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Cocaine-Induced Respiratory Depression in Urethane-Anesthetized Rats: A Possible Mechanism of Cocaine-Induced Death

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TSENG, C.-C., R. W. DERLET, L. G. STARK AND T. E. ALBERTSON. *Cocaine-induced respiratory depression in urethane-anesthetized rats: A possible mechanism of cocaine-induced death.* PHARMACOL BIOCHEM BEHAV **39**(3) 625–633, 1991.— Urethane-anesthetized rats were used to study the mechanism of cocaine-induced death. Continuous recording of the changes in five physiological parameters, including respiratory rate (RR), electroencephalogram (EEG), blood pressure (BP), electrocardiogram (ECG), and body temperature (BT), were conducted after intraperitoneal (IP) administration of a single dose of cocaine HCl (70 mg/kg). In the control group (normothermic with core body temperature 37.7 ± 0.1°C and spontaneously breathing), the death rate was 88% (15/17), and the average time to respiratory arrest was 12.99 ± 1.40 min (mean ± SEM). The first set of experiments investigated the contribution of hypothermia to cocaine-induced death. The hypothermic group (core body temperature 33.9 ± 0.3°C and spontaneously breathing) had a death rate of 81.5% (22/27), and an average time to respiratory arrest of 16.70 ± 1.24 min, which was significantly ($p<0.05$) prolonged. A substantial decrease in respiratory rate was seen in normothermic group, while all the other measured parameters remained relatively stable until respiratory arrest. Sequential arterial blood gas data in this group showed a decrease in PaO_2 from 116.0 ± 5.7 mmHg to 57.7 ± 4.6 mmHg, an increase in $PaCO_2$ from 27.7 ± 2.2 mmHg to 42.7 ± 3.0 mmHg, and a decrease in pH from 7.467 ± 0.039 to 7.357 ± 0.003. To confirm that respiratory depression was an important mechanism of cocaine-induced death in this model, ten normothermic rats underwent mechanical ventilation, and all survived cocaine exposure. This study points to the important role of respiratory depression as a cause of cocaine-induced death.

Cocaine Respiratory depression Hypothermia Urethane Seizures Rat Mechanism of death

COCAINE abuse and the incidence of cocaine-induced death have increased dramatically in the past two decades (11, 13, 25, 32). Acute cocaine intoxication has posed a great challenge to the medical personnel in emergency departments and critical care units mainly because of its fast action, various symptoms, and unpredictability (3, 8, 12).

The treatment of cocaine intoxication has been the subject of debate and speculation. Other than symptomatic treatment, there is no specific antidote for cocaine intoxication that is universally accepted. Some agents have been shown to have various degrees of effectiveness in treating clinical symptoms of acutely cocaine-intoxicated patients, including diazepam (15,42), propranolol (5,34), haloperidol (26), various calcium channel blockers (7,24) and prazocin (40). However, few animal models of cocaine intoxication have been used to demonstrate the protective effects of different approaches of treatment (7,14). Lack of understanding of the precise mechanism of cocaine-induced toxicity contributes to current limitations on appropriate treatment.

Because of the complicated medical situations involved with human cocaine use, including polydrug abuse and the presence of preexisting underlying diseases, human studies have not been successful in defining the precise mechanism of cocaine-induced death. It is also quite difficult to design an animal model that can adequately elaborate the complexity of the human poisoning. All of these facts have made the mechanism of cocaine-induced death a subject of debate. Several possible mechanisms have been suggested, which include hyperthermia (4, 7, 20, 27), seizures or central nervous system (CNS) events (6, 7, 11), respiratory paralysis (1, 10, 17, 39, 43), cardiac arrhythmias (21–24, 38, 41), and cardiovascular disturbances (19, 22, 23).

In addition to hyperthermia, the major organ systems at risk are the CNS and cardiopulmonary system. The evidence of cardiovascular involvement in cocaine-related toxicity has been accumulating in recent years, but the mechanisms of cocaine-induced cardiotoxicity still remain unclear. These may include acute myocardial ischemia and infarction (19), cardiac arrhythmias (21–24, 38), acute and chronic cardiomyopathies (31), rupture of the ascending aorta (16) and stroke (2,36). In this study, a urethane-anesthetized rat model was used to further define and investigate some of the mechanism(s) involved in cocaine-induced death. Intraperitoneal cocaine was used to in part mimic the tissue absorption of the nasal route of cocaine.

METHOD

Animals

Male Sprague-Dawley rats weighing between 200 and 300 g were used. Rats were kept under a 12-hour light-dark cycle and

had access to food and water ad lib.

Chemicals

Urethane, cocaine HCl, and dimethylsulfoxide (DMSO) were purchased from Sigma Chemical Company (St. Louis, MO). Urethane was dissolved in distilled water in a concentration of 0.5 g/ml. Before being administered to the animals, cocaine HCl was dissolved in a physiological saline with pH 5.

Equipment

A Grass polygraph, model 78D, was used to record intermittent EEG, ECG (lead II), blood pressure (Statham Laboratories, Inc., physiological pressure transducer, model No. P23 Dc), and respiratory rates. A Propaq Ultra-portable vital signs monitor, Model 106, was used to constantly monitor body temperature, ECG (lead II) and blood pressure (COBE®, Lakewood, CO, disposable pressure transducer) throughout the experiment. An Edco rodent ventilator, Model 802, was used to give mechanical ventilation. Respiratory rate was recorded by IITC breathing amplifier, Model 680. A Harvard apparatus pump, Model 22, was used to inject drugs or agents at a desired, constant infusion rate.

Surgical Procedures

Prior to general anesthesia, subjects were put in a restraining device and body temperature was monitored via a rectal temperature probe. Urethane was given to each rat at a dose range of 1.2 to 1.5 g/kg. Three PE-50 polyethylene tubes, each attached to a tuberculin syringe containing either cocaine solution, heparinized saline, or DMSO/saline mixture, were prepared. A cocaine-containing intraperitoneal PE-50 tubing was introduced into the peritoneal cavity. The second catheter containing DMSO/saline mixture was inserted into the right jugular vein and the third containing heparinized saline into the right carotid artery. A 16-gauge teflon intravenous tubing was placed in the trachea. On a rodent stereotaxic device, the rat's skull was exposed. Three EEG screw electrodes were introduced above the right motor cortex, left motor cortex, and anterior to bregma. A respiration sensor was placed around the abdomen and chest wall. Subcutaneous needle electrodes were placed on the legs for ECG (lead II) recordings. The body temperature was adjusted by thermal pads beneath and a heat lamp above the rat. The normothermic rats were maintained at a body temperature of 37.7 ± 0.1°C. The heat lamp was removed once the body temperature exceeded the awake body temperature. The thermal pad, wrapped in cloth, was not changed throughout the experiment. In the hypothermic group, body temperature was maintained at 33.9 ± 0.3°C. The experiments were not started until the body temperatures remained stable at the desired temperature.

Experimental Protocols

Rats were divided into three groups: (A) normothermic spontaneously breathing group; (B) hypothermic spontaneously breathing group; and (C) normothermic mechanically ventilated group.

In the control experiments, Group A, 17 subjects were maintained at a body temperature of 37.7 ± 0.1°C. They were then pretreated with 1:1 mixture of DMSO/saline at a dose of 0.5 ml/kg injected at a constant rate over 5 minutes by a Harvard pump (this was to act as control infusion for future pharmacologic studies, and the reason for using such a mixture was to reduce potential toxicity and maintain drug solubility of DMSO). Ten minutes later, they were given 70 mg/kg cocaine HCl in 2 ml/kg normal saline via an intraperitoneal catheter by slow manual push over one minute (this dosage was chosen because it had been shown to result in a death rate of 85% in awake rats in a previous study) (11). Three 0.2-ml blood samples were withdrawn for arterial blood gas analysis from each of the last three animals in this group. The first sample (baseline) was taken before the DMSO/saline mixture was administered. The second sample was taken three minutes after cocaine administration. The last one was taken when the respiratory rate was observed to have decreased to approximately 50% of the precocaine level and breathing was seen to have become shallower (this occurred within 3 minutes of the respiratory arrest in all these animals that died). An equal amount of pH-adjusted physiological saline (0.2 ml) was given after each blood sample. To examine the contribution of hypothermia to cocaine-induced death, 27 rats of Group B, who were cooled to 33.9 ± 0.3°C before experiments began, were compared to the normothermic rats. These animals were also pretreated with 1:1 DMSO/saline mixture. All the remaining treatments were the same as in Group A except that no arterial blood samples were taken.

In the second simultaneously run experiment, 10 animals of Group C were compared to those of Group A. These normothermic rats had the same procedures performed as outlined above except that they were put on mechanical ventilation before receiving cocaine. The mechanical respiratory rate was set at 120 breaths per minute. The tidal volume was determined according to the equation: $V_T = 0.0075B$, where V_T is tidal volume (ml) and B is body mass (g) (9). Mechanical ventilation was administered for 10 minutes before and 60 minutes after cocaine and then turned off to see if the rat was capable of spontaneous breathing. Three arterial blood samples were withdrawn from 4 rats in this group for analysis. The first sample was taken before mechanical ventilation (baseline), the second sample was taken 10 minutes after mechanical ventilation, and the third was taken 15 minutes after cocaine treatment. All parameters were monitored for 120 minutes. The animals were observed for several more hours before they were terminated with an overdose of urethane.

Data Analysis

Data were reported as mean ± standard error of the mean (S.E.M.). The alveolar and arterial PO_2 gradient or $P(A-a)O_2$ gradient was calculated to differentiate the possible causes of hypoxemia according to the following equations:

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} \quad \text{(a)}$$

$$P(A-a)O_2 = PAO_2 - PaO_2 \quad \text{(b)}$$

The alveolar PO_2 (PAO_2) was calculated from equation (a). PIO_2 represents partial pressure of inspired oxygen or 21% oxygen in room air at sea level. R represents the respiratory exchange ratio, which is assumed to be 0.8. The PaO_2 and $PaCO_2$ were measured from the arterial sample (29).

Spike-wave complex (SWC) on EEG recordings was defined as two or more spikes or sharp waves occurring together and repeating at consistent intervals. Spike burst (SB) was a more dramatic form of EEG spiking which was usually a part of a short afterdischarge activity. ECG (lead II) amplitude measurements were done by averaging the height of 10 QRS complexes (heartbeats).

Because of the discrepancy in the time of each cocaine-induced death, the graphs of physiological responses were divided

into two halves (8 minutes each). The first half represents the physiological changes after cocaine administration, and the latter half represents the changes before respiratory arrest. The χ-squared test was used to compare the incidence of death. The statistical significance of all other data were computed by using Student's *t*-test.

RESULTS

The changes in physiological parameters in both the normothermic (A) and hypothermic (B) spontaneously breathing groups treated with a lethal dose of IP cocaine were depicted and compared in Figs. 1 and 2. The changes in physiological parameters in the normothermic mechanically ventilated animals were shown in Fig. 3. An illustrative recording from one normothermic spontaneously breathing rat was provided in Fig. 4. Similarly, an example of recordings from a normothermic mechanically ventilated rat was illustrated in Fig. 5.

(A) Normothermic Spontaneously Breathing Group (N = 15)

The average time to respiratory arrest in this group was 12.99 ± 1.40 minutes (mean $\pm$ SEM). The incidence of death was 88% or 15/17 (Table 1).

Respiratory parameters: Respiratory rate (RR) and arterial blood gas analysis. The anesthetized normothermic rats had an average RR (144 ± 9 breaths/min) which was close to that of the awake rats (160–180 breaths/min by visual counting). Six minutes after cocaine administration, the RR started decreasing until the respiratory arrest. Prior to death, the RR appeared to be the first physiological parameter to show significant depression. Respiratory arrest was immediately followed by dramatic dropping of BP and flattening of EEG waves.

Serial arterial blood gas (ABG) data were shown in Table 2. The ABG data did not change much at 3 minutes after cocaine challenge, whereas within 3 minutes before respiratory arrest the PaO_2, oxygen saturation and pH values decreased dramatically, and the $PaCO_2$ increased. The $P(A-a)O_2$ gradient increased from 3.49 ± 3.49 mmHg to 38.73 ± 1.13 mmHg before respiratory arrest.

Body temperature (BT). The average BT of awake, restrained rats was 37.73 ± 0.10°C. After urethane anesthetization, the average BT went down to 33.62 ± 0.26°C at the end of surgery. In this group, the average BT was brought up to 37.65 ± 0.12°C prior to cocaine challenge. After cocaine treatment, the BT demonstrated a small gradual climb until respiratory arrest. Peak BT was 37.95 ± 0.16°C.

Electroencephalogram (EEG). The EEG data were analyzed on the basis of the changes in frequency and amplitude and the presence or absence of spike-wave complex (SWC) and spike burst (SB) (Tables 3 and 4).

All of the animals used in this experiment had a baseline frequency of 20–30 Hz. After cocaine treatment, this group showed no change in frequency until the time of respiratory arrest when 40% (6/22) had a lower frequency of 10–20 Hz. The EEG amplitude varied greatly after cocaine treatment among animals. It dropped to a flat line a few seconds after respiratory arrest. Although sustained seizure activities including afterdischarges were suppressed by urethane, the presence of epileptiform activities in the form of SWC were still noted in the EEG recordings (Figs. 4 and 5). None of the rats showed any SBs.

Cardiovascular parameters: Blood pressure (BP), heart rate (HR) and ECG voltage. A peak BP increase of 9/11 mmHg (systolic/diastolic) at 3 minutes after cocaine treatment was noted. These BPs remained elevated until one minute prior to respiratory arrest and started dropping a few seconds before respiratory arrest. At the time of the last breath, the BPs were decreased to 87.7 ± 7.7 mmHg systolic and 54.1 ± 6.4 mmHg diastolic, compared to precocaine baseline of 112.1 ± 3.6 mmHg systolic and 73.6 ± 4.5 mmHg diastolic, respectively.

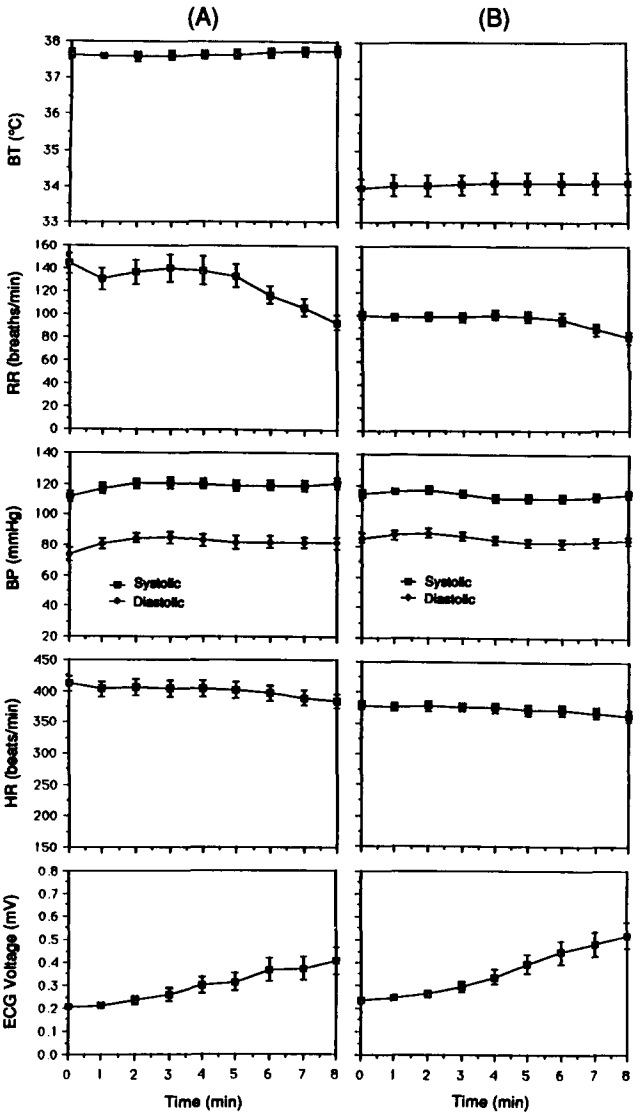

FIG. 1. A comparison of the physiological changes in the first 8 minutes after intraperitoneal administration of a lethal dose of cocaine HCl (70 mg/kg) between (A) normothermic or Group A (N = 15) and (B) hypothermic or Group B (N = 22) spontaneously breathing urethane-anesthetized rats. A decrease in the respiratory rate (RR) after 6 minutes was the most prominent feature among all the measured physiological parameters in the normothermic group. A similar response was seen in the hypothermic group. In the normothermic group (A), only 14 rats were available for recordings at 5 and 6 minutes, and 13 rats were available at 7 and 8 minutes.

The average HR remained essentially stable up to the respiratory arrest (378 ± 12 beats/min at the time of respiratory arrest). The average ECG voltage or amplitude increased steadily with time and reached the peak at the time of respiratory arrest.

(B) Hypothermic Spontaneously Breathing Group (N = 22)

The average time to respiratory arrest in this group, 16.70 ± 1.24

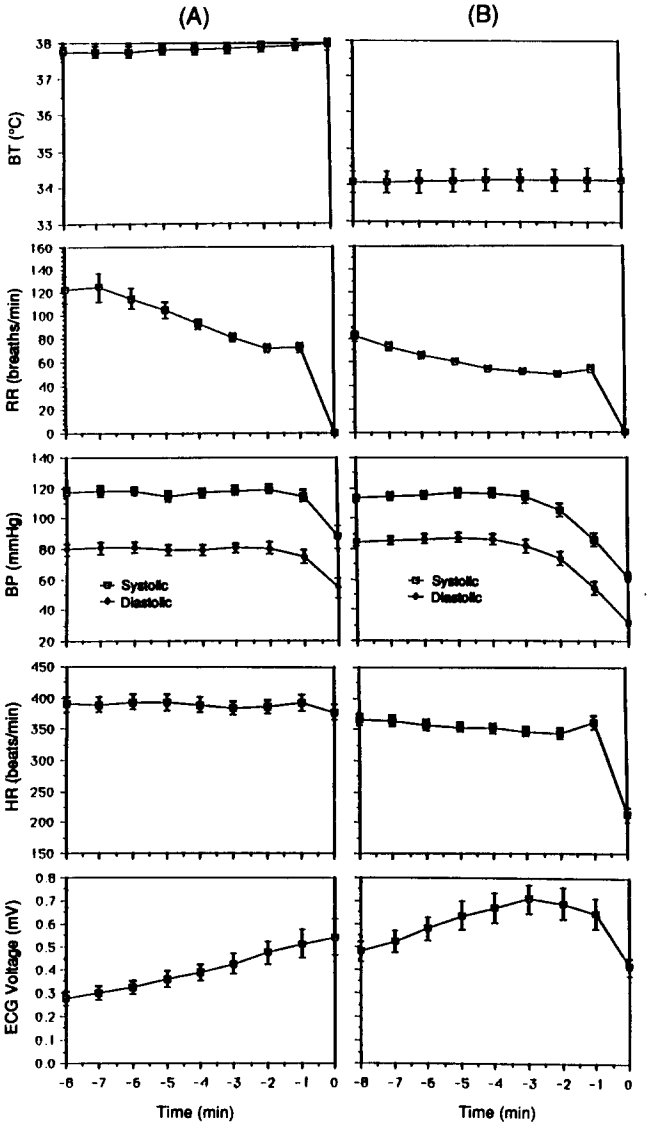

FIG. 2. A comparison of the physiological changes in the last 8 minutes prior to respiratory arrest (time 0) between the (A) normothermic or Group A (N = 15) and (B) hypothermic or Group B urethane-anesthetized rats receiving a lethal dose of cocaine HCl (70 mg/kg) via intraperitoneal route (the latter half of continuous recordings from Fig. 1). The respiratory rate (RR) continued to decrease down to zero (respiratory arrest). In the normothermic group (A), only 13 rats were available for recordings at −8 and −7 minutes, and 14 rats were available at −6 and −5 minutes.

minutes, was significantly ($p<0.05$) prolonged compared to that of normothermic rats (Group A). However, the incidence of death (81.5% or 22/27) was not significantly ($p>0.05$) different from that of Group A.

Respiratory parameters. The average RR before cocaine administration in this group, 100 ± 4 breaths/min, was significantly lower than that of Group A ($p<0.05$). A similar pattern of change was seen in this group as in Group A.

Body temperature (BT). The average BT in this group was 33.94 ± 0.28°C. After cocaine treatment, a small gradual increase in BT was seen. It peaked at 34.15 ± 0.31°C at the time of respiratory arrest.

Electroencephalogram (EEG). No changes in EEG frequency were seen until the last minute when 54.5% (12/22) of the animals showed a decreased frequency of 10–20 Hz and 22.7% (5/22) had an even lower frequency of less than 10 Hz. A similar pattern of amplitude changes was seen as in Group A.

A later appearance (5 minutes prior to death or 12 minutes after cocaine treatment) of SWCs was detected in more than half of the rats (59.1% or 13/22). The majority of this group (81.8% or 18/22) showed SWCs up until two minutes before respiratory arrest. At the time of respiratory arrest, a small percentage (9.1% or 2/22) of rats showed EEG evidence of SWCs. Only one hypothermic rat showed SBs.

Cardiovascular parameters. As in Group A, similar BP changes were seen in this group. However, a more profound decrease in blood pressure, compared to Group A, of approximately 30 mmHg (systolic/diastolic) was seen one minute before respiratory arrest.

Similar changes in average HR and ECG voltage, as noted in Group A, were seen in this group. The EEG voltage began to decrease two minutes before respiratory arrest.

(C) Normothermic Mechanically Ventilated Group (N = 10)

The rate of death dropped significantly ($p<0.01$) from 88% in the normothermic nonmechanically ventilated group (Group A) down to zero in this group.

Respiratory parameters. All ten mechanically ventilated rats regained spontaneous respiration after discontinuance of mechanical ventilation and "survived" (Fig. 3). The serial ABG results for this group are included in Table 2(B).

Body temperature (BT). The greatest increase (1.1°C) in BT was seen at 90 minutes after cocaine administration.

Electroencephalogram (EEG). Three out of 10 mechanically ventilated rats showed a decrease in EEG frequency to 10–20 Hz after 15 minutes of cocaine treatment. After removal of mechanical ventilation, one rat showed a decrease in frequency to 10–20 Hz. A dramatic increase in the average EEG amplitude occurred between 15–30 minutes after cocaine challenge to these animals. After this period, EEG amplitudes decreased somewhat but remained at a high level relative to that prior to cocaine treatment.

With the aid of mechanical ventilation, these surviving rats showed even more SWCs which persisted for longer periods of time. After 90 minutes, only 2 rats still had occasional SWCs. Eight rats showed SBs in the first 60 minutes after cocaine treatment. These SBs occurred for an average of 12.5 ± 3.2 minutes, during which time no spontaneous respiration was detected. After 60 minutes, none of the rats showed SBs.

Cardiovascular parameters. The average BP increased 15/12 mmHg (systolic/diastolic) at 15 minutes after cocaine treatment. It then slowly decreased until it was stabilized at a level slightly higher than that of the precocaine period. The average pulse pressure showed a gradual increase toward the end of the experiment (120 minutes). These animals showed tachycardia which reached a maximal rate of 434 ± 13 beats/min at 20 minutes after cocaine treatment. A maximum increase in the average ECG voltage was also seen approximately 20 minutes after cocaine treatment.

DISCUSSION

Many cocaine-related fatalities have been attributed to convulsions, respiratory arrest (35), and cardiovascular collapse (21). This laboratory has previously reported that cocaine-induced death in freely moving rats was preceded by generalized

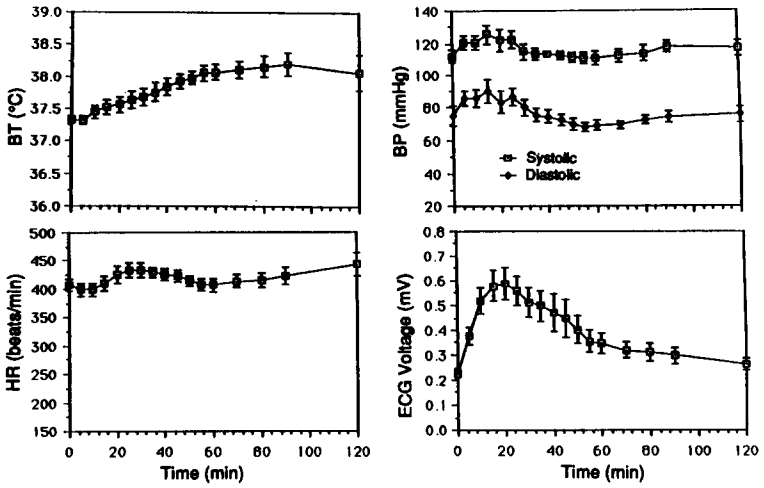

FIG. 3. The physiological changes in the surviving normothermic mechanically ventilated rats or Group C (N = 10).

seizures (11). In the current study, urethane anesthesia was used to block generalized seizures and allow the physiologic changes in the course of cocaine-induced death to be better characterized. In addition, autonomic nervous system reflex activity is thought to remain generally unaltered during urethane anesthesia (39). Respiratory collapse was found to be an important cause of death

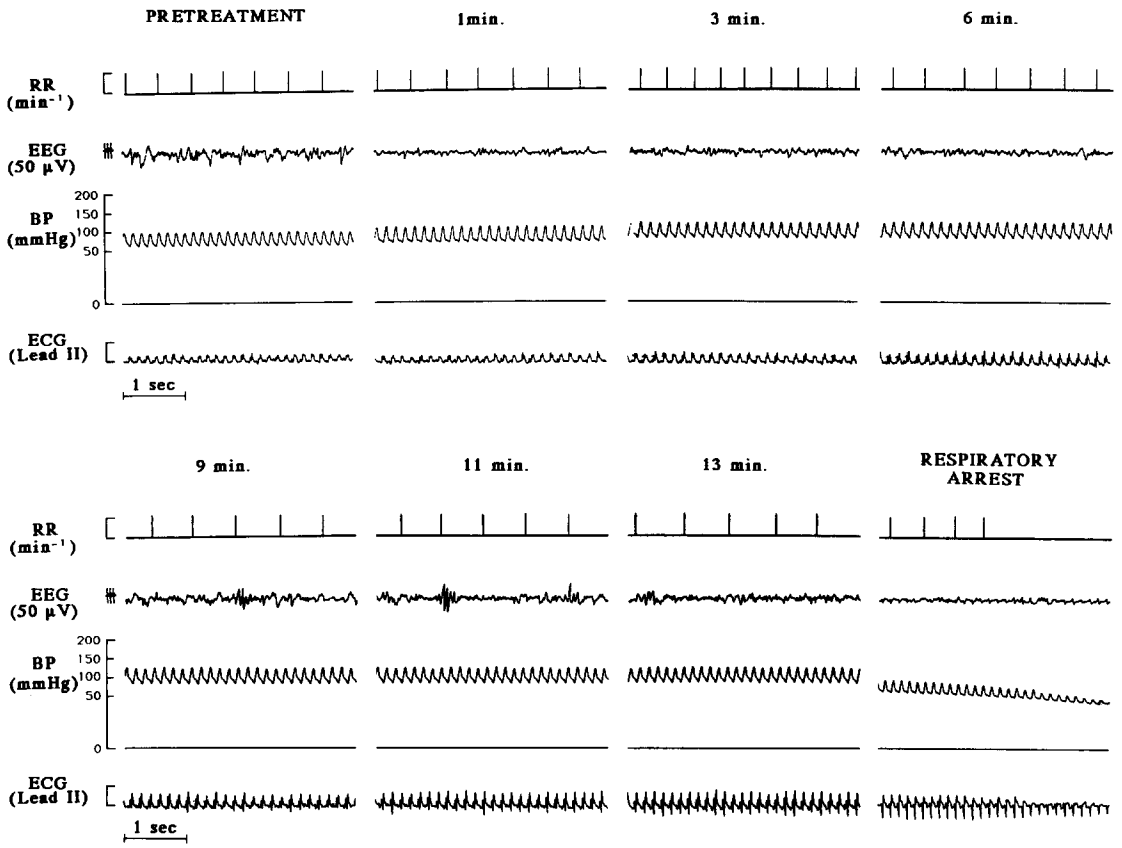

FIG. 4. An illustration of polygraphic recordings of the physiological parameters, including spontaneous respiratory chest wall movements (RR), electroencephalogram (EEG), blood pressure (BP), and electrocardiogram (ECG), from a normothermic spontaneously breathing rat receiving a lethal intraperitoneal dose of cocaine HCl (70 mg/kg).

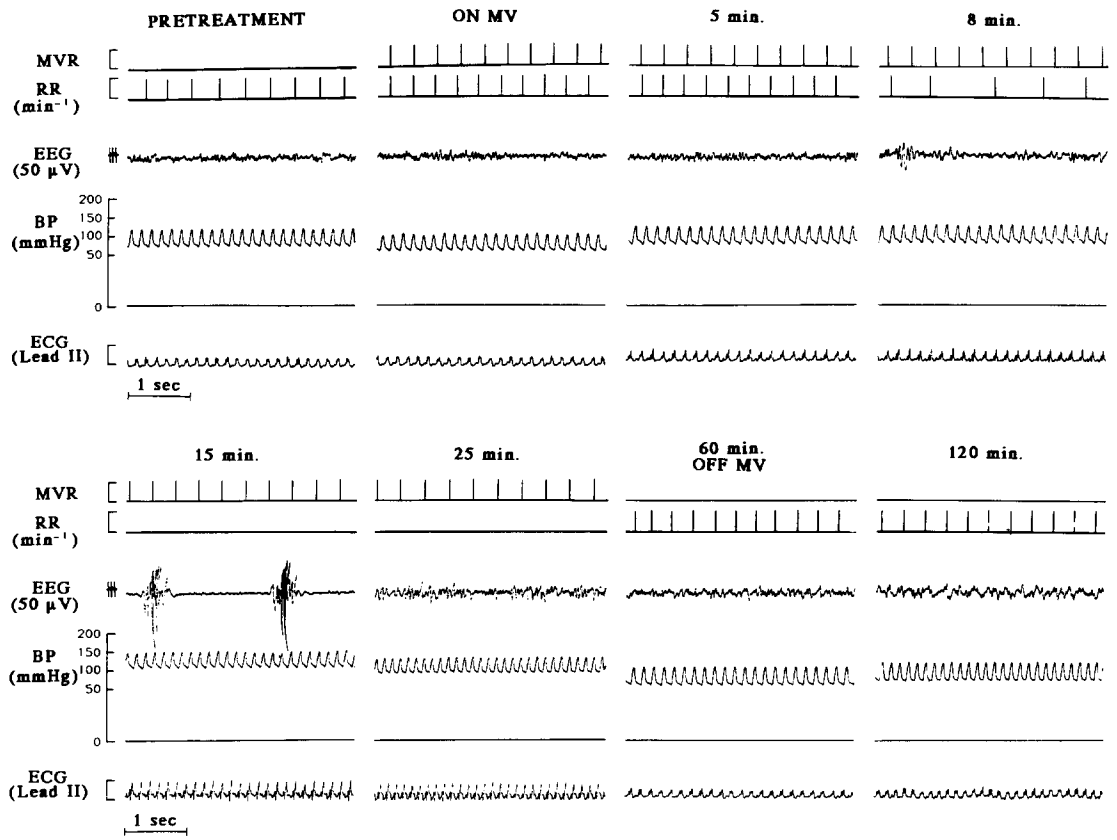

FIG. 5. An illustration of polygraphic recordings of the physiological parameters, including spontaneous respiratory chest wall movements (RR), chest wall movements from mechanical ventilation (MVR), electroencephalogram (EEG), blood pressure (BP), and electrocardiogram (ECG), from a surviving mechanically ventilated rat receiving a lethal intraperitoneal dose of cocaine HCl (70 mg/kg). Spontaneous breathing was recorded as chest wall movements despite mechanical ventilation. The spontaneous RR was noted to begin to decrease at 8 minutes after cocaine treatment. The rat was actually without spontaneous respiration by 15 minutes, relying completely on mechanical ventilation. After removal of mechanical ventilation at 60 minutes, the rat had regained spontaneous respiration and "survived."

in these animals. To substantiate this hypothesis, mechanical ventilation was applied prophylactically to 10 intubated rats. All of them survived what was previously a lethal dose of cocaine.

Some case reports have described seizures as a preterminal event after accidental massive overdose due to rupture of cocaine containers in the body of drug smugglers. Seizures also occur after recreational cocaine abuse (33). Catravas and Waters (7) suggested that seizures were a major determinant of cocaine-induced death in dogs (7). In previous studies with freely moving rats, 90% of the animals receiving a lethal cocaine dose displayed overt seizures (tonic-clonic activity), which were followed immediately by death (11). In the current study, no behavioral seizure activity was seen after a lethal dose of cocaine was administered in urethane-anesthetized rats, presumably because of the nonspecific anticonvulsant properties of urethane. However, despite urethane anesthesia, cortical spiking activity was recorded on the EEG in some animals.

TABLE 1

A COMPARISON OF THE TIME TO RESPIRATORY ARREST AND THE RATE OF DEATH

	Number	Dead/ Alive	% Death	Time to RA (min)*
Normothermic group	17	15/2	88	12.99 ± 1.40
Hypothermic group	27	22/5	81.5	16.70 ± 1.24†

RA: respiratory arrest
*Values are means ± S.E.M.
†$p \leq 0.05$ compared to normothermic group.

Some early reports on cocaine-related deaths speculated that death occurred as a result of respiratory depression, probably from a direct depressant action of cocaine on medullary respiratory centers (28,35) or from secondary respiratory depression from seizures (1, 10, 18, 37, 42). Seifen et al. reported that respiratory arrest was the primary cause of death during cocaine IV infusion in urethane-anesthetized dogs and guinea-pigs (39). Consistent with these observations, the current data demonstrated that respiratory rate was the first parameter to show signs of depression after cocaine if generalized seizures were suppressed. The ABG samples taken within 3 minutes before respiratory arrest showed a significant fall in PaO_2 (hypoxemia) and pH value, as well as an increase in $PaCO_2$, consistent with a picture of acute respiratory failure. In addition, the alveolar-arterial oxygen gradient [$P(A-a)O_2$] analysis revealed a substantial increase prior to respiratory arrest. This indicates a possible presence of pulmonary edema, ventilation-perfusion mismatch or right-to-left shunting (29). The presence of both medullary center depression

TABLE 2

THE ARTERIAL BLOOD GAS DATA OF THE (A) NORMOTHERMIC SPONTANEOUSLY BREATHING GROUP (N = 3) AND THE (B) NORMOTHERMIC MECHANICALLY VENTILATED GROUP (N = 4)

(A) Normothermic Spontaneously Breathing Group (N = 3)

	Precocaine	3 Min Postcocaine	Before RA (within 3 min)
PaO_2 mmHg	116.0 ± 5.7	116.7 ± 6.7	57.7 ± 4.6*
O_2 Sat(%)	98.3 ± 0.3	98.3 ± 0.3	87.7 ± 2.6*
$PaCO_2$ mmHg	27.7 ± 2.2	28.7 ± 1.2	42.7 ± 3.0*
pH	7.467 ± 0.039	7.473 ± 0.012	7.357 ± 0.003*
HCO_3^- mEq	20.3 ± 0.9	21.3 ± 1.5	23.7 ± 1.5
$P(A-a)O_2$ mmHg	3.49 ± 3.49	2.33 ± 2.33	38.73 ± 1.13*

(B) Normothermic Mechanically Ventilated Group (N = 4)

	Precocaine	On MV Precocaine	On MV Cocaine 15 Min
PaO_2 mmHg	95.9 ± 4.3	106.5 ± 6.4	99.1 ± 11.7
O_2 Sat(%)	97.5 ± 0.3	97.8 ± 0.5	97.3 ± 0.6
$PaCO_2$ mmHg	33.6 ± 1.9	33.2 ± 2.0	32.7 ± 5.4
pH	7.44 ± 0.01	7.48 ± 0.01	7.46 ± 0.03
HCO_3^- mEq	22.8 ± 1.6	24.3 ± 1.0	22.5 ± 2.3
$P(A-a)O_2$ mmHg	2.49 ± 4.32	4.25 ± 4.25	12.16 ± 5.22

All data are means ± SEM.

PaO_2 = arterial oxygen pressure; O_2 Sat(%) = percentage of oxygen hemoglobin saturation; $PaCO_2$ = arterial carbon dioxide pressure; HCO_3 = calculated bicarbonate ion; $P(A-a)O_2$ = alveolar-arterial oxygen gradient; MV = mechanical ventilation; RA = respiratory arrest.

*$p \leq 0.01$ compared to precocaine level.

and pulmonary damage may have led to respiratory arrest in this model. The current data have illustrated the potential importance of respiratory involvement in cocaine-related death. This aspect has been mentioned, but not stressed, in previous animal studies (6,30). In addition to respiratory depression, previous reports have postulated hyperthermia as another effect cocaine may contribute in the pathogenesis of death (4, 7, 27). In this study, the protective effect of hypothermia (core body temperature 34°C) against cocaine-induced death was tested. Although hypothermia did demonstrate a certain degree of protection by prolonging the time to respiratory arrest, the overall incidence of death did not change. Alterations in cocaine pharmacokinetics or pharmacodynamics from hypothermia may in part explain this delay.

Cardiovascular stability appeared to be well maintained prior to respiratory arrest at the cocaine dose administered in this study. This was also found to be true in anesthetized dogs and guinea pigs (39). The only cardiovascular parameter to show significant change prior to respiratory arrest was the gradual increase in the amplitude (or "voltage") of the QRS complex. The importance of this observation is not clear. The reason for the absence of other significant cardiovascular changes in this model may result from several factors. It may be due to depression of the central nervous system by the anesthetic, which in turn may modulate the peripheral vascular actions of cocaine (44). The reduction in sympathetic discharge from generalized seizures could alter the cardiovascular response to cocaine. In addition, cardiovascular sensitivity in the rat may not correlate well with physiological changes observed in humans.

The lack of cocaine-induced arrhythmias or significant cardiovascular abnormalities in this study stands in contrast to clinical literature on cocaine toxicity. This discrepancy might be explained by several possibilities: (1) human cocaine victims are often chronically using cocaine which could lead to anatomical alterations (e.g., cardiomyopathy) and make them more suscep-

TABLE 3

THE ELECTROENCEPHALOGRAPHIC CHANGES IN THE (A) NORMOTHERMIC (N = 15) AND THE (B) HYPOTHERMIC SPONTANEOUSLY BREATHING GROUPS (N = 22)

	(A)		(B)	
	% SWC	% SB	% SWC	% SB
Postcocaine (min)				
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	4.5	0
5	13.3*	0*	4.5	0
6	14.3*	0*	4.5	0
7	14.3†	0†	4.5	0
8	46.2†	0†	18.2	0
Before RA (min)				
−8	23.1†	0†	22.7	0
−7	42.9†	0†	31.8	4.5
−6	50.0*	0*	36.4	4.5
−5	46.7*	0*	59.1	4.5
−4	53.3	0	77.3	4.5
−3	73.3	0	72.7	4.5
−2	86.7	0	81.8	4.5
−1	60	0	50	0
0 (RA)	13.3	0	9.1	0

RA: respiratory arrest.

*n = 14; †n = 13.

% SWC: percentage of rats showing spike-wave complexes.

% SB: percentage of rats showing spike bursts.

TABLE 4

THE ELECTROENCEPHALOGRAPHIC CHANGES IN THE NORMOTHERMIC MECHANICALLY VENTILATED GROUP (N = 10)

	% SWC	% SB
Precocaine (min)	0	0
Postcocaine (min)		
5	10	0
10	40	10
15	60	40
20	70	40
25	80	60
30	80	50
40	90	20
50	90	10
60	90	10
90	20	0
120	20	0

MV: mechanical ventilation.
% SWC: percentage of rats showing spike-wave complexes.
% SB: percentage of rats showing spike bursts.

tible to cocaine-induced cardiovascular toxicity; (2) humans may have concomitant diseases (e.g., atherosclerosis of coronary arteries); (3) humans may have other drugs on board increasing cardiovascular toxicity (e.g., alcohol, nicotine, and marijuana, etc.); (4) humans may use routes of administrations and doses that increase cardiovascular toxicity; and (5) rats as a species may be resistant to cocaine-induced cardiovascular toxicity.

It would appear that acute cocaine toxicity in rats is a dose-dependent toxicity phenemenon, with lower doses inducing generalized seizures, moderate doses adding respiratory depression, and even higher doses possibly adding fatal arrhthymias or other fatal cardiac disturbances. Higher doses of cocaine administered to ventilated animals may be required to elicit cardiovascular abnormalities, such as intraventricular conduction defects, myocardial ischemia or infarction, and ventricular tachycardia or fibrillation, in this species.

CONCLUSION

The current study suggests that respiratory depression is an important cause of cocaine-induced death, and hypothermia does not protect against it in urethane-anesthetized rats at the cocaine dose tested. It is suggested that in acute cocaine poisoning the respiratory status be carefully evaluated, monitored, and supported.

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