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Effects of Intravenous Anesthetics on Brain Monoamines in the Rat

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The effects of ketamine, etoxadrol, and thiopental on the concentration and the apparent rates of synthesis of the brain monoamines serotonin, dopamine, and norepinephrine were determined fluorometrically in the rat brain. Ketamine and etoxadrol significantly affected brain monoamine concentrations, but these effects were not consistent between drugs. Ketamine caused a slight increase in serotonin and a decrease in norepinephrine. Etoxadrol had a biphasic action on brain serotonin content, first increasing and later decreasing it, and decreased norepinephrine and dopamine. Brain monoamine content was unaffected by thiopental. The apparent rate of synthesis of brain serotonin was reduced to 50–60 per cent of control levels four hours after administration of ketamine and etoxadrol. These drugs also produced increases in the apparent rate of brain dopamine synthesis, which reached as much as 200 per cent of control six hours after administration. In contrast, thiopental caused only a marginal decrease in the apparent synthesis rate of brain serotonin and a 30 per cent decrease in the apparent synthesis rate of dopamine. Thus, intravenous anesthetics with psychotropic activity, like many other psychotropic agents, produce prominent changes in brain monoamine metabolism. (Key words: Intravenous anesthesia; Ketamine; Etoxadrol; Thiopental; Brain serotonin; Brain dopamine; Brain norepinephrine; Psychotropic drugs.)

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KETAMINE HYDROCHLORIDE, a so-called "dissociative anesthetic,"[1] represents a new class of agents capable of producing a state of detachment from the environment in patients during surgical procedures. Dreamlike experiences have often been reported by patients after recovery from anesthesia. During the post-anesthetic recovery period, confusion or irrational behavior, or both, has also been observed in some patients.

Etoxadrol hydrochloride ({+}-2-{2-ethyl-2-phenyl-1,3 dioxolan-4-yl} piperidine HCl) is currently undergoing clinical trials. Its chemical structure differs from that of ketamine (fig. 1). In laboratory animals, the gross pharmacologic effects of etoxadrol have been reported to resemble those produced by ketamine.[2, 3] Recent clinical reports also verified the similarities of these two drugs.[4, 5] The bizarre behavioral responses of animals treated with ketamine and etoxadrol have not been reported to occur with other inhalation or intravenous anesthetics. Changes in the metabolism of brain monoamines have frequently been associated with administration of psychotropic drugs.[6, 7] Therefore, this study was designed to determine whether such changes—specifically, the apparent rate of synthesis of brain monoamines—could also be demonstrated following the administration of ketamine or etoxadrol. In addition, the effects of ketamine and etoxadrol were compared with those of the short-acting barbiturate, sodium thiopental.

Materials and Methods

Male CFE (Carworth) rats weighing 110–175 g (average 130 g) were used throughout the study. The rats were housed in group cages in a large colony room and were continuously provided with food and water. The lights in the colony room were turned off between 6:00 PM and 6:00 AM. The rats were housed under these conditions for at least three

days before being subjected to any experimental procedure.

The drugs used in this study were ketamine hydrochloride (10, 20, and 40 mg/kg), etoxadrol hydrochloride (5, 10, and 20 mg/kg) and sodium thiopental (40 mg/kg). Drug doses are expressed in terms of these salts. All drugs were dissolved in sterile 0.9 per cent saline solution prior to injection. All treatment groups and control (saline solution) groups received injections intravenously via the tail vein at a constant rate at time zero in a volume of 0.2 ml/100 g body weight.

Rats were sacrificed by decapitation at the indicated times after administration of drug or saline solution. The entire brain was rapidly removed, weighed, and homogenized, as described by Holtzman and Jewett.[8] The brain homogenates were stored in a freezer until they could be assayed for monoamine content. In order to minimize bias due to circadian fluctuations in brain monoamine levels, all animals were sacrificed between 12:00 noon and 3:00 PM. Saline-treated animals comprised a third to half of the animals sacrificed on any one day. Brain concentrations of serotonin (5-HT) and norepinephrine (NE) were determined fluorometrically by the method of Ansell and Beeson.[9] A slight modification of the Ansell and Beeson procedure[10] was used for the determination of dopamine (DA) concentrations. Internal standards were included in every assay. The recoveries of NE, DA, and 5-HT were 104.73 ± 3.75, 44.88 ± 1.90, and 65.92 ± 1.65 per cent, respectively.

The rate of change in the concentration of a neurohumor following the inhibition of its synthesis or breakdown is often a more reliable index of its functional state than is the absolute concentration in the brain. We, therefore, determined the average rate of increase of brain 5-HT in the first hour following the inhibition of monoamine oxidase (MAO).[11] One, two, four, and six hours after the administration of a drug or saline solution, the monoamine oxidase inhibitor pargyline hydrochloride, 75 mg/kg, was injected intraperitoneally in a volume of 0.2 ml/100 g body weight. The rats were sacrificed 0, 20, 40, or 60 minutes later, and the whole brain was analyzed as described above.

The average exponential rates of decline of

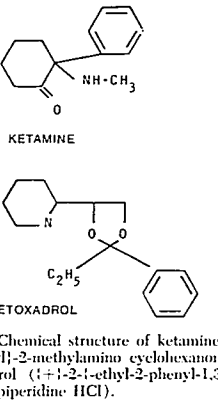

FIG. 1. Chemical structure of ketamine (2-[O-chlorophenyl]-2-methylamino cyclohexanone HCl) and etoxadrol ([+]-2-[-ethyl-2-phenyl-1,3 dioxolanol-4-yl] piperidine HCl).

NE and DA were determined following the inhibition of tyrosine hydroxylase with DL-α-methyltyrosine methyl ester hydrochloride (αMT).[12] One, two, four, and six hours after the administratoin of a drug or saline solution, αMT, 150 mg/kg, was injected intraperitoneally in a volume of 0.2 ml/100 g body weight. The rats were sacrificed 0, 1, 2, or 3 hours later for analysis of the brains.

For the purpose of statistical comparisons of the effects of drugs on brain monoamine concentrations, all of the saline-treated animals from each drug series of experiments were pooled to give control means made up of 27, 23, and 12 observations for the ketamine, etoxadrol, and thiopental experiments, respectively. Comparisons of treatment means with control means were made using Student's t test. To analyze the rate of change of the monoamines after inhibition of synthesis or breakdown, regression lines were determined for each experiment by the method of least squares. The slope of the regression line obtained following a drug treatment was then compared with the slope of the regression line that was generated after treatment with saline solution. For all comparisons, a drug effect was considered significant when $P < 0.05$. The source of the statistical test was Edwards.[13] All means presented in Results are expressed ± SEM.

TABLE 1. Effects of Anesthetics on Brain Serotonin Concentration in the Rat

	Serotonin Concentration (μg/g Tissue)*				
	0 Hour	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Ketamine					
20 mg/kg	0.429 ± 0.008	0.438 ± 0.017	0.423 ± 0.021	0.439 ± 0.016	0.428 ± 0.018
40 mg/kg		0.414 ± 0.014	0.420 ± 0.023	0.443 ± 0.018	0.471 ± 0.011
Etoxadrol					
10 mg/kg	0.415 ± 0.006		0.456 ± 0.016‡	0.388 ± 0.011†	0.371 ± 0.007
20 mg/kg			0.450 ± 0.017†	0.388 ± 0.008†	0.390 ± 0.021
Thiopental					
40 mg/kg	0.465 ± 0.043	0.495 ± 0.013	0.464 ± 0.011	0.476 ± 0.012	

* Means are based on at least six observations and are expressed ± SEM.
† Significantly different from control (0 hour), $P < 0.05$.
‡ Significantly different from control (0 hour), $P < 0.01$.

TABLE 2. Effects of Anesthetics on Brain Dopamine Concentration in the Rat

	Dopamine Concentration (μg/g Tissue)*				
	0 Hour	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Ketamine					
20 mg/kg	0.815 ± 0.015	0.748 ± 0.040	0.837 ± 0.026	0.824 ± 0.020	0.881 ± 0.039
40 mg/kg		0.766 ± 0.031	0.838 ± 0.027	0.777 ± 0.029	0.818 ± 0.015
Etoxadrol					
10 mg/kg	0.798 ± 0.014		0.760 ± 0.014	0.679 ± 0.030§	0.706 ± 0.051†
20 mg/kg			0.769 ± 0.026	0.672 ± 0.031§	0.726 ± 0.030†
Thiopental					
40 mg/kg	0.783 ± 0.064	0.849 ± 0.027	0.835 ± 0.032	0.784 ± 0.021	

* Means are based on at least six observations and are expressed ± SEM.
† Significantly different from control (0 hour), $P < 0.05$.
§ Significantly different from control (0 hour), $P < 0.001$.

Results

The time courses of the effects of ketamine (20 and 40 mg/kg), etoxadrol (10 and 20 mg/kg) and thiopental (40 mg/kg) on brain monoamine concentration are presented in tables 1–3. Ketamine, 20 mg/kg, had no effect on brain 5-HT concentration, but 40 mg/kg produced a significant increase ($P < 0.05$) in brain 5-HT concentration six hours after administration (table 1). Etoxadrol produced a biphasic effect, first elevating (two hours after administration), then lowering (four and six hours after administration), brain 5-HT. Table 2 shows that brain DA concentrations were lowered significantly only by etoxadrol, 10 and 20 mg/kg, at four ($P < 0.001$) and six hours ($P < 0.05$). Brain NE concentrations were significantly lowered by ketamine two hours after administration but returned to normal by four hours (table 3). Etoxadrol had a more prolonged effect and lowered brain NE both two and four hours after administration; NE concentration returned to normal by six hours. Thiopental failed to affect the brain concentration of any of the three monoamines (tables 1–3).

Dose–response curves for ketamine and etoxadrol were determined. Since ketamine ap-

TABLE 3. Effects of Anesthetics on Brain Norepinephrine Concentration in the Rat

	Norepinephrine Concentration (μg/g Tissue)*				
	0 Hour	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Ketamine					
20 mg/kg	0.439 ± 0.009	0.402 ± 0.016	0.391 ± 0.009‡	0.458 ± 0.015	0.431 ± 0.011
40 mg/kg		0.420 ± 0.008	0.390 ± 0.014‡	0.424 ± 0.021	0.421 ± 0.012
Etoxadrol					
10 mg/kg	0.417 ± 0.009		0.374 ± 0.012‡	0.375 ± 0.008§	0.407 ± 0.015
20 mg/kg			0.368 ± 0.011§	0.351 ± 0.012§	0.391 ± 0.015
Thiopental					
40 mg/kg	0.447 ± 0.019	0.413 ± 0.014	0.429 ± 0.025	0.440 ± 0.022	

* Means are based on at least six observations and are expressed ± SEM.
‡ Significantly different from control (0 hour), $P < 0.01$.
§ Significantly different from control (0 hour), $P < 0.001$.

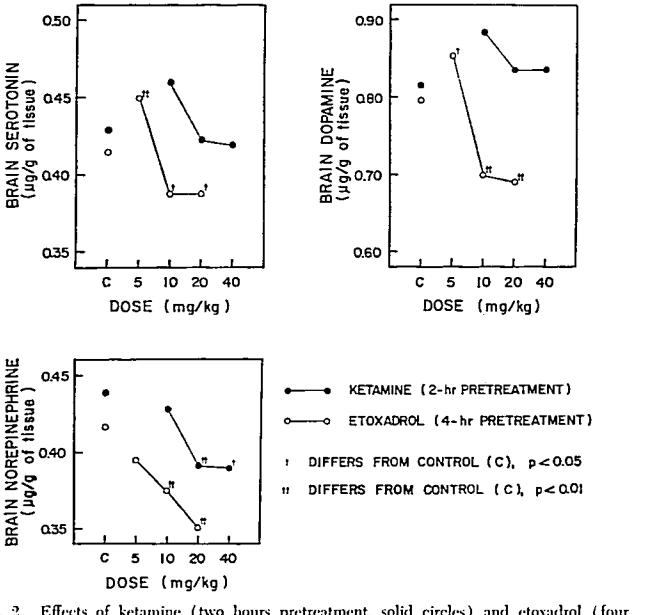

FIG. 2. Effects of ketamine (two hours pretreatment, solid circles) and etoxadrol (four hours pretreatment, open circles) on brain monoamine concentrations in the rat. Each point in the dose–response curves represents the mean of at least six observations. Each point at C represents the mean of at least 12 observations in animals treated with saline solution only. The SEM for each point is presented in tables 1–3.

TABLE 4. Effects of Anesthetics on Rate of Increase of Brain Serotonin in the Rat after Inhibition of MAO*

	Rate of Increase of Serotonin (μg/g Tissue/Hour)			
	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Saline solution	0.293			
Ketamine, 40 mg/kg		0.295	0.174§	0.312
Etoxadrol, 20 mg/kg		0.262	0.151§	0.302
Thiopental, 40 mg/kg	0.240†	0.282	0.283	

* Pargyline (75 mg/kg) was injected at the indicated times after administration of anesthetic. The rate of increase of serotonin was determined for the one-hour period after the administration of pargyline.
† Significantly different from control (saline solution), $P < 0.05$.
§ Significantly different from control (saline solution), $P < 0.001$.

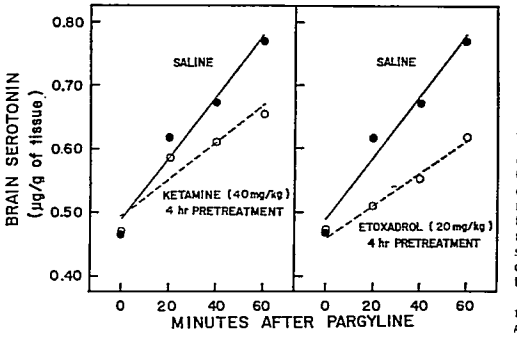

FIG. 3. Rate of increase of brain serotonin in the rat four hours after administration of ketamine (40 mg/kg), etoxadrol (20 mg/kg) or saline solution. Each point represents the mean of three to six observations. The data points for saline solution are identical in the two panels. The Pearson correlation coefficients are 0.844, 0.844, and 0.964 for ketamine, etoxadrol, and saline solution, respectively. The equations of the regression lines were determined by the method of least squares. The rates of increase of brain serotonin after the three treatments were 0.293 (saline solution), 0.174 (ketamine), and 0.151 (etoxadrol) μg/g of tissue/hour.

peared to produce its greatest effect two hours after administration, whereas etoxadrol was most active at four hours, these pretreatment intervals were selected for the dose–response curves. Etoxadrol had biphasic effects on 5-HT and DA levels (fig. 2). The levels were elevated by 5 mg/kg and lowered by 10 and 20 mg/kg. Both ketamine and etoxadrol produced dose-related decreases in brain NE concentration.

The overt behavior of the animals after administration of each of the three drugs was observed. Ketamine-treated animals lost their righting reflex for approximately 1–15 minutes immediately after receiving the drug. The length of time until the righting reflex was recovered was dependent upon the dose used. Upon recovery, the rats became hyperactive: walking backwards, weaving their heads side-to-side, and hyper-responsive to mild environmental stimuli. This behavior persisted for about 2–3 hours. Etoxadrol-treated animals showed a more prolonged course than those treated with ketamine. The animals lost their righting reflex for approximately 10–60 minutes. Upon recovery of the righting reflex, the

TABLE 5. Effects of Anesthetics on Rate of Decline of Brain Dopamine in the Rat after Inhibition of Tyrosine Hydroxylase*

	Rate of Decline of Dopamine (μg/g Tissue/Hour)			
	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Saline solution	0.195 (k_e = 0.244)			
Ketamine 40 mg/kg		0.156 (k_e = 0.195)	0.255 (k_e = 0.280)	0.411§ (k_e = 0.450)
Etoxadrol 20 mg/kg		0.203 (k_e = 0.262)	0.244† (k_e = 0.300)	0.461§ (k_e = 0.499)
Thiopental 40 mg/kg	0.140§ (k_e = 0.156)	0.261 (k_e = 0.271)	0.250 (k_e = 0.296)	

*αMT (150 mg/kg) was injected at the indicated time after administration of anesthetic. The rate of decline of dopamine was determined for the three-hour period after the administration of αMT. k_e is the first-order rate constant for the decline of dopamine levels and is expressed as hr^{-1}.

† Significantly different from control (saline solution), $P < 0.05$.

§ Significantly different from control (saline solution), $P < 0.001$.

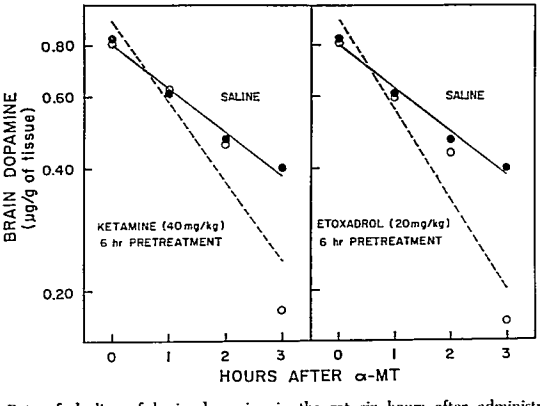

FIG. 4. Rate of decline of brain dopamine in the rat six hours after administration of ketamine (40 mg/kg), etoxadrol (20 mg/kg) or saline solution. Each point represents the mean of three to six observations. The data points for saline solution are identical in the two panels. The Pearson correlation coefficients are 0.935, 0.947, and 0.970 for ketamine, etoxadrol and saline solution, respectively. The equations of the regression lines were determined by the method of least squares. The rates of decline of brain dopamine after the three treatments were 0.195 (saline solution), 0.411 (ketamine), and 0.461 (etoxadrol) μg/g of tissue/hour.

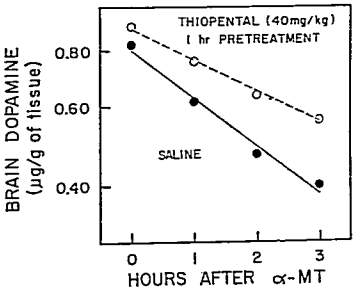

FIG. 5. Rate of decline of brain dopamine in the rat one hour after administration of thiopental (40 mg/kg) or saline solution. Each point represents the mean of three to six observations. The data points for saline solution are identical to those in figure 4. The Pearson correlation coefficients are 0.969 and 0.970 for thiopental and saline solution, respectively. The equations of the regression lines were determined by the method of least squares. The rates of decline of brain dopamine after the treatments were 0.195 (saline solution) and 0.140 (thiopental) μg/g of tissue/hour.

rats displayed behavior similar to that observed in the rats treated with ketamine; however, the duration of the effects was as long as 3–4 hours. In addition, etoxadrol-treated rats manifested rigidity of the tail, a response not seen after treatment with ketamine. Thiopental-treated animals lost their righting reflex for approximately two hours. Upon recovery the rats were hyporesponsive to environmental stimuli.

In control rats (saline pretreated), the average rate of increase in brain 5-HT concentration was 0.293 μg/g/hr following the injection of a MAO inhibitor (pargyline). In animals treated four hours earlier with ketamine (40 mg/kg) or etoxadrol (20 mg/kg), the rate of increase in brain 5-HT concentration after MAO inhibition was significantly slower, only 50 to 60 per cent of that of the saline-treated controls (table 4, fig. 3). This indicates a marked decrease in the utilization of brain serotonin in rats pretreated with ketamine or etoxadrol. In contrast, thiopental attenuated only slightly the rate of 5-HT increase one hour after its administration in pargyline-treated animals.

Following the administration of αMT the brain DA concentration decreased at an average rate of 0.195 μg/g of tissue/hour in saline-treated animals (table 5). The first-order rate constant (k_e, that per cent of the brain monoamine store metabolized per hour) for the decline of DA levels after injection of saline so-

TABLE 6. Effects of Anesthetics on Rate of Decline of Brain Norepinephrine in the Rat after Inhibition of Tyrosine Hydroxylase*

	Rate of Decline of Norepinephrine (μg/g Tissue/Hour)			
	1 Hour after Injection	2 Hours after Injection	4 Hours after Injection	6 Hours after Injection
Saline solution	0.051 (k_e = 0.126)			
Ketamine 40 mg/kg		0.063 (k_e = 0.148)	0.074 (k_e = 0.176)	0.056 (k_e = 0.138)
Etoxadrol 20 mg/kg		0.061 (k_e = 0.151)	0.068 (k_e = 0.161)	0.060 (k_e = 0.147)
Thiopental 40 mg/kg	0.048 (k_e = 0.110)	0.085† (k_e = 0.194)	0.052 (k_e = 0.124)	

* αMT (150 mg/kg) was injected at the indicated time after administration of the anesthetics. The rate of decline of norepinephrine was determined for the three-hour period after the administration of αMT. k_e is the first-order rate constant for the decline of norepinephrine levels and is expressed as hr^{-1}.

† Significantly different from control (saline solution), $P < 0.05$.

TABLE 7. Summary of the Effects of Anesthetics on Brain Monoamine Concentrations and Apparent Rates of Synthesis in the Rat

	Brain Monoamines					
	Serotonin		Dopamine		Norepinephrine	
	Conc.	Apparent Rate of Synthesis	Conc.	Apparent Rate of Synthesis	Conc.	Apparent Rate of Synthesis
Ketamine	↑	↓	—	↑	↓	—
Etoxadrol	↑↓	↓	↑↓	↑	↓	—
Thiopental	—	↓	—	↓	—	↑

lution was 0.244 hr^{-1}. Both ketamine and etoxadrol enhanced the average rate at which DA levels decreased after αMT; this effect was progressive with time (table 5). Six hours after administration of ketamine (40 mg/kg) and etoxadrol (20 mg/kg), the average rates of decline of brain DA were 0.411 μg/g of tissue/hour ($k_e = 0.450$ hr^{-1}) and 0.461 μg/g of tissue/hour ($k_e = 0.499$ hr^{-1}), respectively (table 5, fig. 4). These values represent approximately a 100 per cent increase from those of the saline-treated controls, and indicate a substantial increase in DA utilization or metabolism. Etoxadrol also produced a significant effect four hours after its administration. In contrast, one hour after its administration, thiopental significantly reduced the average rate of decline of brain DA to 0.140 μg/g of tissue/hour ($k_e = 0.156$ hr^{-1}) (table 5, fig. 5).

Brain NE levels decreased at an average rate of 0.051 μg/g tissue/hour ($k_e = 0.126$ hr^{-1}) (table 6) in the control group (*i.e.*, saline pretreated) following injection of αMT. Thiopental (40 mg/kg) was the only drug of the three to alter significantly the rate of NE decline. Two hours after thiopental administration, the rate of decline of this neurohumor increased to 0.085 μg/g tissue/hour ($k_e = 0.194$ hr^{-1}).

Discussion

These experiments show that ketamine and etoxadrol produce varying effects on the absolute levels of brain monoamines but have similar pronounced effects on the metabolism of brain 5-HT and DA. In contrast, thiopental, the short-acting barbiturate, fails to affect the level of any of the three brain monoamines. It produces only a marginal change in the rate of accumulation of 5-HT after MAO inhibition and a change in the rate of decline of brain DA after tyrosine hydroxylase inhibition opposite in direction to the changes observed following administration of ketamine or etoxadrol. A summary of these results is presented in table 7.

The increases in brain 5-HT concentration seen with ketamine were in contrast to the biphasic effects on brain 5-HT levels produced by etoxadrol. However, both ketamine and etoxadrol significantly slow the build-up of 5-HT in pargyline-treated rats (about 50–60 per cent of control level) four hours after their administration. Under steady-state conditions the rate at which the concentration of brain 5-HT increases after the inhibition of MAO may be assumed to be equivalent to, and an indirect measurement of, the rate of biosynthesis of this neurohumor.[11] In the present study, ketamine and etoxadrol produced changes in the total brain content of 5-HT; thus, steady-state conditions were not always in effect. However, since the changes in the total brain levels of 5-HT were small in comparison with the very pronounced and consistent decreases in the rate of accumulation of brain 5-HT after MAO inhibition, it is likely that the latter effect reflects inhibition of 5-HT biosynthesis.

It is of interest that several drugs that produce bizarre behavior in man, *e.g.*, lysergic

acid diethylamide[14] and cyclazocine (unpublished observation), have also been found to reduce the rate of synthesis of 5-HT in the rat brain. The significance of these changes in the disposition of 5-HT with relation to behavior in man is not clear. Diethyl ether, which does not have prominent behavioral effects in man, markedly elevates the synthesis rate of 5-HT in the rat.[15] The same study failed to show changes in the rate of 5-HT synthesis after treatment with cyclopropane or halothane.

Thiopental produced only marginal slowing in the rate of accumulation of 5-HT in the brain when pargyline was injected one hour after its administration. At this time the animals were still unconscious. In contrast, the changes in 5-HT metabolism produced by ketamine and etoxadrol occurred at a time when the animals were widely awake and hyperresponsive to mild environmental stimuli.

As in the case of 5-HT, the effects of ketamine and etoxadrol on total brain catecholamine levels tended to be variable. Ketamine and etoxadrol both produced decreased NE levels in the rat brain two hours after administration, while etoxadrol has more prolonged effects on brain NE levels. In addition, etoxadrol exerts biphasic effects on brain DA levels.

Here, again, the changes in brain catecholamine levels produced by ketamine and etoxadrol compromise the steady-state assumptions necessary to estimate catecholamine systhesis rate from the exponential rate of decline of brain catecholamine levels after the inhibition of tyrosine hydroxylase with αMT. Nevertheless, the very magnitude of the effects of ketamine and etoxadrol on the rate of decline of DA after αMT treatment suggests that these drugs increase the rate of DA synthesis. Furthermore, the effects are progressive with time. The maximum effects occur four to six hours after drug administration, long after the animals have recovered from unconsciousness.

It is of interest that the confusion and irrational behavior that have beeen observed in some patients receiving ketamine or etoxadrol have most often been reported to occur a matter of hours after the drugs were given. On the other hand, thiopental, which does not produce these prominent behavioral effects in either man or animals, decreased the rate of brain DA decline one hour after its administration in animals injected with αMT. At that time the rats were still unconscious.

Since ketamine and etoxadrol produce similar behavioral manifestations in patients, an involvement of brain monoamines in these psychotropic actions would appear to be related to those changes in amine disposition that are produced consistently by both drugs, *i.e.*, the prominent changes in the disposition of brain 5-HT and DA. Although the mechanisms of the changes in amine metabolism and their possible clinical significance are presently obscure, the large magnitude and prolonged time course of the effects reported by us should stimulate further studies which may establish a relationship between changes in the disposition of brain monoamines and the psychotropic effects of certain intravenous anesthetics.

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Drugs and Their Actions

OUABAIN PHARMACOKINETICS A newly devised radioimmunoassay technique for ouabain, with high specificity and sensitivity to less than 0.1 ng/ml of plasma or urine, was used to study the pharmacokinetics of this rapidly acting cardiac glycoside in dogs and man. Following a single intravenous dose, plasma concentrations fell rapidly in both species. The subsequent exponential decline showed a half-life of 18 hours in the dog and 21 hours in man. Following repeated daily intravenous administration to human subjects, plasma and urinary half-lives in the 19–24-hour range were confirmed. These determinations agree well with previously observed time constants of pharmacologic responses. Previous studies of ouabain pharmacokinetics employed tracer doses of ^{3}H-ouabain in experimental animals and human subjects. The values for plasma ouabain half-life in man so obtained have varied widely, limited by the time interval during which plasma radioactivity could be accurately measured after administration of ^{3}H-ouabain. The present radioimmunoassay method seems superior, permitting accurate determination of plasma ouabain concentrations beyond 48 hours after a single subdigitalizing dose of 0.5 mg. (*Selden, R., and Smith, T. W.: Ouabain Pharmacokinetics in Dog and Man. Determination by Radioimmunoassay. Circulation 45: 1176, 1972.*) EDITOR'S NOTE: These data provide an excellent background for knowledge of uptake and distribution but require further modification in relation to total and regional blood flow. Although the blood concentration–toxicity relationships undoubtedly apply, the time constants for uptake and distribution (particularly half-life) will be modified by additional factors, for example kidney function.