Insights into the Mechanisms of Action of the MAO Inhibitors Phenelzine and Tranylcypromine: A Review

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Although the non-selective monoamine oxidase inhibitors phenelzine and tranylcypromine have been used for many years, much still remains to be understood about their mechanisms of action. Other factors, in addition to the inhibition of monoamine oxidase and the subsequent elevation of brain levels of the catecholamines and 5-hydroxytryptamine, may contribute to the overall pharmacological profiles of these drugs. This review also considers the effects on brain levels of amino acids and trace amines, uptake and release of neurotransmitter amines at nerve terminals, receptors for amino acids and amines, and enzymes other than monoamine oxidase, including enzymes involved in metabolism of other drugs. The possible contributions of metabolism and stereochemistry to the actions of these monoamine oxidase inhibitors are discussed.

Key Words: amino acids, monoamine oxidase, neurotransmitter amines, phenelzine, tranylcypromine, uptake

Despite the fact that the non-selective monoamine oxidase (MAO) inhibitors phenelzine (PLZ) and tranylcypromine (TCP) (see Fig. 1) have been used clinically for many years, much remains to be learned about their mechanisms of action. In both cases, it appears that there are much more complex actions than a simple elevation of brain levels of catecholamines and 5-hydroxytryptamine (serotonin, 5-HT) subsequent to inhibition of MAO. These other possible contributing effects are the subject of this review.

Effects on trace amines and amino acids

The inhibition of MAO by drugs such as PLZ and TCP results in an often dramatic elevation of a number of brain amines termed "trace amines" (2-phenylethylamine (PEA), *m*- and *p*-tyramine, octopamine, tryptamine) (Philips and Boulton 1979; Boulton and Juorio 1982) (see Table 1). In addition, PEA is a metabolite of PLZ (Baker et al 1982; Dyck et al 1985). These trace amines can have marked effects on uptake and/or release of the catecholamines and/or 5-HT at nerve endings (Baker et al 1977; Raiteri et al 1977) and/or may act as neuromodulators through direct actions on receptors for the catecholamines and/or 5-HT (Jones 1983; Paterson et al 1990).

Several groups of researchers have noted that administering PLZ to rats results in an elevation of brain levels of the amino acid γ-aminobutyric acid (GABA) (Popov and Matthies 1969; Perry and Hansen 1973; Baker et al 1991; McKenna et al 1991a). Acute and chronic studies suggest that this elevation is the result of an inhibition of the catabolic enzyme GABA-transaminase (GABA-T) (Popov and Matthies 1969; McManus et al 1992). A similar dramatic elevation of brain levels of the amino acid alanine (Wong et al 1990; McKenna et al 1991a) and inhibition of alanine transaminase have been observed (Baker and Martin 1989). These effects of PLZ on GABA and alanine are demonstrated in Fig. 2. It is of interest that there is an increasing amount of evidence suggesting that GABA is involved in the action of anti-panic drugs (Breslow et al 1989), and that PLZ is one of the drugs commonly used to treat panic disorder (Ballenger 1986). We have found that the N^2-acetyl analogue of PLZ is also an effective MAO inhibitor, but lacks the effect of PLZ on GABA (McKenna et al 1991a). Thus, by comparing the effectiveness of N^2-acetyl-PLZ and PLZ in an animal model of panic disorder, it

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Table 1

Effect of tranylcypromine HCl[a] on concentrations of tryptamine and 2-phenylethylamine in rat hippocampus[c]

Treatment	Tryptamine	2-Phenylethylamine
Control	1.5 ± 0.1	1.6 ± 0.4
TCP – 0.25 hours	5.8 ± 0.4[b]	76.8 ± 7.3[b]
TCP – 0.75 hours	10.9 ± 0.6[b]	146.0 ± 11.0[b]
TCP – 1.5 hours	38.1 ± 2.9[b]	214.0 ± 42.0[b]
TCP – 6.0 hours	43.6 ± 8.1[b]	104.0 ± 7.0[b]

[a]20 mg/kg i.p.; [b]$p < 0.001$ relative to controls; [c]values are expressed as ng/g of wet tissue and represent mean ± SEM (n = 5 to 9). Results taken from Philips et al (1980).

should be possible to determine whether the GABAergic effect of PLZ plays an important role in the anti-panic action of PLZ.

Also of interest is the fact that PLZ's inhibition of GABA-T and elevation of GABA can be dramatically reduced by pre-treating rats with another MAO inhibitor (Popov and Matthies 1969; McKenna and Baker 1992). This finding suggests that a metabolite of PLZ produced by MAO is ultimately responsible for the inhibition of GABA-T.

The amino acid tryptophan has been used as an adjunct to therapy for affective disorders and in the treatment of refractory depression (Young 1991). Badawy and Evans (1981; 1982) reported that PLZ and TCP, as with a number of other antidepressants, inhibited rat liver tryptophan pyrrolase activity and produced elevations of brain tryptophan after both acute and chronic administration of the drugs. Grahame-Smith (1971) and Tabakoff and Moses (1976) also reported an increase in the brain levels of tryptophan in rodents at short intervals after the administration of high doses of TCP. The findings of Sherry-McKenna et al (in press) indicate that this tryptophan-elevating effect occurs only with high doses of PLZ and TCP and is relatively short-lived. Dyck and Dewar (1986) found that a high dose of PLZ increased striatal *p*-tyrosine concentrations in rats 12 hours after injection.

Effects on uptake and release of neurotransmitter amines

The structures of PLZ and TCP are similar to those of PEA and amphetamine, and, not surprisingly, they have effects on the uptake and/or release of dopamine, noradrenaline and, to a lesser extent, 5-HT (Hendley and Snyder 1968; Schildkraut 1970; Simpson 1978; Baker et al 1978; 1980; Dyck and Boulton 1980; Reigle et al 1980; Dyck 1984). Some of these effects are shown in Table 2 and Fig. 3. At the doses of PLZ and TCP often used, particularly in studies on laboratory animals, levels of these drugs in the brain that are sufficiently high to affect the uptake and release of these neurotransmitters could be attained (Calverley et al 1981; Dyck 1984). Several reports indicate that high doses of TCP (1.3 mg to 2.4 mg/kg per day) are effective in treating patients suffering from refractory depression (Robinson 1983; Guze and Baxter 1987; Pearlman 1987; Amsterdam and Berwish 1989). Since these doses are well above those reported to inhibit MAO by more than 90% (Giller and Lieb 1980; Giller et al 1982), effects of TCP other than the inhibition of MAO may contribute to the antidepressant effects of TCP at the high doses. Levels of free TCP may also contribute to the side-effects of this drug. In a study examining depressed patients, a correlation was found between mean plasma concentrations of TCP and mean orthostatic drop of systolic blood pressure and a rise in pulse rate (Mallinger et al 1986). Keck et al (1991) found that elevations in blood pressure were significantly correlated with the dose of TCP; they hypothesized that the initial hypertensive response to TCP is mediated by noradrenaline and that the orthostatic hypotensive effect is mediated by a direct interaction between TCP and α-adrenergic receptors.

Effects on receptors for amines and amino acids

Changes in several pre-synaptic and post-synaptic receptors may occur subsequent to the increased levels of the amines and/or amino acid neurotransmitters. These delayed effects may be associated with the lag between administration of the MAO inhibitors and onset of clinical effect.

Down-regulation of β-adrenoreceptors in rat brain cortex has been reported after the acute and chronic administration of PLZ and the chronic administration of TCP (Cohen et al 1982; Frazer and Lucki 1982; Koshikawa et al 1989; McManus and Greenshaw 1991a; Sherry-McKenna et al 1992b). Ordway et al (1991) reported that the chronic administration (21 days) of PLZ and TCP (5 mg/kg per day each) to rats produced a down-regulation of both β_1- and β_2-adrenoceptors in some areas of the brain. Paetsch and Greenshaw (unpublished data, 1992) found that chronic administration (28 days) of TCP (1 mg/kg per day) or PLZ

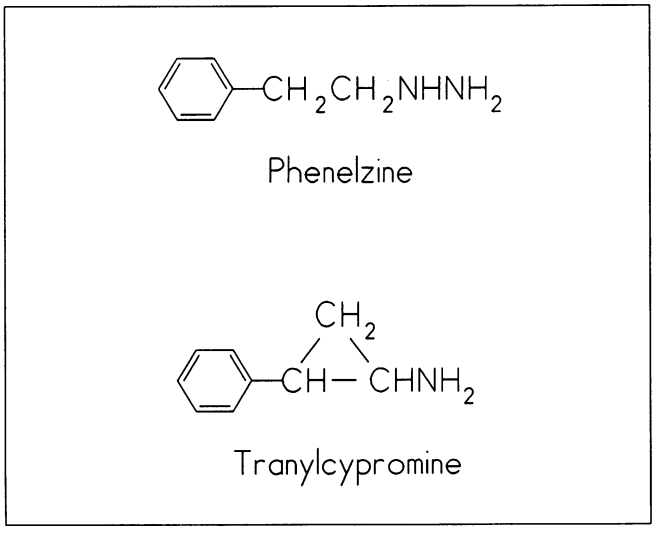

Fig. 1. Structures of phenelzine and tranylcypromine.

(5 mg or 10 mg/kg per day) resulted in β_1- but not β_2-adrenoceptor down-regulation in the cortex and cerebellum; a similar result was reported by Heal et al (1989) in the cortex using a high dose (10 mg/kg per day) of TCP, administered for ten days. After chronic administration (21 days), PLZ, at a dose of 10 mg/kg per day, but not at a lower dose (5 mg/kg per day), attenuated the locomotor suppressant effects of the β-agonist salbutamol (3 mg/kg i.p.) (McManus et al 1991b). Using clonidine as the pharmacological probe, studies on α_2-receptor functioning have been conducted on rats and have indicated that TCP and PLZ both cause a down-regulation of α_2-adrenergic receptors after chronic administration (Greenshaw et al 1988; McKenna et al 1992a). Lloyd et al (1985) reported an up-regulation of $GABA_B$ receptors in the frontal cortex of rats after chronic administration of the MAO inhibitor pargyline, but McManus and Greenshaw (1991a; 1991b) reported that PLZ did not affect $GABA_B$ receptor density or functioning, as measured in neurochemical and behavioral experiments, respectively. The chronic administration of both PLZ and TCP has been reported to cause a decrease in the density of ^{3}H-tryptamine binding sites in the brains of rats (Mousseau et al, in press). Binding studies have demonstrated a down-regulation of 5-HT_2 (Goodnough et al 1992) receptors in rats' brains after the chronic administration of TCP. Based on comprehensive electrophysiological studies, Blier et al (1990) concluded that MAO inhibitors (including PLZ) may act in the CNS by increasing the efficacy of 5-HT neurons through down-regulation of the somatodendritic autoreceptor. Paetsch and Greenshaw (in press) found that the chronic administration of PLZ or TCP results in the down-regulation of both D_1 and D_2 dopamine receptors in the striatum of rats. Chronic administration of some antidepressants has been reported to result in the down-regulation of ^{3}H-flunitrazepam receptors in rats' brains (Suranyi-Cadotte et al 1984). (MAO inhibitors were not tested.) The chronic administration of TCP or PLZ, at relatively low doses sufficient to down-regulate β-adrenergic and tryptamine receptors, has been found to produce no down-regulation of ^{3}H-flunitrazepam receptors in the cortex of rats (McKenna et al 1992b; Todd et al 1992); similar negative results were obtained with TCP (at an i.p. dose of 5 mg/kg b.i.d. for 21 days) by Kimber et al (1987).

Recent experiments were aimed at comparing the effects of high doses (2.5 mg/kg/day) and low doses (0.5 mg/kg/day) of TCP on tryptamine and 5-HT_2 receptors in the cortex of rats. The findings can be summarized as follows: 1. both high and low doses of TCP produce a decrease in the number of tryptamine receptors in cortex (Goodnough et al 1992; Sherry-McKenna et al 1992a), but the effect is more rapid

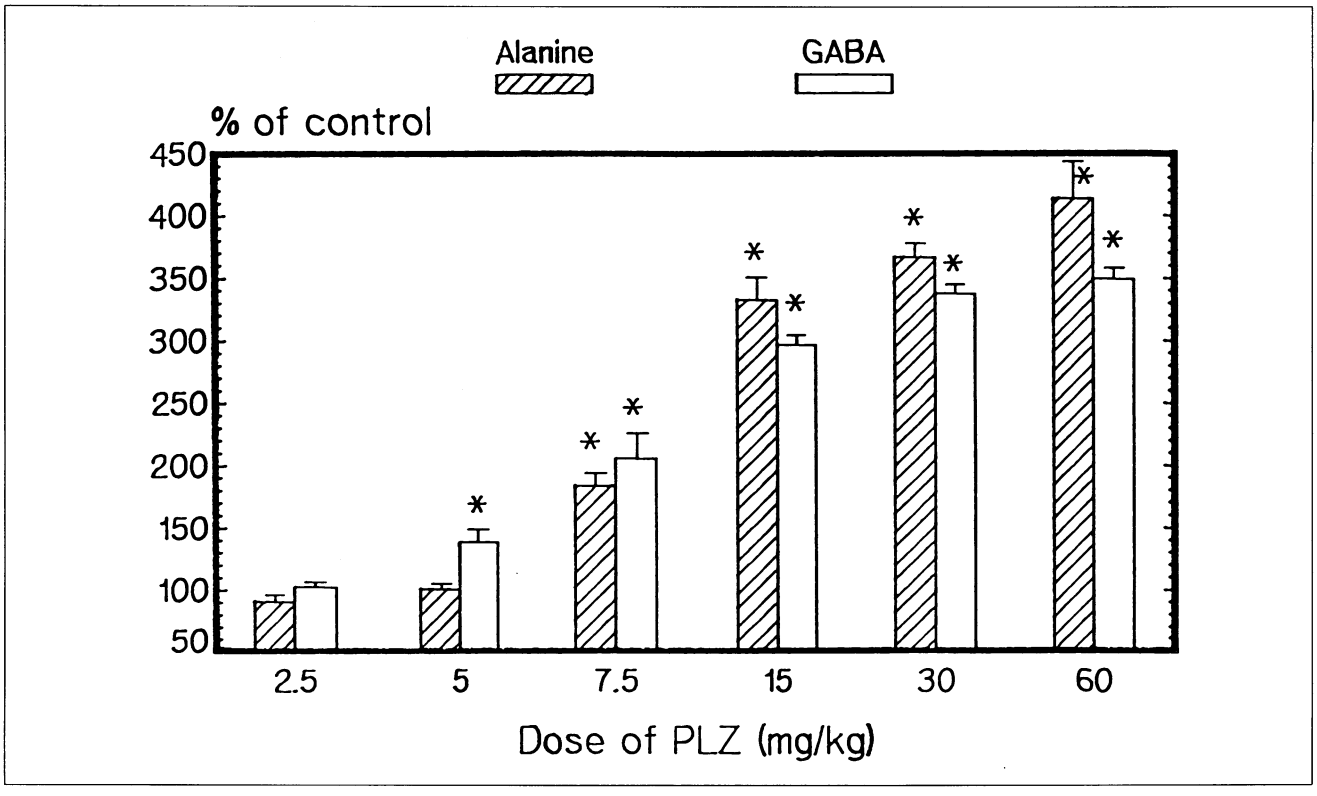

Fig. 2. Rat whole brain levels of GABA and alanine four hours after intraperitoneal administration of various doses of PLZ. The values represent mean percentage (± SEM) of control values (n = 6). *p < 0.05 compared with control values (in physiological saline-treated rats). These figures are based on values taken from Baker et al (1991) and Wong et al (1990).

Table 2

Comparison of the effects of (±)-TCP, PLZ, (±)-pheniprazine (PPZ) and 2-phenylethylamine (PEA) on uptake of catecholamines into prisms prepared from rat brain regions

	IC_{50} (μM)	
Drug	Noradrenaline (hypothalamus)	Dopamine (striatum)
PEA	0.48	1.45
TCP	0.43	4.78
PLZ	2.42	9.20
PPZ	1.24	2.57

Uptake was studied using the procedure described by Baker et al (1980). The results are taken from Baker et al (1978) and represent the means of six experiments conducted in duplicate.

with the high dose (Goodnough et al 1992); and 2. a high dose of TCP produces a greater decrease in 5-HT_2 receptor number in the cortex than the low dose (Goodnough and Baker 1992).

Effects on enzymes other than MAO

PLZ has been reported to inhibit tyrosine amino transferase, aromatic amino acid decarboxylase and dopamine β-hydroxylase (Dyck and Dewar 1986; Yu and Boulton 1992), in addition to inhibiting GABA-T and ALA-T. Aromatic amino acid decarboxylase, GABA-T and tyrosine amino transferase are pyridoxal-dependent enzymes, and PLZ has been shown to deplete blood pyridoxal-5-phosphate levels in humans (Malcolm et al 1990). In their *in vitro* studies of rats, Yu and Boulton (1992) also found that PLZ increased phenylethanolamine N-methyltransferase and catechol O-methyltransferase activities above control values. Robinson et al (1979) reported that chronic administration of TCP is associated with an increase in activity of aromatic amino acid decarboxylase. This observation may be related to the finding that chronic administration (up to 18 days) of TCP (10 mg/kg i.p. daily) to rats produced a much greater elevation of brain tryptamine than did PLZ (15 mg/kg i.p. daily) at the same time periods, despite the fact that both drugs inhibited MAO by more than 90% by day 2 (Baker et al 1984).

There are also reports of PLZ and TCP interacting with enzymes involved in drug metabolism (Gaultieri and Powell 1978; Tollefson 1983; McDaniel 1986). Patients who are prescribed PLZ or TCP may be taking other drugs concomitantly and thus metabolic drug-drug interactions may occur. MAO inhibitors have been reported to inhibit the degradation of such drugs as hexobarbital, ethylmorphine, aminopyrine, meperidine and antipyrine (Eade and Renton 1970; Clark et al 1972; Smith et al 1980; McDaniel 1986). Bélanger and Atitsé-Gbeasson (1982a; 1982b) found that PLZ and TCP inhibited demethylation of *p*-nitroanisole and N,N-dimethylaniline and hydroxylation of aniline in rat liver microsomes. They concluded that both drugs are inhibitors of oxidative microsomal reactions through an interaction with cytochrome P-450. Dupont et al (1987) studied the effects of MAO inhibitors on cytochrome P-450-dependent hydroxylation of bufuralol and antipyrine and 0-deethylation of 7-ethoxycoumarin in rat liver microsomes. Although PLZ and TCP were both able to inhibit hydroxylation of antipyrine, PLZ caused a much more potent inhibition of bufuralol hydroxylation and 7-ethoxycoumarin 0-deethylation than did TCP.

There have been reports of the actions of TCP on prostaglandin synthesis (Ellis et al 1982), and this drug has also been reported to cause a number of biochemical and physiological changes in rabbits that are thought to be the result of a thiamine deficiency (Ali 1985). The administration of PLZ has been reported to cause decreased pseudocholinesterase levels in some patients, which may enhance the effect of drugs such as succinylcholine which are metabolized by this enzyme (Bodley et al 1969).

Metabolism of PLZ and TCP

Much is still unknown about the metabolism of PLZ and TCP and the contribution of metabolites to the overall pharmacological profiles of PLZ and TCP. Numerous studies have been carried out on the acetylator status of patients and their subsequent response to treatment with PLZ (Rose 1982). These investigations were conducted based on the assumption that PLZ is acetylated because it is similar in structure to drugs, such as isoniazid, which are known to be acetylated. In fact, the existence of N-acetyl-PLZ as a metabolite of PLZ had not been adequately demonstrated until very recently, and indications are that it is only a minor metabolite (Narasimhachari et al 1980; Mozayani et al 1988; Coutts et al 1991). PLZ is an unusual drug in that it not only inhibits MAO, but it is also apparently a substrate for MAO. Clineschmidt and Horita (1969a; 1969b), using radiolabelled PLZ, suggested that phenylacetic acid (PAA) is a major metabolite of PLZ. In a later study using mass spectrometry to identify metabolites (Robinson et al 1985), PAA and 4-hydroxyphenylacetic acid (4-OH-PAA) were identified in human urine samples as major metabolites of PLZ. 4-OH-PAA is also of interest because it is a metabolite of the endogenous amine *p*-tyramine (4-OH-PEA). PEA is also a known metabolite of PLZ (Baker et al 1982; Dyck et al 1985), and there is now evidence for the formation of 4-hydroxyphenelzine (4-OH-PLZ) from PLZ (McKenna et al 1990; 1991b). These observations raise the question of the route of formation of 4-OH-PAA. Possible routes are as follows: PLZ → PAA → 4-OH-PAA; PLZ → PEA → *p*-tyramine (and/or PAA) → 4-OH-PAA; and PLZ → 4-OH-PLZ → 4-OH-PAA (with or without *p*-tyramine intermediate). These routes have not been studied thoroughly, nor is there detailed information on the pharmacological activity of metabolites such as 4-OH-PLZ. Another possible route of

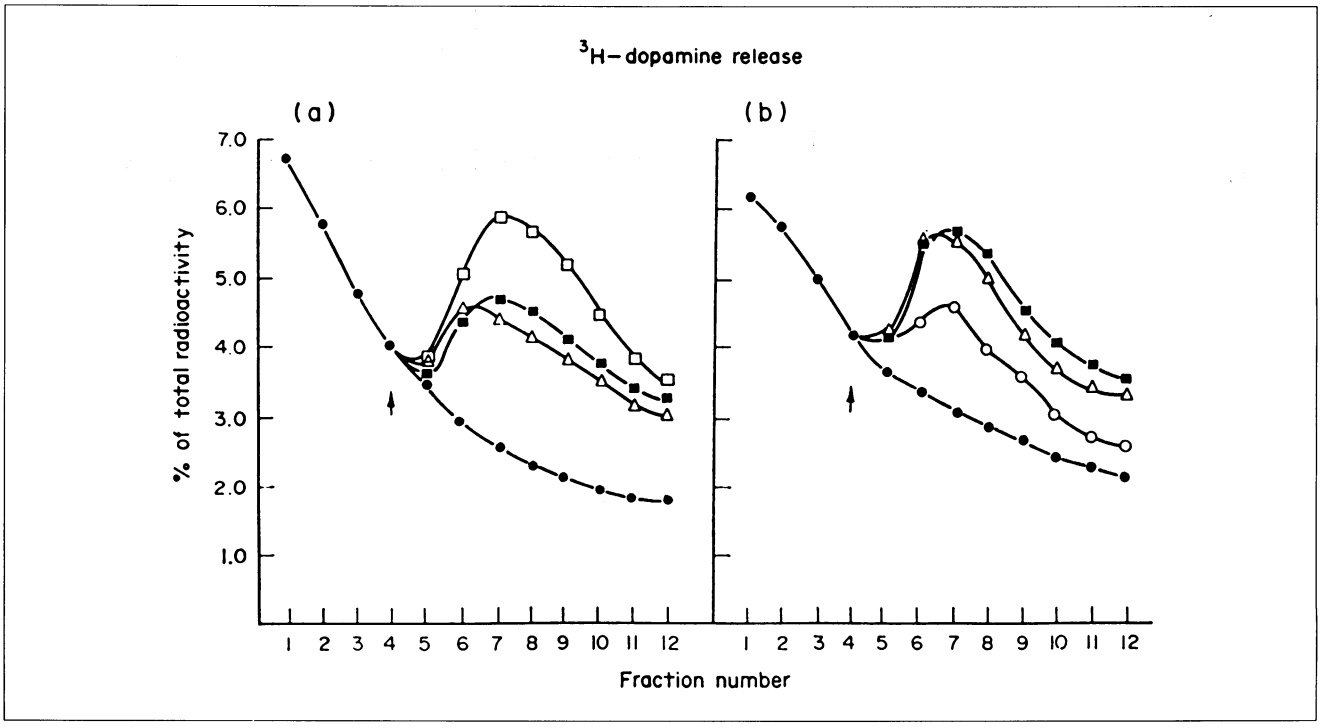

Fig. 3. Effects of some MAO inhibitors on release of ^{3}H-labelled dopamine from prisms prepared from rat striatum. The results are the means of six experiments conducted on separate days in four parallel superfusion chambers. All drugs were present at a concentration of 10 μM; the arrow indicates the fraction at which the drugs were added. Symbols: (a): control (•); (±)-α-ethyltryptamine (Δ); (±)-tranylcypromine (■); (±)-pheniprazine (□); (b): control (•); phenelzine (○); (±) α-ethyltryptamine (Δ); (±)-tranylcypromine (■). (Reprinted from Baker et al (1980) with permission).

metabolism of PLZ is N-methylation, which was recently demonstrated by Yu et al (1991) using enzymes obtained from bovine adrenal glands.

Alleva (1965) reported hippuric acid as a metabolite of TCP, but concluded that amphetamine was not involved as an intermediate in this metabolism. The metabolic formation of amphetamine from TCP continues to be debated. Youdim et al (1979) reported the presence of amphetamine in the plasma of a patient who had overdosed on TCP, but studies conducted by Reynolds et al (1980) on humans and by Sherry-McKenna et al (1992a) on humans and rats have not revealed amphetamine in human urine or rat brain after the administration of pharmacologically relevant doses of TCP. The presence of the N-acetyl (Calverley et al 1981) and ring hydroxylated (Baker et al 1986; Nazarali et al 1987) metabolites of TCP have been demonstrated in rats' brains. Kang and Chung (1984) confirmed the formation of N-acetyl-TCP and also identified N-acetyl-4-hydroxy-TCP as a TCP metabolite in rats' urine. Our preliminary experiments have shown that 4-hydroxy-TCP is an inhibitor of MAO-A and MAO-B, but is weaker than the parent drug in this regard. Studies are in progress to investigate the actions of this metabolite on uptake and release of catecholamines and 5-hydroxytryptamine (5-HT) in the brain. It is known that TCP itself has such actions (Baker et al 1978, 1980; Hendley and Snyder 1968; Horn and Snyder 1972; Schildkraut 1970). The addition of a 4-hydroxy group on the structurally related amine PEA has been reported to enhance its effect on biogenic amine transport in synaptosomes (Raiteri et al 1977).

A better understanding of the metabolism of drugs such as PLZ and TCP may be useful in future drug design studies. Several analogues of TCP in which the 4 position of the phenyl ring is protected from hydroxylation have been investigated, and two of these analogues, namely 4-fluoro-TCP and 4-methoxy-TCP, have proven to be potent MAO inhibitors (Rao et al 1986; Coutts et al 1987; Sherry et al 1990; Sherry-McKenna et al 1992b).

Stereochemistry

TCP is used clinically as the racemate but the (+)-enantiomer has been shown to be more potent than (-)-TCP at inhibiting MAO, whereas (-)-TCP has been demonstrated to be more effective than (+)-TCP as an inhibitor of uptake of catecholamines (Nickolson and Pinder 1984; Smith 1980). Reynolds (1985) has reported that the two enantiomers also differ in their interaction with 5-HT$_1$ receptors in human post-mortem frontal cortex, with (-)-TCP displaying a higher

affinity than (+)-TCP. A recent report (Fischer 1991) indicated that the (+) enantiomer of TCP is more potent than the (-) enantiomer as an anticonvulsant. There is limited information on the pharmacokinetics of (+) TCP and (-) TCP, but results to date, from studies on laboratory animals and humans, indicate differences in clearance rates between the two enantiomers from the brain and plasma (Nickolson and Pinder 1984; Coutts and Baker 1989).

SUMMARY

Although PLZ and TCP have been used extensively in psychiatry for many years, much still needs to be understood about their actions. These drugs have obvious effects on MAO and consequently on levels of neurotransmitter amines, but other potentially important aspects which should be considered are their effects on endogenous amino acids and trace amines, effects on uptake and release of neurotransmitter amines, effects on receptors for amines and amino acids, actions on enzymes other than MAO, metabolism, stereochemistry and interactions with other drugs.

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