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INDUCTION OF PHENCYCLIDINE METABOLISM BY PHENCYCLIDINE, KETAMINE, ETHANOL, PHENOBARBITAL AND ISOSAFROLE

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Abstract—The *in vitro* metabolism of phencyclidine (PCP) was investigated in 9000 *g* supernatant fractions of both control and PCP-, ketamine-, ethanol-, phenobarbital- or isosafrole-pretreated rats. Levels of PCP, *trans*-4-phenyl-4-piperidinocyclohexanol (I), 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (II), *N*-(5-hydroxypentyl)-1-phenylcyclohexylamine (IX), and 5-(1-phenylcyclohexylamino)-valeric acid (X) were monitored by gas chromatographic analysis in all cases. The inhibition of metabolism by N_2, CO, SKF-525A or 2,4-dichloro-6-phenylphenoxyethylamine (DPEA), or deletion of NADPH or protein, implied the involvement of cytochrome P-450 in the reactions. The various inducing agents affected the metabolism of PCP in different ways, implying that at least several isozymes of cytochrome P-450 were involved in the total metabolism. The majority of the consumed PCP was not accounted for by the measured metabolites so that some other metabolic pathways of major quantitative importance must be operative.

Phencyclidine (PCP) has become a major drug of abuse and, as a result, interest has intensified in looking into its mode of action and the mechanism(s) of its biological activity [1].

An investigation of the effect(s) of chronic administration of PCP and other potential inducing agents on both PCP metabolism [2] and PCP levels would help define the potential effects of induction on its metabolic profile. Changes in levels of PCP metabolites or of PCP, as a consequence of induction (including induction by PCP itself), could be responsible for alterations in response to this drug in the event that the metabolite levels induced possess biological activity or levels of PCP are reduced.

There are several studies describing the inducing effects of PCP. Chronic treatment of rats with PCP causes significant increases in the rate of metabolism of hexobarbital, aminopyrine and zoxazolamine by rat liver 10,000 *g* supernatant fraction [3]. A recent study of the effects of chronic ethanol treatment on the disposition of PCP in the rat showed higher levels of PCP metabolites in plasma, brain and adipose tissue in ethanol-treated rats compared to controls, yet a slower rate of PCP clearance was observed [4].

In mice, a recent study reported significant increases in barbiturate and aniline hydroxylase activities, N-demethylase activity, and NADPH–cytochrome *c* reductase levels [5] after chronic PCP administration. Chronic pretreatment of mice with PCP also alters significantly the distribution of PCP and metabolites, particularly in the brain [6]. The LD_{50} of PCP in animals pretreated with SKF-525A (2-diethylaminoethyl-2,2-diphenylvalerate) decreases substantially [7], thus suggesting the involvement of cytochrome P-450 in the metabolism of PCP.

In several studies utilizing *in vitro* techniques to examine the metabolic pathways leading to the excreted products, this laboratory has identified compounds I, II, III, IX and X (Fig. 1) in animal liver preparations† [8, 9] after incubation with PCP and presented evidence that metabolite formation in the rabbit is cytochrome P-450 mediated [10]. Also, X has been found in the urine in both dogs [11] and humans [12] after exposure to PCP and in both rat and rabbit liver homogenates after incubation with PCP† [13].

Since the pharmacologic effects of PCP include induction of liver enzymes in rats and mice, the present study investigated the effects of chronic treatment with PCP and other inducing agents on PCP metabolism in *in vitro* systems. Levels of the individual metabolites I, II, III, VI, IX and X (Fig. 1) were measured in incubates of liver homogenates (9000 *g*) obtained from rats pretreated with the various inducing agents. In addition, evidence is presented that the formation of these metabolites is mediated, directly or indirectly, by cytochrome P-450.

MATERIALS AND METHODS

Chemicals. Potassium chloride, potassium cyanide, potassium phosphate, sodium chloride and magnesium chloride were reagent grade, purchased from the Fisher Scientific Co. (Los Angeles, CA). Monosodium glucose-6-phosphate, yeast alcohol dehydrogenase and $NADP^+$ for incubations were

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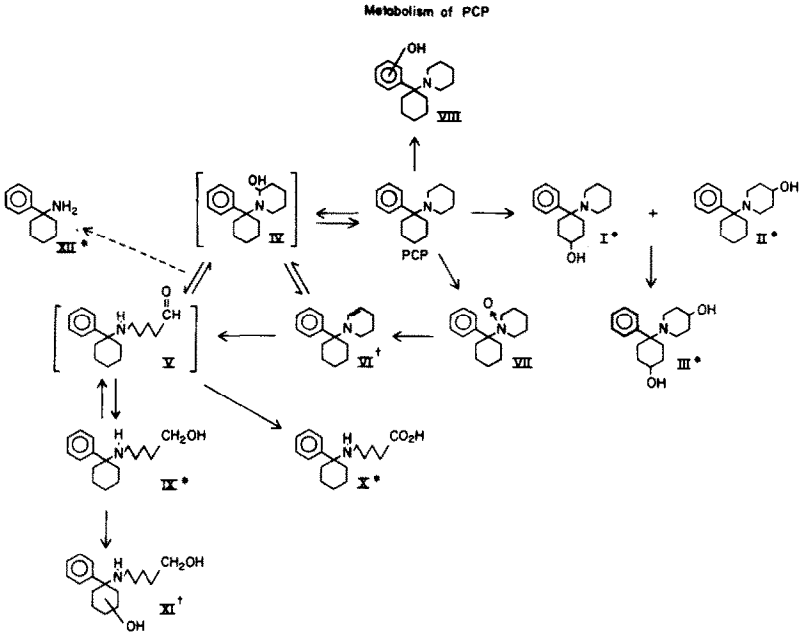

Fig. 1. Proposed metabolism of PCP. Key: (*) positively identified; and (†) tentatively identified.

purchased from the Sigma Chemical Co. (St. Louis, MO). Glass distilled methylene chloride was procured from the Burdick & Jackson Corp. (Muskegon, MI). Benzphetamine was donated by the Upjohn Co. (Kalamazoo, MI). Ketamine (Ketalar) was purchased from Warner Lambert–Parke Davis Laboratories (Ann Arbor, MI). Sodium phenobarbital was obtained from the UCLA Pharmacy. Isosafrole was purchased from the Eastman Kodak Co. (Rochester, NY). BSTFA [*N,O*-bis(trimethylsilyl-trifluoroacetamide] was purchased from the Pierce Chemical Co. (Rockford, IL). 1-Phenylcyclohexylamine hydrochloride (XII), phencyclidine hydrochloride, phencyclidine-$^2H_5$ (phenyl labeled) hydrochloride, *cis* and *trans*-4-phenyl-4-piperidinocyclohexanol (I) [pure *cis* (I) was also obtained], 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (II), and 4-(4′-hydroxypiperidino)-4-phenylcyclohexanol (III) were all supplied by the Research Triangle Institute (Research Triangle Park, NC) as approved by the National Institute on Drug Abuse (NIDA). *N*-(5-Hydroxypentyl)-1-phenylcyclohexylamine (IX) was synthesized and identified as reported earlier [9]. The synthesis, identification, and assay of 5-(1-phenylcyclohexylamino)-valeric acid (X) was reported elsewhere [14].

Animals. Rats (white male Sprague–Dawley, 150–200 g each) were purchased from the Simonsen Corp. (Gilroy, CA).

Metabolism, extraction and assay. Incubation of 1 mM PCP with 9000 *g* rat liver supernatant fraction and subsequent gas chromatographic analysis of PCP, I, II, III, VI and IX were carried out as reported earlier [15]. For mass spectrometric analysis, the identical gas chromatography column (e.g. 5% QF-1. 6 ft glass column) was used, connected to a Hewlett–Packard 5981A GCMS system which contains a selected ion monitoring and microprocessor system. The experimental conditions of gas chromatographic–mass spectrometric (GCMS) analysis were identical (sample derivatization, column and injection temperatures, and carrier gas flow) to those utilized for gas chromatographic analysis, unless stated otherwise. All spectra analyzed were obtained at an ionizing voltage of 15 eV and an ion source temperature of 200°.

Induction protocols. All animals were killed by cervical dislocation approximately 17 hr after the last dose of inducing agent. All animals received drugs dissolved in 0.5 ml isotonic saline except for isosafrole which was dissolved in corn oil. Control animals received either 0.5 ml saline or corn oil injections respectively. Phencyclidine- and ketamine-pretreated rats were injected once daily i.p. for 4 days at 25 and 50 mg/kg i.p., respectively. Phenobarbital rats were induced by 80 mg/kg i.p. injections once daily for 3 days. Isosafrole-pretreated animals received once daily injections of 50 mg/kg p.o. in corn oil for 3 days. Ethanol-induced animals received 11 g/kg daily for 3 weeks in a metrecal liquid diet as described in a previous study [16]. All animals were starved during the period between the last injection and sacrifice.

RESULTS

Identification of metabolites. The methylene chloride extracts of the incubation mixtures were evaporated, derivatized, and injected into the GCMS system. The gas chromatographic retention times and mass spectral fragmentation patterns of the metabolites I, II, III, IX and X were identical to those of authentic samples [8, 9]. The formation of I, II, VI, IX and X from PCP was confirmed by an

incubation of 50% [phenyl-$^2H_5$-]-labeled and 50% unlabeled PCP and monitoring the resulting doublets separated by 5 a.m.u. found in their mass spectra. The GLC retention times and mass spectral characteristics of XI and XII were available for detection of these metabolites from earlier studies [8, 9, 15].

Requirements of the microsomal metabolism of PCP. A summary of the effects of various substances on the rat liver microsomal metabolism of PCP is presented in Table 1. Elimination of the microsomes stopped the reaction, and deletion of the supplemental NADPH-generating system yielded only 4% of the control metabolism. Either decreasing the protein or replacement of the incubation atmosphere by nitrogen or carbon monoxide decreased the reaction rate, indicating the involvement of cytochrome P-450-dependent mono-oxygenase.

The metabolic formation of metabolites I, II, IX and X was increased by phenobarbital pretreatment (~100%) and inhibited by both DPEA (2,4-dichloro-6-phenylphenoxyethylamine) and SKF-525A with IC_{50} values (concentration that inhibits the reaction by 50%) of less than 0.1 and 1.0 mM respectively.

Since ethanol could still be present in the liver after chronic high dose treatment of the animals (such as in this study), the potential effects of the presence of 2 and 20 mM ethanol on the production of I, II, IX and X were examined (Table 1). A small albeit significant decline (30–40%, $P < 0.05$) in the levels of I, II, IX and X was seen after a 60-min incubation in the presence of either 2 or 20 mM ethanol. Incubation in the presence of either 1 or 5 mM pyrazole reduced the hepatic formation of I, II, IX and X about 35% indicating that a small, but significant, portion of this total metabolism may be alcohol dehydrogenase mediated.

Metabolism and comparative induction. PCP disappearance was monitored at a 1 mM concentration in incubates of control and induced tissues (Table 2). Doses of inducers were chosen for maximal inducing effects, but at low enough levels so as to preclude any apparent severe toxicity or significant animal death. Pretreatment of rats with phenobarbital, and subsequent incubation of liver supernatant fractions with PCP for 30 and 60 min, resulted in PCP levels that were ~60% of the control levels at the same incubation times, indicating an increase in the rate of disappearance of PCP of ~70%. Ethanol pretreatment resulted in an increase in the rate of disappearance of ~12% at each incubation time. Pretreatment with PCP or ketamine, for 30 or 60 min, caused an increase in the rate of PCP consumption of ~18 and 14%, respectively, whereas isosafrole pretreatment increased the net PCP consumption ~12% above control consumption at each incubation time. The percent difference between control zero time incubation with and without isosafrole was 15%. After 120 min of incubation, the increases in rates of PCP consumption in phenobarbitol-, ethanol-, and PCP-pretreated tissues remained the same, whereas ketamine- and isosafrole-pretreated animals showed rates of PCP consumption that were like those of control animals.

Levels of I, II, IX and X, as well as relative levels of the tentatively identified VI, were measured by gas chromatography with flame ionization detection after several time periods. The formation of I with time is tabulated in Table 2. The only significant ($P < 0.05$) changes in the levels of I from control values were obtained in incubates of tissues from phenobarbital-induced animals where the levels of I were increased from 100 to 200%. Levels of II over time are tabulated in Table 2, and phenobarbital induction increased levels about 90% at all time points. Pretreatment of animals with PCP or ketamine also increased levels of II in the incubates by approximately 30%, whereas isosafrole pretreatment reduced levels of II by more than half. Ethanol pretreatment apparently had little effect on the formation of II.

Data in Table 2 indicate the formation of IX after

Table 1. Effects of various substances on the microsomal metabolism of phencyclidine (PCP)

Substances	Metabolite formation (% of control)*
Complete	100 ± 8
− Microsomes	0
− NADPH-generating system	4 ± 3
N_2	11 ± 5
CO/O_2 (4:1)	46 ± 10
SKF-525A (1 mM)	0
DPEA (1.0 mM)	0
DPEA (0.1 mM)	0
Pyrazole (1.0 mM)	63 ± 4
Pyrazole (5.0 mM)	59 ± 3
Ethanol (2.0 mM)	70 ± 15
Ethanol (20.0 mM)	61 ± 12
Phenobarbital (3 × 80 mg/kg, i.p. pretreatment)	185 ± 31

* Control = 410 nmoles of I, II, IX and X formed per 0.33 g liver per 60 min at a PCP concentration of 1 mM. Expressed as the mean ± S.E. The data are the means of at least two separate experiments, each of which contained at least two replicate values.

Table 2. Induction of *in vitro* phencyclidine metabolism

Incubation period (min)	Control	Induction by: Phenobarbital	Phencyclidine	Ethanol	Ketamine	Isosafrole
		Phencyclidine*				
0	5.20 ± 0.31	5.27 ± 0.32	5.06 ± 0.20	5.73 ± 0.42	4.89 ± 0.17	4.39 ± 0.20†
30	4.33 ± 0.26‡	2.63 ± 0.11†	3.78 ± 0.27§	3.87 ± 0.29	3.81 ± 0.17§	3.86 ± 0.06
60	4.18 ± 0.30	2.36 ± 0.20†	3.47 ± 0.18†	3.75 ± 0.20	3.67 ± 0.12	3.77 ± 0.09
90	3.82 ± 0.21	2.20 ± 0.22†	3.41 ± 0.12§	3.39 ± 0.19§	3.66 ± 0.12	3.45 ± 0.27
120	3.72 ± 0.20	2.29 ± 0.22†	3.33 ± 0.10§	3.33 ± 0.07§	3.56 ± 0.17	3.44 ± 0.14
		trans-4-Phenyl-4-piperidinocyclohexanol* (I)				
0	--------	--------	--------	--------	--------	--------
30	0.06 ± 0.02	0.16 ± 0.06†	0.02 ± 0.003	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.003
60	0.07 ± 0.02	0.21 ± 0.09†	0.03 ± 0.01	0.06 ± 0.02	0.05 ± 0.01	0.05 ± 0.01
90	0.08 ± 0.01	0.27 ± 0.11†	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.01	0.05 ± 0.004
120	0.08 ± 0.02	0.26 ± 0.10†	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.01	0.05 ± 0.004
		1-(1-Phenylcyclohexyl)-4-hydroxypiperidine* (II)				
0	--------	--------	--------	--------	--------	--------
30	0.14 ± 0.02	0.32 ± 0.03†	0.19 ± 0.01	0.06 ± 0.01	0.19 ± 0.02	0.05 ± 0.004
60	0.16 ± 0.02	0.38 ± 0.04†	0.20 ± 0.01	0.16 ± 0.03	0.20 ± 0.02	0.06 ± 0.01
90	0.17 ± 0.02	0.39 ± 0.04†	0.22 ± 0.01	0.16 ± 0.02	0.22 ± 0.02	0.05 ± 0.01
120	0.16 ± 0.03	0.40 ± 0.05†	0.21 ± 0.01	0.17 ± 0.02	0.21 ± 0.03	0.05 ± 0.01
		N-(Hydroxypentyl)-1-phenylcyclohexylamine* (IX)				
0	--------	--------	--------	--------	--------	--------
30	0.09 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	--------	--------	0.13 ± 0.01
60	0.09 ± 0.003	0.07 ± 0.01	0.07 ± 0.01	--------	0.05 ± 0.01	0.15 ± 0.01
90	0.10 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	--------	0.06 ± 0.01	0.15 ± 0.01
120	0.10 ± 0.005	0.09 ± 0.01	0.08 ± 0.01	--------	0.06 ± 0.01	0.13 ± 0.02
		5-(1-Phenylcyclohexylamino)-valeric acid* (X)				
0	--------	--------	--------	ND¶	ND	
30	0.07 ± 0.02	0.06 ± 0.01	--------			0.06 ± 0.01
60	0.09 ± 0.02	0.10 ± 0.01	0.08 ± 0.02			0.09 ± 0.01
90	0.09 ± 0.02	0.10 ± 0.01	0.08 ± 0.02			0.09 ± 0.02
120	0.10 ± 0.025	0.12 ± 0.00	0.08 ± 0.02			0.11 ± 0.02
		N-(1-Phenylcyclohexyl)-1,2,3,4-tetrahydropyridine* (VI)**				
0	-------	--------	--------	--------	--------	--------
30	0.15 ± 0.02	0.28 ± 0.03†	0.11 ± 0.01	0.25 ± 0.30†	0.28 ± 0.04†	0.19 ± 0.02
60	0.10 ± 0.01	0.16 ± 0.02†	0.11 ± 0.02	0.25 ± 0.32†	0.25 ± 0.05†	0.18 ± 0.01
90	0.07 ± 0.01	0.12 ± 0.03	0.07 ± 0.03	0.23 ± 0.25†	0.15 ± 0.04§	0.12 ± 0.03
120	0.07 ± 0.01	0.08 ± 0.02	0.04 ± 0.01	0.22 ± 0.20†	0.10 ± 0.03	0.12 ± 0.02

* Levels are expressed in μmoles present or formed/0.33 g wet liver, at a substrate concentration of 1.0 mM in rat 9000 *g* liver fraction. Minimum of three experiments. Each point in duplicate ± S.E.M.

† Compared to controls at the same incubation time, $P \leq 0.05$.

‡ $P \leq 0.01$, compared to the control at zero time.

§ $P \leq 0.10$, compared to the control at zero time.

‖ Not detectable by gas chromatography with flame ionization detection.

various incubation periods. Pretreatment with phenobarbital, phencyclidine, or ketamine all had little effect on the rate of formation of IX when compared to controls, or perhaps induced slightly decreased levels of IX at all time points. Ethanol pretreatment either resulted in levels of IX too low to measure or induced the disappearance of IX to possibly form another metabolite (e.g. XI). On the other hand, isosafrole pretreatment increased levels of IX in the incubates by about 50% at most time points.

The relative levels of VI, a dehydropiperidino metabolite tentatively identified earlier [14] by its mass spectral characteristics, are tabulated in Table 2. The relative levels of VI decrease with time in rat, rabbit, cat and monkey liver preparations* and also in all types of induced rat tissues except for those pretreated with ethanol where it reaches a constant level. Levels of VI were increased by phenobarbital, ketamine, ethanol and isosafrole pretreatment after specific incubation periods when compared to incubations with noninduced tissue. PCP pretreatment, however, had no effect on levels of this metabolite.

Measurement of levels of 5-(1-phenylcyclohexylamino)-valeric acid (X) [11–13] produced in PCP-, isosafrole- or phenobarbital-pretreated livers (Table 2) showed no difference from those levels produced in naive rat liver incubations.

DISCUSSION

Phenobarbital pretreatment of animals is known to increase the amount of some of the cytochrome P-450 isozymes found in the liver and to therefore increase the levels of any metabolites whose production is mediated by the induced isozymes. The rate of disappearance of PCP and the levels of I, II and VI were enhanced significantly by phenobarbital pretreatment. Potent inhibition of the formation of I, II, IX and X was observed in the presence of nitrogen, carbon monoxide, SKF-525A, or DPEA indicating that the formation of I, II, and secondarily IX and X is mediated by cytochrome P-450. DPEA has been shown to bind to both microsomes and solubilized cytochrome P-450 and to greatly inhibit the interactions of substrates with cytochrome P-450 [17]. SKF-525A has been shown to be an active inhibitor of a wide range of metabolic transformation reactions of drugs, including chain oxidation, N- and O-dealkylations, and deaminations [18–20].

Coincubation of liver microsomal preparations with the alcohol dehydrogenase inhibitor pyrazole [21, 22] showed a decline of only 8% (not statistically significant) in the formation of I and II after a 60-min incubation but a 35% decline (statistically significant, $P < 0.05$) in the formation of IX and X (see Table 1; the individual data are not shown). These data are consistent with the microsomal cytochrome P-450 mediated formation of IV [14], followed by subsequent metabolism of IV (or its ring opened form, V) to IX and X. Whether the subsequent metabolism of IV (or V) to IX and X is mediated by a dehydrogenase remains to be determined.

Since ethanol has been shown to bind to both microsomal [23] and purified, reconstituted [24] cytochrome P-450, and 10 mM ethanol has been shown to both inhibit the metabolism of meprobamate in liver slices [25] and to decrease the oxidation of alprenolol in hepatocytes [26], we investigated the coincubation of ethanol and PCP in liver preparations from naive animals. A small albeit statistically significant, *ca.* 30% ($P < 0.05$), decline in the formation of I, II, IX and X from PCP occurred after a 60-min incubation. There was also a corresponding decline in the consumption of PCP in these experiments, indicating a statistically significant inhibition of metabolism. However, chronic ethanol consumption induces P-450 in many species, and some evidence suggests that the P-450 species induced by ethanol pretreatment in the rat is a different one than that induced by either phenobarbital or 3-methylcholanthrene pretreatment [27].

In our study, chronic ethanol pretreatment increased the consumption of PCP approximately 100% in rat liver (Table 2) but did not affect the production of either metabolite I or II. No detectable amounts of IX could be found in PCP incubations in ethanol-pretreated rat liver, but this result could be due to induction of the metabolism of IX to XI, or elsewhere. During this work, however, XI was not detected. This lack of formation of IX also could be due to NADPH consumption via ethanol metabolism.

Isosafrole [1,2-(methylenedioxy)-4-propenylbenzene] is known to form a complex with some cytochrome P-450 isozymes in the presence of NADPH and O_2 [28] and thereby inhibit further P-450 metabolism mediated by those isozymes. However, isosafrole pretreatment also induces some forms of cytochrome P-450 [29, 30]. Indeed, isosafrole did not induce the net consumption of PCP in rat liver preparations in this study but did selectively increase the levels of IX and VI (Table 2) without affecting the levels of X.

As discussed earlier, PCP pretreament has been shown to enhance reactions defined as cytochrome P-450 mediated [3, 5]. The disappearance of PCP was increased in incubates of tissue from PCP-pretreated animals by approximately 50% after either a 30-min or a 60-min incubation (Table 2). However, in all tissues, the rate of disappearance of PCP appeared to decrease dramatically after longer incubations. Formation of I, VI, IX and X (Table 2) was essentially unchanged in incubates from PCP-pretreated livers, and levels of II (Table 2) were only slightly increased. Induction by PCP, therefore, appears to be increasing PCP metabolites which we are not measuring in this study. Indeed, since the majority of PCP metabolized was not accounted for by metabolites I, II, III, IX and X (Table 3), some other pathways must be operative.

Pretreatment of rats with ketamine (2-*O*-chlorophenyl-2-methylaminocyclohexanone) results in a 100% increase in the rate of ketamine metabolism *in vitro* [31], as well as an increase in benzphetamine N-demethylation and benzopyrene hydroxylation [32]. In this report, ketamine pretreatment increased the disappearance of PCP slightly (approximately 30% at 30 and 60 min; Table

* R. C. Kammerer, D. A. Schmitz and A. K. Cho, manuscript in preparation.

Table 3. Percentage of PCP metabolized that each metabolite represented after 90-min incubation in each tissue

	Total PCP metabolized after 90 min (μmoles)	% of total PCP metabolized					Total % accounted for
		I	II	IX	X	III	
Control	1.38	5.8	12.3	7.2	6.5	----	31.8
Phenobarbital	3.07	8.8	12.7	2.6	3.3	----	27.4
Phencyclidine	1.65	2.4	13.3	4.2	4.8	----	24.7
Ethanol	2.34	2.6	6.8	0.0	ND	----	9.4*
Ketamine	1.23	4.1	17.9	4.9	ND	----	26.9*
Isosafrole	0.94	5.3	5.3	16.0	9.6	----	36.2

* These numbers are low since no data for the formation of X in this tissue had been obtained.

2), did not appreciably affect the levels of either I or IX, and increased levels of VI at the early time points. Ketamine pretreatment thus appears to affect the metabolism of PCP similarly to the effects of PCP pretreatment.

In summary, the formation of I, II, and secondarily IX and X from PCP was cytochrome P-450 mediated and the various inducing agents affected the metabolism of PCP in different ways, implying that several isozymes are involved in the total metabolism of PCP. These conclusions are consistent with results recently published which show the selective induction of 1-phenyl-3-hydroxycyclohexylpiperidine formation by 3-methylcholanthrene pretreatment in the mouse, whereas phenobarbital pretreatment induces the formation of I and II but not this new metabolite [33]. These results indicate that each inducing agent alters the quantitative distribution of metabolites.

Since 60–70% of the metabolized PCP in either control or induced rat liver preparations was not accounted for by I, II, III, IX and X (Table 3), further metabolic identification and quantitation work need to be done to clarify the total metabolic fate of PCP. It is possible that either unknown metabolic pathways (e.g. VII or VIII, Fig. 1) or pathways not quantitated in this study (e.g. XII) will account for the missing PCP.

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