

Modification of Monoaminergic Activity by MAO Inhibitors Influences Methamphetamine Actions

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Abstract: Methamphetamine (METH) abuse is a serious health and social problem worldwide. At present, however, there are no effective medications for the treatment of METH abuse. Of the intracellular METH target proteins, monoamine oxidase (MAO) is involved in the regulation of monoaminergic tone in the brain, resulting in the modulation of METH-induced behavioral abnormalities in mammals. The METH-induced expression of increased motor activity, stereotypy, and sensitization is closely associated with monoaminergic transmission in the brain. Modification of MAO activity by MAO inhibitors can influence METH action. Of the MAO inhibitors, the propargylamine derivative clorgyline, an irreversible MAO-A inhibitor, effectively blocks METH-induced hyperlocomotion and behavioral sensitization in rodents. Analysis of the associated monoaminergic activity indicates an involvement of altered striatal serotonergic transmission as well as an increased dopaminergic tone. Some effects of MAO inhibitors on METH action appear to be independent of MAO, suggesting complex mechanisms of action of MAO inhibitors in METH abuse. This review describes current research to find effective treatment for METH abuse, using MAO inhibitors.

Keywords: methamphetamine, hyperlocomotion, stereotypy, behavioral sensitization, clorgyline, selegiline, monoamine turnover, monoamine oxidase, 5-HT, striatum.

Introduction

Of amphetamines and their related compounds, *d*-methamphetamine (METH) is one of the most powerful drugs of abuse recognized worldwide on the basis of an increasing number of health and social problems, both acute and chronic (Murray, 1998). In Japan, the third epidemic of METH abuse among the population is in progress (Ujike and Sato, 2004), and about 18000 persons were arrested in 2004 for illegal drug abuse. The U.S. National Survey on Drug Use and Health estimated in 2004 that 1.4 million Americans aged 12 or older had used METH in the past year (NSDUH 2005). The direct CNS effects of METH include increased wakefulness, increased respiration, enhanced body movements, hyperthermia, euphoria, and decreased appetite, as well as the following psychiatric sequelae: confusion, anxiety, paranoia, delirium, increased agitation, and aggressiveness (NIDA 2004). Recently, evidence has accumulated that METH can cause neurodegeneration in the brain (Davidson et al. 2001; Kita et al. 2003; Cadet et al. 2005). In addition, increased infectious diseases such as HIV and hepatitis B and C are likely to be consequences of increased METH abusers through sharing contaminated syringes (Poshyachinda, 1993). At present, however, there are no effective medications for the treatment of METH abuse (Kantak, 2003).

The molecular basis of amphetamine action has been investigated. METH targets in subcellular components include the cocaine-sensitive dopamine transporter (DAT) located in presynaptic plasma membranes, the vesicular monoamine transporter-2 (VMAT-2) located in vesicular membranes, and the monoamine oxidase (MAO) enzyme located in mitochondrial outer membranes (Seiden et al. 1993). The direct action of METH on DAT reverses dopamine transport, resulting in enhanced release of dopamine from presynaptic terminals into extracellular space (Sulzer et al. 1995; Jones et al. 1998; Khoshbouei et al. 2003). METH also enters the presynaptic neurons via lipophilic diffusion and through DAT as a structural analogue of dopamine (Zaczek et al. 1991a, b), thereby allowing the drug to enter synaptic vesicles through VMAT-2 and/or by diffusion. The resulting METH-induced disruption of vesicular pH produces enhanced release of dopamine from the vesicles through VMAT-2 (Sulzer et al. 1995; Jones et al. 1998). Once inside the presynaptic terminals, METH inhibits (i) VMAT-2; resulting

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in a decrease in vesicular dopamine uptake (Brown et al. 2002; Ugarte et al. 2003), and (ii) MAO, which catalyzes the oxidative deamination of monoamines, resulting in increased levels of monoamines such as dopamine and serotonin (5-hydroxytryptamine, 5-HT) and a decrease in their metabolites (Felner and Waldmeier, 1979; Egashira et al. 1987). Overall, the actions of METH on these three target proteins result in the massive outflow of dopamine from the presynaptic terminal into the synaptic cleft (Kuczenski et al. 1995). The activation of dopamine receptors by aberrant levels of released dopamine in mesolimbic and mesocortical areas is closely related to METH-induced abnormal behavior and the rewarding property of the drug in rodents and humans (Robinson and Becker, 1986; Seiden et al. 1993; Self and Nestler, 1995; Giros et al. 1996; Everitt and Robbins, 2005).

Pre-clinical investigations suggest that DAT blockers such as vanoxerine (also known as GBR 12909) are effective for the prevention of cocaine effects such as cocaine-self administration and cocaine-induced increases in extracellular dopamine levels, because cocaine exerts its effects predominantly through an interaction with DAT (Gorelick et al. 2004). Pre-clinical evaluation of vanoxerine as a potential medication for METH addiction is also in progress (Baumann et al. 2002). Alternatively, mechanism(s) other than DAT have been proposed for METH action in transgenic studies (Searce-Levie et al. 1999; Budygin et al. 2004), because METH targets are multiple (Seiden et al. 1993).

In the recent literature, some attempts have been made to find an effective treatment for METH abuse through one of the three targets listed above. This review describes current insights into the pharmacology of MAO inhibitors from the behavior of rodents administered with various doses of single and repeated METH, since relatively moderate and high doses of single and repeated METH administration in rodents serve as an animal model for METH abuse in humans (described below). Although amphetamines inhibit MAO reversibly, a role for MAO inhibition in amphetamine-induced behaviors has not brought much scientific interest since amphetamine-induced MAO inhibition is weak (Mantle et al. 1976; Miller et al. 1980). However, recent evidence that METH (or *d*-amphetamine) in combination with MAO inhibitors produces unique behavioral

effects, and implicates a role for MAO inhibitors in the protection against and improvement of METH abuse, especially, through the actions on the striatal serotonin system.

METH-Treated Rodents as Animal Models of METH Abuse

The use of naïve rodents administered with single or repeated METH serves as an animal model for METH abuse in humans, since animal models show abnormal behavior such as increased motor activity (Abekawa et al. 1995; Kitanaka et al. 2003, 2005a), repetitive and compulsive behavior called stereotypy (Nishikawa et al. 1983; Kuczenski et al. 1995; Abekawa et al. 1995; Tatsuta et al. 2005, 2006), self-injurious behavior (Halladay et al. 2003; Mori et al. 2004), and rewarding properties (Ranaldi and Poeggel, 2002; Justinova et al. 2003; Kitanaka et al. 2006), which resemble human symptoms of amphetamine psychosis (Randrup and Munkvad, 1967; Groves and Rebec, 1976; Winchel and Stanley, 1991). In addition to the effects of METH listed above, repeated administration of METH also induces a progressive augmentation of locomotor activity in response to treatment, a phenomenon referred to as behavioral sensitization (Post, 1980; Shimosato and Saito, 1993; Ohno and Watanabe, 1995; Itzhak, 1997; Ito et al. 2000; Itzhak and Ali 2002; Kitanaka et al. 2003, 2005b; Okabe and Murphy, 2004). The progressive augmentation of locomotor activity in response to repeated METH in rodents resembles the METH-induced psychiatric symptoms which show progressive quantitative alteration in METH addicts (Ellinwood and Kilbey, 1977; Robinson and Becker, 1986; Itzhak and Ali, 2002; Ujike and Sato, 2004).

MAO, MAO Inhibitors, and Amphetamines

In mammals, the MAO enzyme exists in two isoforms, termed MAO-A and MAO-B, which differ in substrate specificity (Johnston, 1968; Murphy, 1978) and have been identified as separate gene products (Shih et al. 1999). Selective and non-selective MAO inhibitors have been developed for pre-clinical and clinical purposes, especially as treatments for major depression and Parkinson's disease (Finberg and Youdim, 1983; Worms et al. 1987; Pletscher 1991; Aubin et al. 2004). The first MAO inhibitor to be discovered

was the hydrazine derivative iproniazid, which was originally developed for the treatment of tuberculosis. Iproniazid and the related compounds are highly toxic to the liver when taken excess (Sinha, 1987), resulting in the withdrawal of many hydrazine derivatives from the clinic. Then, the propargyl compounds were developed as MAO inhibitors with less undesirable side-effects (Swett et al. 1963). Among them, pargyline (*N*-methyl-*N*-2-propynylbenzylamine) and clorgyline (*N*-methyl-*N*-propargyl-3-(2, 4-dichlorophenoxy) propylamine) were reported to be irreversible inhibitors of MAO-A/B (non-selective) and MAO-A, respectively. Selective irreversible MAO-B inhibitors were also developed (Knoll et al. 1965). One of them is selegiline (*N*, α -dimethyl-*N*-2-propynylphenethylamine; also known as *l*-deprenyl), which is a propargyl derivative of *l*-amphetamine.

Besides being potent monoamine releasing agents, amphetamines are also relatively potent, non-selective MAO inhibitors (Seiden et al. 1993), while the inhibition is weak compared with the actions of synthetic MAO inhibitors (Mantle et al. 1976; Miller et al. 1980).

While a valuable review highlights the advantages of MAO inhibitors (Youdim et al. 2006), these propargyl compounds have received little attention in the literature in recent years because of (1) the side effects associated with this drug class, including possible hypertensive crisis, (2) the development of new and more specific types of agents for the treatment of mental diseases and, (3) the complex mechanism of action of MAO inhibitors, that are at least partially unresolved.

As for the clinical use of psychostimulant-MAO inhibitor combinations, amphetamine and MAO inhibitor combination therapy has been used to augment antidepressant treatment (Feinberg, 2004). Other clinical trials of amphetamine and MAO inhibitor combination appear to be highly restricted because of the lack of therapeutic benefits. In the animal experiments, however, the effects of clorgyline, selegiline, and pargyline on METH-induced behavior have been well documented.

Modification of METH Action by Clorgyline

As shown in Table 1, clorgyline has no effect on spontaneous locomotor activity in naïve mice and rats (Table 1). However, when co-administered with METH, clorgyline exerts significant inhibi-

tory effects on METH (1 mg/kg, i.p.)-induced hyperlocomotion after single and repeated (5 days) clorgyline administration (Kitanaka et al. 2005a). The effect of clorgyline on METH-induced behaviors lasts up to 40 min after METH challenge, suggesting that the development of METH-induced hyperlocomotion was effectively inhibited by clorgyline pretreatment (Kitanaka et al. 2005a). It should be noted that no enhanced stereotypic behavior including “mouthing” behavior in parallel with the decrease in hyperlocomotion after METH in mice pretreated with clorgyline was observed in terms of the rearing index (Kitanaka et al. 2005a). This effect was not observed with selegiline (Kitanaka et al. 2005a).

In this study, the association between the inhibitory action of clorgyline and MAO-A activity in the brain was simultaneously investigated. For this purpose, the activity of monoaminergic transmission was evaluated in terms of apparent monoamine turnover. With respect to 5-HT metabolism, the ratio of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of 5-HT, to 5-HT is a good index of apparent 5-HT turnover (De Vries and Odink, 1991; Torres et al. 2002). 5-HT turnover was significantly increased in the regions of the striatum and nucleus accumbens after single METH administration due to a significant decrease in 5-HT levels (Kitanaka et al. 2003). Clorgyline pretreatment, in turn, significantly increased and decreased 5-HT and 5-HIAA contents, respectively, by inhibiting MAO-A, resulting in a significant decrease in the 5-HT turnover index in the striatum and nucleus accumbens (Kitanaka et al. 2005a). This effect of clorgyline on 5-HT turnover is closely correlated with the drug's inhibitory action on METH-induced hyperlocomotion, evaluated by ANOVA analysis (Kitanaka et al. 2005a). This finding suggests that the improvement of METH-induced abnormal 5-HT turnover in the striatal region by clorgyline treatment may play a role in the suppression of METH-induced increase in motor activity. Since selegiline had no effect on 5-HT turnover *in vivo*, METH-induced hyperlocomotion and 5-HT turnover were not affected by selegiline pretreatment (Kitanaka et al. 2005a; Table 1).

Clorgyline action on METH-induced hyperlocomotion in mice (Kitanaka et al. 2005a) appears paradoxical, because clorgyline and METH were assumed to inhibit MAO-A activity additively, presumably resulting in enhanced METH toxicity (i.e. hypermotility) with clorgyline pretreatment.

Table 1. Effects of MAO inhibitors on behavior of naive and METH (or *d*-amphetamine)-challenged rodents.

Measurement	MAOI	Species, Dose and Injection Schedule	Effect ^a	Reference
Naive				
Locomotion	Clorgyline	Rat, 4 mg/kg, ip x 1 d	NC	Segal et al. 1992
	Clorgyline	Mouse, 1 mg/kg, sc x 1 d or 5 d	NC	Kitanaka et al. 2005a
	Selegiline	Rat, 0.25 mg/kg, sc x 42 d	NC	Timár et al. 1986
	Selegiline	Rat, 1–20 mg/kg, sc x 1 d	NC	Timár et al. 1996
	Selegiline	Rat, 10 mg/kg, ip x 1 d	Increase	Okuda et al. 1992
	Selegiline	Rat, 10 mg/kg, ip x 1 d	Increase	Themann et al. 2002
	Selegiline	Mouse, 0.3 mg/kg, sc x 1 d or 5 d	NC	Kitanaka et al. 2005a
	Pargyline	Rat, 10 mg/kg, sc x 24 d	Increase	Barbelivien et al. 2001
	Selegiline	Rat, 1–10 mg/kg, sc x 1 d	ND	Timár et al. 1996
	Selegiline	Rat, 20 mg/kg, sc x 1 d	Increase	Timár et al. 1996
Stereotypy				
	Clorgyline	Mouse, 1 mg/kg, sc x 5 d	ND	Kitanaka et al. 2005b
	Selegiline	Rat, 10 mg/kg, ip x 8 d	Increase	Themann et al. 2002
CPP index	Clorgyline	Mouse, 0.1–10 mg/kg, sc x 6 d	Increase	Kitanaka et al. 2006
	Selegiline	Rat, 1–20 mg/kg, sc x 4 d	ND	Timár et al. 1996
	Selegiline	Mouse, 10 and 25 mg/kg, ip x 5 d	Increase	Wu and Zhu 1999
# of CAR	Selegiline	Rat, 1–20 mg/kg, sc x 5 d	ND	Timár et al. 1996
DSE ^b	Selegiline	Rat, 10–30 mg/kg, ip x 1	Increase	Yasar et al. 1993
After METH (or <i>d</i> -Amphetamine) challenge				
Hyperlocomotion	Clorgyline	Rat, 4 mg/kg, ip x 1 d	Decrease	Segal et al. 1992
	Clorgyline	Mouse, 1 mg/kg, sc x 1 d or 5 d	Decrease	Kitanaka et al. 2005a,b
	Selegiline	Mouse, 0.3 mg/kg, sc x 1 d or 5 d	NC	Kitanaka et al. 2005a
	Pargyline	Mouse, 50 mg/kg, ip x 1 d	NC	Lew et al. 1971
	Clorgyline	Rat, 4 mg/kg, ip x 1 d	Increase	Segal et al. 1992
	Clorgyline	Rat, 0.1–10 mg/kg, sc x 1 d	NC	Tatsuta et al. 2005
	Clorgyline	Mouse, 0.1 not 1–10 mg/kg, sc x 1 d	Decrease	Tatsuta et al. 2005
	Selegiline	Rat, 0.25–5 mg/kg, sc x 1 d	Decrease	Timár et al. 1993
	Selegiline	Mouse, 0.1, 1 and 10 mg/kg, sc x 1 d	NC	Tatsuta et al. 2005
	Clorgyline	Mouse, 1 mg/kg, sc x 5 d	Decrease	Kitanaka et al. 2005b
Behavioral sensitization	Clorgyline	Mouse, 0.1–10 mg/kg, sc x 6 d	NC	Kitanaka et al. 2006
CPP index	Clorgyline	Rat, 3 and 5.6 mg/kg, ip x 1	Increase	Yasar et al. 1993
DSE ^b	Selegiline	Mouse, 2 mg/kg, sc, x 13 d	NC	Grasing et al. 2001
Mortality	Selegiline	Mouse, 0.02 and 0.2 mg/kg, sc, x 13 d	Decrease	Grasing et al. 2001

This table compares the published effects of MAO inhibitors (MAOI) on naive and METH-treated mice. CAR: conditioned avoidance responses; CPP: conditioned place preference; DSE: discriminative stimulus effect; NC: no change; ND: not detected; ip: intraperitoneal injection; sc: subcutaneous injection. "Selegiline" means "R-isomer of selegiline" in this table.

^aComparison between MAOI- and vehicle-pretreated subjects.

^bMice were used after they were trained under a 5-response, fixed ratio schedule of stimulus-shock termination or a 10-response, fixed ratio schedule of food presentation to discriminate between *d*-amphetamine (1 mg/kg) and saline in a two-lever, conditioning procedure.

Indeed, for apparent dopamine turnover, an additive inhibition of the ratio of 3, 4-dihydroxyphenylacetic acid (DOPAC), a metabolite of dopamine, to dopamine by single METH administration after clorgyline pretreatment was observed in the regions of the striatum and nucleus accumbens in mice (Kitanaka et al. 2005a).

In light of these findings, why did the 5-HT content selectively decrease in the regions of the striatum and nucleus accumbens in mice after a relatively moderate dose of METH (1 mg/kg)? A depletion effect similar to this is often interpreted as evidence that the neurotoxic dosage of METH induces neurodegeneration in the terminals of monoaminergic neurons. In the rat brain striatum, neurotoxic METH destroys the terminal arbors of fine 5-HTergic axons that arise from the dorsal raphe nucleus, resulting in the acute depletion of 5-HT from the axons (Axt and Molliver, 1991; Brown and Molliver, 2000). Similar neurodegeneration is observed in the dopaminergic axons of rats (Ricourte et al. 1982, 1984; Xu et al. 2005), with a significant decrease in the striatal dopamine content (Broening et al. 2005). Neurotoxic dosages of METH in mice (four injections of 15 mg/kg METH every 2 h or a single administration with 30 mg/kg) have been shown to produce a significant decrease in the striatal contents of dopamine and 5-HT (Fumagalli et al. 1998), similar to the observations in rats. Unfortunately, the possible neurodegenerative effects of METH at a moderate dose (1 mg/kg) on the striatal neuronal system in mice has not yet been studied.

Provided that monoaminergic axons in the striatum express properties that determine which are relatively vulnerable to METH at even moderate doses, there exists an obvious difference between dopamine and 5-HT fibers which result in the METH vulnerability. Since there is evidence of 10-30-fold higher content of dopamine than 5-HT in the mouse striatum (Kitanaka et al. 2003, 2005a, 2006), the density of dopamine-containing fibers might be higher than that of 5-HT-containing fibers, provided that the percentages of synapses occupied by dopamine and 5-HT present in the brain are identical (Krieger, 1983). It is possible that the low density of striatal 5-HT fibers can be damaged more seriously than the dopamine fibers by METH at moderate doses. Striatal 5-HT neurotransmission is suggested to play a crucial role in the regulation of METH-induced hyperlocomotion in mice (Kitanaka et al. 2005a). Therefore, it is possible

that MAO-A inhibition increases the content of 5-HT, resulting in a significant improvement in 5-HT neurotransmission which protects against METH-induced hyperlocomotion via the activation of 5-HT turnover.

Several investigations have shown that the development of sensitization to the locomotor stimulating effect of METH in rodents can be blocked effectively by pharmacological agents such as a protein synthesis inhibitor cycloheximide, nitric oxide synthase inhibitors *N*^G-nitro-L-arginine and 7-nitroindazole, and a benzodiazepine clonazepam administered prior to, or simultaneously with METH (1 mg/kg once per day for 5–10 consecutive days or 2 mg/kg once per day, 5 times at intervals of 3–4 days) (Shimosato and Saito, 1993; Ohno and Watanabe, 1995; Itzhak, 1997; Ito et al. 2000). Unfortunately, a protocol involving agent pretreatment or co-treatment is not easily applied to human METH addictions. To overcome this, we applied a modified treatment protocol to mice which have already acquired behavioral sensitization to METH (1 mg/kg, i.p. once per day for 5 consecutive days). During the drug-free period (4 days) after the repeated METH administration, the mice were treated with 1 mg/kg of clorgyline once per day. This treatment successfully blocked the expression of behavioral sensitization to METH (Table 1; Kitanaka et al. 2005b).

It is suggested that behavioral sensitization may have some common properties with learning and memory (Lidow et al. 1998); therefore, the cerebral cortex is one region of interest. After the METH challenge, significantly enhanced dopamine metabolism (i.e. increased overall dopamine turnover, the ratio of homovanillic acid (HVA) to dopamine) was observed in the cerebral cortex of METH-sensitized mice compared with non-sensitized animals (Kitanaka et al. 2005b). In particular, cerebral cortical dopamine metabolism increased approximately 3-fold in sensitized mice treated with repeated clorgyline compared with mice without clorgyline treatment. It is likely that brain dopamine in mice, which is not metabolized by MAO-A after repeated clorgyline treatment (Kitanaka et al. 2005a) was, in turn, exposed to catechol-*O*-methyltransferase (COMT), another dopamine metabolizing enzyme. In the cerebral cortex, dopamine metabolism is more sensitive to COMT than that in the striatum or hypothalamus (Gogos et al. 1998), or cerebral cortical MAO activity is lower than in other regions.

Therefore, dopamine released in the cerebral cortex by a single METH challenge was metabolized largely by COMT after clorgyline treatment, resulting in inhibition of the expression of behavioral sensitization to METH. It is of interest to note the possible relationship between the activities of MAO-A and COMT, influenced by each other, in the brain; however, to our knowledge, there is no direct evidence of molecular interaction between the two enzymes. Clorgyline exhibits no behavioral sensitization *per se* (Table 1).

In rats, Segal et al. (1992) reported that clorgyline (4 mg/kg) pretreatment significantly reduced locomotion (increased crossover plus rearing) during the first 1-h interval after the amphetamine challenge (0.25 and 2.5 mg/kg) in parallel with a significant increase in the total period of the observed stereotypy (Table 1). This effect is interpreted by experimental evidence that MAO-A inhibition by clorgyline increases the extracellular dopamine concentration in the nucleus accumbens, assessed by *in vivo* microdialysis. In contrast, no change in the intensity of METH (10 mg/kg)-induced stereotypy was observed in rats pretreated with clorgyline (0.1–10 mg) (Table 1; Tatsuta et al. 2005). In mice, the lowest dose of clorgyline tested (0.1 mg/kg) significantly increased and decreased hyperlocomotion and stereotypy, respectively, during the first 20-min interval at which the mice showed a submaximal intensity of stereotypy (Tatsuta et al. 2005). However, clorgyline pretreatment (1 and 10 mg/kg) did not significantly alter horizontal hyperlocomotion in mice during the first 20-min interval after METH challenge (10 mg/kg) compared with the mice pretreated with vehicle (saline). The molecular action of the clorgyline is likely to be independent of MAO-A because (1) change in the intensity of METH-induced stereotypy was not correlated with the change in the striatal monoamine turnover during the first 20-min interval (Tatsuta et al. 2006) and, (2) the clorgyline (0.1 mg/kg)-induced shift in the METH response was not correlated with the degree of MAO-A inhibition estimated by apparent monoamine turnover (Tatsuta et al. 2005).

Possible interactions of clorgyline with sigma receptors (Itzhak and Kassim, 1990; Itzhak et al. 1991), imidazoline I₂ receptors (Alemany et al. 1995; MacInnes and Duty, 2004), and/or MAO inhibitor-displaceable quinpirole binding sites (Culver and Szechtman, 2003) should not be neglected to understand the mode of action of

clorgyline, since these binding sites are involved in psychiatric disorders (Eglen et al. 1998; Bermack and Debonnel, 2005). Clorgyline displays high affinity for both MAO-A and sigma receptors with relatively identical affinities (IC₅₀ value of 10 nM and 3 nM, respectively) (Egashira et al. 1987; Itzhak et al. 1991), and clorgyline-sensitive sigma receptors are suggested to coexist with a subcellular fraction with MAO activity (Itzhak et al. 1991). Therefore, the doses of clorgyline used in the *in vivo* studies appear to fully activate the sigma receptors.

For the METH-induced rewarding property, clorgyline pretreatment (0.1–10 mg/kg) failed to block the METH (0.5 mg/kg)-induced increase in the conditioned place preference (CPP) index in mice (Table 1; Kitanaka et al. 2006). The monoamine turnover index (ratios of DOPAC to dopamine, HVA to dopamine, and 5-HIAA to 5-HT) in the striatum and nucleus accumbens was not different between mice conditioned with and without METH, indicating that the inhibitory effect of various doses of clorgyline on MAO activity was independent of METH (0.5 mg/kg) action. It should be noted that the saline/saline pairing groups pretreated with clorgyline at a dose of 1 mg/kg showed an increased CPP index, similar to the result from METH/saline pairing group (Kitanaka et al. 2006). This might mean that the mice in the saline/saline pairing group entered and stayed in each CPP compartment independent of the given visual and texture cues on the testing day after the pretreatment with 1 mg/kg clorgyline.

Modification of METH Action by Selegiline

Selegiline in appropriate doses exhibits amphetamine-like properties *per se*, such as increased motor activity, rewarding effect, and behavioral sensitization (Table 1), since selegiline is metabolized in part to *l*-METH and *l*-amphetamine (Reynolds et al. 1978; Elsworth et al. 1982; Lajtha et al. 1996; Gerlach et al. 1996; Baker et al. 1999). Because of the potential of the selegiline metabolites for abuse liability, it is likely that selegiline could enhance METH action when given in combination. Indeed, selegiline (20 mg/kg) induced the stereotyped head movement in rats, while the stereotypy was not observed when the rats were administered with 1–10 mg/kg of selegiline (Table 1; Timár et al. 1996). Selegiline in doses of

1–20 mg/kg had no effect on locomotion, CPP index, nor the number of conditioned avoidance responses (Timár et al. 1996).

Increased discriminative stimulus effects were reported using 3 and 5.6 mg/kg of selegiline in combination with *d*-amphetamine (1 mg/kg) compared with *d*-amphetamine alone in mice which have been trained under a 5-response, fixed ratio schedule of stimulus-shock termination or a 10-response, fixed ratio schedule of food presentation to discriminate between *d*-amphetamine (1 mg/kg) and saline in a two-lever, conditioning procedure (Table 1; Yasar et al. 1993). Also, high doses of selegiline (17–30 mg/kg) produced full generalization to *d*-amphetamine (Yasar et al. 1993). These observations as well as those of Timár et al. (1996) suggest that the amphetamine-like properties can be observed when selegiline *l*-isomer in high doses is treated.

Small doses of selegiline fail to induce any amphetamine-like hyperlocomotion (Timár et al. 1986). Timár et al. (1993) reported that selegiline at small doses can decrease amphetamine-induced stereotypy in rats, without change in the index of dopamine turnover in the olfactory tubercle, compared with saline-pretreated animals. They suggest that the uptake of amphetamine might be reduced by pretreatment with selegiline, resulting in the decrease of stereotyped behavior; however, the same selegiline treatment protocol as that reported by Timár et al. (1993) enhances striatal dopamine turnover (Zsilla et al. 1982). Therefore, the relationship between selegiline action on amphetamine-induced stereotypy and MAO-B activity needs to be clarified by further studies. Only one report shows the effect of selegiline on the lethal action of METH. Repeated administration with lower doses of selegiline (0.02 and 0.2 mg/kg) to mice treated with toxic METH dosage (10 mg/kg \times 4 within one day, two-hour intervals) blocked the METH-induced increase in mortality (Table 1; Grasing et al. 2001). This selegiline effect was not detected at 2 mg/kg, suggesting that the mode of action is MAO-B independent. Regarding this point, Lamensdorf et al. (1999) reported that increased DAT expression was observed after chronic (21 days) treatment with selegiline (0.25 mg/kg). This might explain the results of Timár et al. (1993) and of Grasing et al. (2001), since the increased DAT expression induces increased extracellular dopamine clearance in the brain. Molecular mechanism(s) of the

enhanced DAT expression by selegiline are unclear, although selegiline has been shown to alter the expression of mRNA for a variety of proteins including tyrosine hydroxylase and L-aromatic amino acid decarboxylase (Vrana et al. 1992; Li et al. 1992).

In mice, stereotypy can be induced by METH at doses of 10 mg/kg by a single injection (Tatsuta et al. 2005). When administered of mice with 20 mg/kg METH, the mice show self-injurious behavior (Mori et al. 2004). Tatsuta et al. (2005) reported that a wide range of selegiline (0.1–10 mg/kg) showed no enhancement of METH-induced stereotyped behavior nor a shift of the abnormal behavior from stereotypy to self-injurious behavior in mice, suggesting that 10 mg/kg of selegiline could not have an amphetamine (10 mg/kg)-like property after the systemic injection and following metabolism.

Modification of METH Action by Non-selective MAO Inhibitors

Lew et al. (1971) reported that pretreatment of mice with 50 mg/kg of pargyline, a non-selective MAO inhibitor, had no effect on *d*-amphetamine-induced hyperlocomotion in mice (Table 1). However, treatment of rats with 10 mg/kg of pargyline increases locomotor activity *per se* (Table 1; Barbelivien et al. 2001); this effect might be interpreted by evidence that MAO-A inhibition by clorgyline (and probably by pargyline at high doses) increases extracellular dopamine concentration in the nucleus accumbens (Segal et al. 1992). The possible effect of metabolites of pargyline (benzylamine, *N*-methylbenzylamine, and *N*-propargylbenzylamine) on spontaneous locomotion in rodents can not be ruled out, but no reports have not been published.

Aubin et al. (2004) reported the behavioral profile of a newly developed, mixed-reversible MAO-A/B inhibitor, SL25.1131, in mice. The agent can improve decreased dopaminergic tone in the striatum by inhibiting MAO-A and -B and locomotion disrupted by treatment with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Mixed MAO inhibitors possess attractive potential properties for the treatment of METH abuse, since selective, irreversible MAO inhibitors can block METH (or *d*-amphetamine)-induced abnormal behavior in rodents (Table 1), although the mechanisms of action are complex.

Conclusions

METH-induced motor activity, stereotypy, and sensitization are closely associated with monoaminergic transmission. Modification of MAO activity by MAO inhibitors can influence METH action. Although some pre-clinical studies cited in this review suggest the feasibility of MAO inhibitors for the treatment of METH abuse, careful attention should be directed to the potential risk similar to that reported in the treatment of depressive disorder. Based on the current research on the mechanisms of MAO inhibitors, they exhibit a putative 'novel' mode of action which is independent of MAO and might influence monoaminergic-related behavior, as well as 'classical' MAO inhibition. For pre-clinical studies of the exact mode of action of MAO inhibitors and the effects of the MAO inhibitors on METH-induced abnormal behavior, METH-induced abnormal behavior in rodents may serve as an appropriate animal model for METH abuse in humans.

Acknowledgments

Research by one of the authors (NK) described herein was supported in part by a Grant-in-Aid for Researchers, Hyogo College of Medicine. We thank anonymous reviewers for their very helpful comments on an earlier version of the manuscript.

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