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Acute Cocaine Toxicity: Antagonism by Agents Interacting With Adrenoceptors

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DERLET, R. W. AND T. E. ALBERTSON. *Acute cocaine toxicity: Antagonism by agents interacting with adrenoceptors.* PHARMACOL BIOCHEM BEHAV **36**(2) 225–231, 1990.—Agents which interact with alpha- or beta-adrenoceptors were evaluated for efficacy in preventing seizures and death from a lethal dose of cocaine. Rats were first pretreated with the test drug(s), then subjected to an intraperitoneal LD_{86} of cocaine (70 mg/kg). In this model, control vehicle-pretreated animals developed seizures within six minutes, followed by death within 10 minutes. Significant protection against death was afforded by pretreatment with clonidine (0.25 mg/kg), prazocin (5.0 to 20 mg/kg), propranolol (8.0 to 32 mg/kg), or labetalol (40 mg/kg). Surviving animals still experienced seizures as judged through behavior and EEG recordings. Phentolamine did not affect the incidence of seizures or death. Two nonadrenoceptor agents were also studied: hydralazine reduced the incidence of death and seizures at 5.0 and 10 mg/kg, but reserpine did not alter the incidence of death or seizures. A combination of prazocin and propranolol did not provide additional protection compared to single agents. We conclude that the pathogenesis of acute cocaine death is complex, and that this toxicity can be antagonized by agents having either central or peripheral effects.

Adrenoceptors Cocaine Death Rats Seizures

ACUTE cocaine toxicity results through multifactorial and not thoroughly understood mechanisms. Cocaine induces release and blocks the reuptake of specific catecholamines at selected central synaptic junctions, resulting in catecholamine accumulation, thus producing receptor cell hyperstimulation (7). Many catecholamine-rich sites within the central nervous system are affected, but the relative importance of these sites to acute cocaine toxicity is not known (29). In addition, circulating catecholamine levels increase resulting in cardiovascular hyperstimulation (10,19). The relative contribution of central nervous system compared to the cardiovascular hyperstimulation in causing drug toxicity and ultimate death is also not well understood. Death in humans from cocaine has been attributed to seizures, hypertension, cerebral vascular spasm, hemorrhage, vascular collapse, acidosis, or cardiac ischemia from coronary arterial spasm (2).

Adrenoceptors are important in modulation of cardiovascular activity (30). Animal models of cocaine intoxication have produced conflicting results on the effectiveness of agents interacting with adrenoceptors (1, 3, 23). The relative importance of adrenoceptor-specific agonists or antagonists in modulating the toxic effects of cocaine needs further clarification. This laboratory has utilized a model of acute cocaine intoxication in the rat to evaluate the protective characteristics of pretreatment with several drugs, including those which act on either alpha-adrenoceptors, beta-adrenoceptors, or both.

METHOD

Male Sprague-Dawley rats weighing between 200 and 300 grams were used in these experiments. The animals were cared for following the guidelines and approval of our campus animal control committee and were in compliance with Federal guidelines. Rats were kept under 12-hour light/dark cycles and had ad lib access to food and water. The various test drugs were administered IP 30 minutes prior to cocaine dosing.

The efficacy of pharmacologic agents in antagonizing the effects of cocaine was tested using a model of acute cocaine toxicity previously described by this laboratory (6). In this model, the 70 mg/kg of cocaine administered IP represents approximately an LD_{86}.

Rats were pretreated IP with either vehicle [dimethylsulfoxide (DMSO), Sigma Chemical Company] 1.0 ml/kg as a control, clonidine (0.25 to 1.0 mg/kg), hydralazine (1.0 to 20 mg/kg), labetalol (5.0 to 40 mg/kg), prazocin (1.0 to 20 mg/kg), phentolamine (2.5 to 5.0 mg/kg), propranolol (1.0 to 32 mg/kg), yohimbine (1.0 to 5.0 mg/kg), or pretreated with propranolol (8.0 mg/kg) in combination with prazocin (5.0 mg/kg) or yohimbine (2.5 mg/kg). Thirty minutes after the test drug(s) was given, the rats were challenged with cocaine hydrochloride (cocaine-HCl, Sigma Chemical Company) 70 mg/kg, IP, in 1.0 ml/kg of saline. Test drugs uniformly went into solution in DMSO (1.0 ml/kg). Doses of these drugs were selected to cover a wide range and to be consistent with previously established dosing in rodents (9, 15, 19, 25). Additional groups of 10 rats each received reserpine 2.5 or 5.0 mg/kg 24 hours prior to 70 mg/kg cocaine administration to assess the effect of reserpine-induced catecholamine depletion.

Animals were observed in Plexiglas cages prior to and after

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cocaine dosing. Evidence of sedation, decreased muscle tone, and gait ataxia were recorded before cocaine dosing. After cocaine dosing, times were recorded for the onset of clinically obvious seizures and death. All animals were observed for 180 minutes after cocaine treatment and checked daily thereafter for five days.

In the second set of experiments, rats had cortical and amygdaloid electrodes implanted as previously described (6). These rats were anesthetized with 3.6 ml/kg, IP, Chloropent® [pentobarbital (8.9 mg/ml)/chloral hydrate (42.5 mg/ml)/ethanol (14.3%)]. The skulls were exposed through sharp and blunt dissection and drilled. A right amygdaloid electrode (1.0 mm posterior to bregma, 4.75 mm lateral to midline, and 7.5 mm deep from the surface of the brain) was placed. Cortical electrodes were introduced above the right and left motor cortex, and anterior to bregma. The screw electrodes were connected by wires to Amphenol® connectors and cemented in place to the skull with Dentoplast® acrylic. Rats were allowed to recover for at least 10 days before being studied.

Two to four rats each were pretreated with DMSO (1.0 ml/kg, IP) or labetalol (20 mg/kg), prazocin (10 mg/kg), propranolol (16 mg/kg), or yohimbine (2.5 mg/kg) all dissolved in DMSO (1.0 ml/kg), IP, 30 minutes before cocaine intoxication (70 mg/kg). The EEG activity and behavioral consequences of the cocaine treatment were monitored for up to 45 minutes. Seizures were ranked one through five using a variation of the ranks defined by Racine (20): 1) mouth and facial movement, 2) head nodding, 3) forelimb clonus, 4) rearing, with forelimb movements, 5) rearing and/or falling on side with full motor seizure.

Data is reported as overall percent of seizures and death for each group. Mean time to seizures and death includes standard error. Time comparisons were performed using one-way ANOVA. Individual comparisons of mean values were done by Dunnett's test when appropriate F scores were significant ($p \leq 0.05$). The Chi-squared test was used to compare the incidence of seizures and deaths after drug pretreatment compared to DMSO control rates.

RESULTS

In this group of experiments, DMSO-pretreated animals served as controls and developed convulsions in 6.4 ± 0.4 min which persisted, except for brief pauses, generally until animals died as a result of what appeared to be a cardiopulmonary arrest 9.9 ± 0.6 min after cocaine administration. The effects of various agents studied are presented in Table 1. All animals that convulsed reached a rank of five within five seconds.

Pretreatment with clonidine offered significant protection against cocaine-induced seizures and death at a dose of 0.25 mg/kg. At a dose of 0.5 mg/kg several animals died without having seizures. These animals became sedated five minutes after receiving cocaine, and spontaneous movement decreased until animals sustained a cardiopulmonary arrest.

Labetalol did not significantly alter the incidence of seizures or death, except at the highest dose of 40 mg/kg. At this dose, animals demonstrated loose muscle tone and signs of sedation just prior to cocaine administration. Following cocaine, animals lay on their sides, eyes open, and were observed to have repeated rotational motion of forelimbs (swimming behavior) which persisted 30 minutes unless animals convulsed and died.

Prazocin-pretreated animals had a significant prolongation of the time to seizures and death at doses greater than 5.0 mg/kg; however, the actual incidence of seizures was not significantly affected. Prazocin had a significant effect in decreasing death at doses above 5.0 mg/kg. Surviving animals displayed swimming behavior up to 30 minutes after cocaine, then lay on their sides with increased respirations for 60 minutes before spontaneously crawling and recovering.

Phentolamine pretreatment did not significantly alter the incidence or time of seizures or death.

Propranolol significantly reduced the incidence of death at the highest doses tested. Precocaine evaluation of these animals demonstrated loose muscle tone, but animals were up and moving in cages. Following cocaine, the behavior of surviving animals was similar to the labetalol group, with animals demonstrating swimming behavior punctuated by rank five seizures.

Animals receiving yohimbine showed increased activity prior to and after receiving cocaine. They displayed increased running in cages, quicker movements, and piloerection. Yohimbine failed to protect against cocaine toxicity.

Two drugs not affecting adrenoceptors were also studied. Hydralazine pretreatment evoked obvious skin vasodilatation at doses of 5.0, 10, and 20 mg/kg. This was evidenced by striking erythema of ears and feet. The incidence of death was 30% in animals receiving 10 and 20 mg/kg. These groups also had significantly prolonged time to initial seizure as shown in Table 1.

Animals that received reserpine 24 hours prior to cocaine were abnormal at the time of cocaine injection. These animals had diarrhea, stereotypic behavior, and kept their eyes shut. The effects were most noticeable in the group that received the highest dose tested (5.0 mg/kg). These animals had an overall weight loss of 10% body weight over the 24 hours after pretreatment. Following administration of cocaine, these animals developed seizures and death at the same rate and time as control animals.

The final set of experiments were done to determine the EEG activity in cocaine intoxicated rats. Four animals were pretreated with DMSO, and two with labetalol, prazocin, propranolol, or yohimbine 30 minutes prior to injection of 70 mg/kg of cocaine. DMSO, labetalol, prazocin, propranolol, and yohimbine pretreated rats all had clinically overt rank five seizures (Table 2). One pretreated with prazocin and one pretreated with propranolol survived, while none of the DMSO-, labetalol-, or yohimbine-pretreated rats survived. Analysis of the EEG showed a rapid onset of cortical and limbic spiking activity leading to sustained afterdischarge activity. A continuum of electrical activity beginning with one to two seconds of five to 10 Hz cortical and limbic spike and burst activity which increased in frequency to become four- to six-second bursts of 10- to 15-Hz afterdischarges were noted in all animals including the survivors. A comparison of EEG activity during the initial stereotypic behavior phase to the full rank five seizure with the sustained EEG afterdischarge is shown in Fig. 1. Abnormal behavior consisted of circling, occasional forelimb clonus, followed by sedation, swimming-like limb movements, and ataxia. This did not correspond to obvious cocaine-induced EEG spikes. Animals that developed obvious clinical rank five convulsions and ultimately died had episodes of prolonged (greater than six seconds) sustained afterdischarge.

DISCUSSION

This model of acute cocaine toxicity shows that many agents which interact with adrenoceptors alter the toxic effects of high dose cocaine. The finding that cocaine toxicity can be modified by alpha- and beta-adrenoceptor antagonists provides additional insight into the potential mechanisms of cocaine toxicity. This study summarized in Table 3 provides indirect evidence that adrenoceptor hyperstimulation may to some degree contribute to cocaine-induced death.

Cocaine toxicity has been explained through hyperstimulation of central nervous system pathways. The reuptake of norepinephrine and dopamine at selective central and peripheral nervous system neurotransmission sites are blocked, resulting in excess

TABLE 1

COCAINE TOXICITY AND AGENTS AFFECTING ALPHA- AND BETA-ADRENOCEPTORS

Pretreatment	N	Precocaine Drug Effect[a]	Percent Seizure	Time[a] to Seizure	Percent Death	Time[a] to Death
DMSO (control)	75	O	96	6.3 ± 0.3	86	9.8 ± 0.5
Clonidine						
0.25 mg/kg	8	O	25†	15.6 ± 0.4†	50*	10.5 ± 2.0
0.5 mg/kg	8	M	38†	11.5 ± 2.5*	63	11.4 ± 2.0
1.0 mg/kg	8	M	75	12.0 ± 2.0†	63	13.5 ± 3.6
				$F(3,64)=16.02$, $p\leq 0.01$		$F(3,59)=1.06$, NS
Labetalol						
5.0 mg/kg	10	O	100	7.1 ± 0.3	70	12.0 ± 0.6
10.0 mg/kg	10	O	80	6.1 ± 0.2	70	11.0 ± 0.8
20.0 mg/kg	15	M	73	6.0 ± 0.2	73	9.4 ± 0.8
40.0 mg/kg	10	M	50†	7.7 ± 1.0	40†	15.0 ± 3.0
				$F(4,85)=0.74$, NS		$F(4,73)=2.10$, NS
Prazocin						
1.0 mg/kg	10	O	70	6.6 ± 1.0	80	9.3 ± 1.5
5.0 mg/kg	10	M	80	11.8 ± 1.7†	40†	13.0 ± 3.1
10.0 mg/kg	20	M	75	13.5 ± 1.4†	30†	13.4 ± 2.4
20.0 mg/kg	10	M	70	13.3 ± 2.2†	50*	14.7 ± 1.3*
				$F(4,89)=16.9$, $p\leq 0.01$		$F(4,67)=2.64$, $p\leq 0.05$
Phentolamine						
2.5 mg/kg	10	V	70	6.6 ± 1.9	60	9.4 ± 2.2
5.0 mg/kg	10	V	80	5.0 ± 0.5	70	8.4 ± 1.1
				$F(2,79)=0.81$, NS		$F(2,68)=0.39$, NS
Propranolol						
1.0 mg/kg	10	O	70	9.0 ± 2.0	70	17.5 ± 5.5†
2.0 mg/kg	10	M	100	8.2 ± 1.0	60	11.4 ± 1.2
4.0 mg/kg	10	M	80	6.5 ± 0.7	80	10.1 ± 0.9
8.0 mg/kg	10	M	60*	9.1 ± 2.5	40†	8.6 ± 1.6
16.0 mg/kg	20	M	80	9.1 ± 1.2*	55*	8.3 ± 0.8
32.0 mg/kg	10	M	90	11.3 ± 1.6†	40†	11.4 ± 2.6
				$F(6,106)=3.62$, $p\leq 0.01$		$F(6,82)=2.46$, $p\leq 0.05$
Yohimbine						
1.0 mg/kg	8	O	88	8.7 ± 0.8	88	13.3 ± 1.9
2.5 mg/kg	10	A	100	7.2 ± 0.5	100	9.4 ± 0.7
5.0 mg/kg	10	A	70	6.8 ± 1.2	70	9.9 ± 1.5
10.0 mg/kg	10	A	100	5.5 ± 0.6	100	8.2 ± 0.6
				$F(4,96)=2.46$, NS		$F(4,85)=1.74$, NS
Combinations:						
Propranolol 8.0 mg/kg Prazocin 5.0 mg/kg	10	M	80	14.6 ± 1.5†	40†	14.6 ± 1.8*
Propranolol 8.0 mg/kg Yohimbine 2.5 mg/kg	10	A	90	13.3 ± 0.8†	80	15.4 ± 0.5*
Other Drugs:						
Hydralazine 1.0 mg/kg	10	O	80	7.2 ± 0.9	60	8.3 ± 0.9

TABLE 1
(CONTINUED)

Pretreatment	N	Precocaine Drug Effect[a]	Percent Seizure	Time[a] to Seizure	Percent Death	Time[a] to Death
5.0 mg/kg	20	V	95	13.2 ± 1.0†	30†	14.9 ± 2.8†
10.0 mg/kg	10	V	60*	12.8 ± 1.9†	30†	13.0 ± 3.7
20.0 mg/kg	10	V	90	8.6 ± 0.9	90	11.7 ± 1.0
				F(4,104) = 20.74, $p \leq 0.01$		F(4,77) = 2.81, $p \leq 0.05$
Reserpine						
2.5 mg/kg	10	R	70	5.7 ± 1.0	60	7.7 ± 0.7
5.0 mg/kg	10	R	90	7.2 ± 0.6	70	9.6 ± 0.7
				F(2,80) = 0.88, NS		F(2,68) = 0.82, NS

All test drugs given 30 minutes before cocaine challenge except reserpine which was given 24 hours before testing.
*$p \leq 0.05$ compared to DMSO control by Dunnett's test or Chi-squared test.
†$p \leq 0.01$ compared to DMSO control by Dunnett's test or Chi-squared test.
N = number; NS = not significant; ± standard error.
[a]Effect of test drug on animals at time of cocaine injection: S = sedated, M = muscle tone decreased, V = peripheral vasodilated, O = no gross effect, A = agitated, R = refer to text.

catecholamine stimulation (8, 18, 26). Toxic effects of confusion, agitation, hallucinations, and seizures are thought to result from increased catecholamine activity in specific pathways in the brain such as the mesolimbic or mesocortical pathway. In animal models, seizures occur before death (6). Our findings show that despite seizures, death can be prevented by agents which have peripheral cardiovascular effects. The interrelationship between central nervous system and cardiovascular hyperstimulation is not well understood (6). The cardiovascular toxicity of cocaine could occur through the release of catecholamines centrally, peripherally, or through a direct effect. Final end-organ toxicity may also result from metabolic derangements caused by seizures, hyperthermia, and/or hypertension (16). In addition, cardiac myofibrils of cocaine-treated animals have shown necrosis believed to be the effect of excessive beta-adrenoceptor stimulation (11). The degree of alpha- compared to beta-adrenoceptor hyperstimulation in the pathogenesis of cocaine-induced death can be partially understood by comparing the effects of respective pharmacologic agents as studied in this model.

Prazocin, a postsynaptic alpha-1 antagonist, was effective in all doses above 5.0 mg/kg in significantly reducing the incidence of cocaine-induced death. Prazocin exerts peripheral and central

TABLE 2
EEG AND BEHAVIOR OF INDIVIDUAL ELECTRODE IMPLANTED RATS AFTER COCAINE 70 mg/kg

Pretreatment	Animal Number	Behavior[a]	Seizure Rank	EEG Before Cocaine[a]	EEG With Clin Seiz.	Death
DMSO	1	ST	5	NL	Spike/AD	Yes
1.0 ml/kg	2	ST	5	NL	Spike/AD	Yes
	3	ST	5	NL	Spike/AD	Yes
	4	ST	5	NL	Spike/AD	Yes
Labetalol	5	SW	5	NL	Spike/AD	Yes
20 mg/kg	6	SW	5	NL	Spike/AD	Yes
Prazocin	7	SW	5	NL	Spike/AD	No
10 mg/kg	8	SW	5	NL	Spike/AD	Yes
Propranolol	9	SW	5	NL	Spike/AD	No
16 mg/kg	10	SW	5	NL	Spike/AD	Yes
Yohimbine	11	A	5	NL	Spike/AD	Yes
2.5 mg/kg	12	A	5	NL	Spike/AD	Yes

[a]For time between cocaine injection and seizure onset.
SW = swimming behavior; A = agitated; ST = stereotypic behavior; NL = normal.
Spike/AD = spikes, afterdischarge or both.
Seizure Rank: 1 to 5 scale (see the Method section).

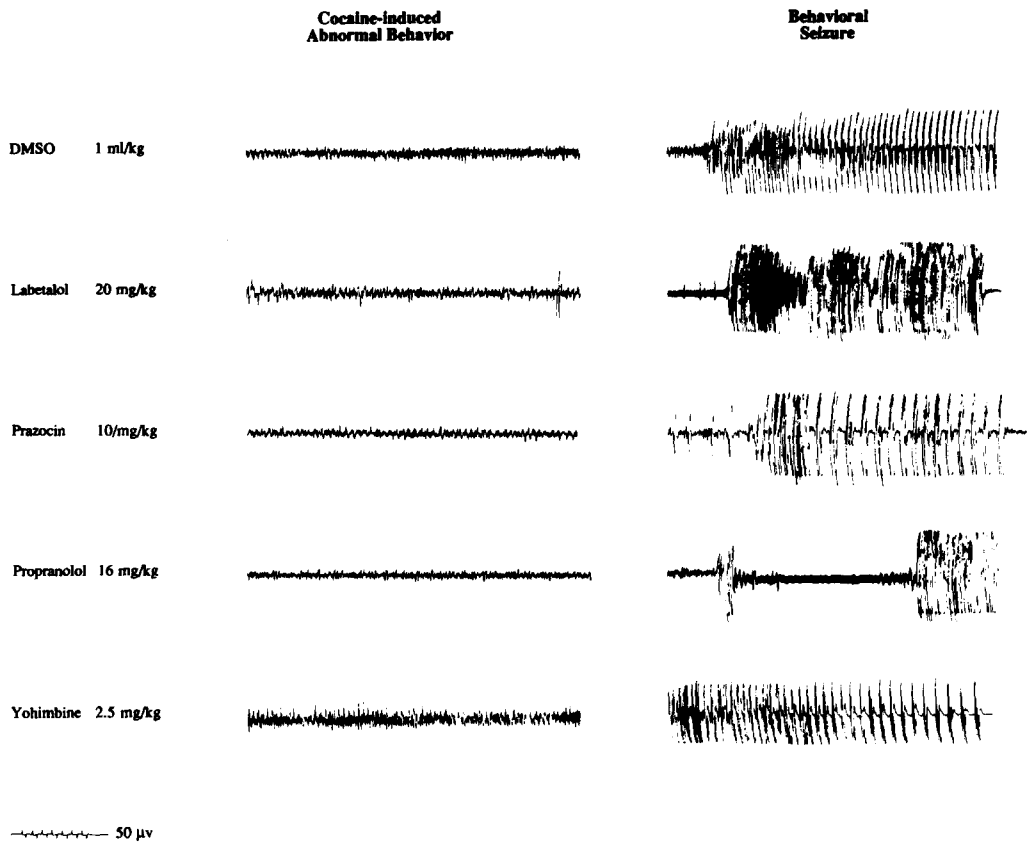

FIG. 1. Post 70 mg/kg cocaine EEG obtained during stereotypical abnormal behavior of circling and occasional forelimb clonus followed by sedation, swimming-like limb movements, and ataxia occurred after pretreatment with all five agents. Sustained afterdischarges were noted with clinically obvious rank five seizures. Scale marks 50 mV increases/decreases from baseline, each one second apart.

alpha-1 antagonistic effects, causing a reduction in arterial blood pressure by reducing systemic vascular resistance (24). The protective effect of prazocin could result from site specific antagonism, or through its hypotensive actions.

Hydralazine offered similar protection against death, presumably through nonspecific vasodilation-induced decreases in blood pressure or altered cocaine pharmacodynamics. Prazocin and hydralazine also both delayed the onset of clinically overt seizures when compared to controls. In the doses tested, neither prazocin nor cocaine alone induced sedation in the animals. In combination, sedation and a peculiar "swimming" behavior were observed in animals, many of which did not die. Animals were not having electrical seizures without the motor component as shown by the EEG studies. The paradox of the stimulant cocaine enhancing sedation produced by other agents has been previously described (28).

The combined peripheral alpha-1 and alpha-2 antagonist phentolamine failed to provide significant protection against cocaine-induced seizures or death. This is consistent with the work of Robin *et al.* who found that phentolamine provided no protective effect against death in mice exposed to high doses of cocaine (23). Behavioral effects induced by cocaine or amphetamine which can be antagonized by prazocin have been observed in other studies not to be altered by phentolamine (27). Phentolamine, in contrast to prazocin, also blocks alpha-2 receptors. The alpha-2 antagonist yohimbine also failed to provide protection against either seizures or death.

Propranolol, a nonselective beta-adrenoceptor antagonist, also had significant efficacy in providing a dose-dependent reduction in the incidence of death in this model. Propranolol blocks the effect on end organs of beta-1 and beta-2 stimulation at the central and peripheral adrenoceptor (17). The current study is consistent with the study by Robins (23) which showed that propranolol pretreatment significantly reduced the incidence of death in mice given a lethal dose of cocaine. These observations differ from a previous report by Catrauas (3) in which propranolol pretreatment failed to protect dogs from cocaine-induced death. In contrast to the current study, Catrauas and Waters utilized a slow intravenous infusion of cocaine and pretreated the dogs with propranolol one to two hours before the cocaine infusion was begun, which may have provided inadequate levels of propranolol.

In the doses of propranolol utilized, animals became sedated and had swimming behavior following injection of cocaine. Neither cocaine nor propranolol when given alone induced this behavior. EEG's on animals with this behavior showed normal, approximately 10 Hz waves which were similar to those seen in prazocin pretreated animals. The underlying mechanisms inducing this behavior are unknown.

Labetalol, a beta-adenoceptor nonselective antagonist, also has very weak alpha-1 antagonizing effects when given parenterally (21). Based on the results with propranolol pretreatment, this agent would be expected to antagonize cocaine toxicity. Labetalol was effective only at the very highest dose tested (40 mg/kg), which was five times the threshold effective dose of propranolol.

TABLE 3

SUMMARY OF EFFECTS OF ADRENOCEPTOR PRETREATMENT ON COCAINE TOXICITY

Pretreatment	Mechanism Action(s)	Site	Results: Incidence Seizure	Time to Seizure	Incidence Death	Time to Death
Clonidine	Alpha-2 agonist	C,P	↓ ↓	↑ ↑ ↑	↓	NS
Prazocin	Alpha-1 antagonist	C?,P	NS	↑ ↑ ↑	↓ ↓ ↓	↑
Phentolamine	Alpha-1 and Alpha-2 antagonist	P	NS	NS	NS	NS
Propranolol	Beta antagonist	C?,P	↓	↑ ↑	↓ ↓ ↓	↑
Labetalol	Beta and limited Alpha-1 antagonist	C?,P	↓	NS	↓	NS
Yohimbine	Alpha-2 antagonist	C?,P	NS	NS	NS	NS
Propranolol + Prazocin[a]	(see above)		NS	NS	↓	NS
Propranolol + Yohimbine	(see above)		NS	↑	NS	↑
Hydralazine	Nonadrenoceptor vasodilator	P	↓	↑ ↑	↓ ↓	↑
Reserpine	Catecholamine depletion	C,P	NS	NS	NS	NS

[a]No change compared to prazocin alone.

C = central; P = peripheral.

↓ = Significant decrease with one dose. ↓ ↓ = Significant decrease with two doses. ↓ ↓ ↓ = Significant decrease with three doses. ↑ = Significant increase with one dose. ↑ ↑ = Significant increase with two doses. ↑ ↑ ↑ = Significant increase with three doses.

NS = No significant effect.

This is consistent with studies in animals showing propranolol to be three to five times as potent as labetalol (22). In the current model, the weak alpha-1 antagonist effect of labetalol does not appear to provide enhanced protective effects above the pure nonselective beta antagonist effect. This finding is consistent with our failure to find enhanced protection when propranolol is given in combination with prazocin.

Yohimbine, an alpha-2 antagonist, blocks selective adrenoceptors, and thus induces stimulatory effects in specific peripheral and central nervous system circuits lending to clinical effects of hypertension and agitation (32). The peripheral alpha-2 blocking effects of yohimbine enhance the effects of circulatory catecholamines by preventing presynaptic alpha-2 negative feedback. Yohimbine might be expected to enhance the stimulatory actions of cocaine since antagonism of these receptors may enhance catecholamine-induced vascular smooth muscle contractions (30,31). We cannot explain our finding that yohimbine-pretreated animals showed no change in the incidence of seizures and death compared to controls.

Clonidine is a centrally active alpha-2 selective agonist with antihypertensive effects. Clonidine also exerts limited anticonvulsant effects in many seizure models (14). In this model, clonidine significantly reduced the incidence of seizures consistent with observations in other seizure models (14), although a paradoxical effect was seen at the highest dose. However, at high doses, an alpha-1 agonist effect has been described (31).

Reserpine was administered to assess the effect of central and peripheral presynaptic catecholamine depletion on cocaine toxicity. Animal behavior 24 hours after reserpine injection was consistent with this effect. Despite this depletion, cocaine toxicity was not altered. The stimulatory effects of cocaine occur despite depletion of presynaptic norepinephrine and dopamine from specific central nerve terminals, suggesting that toxic effects of cocaine may not require normal presynaptic catecholamine stores or may be mediated through sites distant to those depleted by reserpine.

In conclusion, the mechanisms by which lethal dose cocaine induces seizures and death are complex and do not appear to be entirely adrenoceptor mediated. Alpha-1, alpha-2, and beta-adrenoceptors appear important in the pathogenesis of toxicity since toxicity can be reduced by certain adrenoceptor agonists and antagonists. The lack of absolute antagonism by either alpha-1 or beta-antagonists alone or in combination and the effects of the nonadrenoceptor vasodilator hydralazine suggests that additional and perhaps nonspecific mechanisms contribute significantly to cocaine-induced toxicity and death. Further evidence regarding the complex pathogenesis of high-dose cocaine is derived from the absence of protective effect seen after central and peripheral catecholamine depletion induced by reserpine. Further studies into the mechanism of cocaine-induced seizures and death which include measurement of more specific physiologic, electrical, and biochemical parameters are needed to better define and clarify the pathophysiologic mechanisms of cocaine.

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