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BIODISPOSITION OF KETAMINE IN THE RAT: SELF-INDUCTION OF METABOLISM[1, 2, 3]

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ABSTRACT

MARIETTA, M. P., P. F. WHITE, C. R. PUDWILL, W. L. WAY AND A. J. TREVOR: Biodisposition of ketamine in the rat: Self-induction of metabolism. J. Pharmacol. Exp. Ther. **196:** 536-544, 1976.

Four pharmacologic actions of intravenous ketamine (30 mg/kg) were studied in the rat. To elucidate the mechanism(s) terminating the pharmacologic effects, animals were pretreated with ketamine and agents anticipated to modify hepatic microsomal metabolism, including phenobarbital and SKF 525A. SKF 525A pretreatment markedly prolonged ataxia, analgesia and agitation, in addition to significantly elevating brain and plasma ketamine levels subsequent to the initial 10 minutes following injection; thus hepatic metabolism appeared to play a prominent role in the termination of the posthypnotic effects of the drug. While significantly shortening the durations of the three posthypnotic events, phenobarbital and ketamine pretreatments also lowered the brain and plasma levels of ketamine. With all pretreatments, brain ketamine levels were almost identical at the cessation of hypnosis (25 μg/g of tissue) and ataxia (8-10 μg/g of tissue). No pretreatment altered either the duration of loss of righting reflex (hypnosis) or brain and plasma ketamine levels during the initial 10 minutes after injection. Approximately 70% of the injected drug was recovered from four tissues, skeletal muscle, gut, skin and liver, at 10 minutes after injection; thus redistribution from brain to other tissues appeared to play a major role in the cessation of hypnosis. Ketamine pretreatment caused a 2-fold increase in the rate of its *in vitro* hepatic microsomal metabolism. Brain and plasma ketamine levels 30 minutes after injection were nearly identical in rats pretreated with ketamine and phenobarbital, although phenobarbital pretreatment resulted in a 4-fold increase in *in vitro* ketamine hepatic metabolism.

Previous work from our laboratories on the dissociative anesthetic ketamine [2-(O-chlorophenyl)-2-(methylamino)-cyclohexanone] suggested that at least two mechanisms, redistribution from brain to other tissues and hepatic metabolism, are involved in the termination of the pharmacologic effects of the drug in rats

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[2] A preliminary report of these studies was presented at the fall meeting of the American Society for Pharmacology and Experimental Therapeutics, August 1974, in Montreal, Canada.
[3] This is publication no. 75-11 from the Departments of Pharmacology & Anesthesia.
[4] This work represents partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(Cohen and Trevor, 1974). If redistribution and metabolism do play major roles in the cessation of the pharmacologic effects of ketamine, it is natural to question which body tissues serve as reservoirs or "sinks" for the drug and to consider the effects of agents which modify hepatic drug metabolism on brain and plasma levels of ketamine. These questions were approached by the determination of the levels of ketamine in various tissues at selected time intervals after intravenous administration and by examination of brain and plasma levels of ketamine in rats pretreated with drugs anticipated to modify hepatic drug metabolism.

The pharmacologic actions of ketamine have been reported to include posthypnotic agitation (Cohen and Trevor, 1974) and analgesia (Corssen *et al.*, 1968; White *et al.*, 1975). These properties were examined in this study by objective methods including electronic motility measurement and tail thermal stimulation. In addition, the influence of hepatic function on the durations of analgesia and agitation after ketamine administration was examined using drugs expected to modify hepatic drug metabolism.

While the clinical use of ketamine does not ordinarily invoke chronic administration, Cronin *et al.* (1972) described repetitive ketamine anesthesia for radiotherapy in small children. To answer the question of whether or not the repetitive administration of ketamine would alter its pharmacologic and pharmacokinetic properties, we investigated the effects of ketamine pretreatment on the duration of its pharmacologic effects, the brain and plasma levels of ketamine and the rate of *in vitro* N-demethylation of ketamine to its primary metabolite in rats.

Materials and Methods

Intact animal experiments. Male Sprague-Dawley rats, weighing 100 to 150 g, provided Purina Rat Chow and water *ad libitum*, allowed no bedding material and housed in air-conditioned quarters with automatic light regulation when not in the laboratory, were used exclusively. To investigate the effects of intravenous ketamine, animals were immobilized for injection and the durations of loss of righting reflex and ataxia were measured according to methods described previously (Cohen *et al.*, 1973). Locomotor activity was measured with an Electronic Motility Meter Fc 40 (Motron produckter, Stockholm, Sweden). Baseline activity, determined for each rat prior to injection, was subtracted from the activity recorded for each of six consecutive 10-minute intervals subsequent to ketamine administration and expressed as motility meter counts per 10-minute interval.

Analgesia was assessed by means of a tail-flick method modified after D'Amour and Smith (1941) and Way *et al.* (1969). A mean base-line response, 1.0 ± 0.1 second (S.E.), to tail thermal stimulation was established for each animal before intravenous ketamine. Tail-flick response was then measured at the instant the animal recovered its righting reflex and at subsequent 4-minute intervals. Analgesia was judged to have ceased when tail response time returned to within 0.2 second of base-line response.

In vivo **tissue distribution.** Rats receiving intravenous ketamine (30 mg/kg) were decapitated at various times after caudal vein injection. Heparin-treated blood samples, obtained by exsanguination following decapitation and representative tissue samples (whole brain, liver, skeletal muscle, kidney, heart, gut and skin) were collected and homogenates (10% w/v) were prepared from all tissues, except skin (5% w/v), in 0.1 N HCl. Plasma samples, collected by centrifuging the blood samples at 1000 × *g* for 10 minutes, and tissue supernatant samples, obtained by ultracentrifuging homogenate samples at 100,000 × *g* for 60 minutes, were then either extracted immediately or refrigerated and extracted the following day for chromatographic assay of ketamine and its metabolites as described below.

In vitro **ketamine metabolism.** To examine the effects of pretreatment with ketamine, phenobarbital and 2-diethylaminoethyl-2,2-diphenylvalerate HCl (SKF 525A) on the hepatic metabolism of ketamine, microsomes were prepared using a modification of the procedure described by Fouts (1971). Rats were decapitated and exsanguinated and their livers were excised immediately, placed on ice and cleaned of external blood. Homogenates (10% w/v) in 160 mM KCl-50 mM Tris-HCl, pH 7.40, were prepared from individual livers. The homogenates were centrifuged at 9000 × *g* for 20 minutes and the supernatants then recentrifuged at 9000 × *g* for an additional 15 minutes. Microsomes were sedimented by centrifugation of the postmitochondrial (9000 × *g*) supernatant at 105,000 × *g* for 60 minutes, the microsomal supernatant was discarded, and the pellet was resuspended in 160 mM KCl-50 mM Tris-HCl buffer. The final suspension volume was adjusted so that each milliliter contained 1 to 4 mg of microsomal protein determined by the method of Lowry *et al.* (1951).

Metabolism of ketamine was estimated by incubating 0.8 ml of the prepared suspension with a saturating concentration of ketamine (2.5 mM) in a Dubnoff metabolic incubator for 15 minutes under air. The Erlenmeyer flasks also contained glucose-6-phosphate (12.5 mmol), $MgCl_2$ (25 mmol), glucose-6-phosphate dehydrogenase (1 I.E.U.) and nicotinamide adenine

dinucleotide phosphate (1 mmol) adjusted to a final reaction volume of 2.5 ml with 160 mM KCl–50 mM Tris-HCl, pH 7.40. Under these conditions, the K_m for the reaction was 0.14 mM and the value was unchanged by pretreatments with phenobarbital or ketamine. The reaction was initiated by the addition of ketamine to the reaction vessel; samples (0.1 ml) were taken at zero time and 15 minutes and transferred into 0.9 ml of 0.1 N HCl for assay of ketamine and its metabolites.

Assay of ketamine and its metabolites. All samples were extracted and derivatized for assay of ketamine base and its metabolites using the modification by Cohen *et al.* (1973) of the gas chromatographic procedure of Chang and Glazko (1972). Duplicate assays demonstrated good reproducibility with a variation of ±3%. Analytical recovery of ketamine and its metabolites from tissue homogenates and plasma ranged from 96 to 99%.

Pretreatment schedules. Animals pretreated with phenobarbital were injected i.p. twice daily for 3 days with drug (35 mg/kg/injection) with the final injection given 18 hours prior to ensuing experimentation. Likewise, ketamine was administered i.p. twice daily for 3 days at a dose of 40 mg/kg/injection with one final injection also 18 hours preceding further experimental manipulation. 2-Diethylaminoethyl-2,2-diphenylvalerate HCl (SKF 525A) was injected i.p. at a dose of 25 mg/kg 60 minutes prior to subsequent experimentation. Control animals were concurrently injected with equal volumes of 0.9% NaCl.

Chemicals. All reagents were obtained from available commercial sources. Ketamine hydrochloride (Ketalar) was supplied by Parke, Davis & Company (Detroit, Mich.) and SKF 525A (Proadifen) was a gift from Smith Kline and French Laboratories (Philadelphia, Pa.).

Results

Ketamine distribution in selected tissues. After intravenous ketamine (30 mg/kg), peak

TABLE 1

Percent recovery of ketamine from selected tissues

Ketamine (30 mg/kg) was injected into the caudal vein of rats subsequently sacrificed at the indicated times after injection to collect tissues for assay. Data express ketamine and metabolite I recovered from each tissue as percentages of the total amount of ketamine administered. Calculations are based on the mean drug concentrations shown in figure 1, and the tissue weights per 100 g of rat cited in the text.

	1 Min[a]	5 Min	10 Min	20 Min	30 Min	60 Min
Ketamine percent recovery (tissue)						
Muscle	33.0	37.1	37.8	26.6	16.2	11.4
Skin	6.0	8.3	12.1	16.2	12.5	6.2
Liver	4.3	7.2	7.7	2.9	2.4	1.7
Gut	8.1	10.8	10.9	10.1	6.2	
Kidneys	4.9	3.3	2.8	1.5	1.3	0.7
Heart	1.1	0.6	0.5	0.4	0.2	0.1
Brain	4.0	2.0	0.7	0.3	0.3	0.1
Plasma	2.2	1.3	0.8	0.5	0.4	0.3
Total percent accounted for	63.6	70.6	73.3	58.5	39.5	20.5
Metabolite I[b] percent recovery (tissue)						
Muscle	0.5	3.6	5.6	7.5	8.4	8.4
Skin	0	1.2	1.8	3.3	4.0	6.7
Liver	0.6	4.6	6.7	7.3	8.9	6.0
Gut	0.5	1.6	3.1	4.8	5.6	
Kidneys	0	0.4	0.7	1.0	1.4	1.4
Heart	0	0.2	0.3	0.2	0.2	0.2
Brain	0	0.2	0.3	0.2	0.2	0.2
Plasma	0.1	0.4	0.7	0.8	1.0	1.1
Total percent accounted for	1.7	12.2	19.2	25.1	29.7	24.0

[a] Time after injection.

[b] Calculated as ketamine (moles) metabolized to metabolite I.

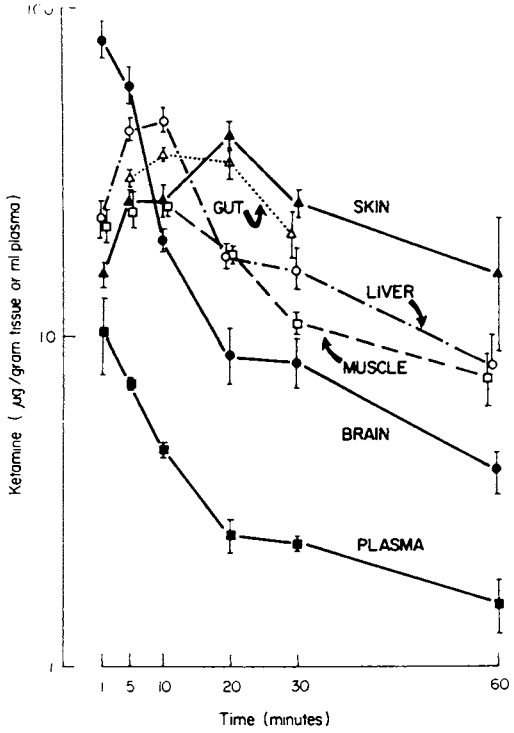

FIG. 1. Distribution of ketamine after its caudal vein administration (30 mg/kg) to rats. At the indicated times, animals were decapitated for gas chromatographic assay of ketamine levels in selected tissues. Values are means for five animals with vertical bars representing ±S.E.M.

levels were achieved in brain within 1 minute and declined rapidly during the initial 10 minutes after injection (table 1; fig. 1). Simultaneously, levels of injected ketamine in skeletal muscle, liver, gut and skin were rising to the plateau levels eventually achieved 10 to 20 minutes after drug administration (fig. 1). Subsequently, levels of drug in all tissues declined slowly, paralleling the plasma decay of ketamine. A similar, but more protracted distribution pattern was observed in tissues assayed after the intramuscular administration of ketamine (White *et al.*, 1976).

Data from table 1 show that less than 1% of the ketamine administered i.v. remained in the plasma at 10 minutes after injection, and at that time nearly 70% of the parent drug was localized within skeletal muscle, skin, gut and liver.[5] Such tissues appear to serve as major reservoirs for ketamine. Estimation of percent recovery of ketamine 10 minutes subsequent to intravenous administration shows that 73% of the injected drug was recovered as the parent molecule, while nearly 20% of the dose was recovered as metabolite I. In addition, although not presented, determinations of ketamine and metabolite I levels in "whole rat homogenates" prepared from animals killed 10 minutes after intravenous ketamine administration (30 mg/kg) disclosed 74% of the injected drug recovered as ketamine and 24% recovered as metabolite I.

Pharmacologic actions of intravenous ketamine in pretreated rats. The durations of four pharmacologic effects of intravenous ketamine (30 mg/kg) were determined in animals pretreated with ketamine, phenobarbital and SKF 525A. No pretreatment had any significant effect on the duration of loss of righting reflex (hypnosis) after injection (table 2). However, SKF 525A pretreatment caused marked prolongation of the durations of ataxia and analgesia ($P < .01$) as well as the duration of posthypnotic locomotor activity (fig. 2). In control experiments, it was determined that SKF 525A itself had no significant influence on locomotor activity. Phenobarbital and ketamine pretreatments resulted in significant decreases in the durations of ataxia, analgesia and locomotor activity after ketamine administration (table 2; fig. 3). Ataxia observed after intravenous ketamine was considered to be of central origin since examination of the isolated rat phrenic nerve-diaphragm preparation (Bulbring, 1946) showed that levels of ketamine and metabolite I that occur in skeletal muscle *in vivo* had no effects on neuromuscular transmission. Posthypnotic analgesia and enhanced locomotor activity after ketamine administration appeared to be specific properties of the drug. The intravenous administration of hypnotic doses of thiopental to rats caused no posthypnotic analgesia and a minor decrement, rather than an increase, in locomotor activity compared to control animals.

Plasma and brain levels of ketamine in rats pretreated with ketamine and SKF 525A. After intravenous ketamine (30 mg/kg) to rats, plasma levels of the drug declined rapidly ($T_{\frac{1}{2}}$ approximately 10 minutes) and neither pretreatment schedule significantly altered the plasma levels of ketamine during the initial 10-minute period after injection (fig. 4). At

[5] In this and subsequent calculations, the following data from our laboratory and Goldstein and Aronow (1960) are used: for 100 g of rat, plasma 5, muscle 45, kidneys 2, liver 5, skin 12, brain 1, heart 1, gut 9 g.

TABLE 2

Effect of ketamine HCl, phenobarbital and SKF 525A pretreatments on pharmacologic effects of i.v. ketamine

Ketamine hydrochloride (30 mg/kg) was injected into the caudal vein of pretreated rats and durations of effects were measured from the end of injection as detailed under "Materials and Methods." Values for durations of loss of righting reflex and ataxia represent means ± S.E.M. of four animals; those for duration of analgesia are means ± S.E.M. for 11 rats.

Pretreatment	Duration of loss of Righting Reflex	Duration of Ataxia	Duration of Analgesia[a]
	(min)	(min)	(min)
Control	8.0 ± 1.7	27.2 ± 5.0	29.1 ± 3.4
SKF 525A	9.9 ± 2.1[b]	58.1 ± 7.5[c]	59.5 ± 4.6[c]
Ketamine	8.1 ± 2.0[b]	18.1 ± 3.0[c]	13.2 ± 2.9[c]
Phenobarbital	7.9 ± 1.8[b]	19.3 ± 2.5[c]	15.6 ± 2.8[c]

[a] Analgesia experiments performed separately.
[b] P value > .15 by Student's unpaired *t* test.
[c] P value < .01 by Student's unpaired *t* test.

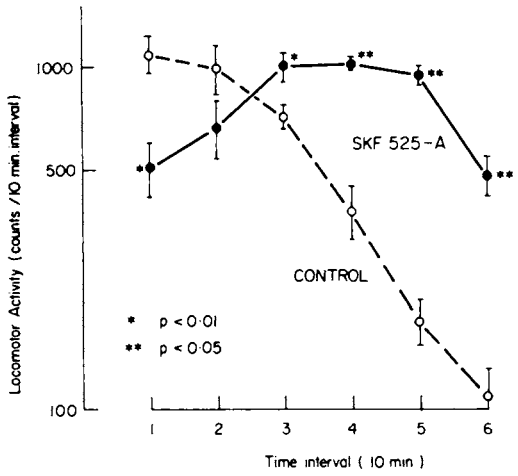

FIG. 2. Locomotor activity after caudal vein injection of ketamine (30 mg/kg) in rats pretreated with SKF 525A. Motility meter activity was recorded for individual rats during each of six consecutive 10-minute intervals subsequent to cessation of ketamine hypnosis and is expressed as counts per 10-minute interval. Values represent means (±S.E.M.) of five experiments.

subsequent time points, SKF 525A pretreatment significantly elevated plasma ketamine levels up to and including 60 minutes. By contrast, ketamine pretreatment lowered plasma levels of injected ketamine although the effect was not statistically significant at the 60-minute time point.

A similar pattern was observed for brain levels of ketamine (fig. 5). Levels of the drug were maximal within 1 minute after intravenous injection and declined rapidly during the initial 10 minutes ($T_{\frac{1}{2}}$ approximately 8 minutes). Although neither pretreatment schedule significantly modified the levels of ketamine during the first 10-minute interval, SKF 525A pretreatment significantly increased brain ketamine levels at all time points examined after 10 minutes. While ketamine pretreatment decreased brain levels of ketamine at 20, 30 and 60 minutes, only the 30-minute ketamine brain level was significantly decreased ($P < .05$). Estimation of brain levels of ketamine at time points of recovery of righting reflex indicated no differences between control animals and those pretreated with ketamine or SKF 525A (25 mg/kg). In all groups of animals, brain levels of ketamine were nearly identical (approximately 9 μg/g of tissue) at the point of cessation of ataxia.

In vitro **metabolism of ketamine.** The *in vitro* N-demethylation of ketamine by rat hepatic microsomes was investigated in rats pretreated with phenobarbital and ketamine. Data in table 3 show that ketamine pretreatment increased the rate of ketamine N-demethylation by 112% ($P < .05$) whereas phenobarbital pretreatment caused a more than 360% increase in ketamine metabolism ($P < .05$). SKF 525A pretreatment has been shown to decrease the rate of N-demethylation of ketamine by more than 30% (Cohen and Trevor, 1974).

Comparison of metabolite I levels in plasma and brain after phenobarbital and ketamine pretreatments. Both pretreatments significantly decreased levels of ketamine and metabolite I in plasma and brain 30 minutes after intravenous ketamine (table 4). However, statistical differences in brain and plasma levels

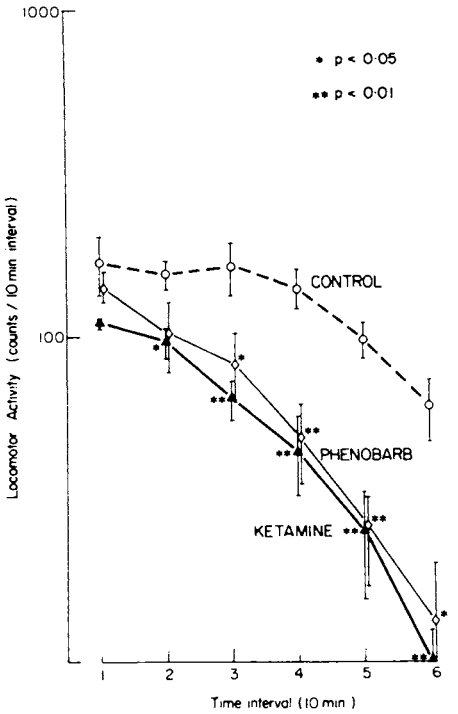

FIG. 3. Locomotor activity after caudal vein administration of ketamine (30 mg/kg) to rats pretreated with ketamine and phenobarbital. Motility meter activity was recorded for individual rats during each of six consecutive 10-minute intervals subsequent to cessation of ketamine hypnosis and is expressed as counts per 10-minute interval. Values represent means (± S.E.M.) of five experiments.

of ketamine and metabolite I were not demonstrated between the group of animals pretreated with phenobarbital and that pretreated with ketamine. Decreased plasma levels of metabolite I, along with decreased levels of ketamine, suggest that ketamine and phenobarbital pretreatments may augment the metabolism of ketamine both at the N-demethylation step and at a level of the further metabolic conversion of metabolite I.

Discussion

Four pharmacologic actions of intravenous ketamine (30 mg/kg) were studied in rats, namely the duration of righting reflex (hypnosis) and three posthypnotic events, ataxia, analgesia and locomotor activity. Pretreatment with ketamine and drugs anticipated to modify hepatic microsomal drug metabolism (Axelrod *et al.*, 1954; Conney, 1967) had no effect on the duration of loss of righting reflex but markedly altered the durations of the posthypnotic drug effects (table 2; figs. 2 and 3). Moreover, ketamine and SKF 525A pretreatment influenced brain and plasma levels of intravenous ketamine only subsequent to the initial 10 minutes following intravenous injection (figs. 4 and 5). Irrespective of pretreatment schedule, brain levels of ketamine were similar in all animals at the cessation of hypnosis as well as ataxia (fig. 5). Thus, two separate biodispositional events appear to be involved in the termination of the pharmacologic actions of intravenous ketamine. Intact animal data coupled with those on brain and plasma levels following intravenous ketamine (30 mg/kg) suggest that hepatic metabolism plays a prominent role in the termination of the posthypnotic effects of ketamine. However, because agents anticipated to modify hepatic drug metabolism had no influence on the duration of loss of righting reflex (hypnosis), other biodispositional phenomena apparently play important roles in the termination of hypnosis.

Because of its lipid solubility, rapid entry into

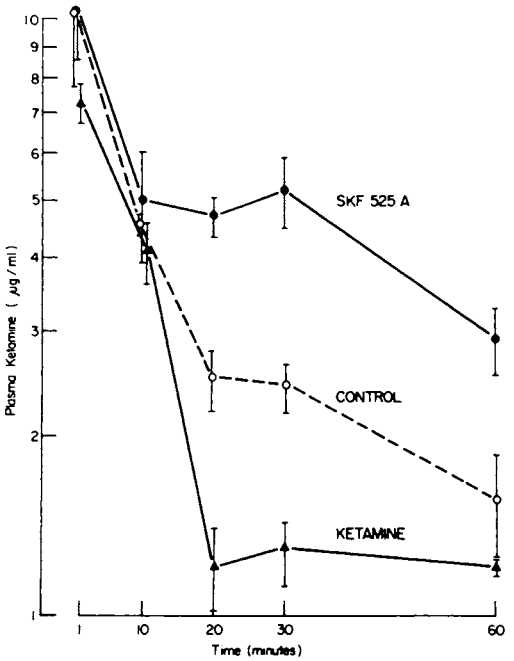

FIG. 4. Plasma levels of ketamine after caudal vein administration of ketamine (30 mg/kg) to rats. Animals pretreated with ketamine and SKF 525A were decapitated at the indicated times after i.v. injection for gas chromatographic assay of plasma ketamine levels. Values are means of four experiments and vertical bars represent ±S.E.M.

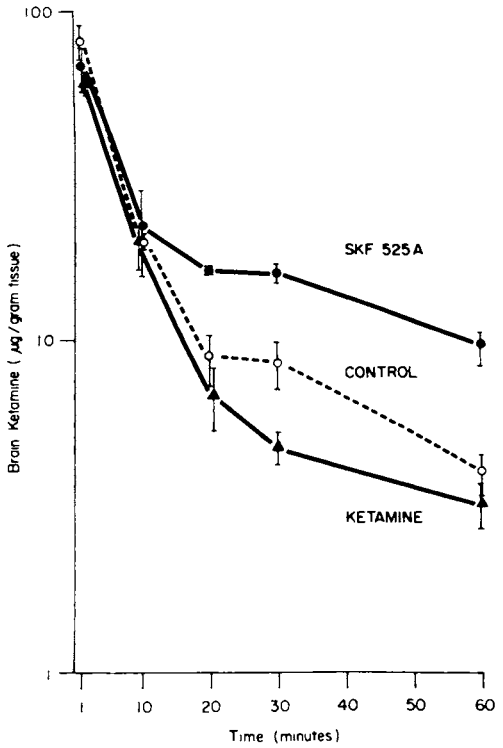

FIG. 5. Brain levels of ketamine after caudal vein administration of ketamine (30 mg/kg) to rats. Animals pretreated with ketamine and SKF 525A were decapitated at the indicated times after i.v. injection for gas chromatographic assay of brain ketamine levels. Values are means of four experiments and vertical bars represent ±S.E.M.

brain tissue and relatively short duration of action, ketamine has been compared with short-acting thiobarbiturates (Cohen and Trevor, 1974; Dundee, 1971). It is conceivable, therefore, that redistribution events operate to terminate ketamine hypnosis as in the case of the thiobarbiturate, thiopental (Price *et al.*, 1959; Goldstein and Aronow, 1960). Peak levels of ketamine occur in brain, heart, kidney and plasma within 1 minute after intravenous ketamine (30 mg/kg) and, subsequently, fall rapidly during the initial 10 to 20 minutes after injection (fig. 1; table 1). Simultaneously, levels of ketamine in gut, liver, skin and muscle rise to plateau levels within 5 to 20 minutes following injection. Ten minutes after intravenous administration, nearly 70% of the parent drug is localized within the gut, liver, skin and skeletal muscle (table 1). Thus it appears likely that these four tissues serve as reservoirs for both injected ketamine and ketamine which has redistributed from brain into plasma.

In a previous study, Chang and Glazko (1974) reported ketamine administration (50 mg/kg i.v. at 16- to 24-hour intervals for three doses) to lack stimulatory effects on the hepatic metabolism of N-methylaniline. Their results suggested that ketamine pretreatment does not enhance the activity of microsomal enzymes responsible for N-demethylation in the rat when estimated 42 hours after the final intravenous ketamine injection. However, our results indicate that this is not the case (table 2; figs. 4 and 5). Investigation of the *in vitro* microsomal metabolism of ketamine revealed more than 2-fold increase in ketamine N-demethylation (table 3) following pretreatment scheduling as described under "Materials and Methods." These results do suggest that the chronic clinical administration of ketamine may alter *in vivo* metabolism, an effect which may require dosage adjustments for ketamine and, possibly, other drugs metabolized by liver microsomal enzyme systems.

Although the pretreatment of rats with phenobarbital resulted in more than a 4-fold increase in the *in vitro* metabolism of ketamine (table 3), comparison of phenobarbital and ketamine pretreatments shows no significant differences in their influence on the durations of pharmacologic actions following intravenous ketamine injection (table 2; fig. 3). Furthermore, 30 minutes after the i.v. administration of

TABLE 3

Rate of N-demethylation of ketamine by liver microsomes following pretreatments with phenobarbital and ketamine

The rate of N-demethylation of ketamine to metabolite I by rat liver microsomes was estimated as detailed under "Materials and Methods." Values are means of four animals ± S.E.M.

Pretreatment[a]	Ketamine N-Demethylation (*nmol/mg of protein/hr*)	Percent Change from Control
Control	182.3 ± 32.5	
Ketamine	387.1 ± 33.9[b]	+112%
Phenobarbital	850.6 ± 40.5[b]	+367%

[a] Detailed under "Materials and Methods."

[b] P value < .05 by Student's unpaired *t* test.

TABLE 4

Effect of ketamine and phenobarbital pretreatments on ketamine and metabolite I levels in brain and plasma

Ketamine hydrochloride (30 mg/kg) was injected into caudal vein of pretreated rats which were sacrificed 30 minutes following the injection to collect brain and plasma samples for assay of ketamine and metabolites as detailed under "Materials and Methods." Values are means ± S.E.M. for six rats.

Pretreatment	Brain		Plasma	
	Ketamine	Metabolite I	Ketamine	Metabolite I
	(μg/g)		(μg/ml)	
Control	7.75 ± 0.47	6.85 ± 0.92	2.19 ± 0.17	4.99 ± 0.72
Ketamine	4.78 ± 0.54[a]	3.05 ± 0.29[a]	1.30 ± 0.15[a]	2.82 ± 0.18[a]
Phenobarbital	4.95 ± 0.46[a, b]	2.15 ± 0.25[a, c]	1.20 ± 0.11[a, b]	2.37 ± 0.42[a, b]

[a] Differs from control; P value < .01 by Student's unpaired *t* test.
[b] Differs from ketamine; P value > .41 by Student's unpaired *t* test.
[c] Differs from ketamine; P value > .06 by Student's unpaired *t* test.

ketamine to pretreated rats, brain and plasma levels of ketamine and metabolite I were similar for both pretreatments (table 4). These observations raise the question of the validity of predicting *in vivo* metabolic events by extrapolating directly from *in vitro* studies without careful consideration of the many factors affecting drug metabolism (Gillette, 1971).

In conclusion, two biodispositional phenomena, redistribution events and hepatic metabolism, play prominent roles in the termination of the central pharmacologic actions of intravenous ketamine. Hepatic metabolism plays a major role in the termination of the three posthypnotic events—ataxia, analgesia and agitation—observed in this study, while redistribution of ketamine from brain to other tissues, primarily skeletal muscle, gut, skin and liver, terminates hypnosis. Pretreatment of rats with ketamine increases both the *in vitro* hepatic microsomal metabolism of ketamine and the *in vivo* rate of plasma decay of ketamine following its injection i.v. In addition, ketamine pretreatment shortens the durations of the three posthypnotic effects of intravenous ketamine observed in this study but does not influence the duration of hypnosis after drug administration.

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