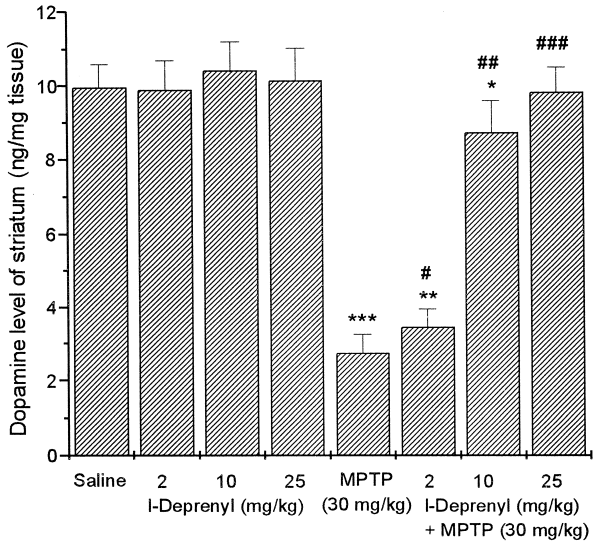

Fig. 5. Effects of MPTP and L-deprenyl on the dopamine levels of striata in mice. The bars represent the mean ± S.E.M., $n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with saline group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ compared with MPTP group.

4. Discussion

Although metabolites of L-deprenyl such as L-amphetamine and L-methamphetamine can induce dependence and abuse, L-deprenyl itself seems to have no abuse potential when used clinically for the treatment of parkinsonism. However, series of studies on L-deprenyl in experimental animals have provided preclinical data predictive of human abuse liability (Winger et al., 1994; Zheng et al., 1995). L-Deprenyl, but not other monoamine oxidase B inhibitors, has dose-dependent amphetamine-like (Porsolt et al., 1984; Yasar et al., 1993a), methamphetamine-like (Yasar and Bergman, 1994) and cocaine-like (Johanson and Barrett, 1993; Yasar et al., 1994) discriminative stimulus properties in rats, monkeys and pigeons. High doses of L-deprenyl can also maintain drug-seeking and drug-taking behaviors by intravenous self-administration in monkeys (Winger et al., 1994). These results indicate that such effects are predominantly induced by amphetamine metabolites of L-deprenyl with effects other than the inhibition of monoamine oxidase B, and also suggest that the relatively weak reinforcing potency of L-deprenyl is due to the slow formation of its amphetamine metabolites.

In our studies, conditioned place preference was used to further investigate the reinforcing effect of L-deprenyl. The results demonstrated that L-deprenyl had a dose-dependent amphetamine-like reinforcing effect in C57 mice, and that its reinforcing potency was approximately one-fifth that of L-amphetamine (Fig. 1). Although the data from this re-

spondent reinforcement paradigm are not completely consistent with those from the operated reinforcement model (Winger et al., 1994), conditioned place preference has been proved to be a more useful and convenient technique than self-administration for evaluating the reinforcing properties of some drugs. Conditioned place preference can avoid some limitations of the self-administration procedure, such as a typical inverted U-shaped dose–effect curve (Yokel, 1987) and possible false negative results, also the apparatus is simple and the procedure short-lasted (File, 1986; Tao and Zheng, 1996).

Drug reward involves multiple brain neurotransmitter systems (White et al., 1991; Shippenberg et al., 1993; Bardo, 1998) and neuroanatomical brain regions (White et al., 1991; Kalivas, 1993; McGregor et al., 1996). Since dopamine acted as a critical mediator in drug reward, the dopamine antagonist, haloperidol, was used in this study to investigate the neurochemical mechanism of the reinforcing effect of L-deprenyl. Our finding that haloperidol (1 mg/kg i.p.) effectively blocks the reinforcing effects of L-deprenyl and L-amphetamine (Figs. 2 and 3) clearly implies a role for dopamine receptors in L-deprenyl-induced reward. The results also suggest that a similar mechanism is involved in the effects of these two drugs. MPTP-lesioned C57 mice were also used to detect whether the reinforcing effect of L-deprenyl was mediated by the mesolimbic or by the nigrostriatal dopaminergic system. Our results demonstrated that MPTP treatment induced a significant depletion of the striatal dopamine level in C57 mice, which could be antagonized by the neuroprotective actions of L-deprenyl (Gerlach et al., 1996; Wu et al., 1999), but did not modify the reinforcing effect of L-deprenyl (Figs. 4 and 5). These results suggest that the dopamine level in the nigrostriatal pathway plays no role in the place preference induced by L-deprenyl, which is consistent with the previous suggestion that the mesolimbic dopaminergic system is a critical pathway underlying drug reward (Liu and Zhang, 1996; Bardo, 1998) and that the nigrostriatal dopaminergic system may not be involved in modification of the reinforcing effects, especially those of stimulants (Carr and White, 1986; Bals-Kubik et al., 1993). The results also imply that MPTP has a relatively selective neurotoxicity in the nigrostriatal system, or that the dopamine neurons of the mesolimbic system are more resistant than those of the nigrostriatal system. These suggestions are supported by results of other studies that show not only different vulnerability to neurotoxins between central dopaminergic pathways (Hung et al., 1995), but also differences in gene expression (Hung and Lee, 1996), oxidative stress and antioxidative response (Hung and Lee, 1998).

To try to resolve the controversy about the abuse liability of L-deprenyl found in preclinical studies and for clinical applications, we suggest that not only the nigrostriatal dopaminergic system but also the mesolimbic dopaminergic system of patients with Parkinson's disease is damaged to a certain degree (Chinaglia et al., 1992; Menza et al., 1993). The fact that the mesolimbic dopaminergic system, the critical pathway underlying drug reward, is not intact in these patients might explain the small number of cases of L-deprenyl abuse reported. However, evidence from the general population belies the abuse potential of L-deprenyl. L-Deprenyl appears to be popular as a 'smart drug', which is sought out for its ability to produce desirable effects relating to cognition, mood, attention, libido (Morgenthaler, 1992; Schneider et al., 1994). Therefore, the abuse liability of L-deprenyl should be further evaluated, especially in the general population.

In conclusion, the present studies demonstrated that L-deprenyl has amphetamine-like reinforcing properties and that the mesolimbic dopaminergic pathway, but not the nigrostriatal dopaminergic pathway, may play an important role in the reinforcing effect of L-deprenyl.

References

Anne Johnson, E., Wu, E.Y., Rollema, H., Booth, R.G., Trevor, A.J., Castagnoli, N., 1989. 1-Methyl-4-phenylpyridinium (MPP^+) analogs: in vivo neurotoxicity and inhibition of striatal synaptosomal dopamine uptake. Eur. J. Pharmacol. 166, 65–74.

Antkiewicz-Michaluk, L., Romanska, I., Vetulani, J., 1997. Ca^{2+} channel blockade prevents lysergic acid diethylamide-induced changes in dopamine and serotonin metabolism. Eur. J. Pharmacol. 332, 9–14.

Bals-Kubik, R., Albertiner, A., Herz, A., Shippenberg, T.S., 1993. Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. J. Pharmacol. Exp. Ther. 264, 489–495.

Bardo, M.T., 1998. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. Crit. Rev. Neurobiol. 12, 37–67.

Birkmayer, W., Riederer, P., Youdim, M.B.H., Linauer, W., 1975. The potential of the anti-akinetic effect of L-DOPA treatment by an inhibitor of MAO-B, (−)deprenyl. J. Neural Transm. 36, 303–326.

Carr, G.D., White, N.M., 1986. Anatomical disassociation of amphetamine's rewarding and aversive effects: an intracranial microinjection study. Psychopharmacology 89, 340–346.

Chinaglia, G., Alvarez, E.J., Probst, A., Palacios, J.M., 1992. Nigrostriatal and mesolimbic dopamine uptake binding sites are reduced in Parkinson's disease and progressive supranuclear palsy: a quantitative autoradiographic study using [^{3}H]mazindol. Neuroscience 49, 317–327.

File, S.E., 1986. Aversive and appetitive properties of anxigenic and anxioltic agents. Behav. Brain Res. 21, 189–194.

Gerlach, M., Youdim, M.B.H., Riederer, P., 1996. Pharmacology of selegiline. Neurology 47, S137–S145, Suppl. 3.

Heikkila, R.E., Manzino, L., Cabbat, F.S., Duvoisin, R.C., 1984. Protection against the dopaminergic neurotoxicity 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine by monoamine oxidase inhibitors. Nature 311, 467–469.

Heinonen, E.H., Anttila, M.I., Lammintausta, A.S., 1994. Pharmacokinetic aspects of L-deprenyl (selegiline) and its metabolites. Clin. Pharmacol. Ther. 56, 742–749.

Hung, H.C., Lee, E.H., 1996. The mesolimbic dopaminergic pathway is more resistant than the nigrostriatal dopaminergic pathway to MPTP and MPP^+ toxicity: role of BDNF gene expression. Brain Res. Mol. Brain. Res. 41, 14–26.

Hung, H.C., Lee, E.H., 1998. MPTP produces differential oxidative stress

and antioxidative responses in the nigrostriatal and mesolimbic dopaminergic pathways. Free Radic. Biol. Med. 24, 76–84.

Hung, H.C., Tao, P.L., Lee, E.H., 1995. 1-Methyl-4-phenylpyridium (MPP^+) uptake does not explain the differential toxicity of MPP^+ in the nigrostriatal and mesolimbic dopaminergic pathways. Neurosci. Lett. 196, 93–96.

Johanson, C.E., Barrett, J.E., 1993. The discriminative stimulus effects of cocaine in pigeons. J. Pharmacol. Exp. Ther. 267, 1–8.

Kalivas, P.W., 1993. Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. Brain Res. Rev. 18, 75–82.

Knoll, J., 1983. Deprenyl (selegiline): the history of its development and pharmacological action. Acta Neurol. Scand. 95 (Suppl.), 57–80.

Knoll, J., 1988. Striatal dopamine dependency of life span in male rats: longevity study with L-deprenyl. Mech. Ageing Dev. 46, 237–262.

Liu, Z.H., Zhang, K.G., 1996. Conditioned place preference and its neurochemical mechanisms. Chin. Bull. Drug Depend. 5, 193–196.

Mann, J.J., Aarons, S.F., Wilner, P.J., 1989. A controlled study of the antidepressant efficacy and side-effects of L-deprenyl. Arch. Gen. Psychiatry 46, 45–50.

McGregor, A., Baker, G., Roberts, D.C.S., 1996. Effects of 6-hydroxydopamine lesions of the medial prefrontal cortex on intravenous self-administration under a progressive ratio schedule of reinforcement. Pharmacol. Biochem. Behav. 53, 5–9.

Mendlenicz, J., Youdim, M.B.H., 1983. L-Deprenyl, a selective monoamine oxidase type B inhibitor, in the treatment of depression: a double-blind evaluation. Br. J. Psychiatry 142, 508–511.

Menza, M.A., Golbe, L.I., Cody, R.A., Forman, N.E., 1993. Dopamine-related personality traits in Parkinson's disease. Neurology 43, 505–508.

Monteverde, A., Gnemmi, P., Rossi, F., 1990. Selegiline in the treatment of mild to moderate Alzheimer-type dementia. Clin. Ther. 12, 315–332.

Morgenthaler, J., 1992. Smart drug update. Mondo 2000 5, 36–37.

Myllyla, V.V., Sotaniemi, K.A., Tuominen, J., Heinonen, E.H., 1989. Selegiline as primary treatment in early phase of Parkinson's disease —an interim report. Acta Neurol. Scand. 126, 177–182.

Nickel, B., Szelenyi, I., Schulze, G., 1994. Evaluation of physical dependence liability of L-deprenyl (selegiline) in animals. Clin. Pharmacol. Ther. 56, 757–767.

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

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

Risner, M.E., Jones, B.E., 1977. Characteristics of β-phenylethylamine self-administration by dog. Pharmacol. Biochem. Behav. 36, 1731–1735.

Salonen, J.S., 1990. Determination of amine metabolites of selegiline in biological fluids by capillary gas chromatography. J. Chromatogr. 527, 163–168.

Schneider, L.S., Tariot, P.N., Goldstein, B., 1994. Therapy with L-deprenyl (selegiline) and relation to abuse liability. Clin. Pharmacol. Ther. 56, 750–756.

Shannon, H.E., De Georgio, C.M., 1982. Self-administration of the endogenous trace amines β-phenylethylamine, *N*-methylphenylethylamine and phenylethanolamine in dogs. J. Pharmacol. Exp. Ther. 222, 52–60.

Shippenberg, T.S., Bals-Kubik, R., Herz, A., 1993. Examination of neurochemical substrates mediating the motivational effects of opioids: roles of the mesolimbic dopamine system and D_1 vs. D_2 dopamine receptors. J. Pharmacol. Exp. Ther. 265, 53–59.

Tao, Q., Zheng, J.W., 1996. Conditioned place preference paradigm. Chin. Bull. Drug Depend. 5, 68–73.

Tariot, P.N., Schneider, L.S., Patel, S.V., Goldstein, B., 1993. Alzheimer's disease and L-deprenyl: rationale and findings. In: Szelenyi, I. (Ed.), Inhibitors of Monoamine Oxidase B. Birkhauser, Basal, pp. 301–317.

The Parkins Study Group, 1989. Effect of deprenyl on the progression of disability in early Parkinson's disease. New Engl. J. Med. 321, 1363–1371.

The Parkinson Study Group, 1993. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. New Engl. J. Med. 328, 176–183.

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

White, N.M., Packard, M.G., Hiroi, N., 1991. Place conditioning with dopamine D_1 and D_2 agonists injected peripherally or into nucleus accumbens. Psychopharmacology 103, 271–276.

Winger, G.D., Yasar, S., Negus, S.S., Goldberg, S.R., 1994. Intravenous self-administration studies with L-deprenyl (selegiline) in monkeys. Clin. Pharmacol. Ther. 56, 774–780.

Wu, W.-R., Zhu, X.-Z., Guan, H.-J., Wang, R.-G., Ji, X.-Q., 1999. Neuroprotective rather than neurorescue or neurorestorative effect of selegiline against MPTP-induced dopaminergic toxicity. Acta Pharmacol. Sin. 20, 138–142.

Yasar, S., Bergman, J., 1994. Amphetamine-like effects of L-deprenyl in drug discrimination studies. Clin. Pharmacol. Ther. 56, 768–773.

Yasar, S., Schindler, C.W., Thorndike, E.B., Szelenyi, I., Goldberg, S.R., 1993a. Evaluation of stereoisomers of deprenyl for amphetamine-like discriminative stimulus effects in rats. J. Pharmacol. Exp. Ther. 265, 1–6.

Yasar, S., Winger, G., Nickel, B., Schulze, G., Goldberg, S.R., 1993b. Preclinical evaluation of L-deprenyl: lack of amphetamine like abuse potential. In: Szelenyi, I. (Ed.), Inhibitors of Monoamine Oxidase B. Birkhauser, Basal, pp. 215–233.

Yasar, S., Schindler, C.W., Thorndike, E.B., Goldberg, S.R., 1994. Evaluation of deprenyl for cocaine-like discriminative stimulus effects in rats. Eur. J. Pharmacol. 259, 243–256.

Yokel, R.A., 1987. Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preference. In: Bozarth, M.A. (Ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. Springer-Verlag, New York, NY, pp. 1–22.

Zheng, J.W., Lu, S.N., Groldberg, S.R., 1995. Abuse liability of L-deprenyl. Clin. Bull. Drug Depend. 4, 254–256.