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Respiratory Patterning Following Cerebral Ventricular Administration of Cocaine

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RICHARD, C. A., R. K. HARPER, V. L. SCHECHTMAN, H. NI AND R. M. HARPER. *Respiratory patterning following cerebral ventricular administration of cocaine.* PHARMACOL BIOCHEM BEHAV 45(4) 849–856, 1993.—Intravenous (IV) cocaine in the conscious cat causes extreme tachypnea and reduction in breath-to-breath variability. In this study, we examined respiratory patterning following administration of cocaine into the cerebral ventricles. Intraventricular cocaine elicited a tachypnea that was nearly identical to that for IV cocaine. At the high dose, peak respiratory rate increased by 380%. Breath-to-breath variability was dramatically reduced by cocaine, especially in the early stages of the intoxication; during these stages, the tachypnea was occasionally interrupted by prolonged inspiratory efforts.

Procaine was administered as a control for the anesthetic effects of cocaine and caused an initial tachypnea that was similar to that for cocaine. For both cocaine and procaine, the mean ratios of inspiratory to expiratory durations were unaffected, indicating that the tachypnea was accomplished by approximately equal reductions in inspiratory and expiratory durations.

We conclude that the tachypnea following cocaine administration results principally from central rather than peripheral mechanisms. In addition, the data suggest that anesthetic actions mediate the principal respiratory effects of cocaine.

Tachypnea Respiration Cats Procaine Anesthesia

COCAINE intoxication in humans is accompanied by substantial cardiovascular changes that are consistent with the sympathoexcitatory actions of cocaine. These autonomic changes have been experimentally examined by several investigators in various animal models as well as in humans (8,18,25,36). Cocaine also exerts a profound influence on the respiratory control system in humans and animals. This respiratory effect is usually manifested as a rapid, shallow breathing pattern that is occasionally followed by respiratory depression (1,2,10,25). Several respiratory malfunctions and pathologies have been associated with cocaine intoxication, such as pulmonary edema and acidosis. Cocaine-related deaths in humans and animals may result, at least partially, as a consequence of these respiratory effects (15,23,30). Few studies, however, addressed the mechanisms by which cocaine affects respiratory control.

Previously, we observed a pronounced, long-lasting tachypnea after intravenous (IV) administration of cocaine in cats (13,27). The tachypnea began with a short latency (approximately 1 min) and contained occasional inspiratory efforts that were much longer in duration than adjacent breaths. These isolated "deep" inspirations were usually confined to the early portion of the cocaine intoxicated state. Excluding these occasional prolonged breaths, variability was markedly reduced in the early postcocaine periods, a phenomenon that intensified over the first 1–2 h. The rate and variability results indicate that cocaine induces a powerful drive to respiratory phase-switching mechanisms that are occasionally interrupted by factors that act to prolong inspiration for a single cycle.

Although we measured changes in respiratory patterning in response to IV cocaine, the mechanisms by which cocaine exerts the tachypneic and variability effects remain unclear. To address this question, it is necessary to partition the effects of cocaine into central and peripheral effects. Cocaine induces marked vasoconstriction (25,26,28) and affects diaphragmatic and skeletal muscle activity (24). The changes associated with these peripheral phenomena may account for all or part of the respiratory effects observed. Indirect respiratory effects are also possible via peripheral actions on the myocardium (4,17,25) or phrenic nerve traffic (24). Therefore, we administered three dose levels of cocaine directly into the cerebral

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ventricles in conscious, freely behaving cats to distinguish the central and peripheral actions of this agent.

METHOD

These studies were carried out on five adult cats weighing between 2.7 and 5.0 kg. Each cat was anesthetized for surgery with an IV injection of sodium pentobarbital (25 mg/kg), supplemented as necessary. Two pairs of insulated, stainless steel wires (Cooner Wire, Chatsworth, CA) were placed into the lateral costal diaphragm using an abdominal approach. These wires were used to record diaphragmatic electromyographic (DEMG) activity, and similar wires placed in the nuchal musculature were used to assess postural motor tone. Recordings of cortical electrical activity [electroencephalogram (EEG)] were made from two stainless steel screws implanted in the skull, and the electrocardiographic (ECG) activity was monitored by recording the signal between a diaphragmatic and a nuchal EMG lead. A stainless steel guide tube (23 ga; 0.64 mm) was stereotaxically placed in either the left or right lateral ventricle, cemented in place with dental acrylic, and sealed with a stylus. In two animals, cannulae were placed in a carotid artery and led to the head cap. The cannulae were flushed daily with heparinized saline to maintain patency and were used to collect arterial blood samples of 0.3 cc for blood gas analysis. All electrode leads were soldered into a 20-pin connector and cemented in place on the head.

During 2 weeks of recovery, animals were habituated to a 1-m^3 recording chamber. This chamber was fitted with a commutator and was designed to allow recording from unanesthetized, unrestrained animals. Electrode signals were passed to a Grass 78 polygraph and signals were bandpass filtered (EMG 10 Hz–1 kHz) and simultaneously written on polygraph paper and stored on analog tape. Signals were also digitized at or above rates dictated by the Nyquist frequency (12) and stored on optical computer disks. Baseline recordings were carried out for at least 30 min prior to any cocaine or control drug administration. After the baseline recording, one of three doses of cocaine HCl in artificial cerebrospinal fluid (CSF) was injected into the cerebral ventricle through a 27-ga injection cannula inserted into the guide tube. Each administration was delivered over approximately 15 s (range 13–17 s). Doses of cocaine were 0.625, 1.25, and 2.50 mg dissolved in artificial CSF in volumes of 0.025, 0.05, and 0.10 cc, respectively. Arterial blood samples were collected at two points during baseline, at 13, 33, and 63 min after drug administration, and at the end of the recording. Control administrations consisted of identical doses of procaine dissolved in artificial CSF (in three cats) and CSF alone (in two cats). Recordings were carried out for 2.5 h after cocaine or control administration. All surgical procedures and data collection were performed in strict accordance with NIH Guidelines as described in *Guide for the Care and Use of Laboratory Animals*.

DEMG was studied in two forms: a) The "raw" digitized signal was used to index DEMG amplitude during a respiratory cycle; and b) the raw DEMG signal was rectified and smoothed with a moving average digital filter to allow software determination of inspiratory and expiratory onset for timing analysis. To index the DEMG amplitude, the mean amplitude of the signal was computed for each of 90 consecutive inspiratory efforts and averaged. Because significant differences in electrode position and coupling to the muscle occur between animals (which alter measured EMG activity), between-subject comparisons were not made with the individually averaged amplitudes; instead, amplitude comparisons between animals were made as a percent change from baseline measurements. From the peak trough detection applied to the rectified and smoothed signal, several measures of respiratory timing were derived for each breath: inspiratory duration (T_I), expiratory duration (T_E), total cycle time (T_{Tot}), duty cycle (T_I/T_{Tot}), and the ratio of inspiratory to expiratory times (T_I/T_E). Epochs of data were chosen for analysis from the baseline period and at 10, 30, 60, and 150 min after cocaine administration. These epochs were at least 90 s in length and commonly 180 s in duration. In addition to the summary statistics on the above-mentioned variables, dynamic aspects were examined. Breath-to-breath intervals within an epoch were plotted against the breath (interval) number to illustrate any pattern of short-term change in timing characteristics and identify discrete, isolated changes in respiratory activity that would be masked by summary statistics.

Summary statistical analyses were accomplished with two-way analysis of variance (ANOVA) (dose × time) using time as the repeated measure utilizing the BMDP2V package (6), followed with analysis of simple effects. Means and SEs were based upon one trial from each cat receiving that dose; therefore, SE represents between animal variance. Significance was assigned when $p < 0.05$.

RESULTS

Intraventricular cocaine induced a significant tachypnea at all dose levels with a minimal latency of 45 s. This tachypnea persisted for over 2 h, but respiratory rates slowed and approached (but were still significantly above) baseline values at 2.5 h after administration (Fig. 1 and Table 1). T_{Tot} values were significantly shorter than baseline values at all time points, and no significant differences emerged between dose levels. The shortening of T_{Tot} was accomplished by equal reductions in T_I and T_E because cocaine (at any dose) did not significantly alter T_I/T_E or T_I/T_{Tot} ratios at any time point. The magnitude of the tachypnea was pronounced, averaging

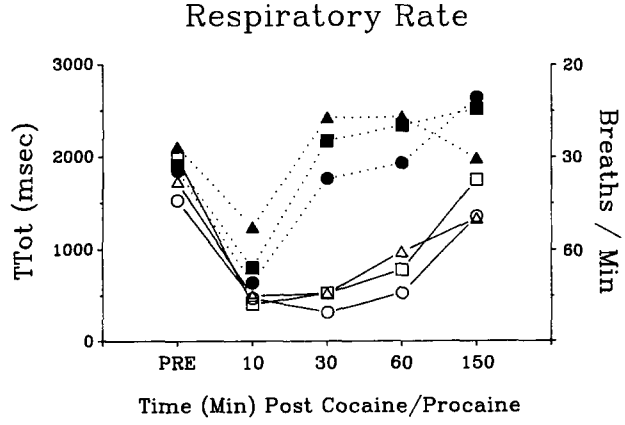

FIG. 1. Mean T_{Tot} values for all doses of cocaine and procaine. T_{Tot} was significantly different from baseline (PRE) at all time points for all doses of cocaine, but only at 10 min for all doses of procaine. (○), high-dose cocaine; (□), medium-dose cocaine; (△), low-dose cocaine; (●), high-dose procaine; (■), medium-dose procaine; (▲), low-dose procaine. For both drugs, high dose = 2.50 mg, medium dose = 1.25 mg, and low dose = 0.625 mg.

TABLE 1

TOTAL RESPIRATORY CYCLE TIME (T_{tot}) (MEANS ± SEM IN ms)

Dose	PRE	10 Min	% Pre	30 Min	% Pre	60 Min	% Pre	150 Min	% Pre
Cocaine									
High	1,527.7	471.2	−61.1	387.6	−67.9	529.7	−63.6	1,357.4	−7.4
	309.7	94.9	12.3	63.0	9.4	134.9	5.7	238.6	9.7
Medium	1,985.4	408.2	−76.2	527.5	−72.7	781.0	−61.5	1,752.4	−10.2
	227.9	58.9	7.2	112.1	5.1	193.3	7.9	197.7	6.8
Low	1,732.4	496.5	−69.3	526.0	−70.1	974.7	−45.2	1,334.9	−23.5
	136.0	102.9	7.8	142.2	6.9	232.5	10.2	317.8	17.3
Procaine									
High	1,850.4	641.4	−62.0	1,764.2	−3.1	1,932.7	4.1	2,646.3	44.3
	217.7	188.2	13.0	256.1	14.8	421.9	21.4	295.5	12.0
Medium	1,908.8	803.2	−57.4	2,172.6	14.2	2,342.9	23.0	2,524.3	32.2
	27.7	235.8	12.9	211.4	12.4	202.1	11.5	150.2	7.5
Low	2,107.4	1,240.4	−44.3	2,425.7	21.6	2,432.9	26.1	1,985.0	−0.8
	451.1	426.5	11.0	301.2	12.1	144.3	16.8	275.3	11.2
CSF									
	1,579.1	1,834.7	16.2	2,112.1	33.3	2,357.5	48.4	2,157.7	35.8
	40.6	45.1	0.1	191.1	8.7	327.7	16.9	317.5	16.6

3.15 breaths/s at 30 min postadministration of the high dose, compared to only 0.65 breaths/s prior to administration.

DEMG amplitude was also significantly affected by cocaine in that the amplitude increased dramatically for the high and low dosages and moderately for the medium dose. Across all doses, DEMG amplitude was significantly different from baseline at 10, 30, and 60 min but not at 150 min. Amplitude changes for the high cocaine dose were variable, with the 10- and 60-min values approaching 200% over baseline, while the 30-min value was 50% over baseline and 2.5 h was 13% below baseline (Fig. 2). The reduction in respiratory cycle time and the increase in DEMG amplitude resulted in little change in blood gas levels at any of the time points. Procaine administration produced changes in DEMG amplitude that were extremely variable. One cat exhibited consistent increases in DEMG amplitude, one cat exhibited consistent decreases, and the third demonstrated increases at the high dose and decreases at the other doses. Therefore, the group mean percent change in this variable was not statistically different for any dose of procaine.

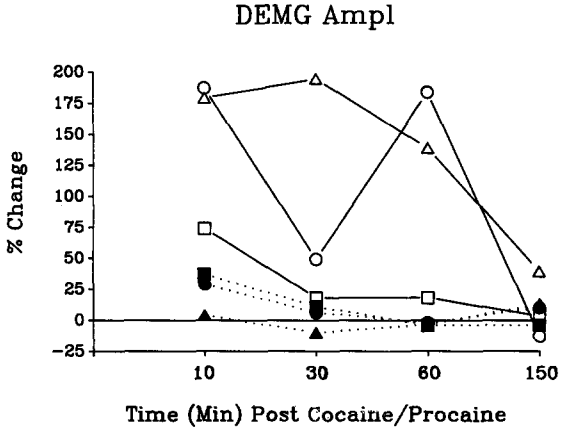

FIG. 2. Mean percent change of diaphragmatic electromyographic (DEMG) amplitude (Ampl) from baseline. Significant differences were found at 10, 30, and 60 min for all doses of cocaine, but procaine administration did not produce significant changes. Symbols as in Fig. 1.

The pronounced tachypnea was accompanied by a reduction in breath-to-breath variability that was evident at 10, 30, and 60 min postadministration for the high dose (four of five trials) and at 10 and 30 min for both the medium dose (four of four trials) and the low dose (four of five trials; see Fig. 3). During the 10- and/or 30-min epochs, the reduction in variability was interrupted by occasional, single, prolonged inspirations, identical to those observed after IV cocaine administration (see Fig. 3, 10-min panel).

The breath-to-breath variability in the T_I/T_E and T_I/T_{Tot} ratios, as assessed from plots identical to those in Fig. 3, was unchanged by cocaine at any time point except for two cases of a reduction in variability (both at the high dose). However, a significant effect on the overall relationship between T_I and T_E emerged from regression analysis. In 13 of 14 trials, there was a significant positive correlation ($p < 0.05$) between T_I and T_E, consistent with normal respiratory function, either in the precocaine epochs (8 of 14) or in the 150-min epochs [12 of 14; at 150 min, variability in T_I/T_E ratios had returned to baseline levels (data not shown)]. However, in 9 of the 14 trials, cocaine administration resulted in inversion of the correlation to a significant negative correlation ($p < 0.05$) at 10 or 30 min (or both) after injection (Fig. 4 and Table 2). In only 4 of 14 trials was a significant positive correlation in the precocaine or 150-min epochs not accompanied by a significant negative correlation in the early epochs (10 and/or 30 min). In addition, significant negative correlations were never observed outside of the early epochs.

Intraventricular cocaine administration produced a stereotypical behavioral reaction, including pupillary dilation, ex-

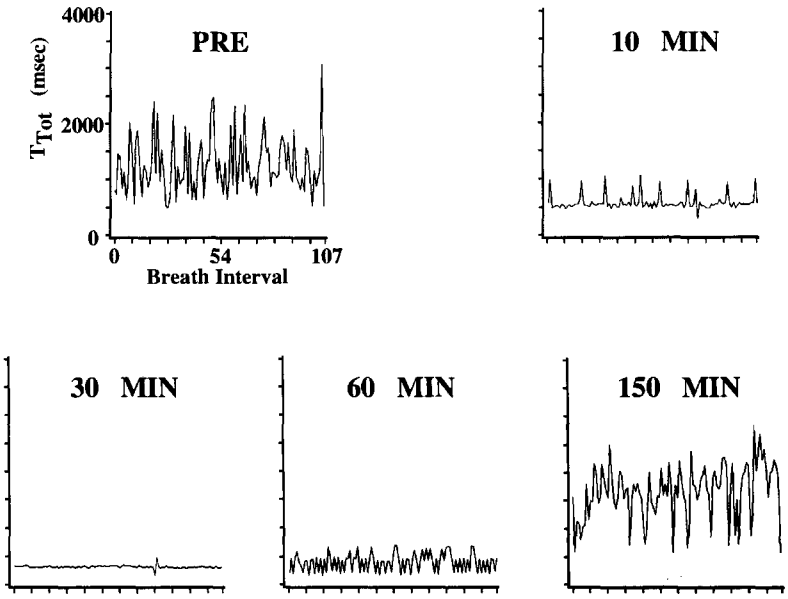

FIG. 3. Breath-to-breath interval plots of T_{Tot} from a single cat showing the reduction in breath-to-breath variability resulting from cocaine (high dose). Note the isolated occurrences of peaks in the 10-min plot, indicating long respiratory cycles; these peaks resulted from single, prolonged inspiratory efforts, characteristic of the early phases of cocaine intoxication.

cessive salivation, EEG activation, and occasional emesis, micturition, or defecation. The animals exhibited little locomotor or any other phasic motor behavior; instead, they lay in a prone position (usually with forelegs extended) and remained relatively unresponsive to environmental stimuli. These behavioral effects occurred with a minimal latency of 20 s. There was no evidence of seizure activity in either the EEG or EMG records.

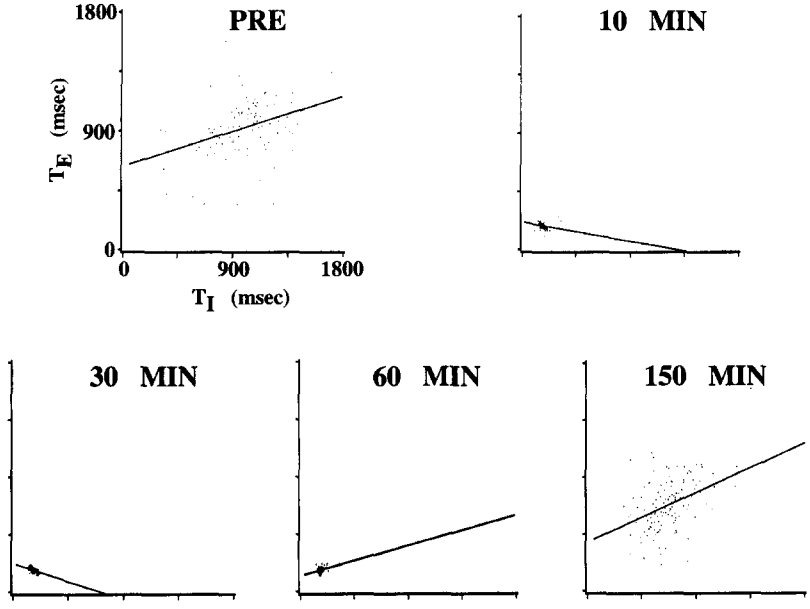

FIG. 4. Regression analysis of T_I vs. T_E from a single cat showing the inversion of the positive relationship between T_I and T_E during the early epochs of a high-dose cocaine administration and the subsequent return to baseline. Regression equations are as follows: PRE, $y = 0.287x + 562.1$; 10 min, $y = -0.163x + 191.5$; 30 min, $y = -0.312x + 198.5$; 60 min, $y = 0.260x + 105.7$; 150 min, $y = 0.423x - 406.5$.

TABLE 2

T_I/T_E REGRESSION ANALYSIS

Cat		PRE	10 Min	30 Min	60 Min	150 Min
High-dose cocaine						
10991	*r*	0.46*	0.06	–	0.03	0.37*
	n	179	201	–	353	199
10751	*r*	0.14	−0.02	0.13	0.21	0.08
	n	162	244	187	231	121
6	*r*	0.26*	0.50*	−0.56*	0.41*	0.48*
	n	139	220	197	195	108
451	*r*	−0.20	0.48*	−0.25*	0.42*	0.79*
	n	65	276	226	160	80
482	*r*	0.35*	−0.22*	−0.33*	0.27*	0.40*
	n	97	195	321	262	135
Medium-dose cocaine						
113	*r*	−0.03	−0.17*	0.14*	0.31*	0.19*
	n	96	820	855	453	134
6	*r*	0.19*	0.32*	0.14*	0.14*	0.25*
	n	140	296	546	581	142
451	*r*	0.44*	−0.14*	0.28*	0.53*	0.66*
	n	80	230	165	138	76
482	*r*	0.14	0.03	0.35*	0.23*	0.29*
	n	119	461	219	179	145
Low-dose cocaine						
10991	*r*	0.02	−0.19*	0.44*	0.12	0.16*
	n	109	165	113	128	141
10751	*r*	0.56*	0.35*	0.03	0.03	0.04
	n	122	96	260	190	202
113	*r*	0.10	0.04	−0.38*	0.24*	0.37*
	n	89	247	267	195	109
451	*r*	0.18*	−0.24*	0.35*	0.68*	0.39*
	n	80	275	171	92	75
482	*r*	0.32*	−0.04	−0.30*	0.38*	0.43*
	n	120	249	248	127	92

r, Pearson's correlation coefficient; *n*, number of respiratory cycles.
*Significant correlation coeffienct ($p < 0.05$).

After procaine administration, cats assumed a posture similar to that exhibited after cocaine administration; that is, they remained quietly prone for long periods. Procaine administration also produced a significant shortening of T_{Tot} values at all dose levels (see Fig. 1). The tachypnea following high-dose procaine administration was identical to that for high-dose cocaine, but did not persist for several hours, as in the case for cocaine; the percent changes in T_{Tot}, T_I, and T_E were similar to those for cocaine only at 10 min. By 30 min after procaine administration, T_{Tot}, T_I, and T_E values under the procaine conditions rebounded to levels significantly above baseline ($p < 0.05$); that is, breathing slowed beyond baseline rates during recovery.

Procaine also produced changes in breath-to-breath variability that were similar to those observed with cocaine. Thus, variability was markedly reduced at 10 min in seven of the nine procaine trials, as indicated in Fig. 5. While procaine reduced the variability in T_{Tot} at 10 min, the single, isolated, prolonged inspirations that occurred after cocaine administration rarely appeared. When inspiratory prolongations did occur, they usually occurred in groups of two or more "deep" inspiratory efforts. In addition, these inspiratory prolongations were accompanied by roughly equal prolongations in T_E that resulted in no significant change in the slope of the T_I/T_E regression lines (see the Discussion section). Procaine administration also did not significantly affect mean T_I/T_E or T_I/T_{Tot} ratios.

Administration of artificial CSF in volumes identical to those used for the high dose of cocaine had no significant effect on any variable.

DISCUSSION

The purpose of this study was to partition the respiratory effects of cocaine into peripheral and central actions and partition the contributions from local anesthetic action. Intraventricular cocaine administration produced results that paralleled those for IV cocaine in almost every respect (27); specifically, dramatic and significant reductions in mean values for T_{Tot}, T_I, T_E, and breath-to-breath variability occurred, all of which were similar to those that occurred following IV cocaine administration. As with IV cocaine, the reduction in T_{Tot} resulted from equal reductions in T_I and T_E. The mean ratio of T_I to T_E was not altered by either route of administration, and the breath-to-breath variability of ratios were also unaffected. The only difference in respiratory patterning be-

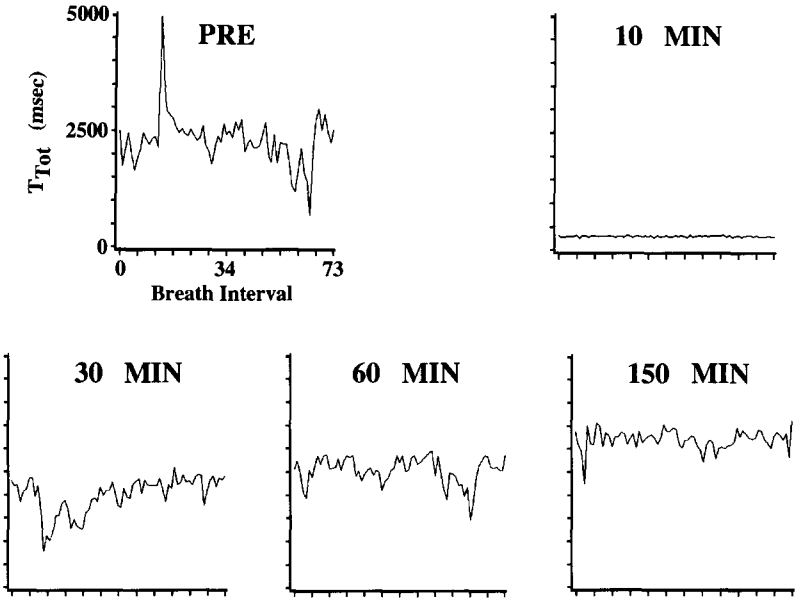

FIG. 5. Breath-to-breath interval plots of T_{Tot} in a single cat under procaine (high dose). At 10 min, the plot indicates the tachypnea but lacks the inspiratory (and T_{Tot}) prolongations resulting from cocaine (see Fig. 3).

tween the two administration routes appeared in the time course of the response. Respiratory changes resulting from IV cocaine continued to intensify for 1–2 h and showed little recovery as much as 3 h after administration; intraventricular cocaine administration, however, produced peak respiratory changes within 10–30 min and by 150 min had almost returned to baseline. Injections of CSF alone were used to control for the effect of the volume of the injection and caused no significant change in any variable. Therefore, we conclude that the largest component of the respiratory effects of cocaine results from central actions.

While cocaine did not affect the mean T_I/T_E ratios nor the breath-to-breath variability in T_I/T_E, the relationship between T_I and T_E was modified, as revealed by regression analysis. In the baseline and late intoxication epochs (60, 150 min), T_E increased with increasing T_I, as expected (14); however, in the early intoxication epochs this relationship altered. During those early epochs, isolated, relatively slow inspiratory efforts (> 2 SD above the mean) commonly occurred, interspersed within the otherwise extremely constant T_{Tot} profile (see Fig. 3). These long inspiratory efforts were accompanied by three types of paradoxical changes in T_E, which accounted for the weakening of the strong positive correlation between T_I and T_E and the correlation's ultimate reversal: a) T_E increased slightly [much less than would be expected based on the usual relationship between T_I and T_E (14)]; b) T_E did not change, as compared to immediately preceding T_E values; or c) T_E actually decreased substantially—in many cases, the T_E following a prolonged inspiratory effort was more than 1 SD *faster* than the mean. In most cases, each of the three T_E responses could be found in a single epoch exhibiting the reversal of slope.

One possible explanation for the prolonged inspiratory efforts is that those isolated events are reflex responses to atelectasis, possibly due to neurogenic pulmonary edema (2). At this time, we can offer no explanation for the observation of paradoxical T_E changes accompanying deep inspirations; we are unaware of any previous reports of this phenomenon. However, if the inspiratory prolongations are reflex responses to atelectasis and the "deeper" inspirations facilitate expiratory airflow, then it is possible that this paradoxical decrease in T_E is related to the Breuer–Hering deflation reflex (9,16). Because this phenomenon did not occur after procaine administration, the paradoxical T_E values accompanying the prolonged T_I values may result from either the sympathomimetic or CNS stimulant properties of cocaine.

While cats appeared to exhibit rapid, "shallow" breathing, analysis of the DEMG amplitude data showed large increases in many cases and some degree of increase in 13 of 14 cases. Therefore, the shallow breath pattern could result from mechanical limitations on effective ventilation. We speculate that, during cocaine intoxication, accessory respiratory muscle participation in ventilation is reduced and DEMG activity reflexively increased to compensate for this loss. Cocaine is known to provide powerful tonic activation of skeletal muscles, especially extensor groups (10,13). Thus, it is likely that cocaine tonically activates intercostal, abdominal, and pectoral musculature; these tonic activations may then interfere with phasic ventilatory activity in affected accessory respiratory musculature.

The high doses of procaine and cocaine produced virtually identical percent changes in T_{Tot}, T_I, and T_E at the 10-min epoch. The medium and low doses of procaine also produced significant shortening of the respiratory cycle, but those changes were smaller in magnitude than were those elicited by identical doses of cocaine. The most dramatic difference in the timing effects of the two drugs was the rapid recovery and rebound (< 30 min) that followed the procaine-induced tachypnea. Although procaine appears to produce a somewhat less potent and certainly shorter-lasting effect on breath frequency, it seems likely that the tachypnea resulting from cocaine administration is related to anesthetic effects.

In the high-dose procaine group, two of the three cats ex-

hibited an increase in DEMG amplitude at some point, but only one cat continued to show consistent increases at the other doses. Because our data show that both cocaine and procaine can increase DEMG activity, whatever mechanism underlies the increase in DEMG amplitude might also be related to the anesthetic effects of these agents but without more consistent data this remains speculative. At least in the cat, the powerful alterations in breath frequency and DEMG amplitude are not independent of homeostatic control mechanisms. We speculate that cocaine (and procaine) directly affect respiratory phase-switching and accessory respiratory muscles and that DEMG amplitude increases to maintain blood gas values.

In this study, the baseline T_{Tot} values reported for individual animals showed considerable variability; both the means and the high variability were consistent with previous reports from this laboratory (21) and others (14). Jennings and Szlyk (14) observed that baseline breath frequencies are widely distributed both between and within cats. Further, they found that the T_I/T_E ratio varies with breath frequency in that T_E usually exceeds T_I (ratio < 1.0) at frequencies less than about 30 breaths/min and that T_I exceeds T_E at higher frequencies. In general, our data are consistent with these results because in the few instances that baseline T_I/T_E ratios were less than 1.0 (4 of 22 trials) those ratios were associated with breath frequencies of 24–30 breaths/min (data not shown). However, our data included many instances of breath frequencies at, or slower than, 25 breaths/min that were accompanied by T_I/T_E ratios > 1.0. Szlyk and Jennings (32) also reported that hypercapnic drive to respiration results in little change in mean T_I/T_{Tot} ratios. They found that hypercapnia-induced tachypnea results from approximately equal reductions in T_I and T_E when frequency is high [>30 breaths/min; see Fig. 6 of (32)]. Therefore, cocaine intoxication produces a respiratory drive with timing effects similar to at least one other type of tachypnea.

In addition to the anesthetic and sympathomimetic effects, cocaine induces general CNS stimulant effects (28) that might underlie the respiratory excitation observed in our studies. Lesse and Collins (19) found that IV cocaine increases the excitability of particular limbic structures, the amygdala and hippocampus, without affecting other limbic areas, such as the septum. This specific increase in excitability could account for the tachypnea because stimulation of the central nucleus of the amygdala can pace respiratory rhythm (11). In addition, stimulation of various amygdaloid regions can elicit tachypnea (22,33). However, procaine is not usually regarded as having significant CNS stimulant effects similar to cocaine (28), and this agent produced tachypnea similar to that seen following cocaine administration.

Obviously, respiratory phase-switching mechanisms are receiving powerful activation during cocaine intoxication. A region exists in the parabrachial pons that contains important components of respiratory phase-switching mechanisms (3,5, 7). Respiratory reflexes that result in high respiratory rates, including hypercapnic hyperpnea (29,34,35), are probably mediated by the parabrachial pons. St. John and Wang (29), for example, found that parabrachial pontine lesions elevate $PACO_2$ levels and that these lesions significantly reduce the frequency response to hypercapnia without consistently altering the tidal volume responses. Respiratory changes accompanying sleep may also be partially mediated by parabrachial pontine mechanisms (20,31). Therefore, we hypothesize that cocaine enhances respiratory rate via activation of rostral brain and pontine networks. Because it is unlikely that cocaine diffuses from the cerebral aqueduct to parabrachial pontine cells, cocaine probably acts on some structure bordering the ventricles that provides tonic input to the pons. The respiratory effects of procaine indicate that the primary effect of these agents is inhibitory, that is, anesthetization. Thus, the simplest explanation of cocaine tachypneic effects is that an inhibitory input from a circumventricular area to the parabrachial pons has been inhibited.

The possibility exists that the tachypneic effects observed with intraventricular administration mimics those of IV administration because cocaine is absorbed from cerebrospinal fluid into the vascular system and then modifies peripheral mechanisms. That possibility is unlikely because IV-administered cocaine resulted in a tachypneic response with a latency of 1 min while the minimal latency for ventricular induced tachypnea was 45 s. These latency data are suggestive (but not definitive) that cocaine acts principally on central rather than peripheral mechanisms. Further supportive evidence comes from an allied study (Poe et al., submitted) that shows that a 1.5-mg/kg IV dose of cocaine elicited a substantially reduced respiratory response as compared to the 0.625-mg dose administered into a cerebral ventricle in this study. Because cocaine readily passes the blood–brain barrier, the tachypnea accompanying both IV and ventricular administration most likely results from central origins.

In summary, our data show that intraventricular administration of cocaine causes an extreme tachypnea, apparently of central origin. The tachypnea is occasionally interrupted by inspiratory prolongations in the early phases of the intoxication, and these extended inspiratory efforts may be of peripheral reflex origin. The high respiratory rate most likely results from anesthetic effects on central neuronal mechanisms, and these effects appear to have minimal effect on arterial blood gas homeostasis.

ACKNOWLEDGEMENTS

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