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Upper Airway and Diaphragmatic Muscle Activity Following Acute Cocaine Administration

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HARPER, R. M., R. R. TERREBERRY, C. A. RICHARD AND R. K. HARPER. *Upper airway and diaphragmatic muscle activity following acute cocaine administration.* PHARMACOL BIOCHEM BEHAV **39**(1) 137–142, 1991.—These studies examined activity of the diaphragm and a laryngeal dilator, the posterior cricoarytenoid, following 3 levels of intravenous and cerebral ventricular administration of cocaine. Both administration routes induced extremely high respiratory rates with enhanced tonic and phasic electromyographic activity, and affected patterning similarly in upper airway and diaphragmatic muscles. Both intravenous and intraventricular administration induced a rise in core and brain temperature related to the route of administration; however, the tachypnea was only loosely related to the hyperthermia. Intraventricular administration resulted in a more rapid onset of peak respiratory rates, and a faster decline than an intravenous route. Different dose levels elicited similar elevated respiratory rates, but higher intravenous doses also resulted in extensive hypertonicity with intermittent phasic movements. Tachypnea continued between these phasic efforts. The phasic events associated with high doses were accompanied by sustained inspiratory efforts; however, no evidence of obstructive apnea was found. These data suggest that cocaine can modify respiratory patterning by inducing a centrally mediated tachypnea and by eliciting sustained, intermittent inspiratory efforts.

Respiration Cocaine Temperature Upper airway Diaphragm Cats

BOTH rapid, shallow breathing (14,17) and apnea have been reported to result from cocaine administration, the latter being frequently observed following generalized convulsions after high-dose administration (2,10). Respiratory "failure" is a common description associated with fatal cocaine intoxication in the clinical population; however, the particular dysfunctions in respiratory "failure" are seldom discussed.

It is important to determine whether the purported disturbance of respiratory control mechanisms following cocaine administration results from diminished or altered influences on the diaphragmatic musculature, from obstruction of the upper airway, or from an alteration in upper airway muscle cyclic timing. Upper airway muscles are innervated by different cranial nerve motoneurons, receive different modulatory influences from rostral brain and other structures, and respond to chemical and somatic stimuli differently from the diaphragmatic musculature (1, 9, 13). An agent which has the potential to modify central and peripheral neurotransmission, such as cocaine, might exert a very different modulation of upper airway musculature from diaphragmatic muscles.

The direct effect of cocaine on respiration that leads to the description of "failure" could thus result from a number of potential mechanisms, the most likely being 1) extreme tachypnea with such small tidal volumes as to lead to ventilatory insufficiency, 2) upper airway obstruction, brought about by sustained diaphragmatic efforts with extreme negative pressure on an upper airway that has greatly suppressed muscle tone and is thus more compliant, or 3) apneusis or apnea associated with convulsions which lead to desaturation from lack of cyclic airflow.

The objective of these studies was to document the patterning of upper airway and diaphragmatic musculature following high-dose cocaine administration to distinguish between these potential mechanisms of respiratory disturbance. The impetus for this research derives from the potential for asphyxia following cocaine administration and the clinical evidence of respiratory disturbance following cocaine abuse.

METHOD

Seven adult cats were used for intravenous administration and 4 of these cats were used for intraventricular delivery. Cats of either sex weighing 3.0–4.5 kg were used. Under sodium pentobarbital anesthesia (initial dose = 25 mg/kg, intravenous), a pair of insulated, flexible, multistranded stainless-steel wires were placed unilaterally into the posterior cricoarytenoid (PCA) muscles of the larynx, a primary upper airway dilator muscle, and 4 sets of similar wires were placed into the lateral costal diaphragm to assess electromyographic (EMG) activity. To record limbic and cortical electrical activity, bipolar stainless-steel electrodes were

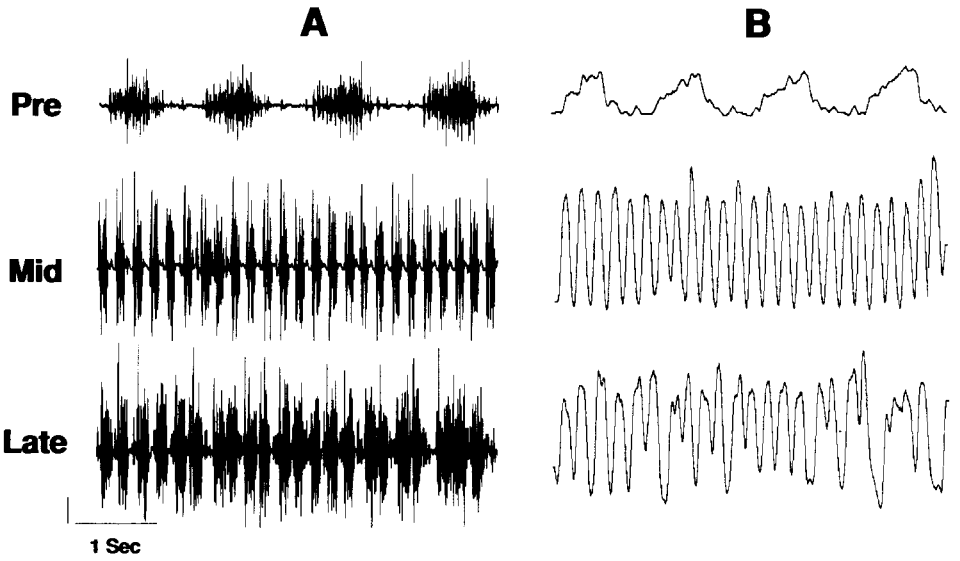

FIG. 1. Traces of raw diaphragmatic electromyographic activity (A) and rectified, digitally low-pass filtered forms of that activity (B) in precocaine waking baseline (Pre), 20 min post 10 mg/kg intravenous administration (Mid), and 150 min postcocaine administration (Late). Traces are plotted to the same absolute scale. Cocaine results in marked tachypnea (approximately 1/s Pre to 5/s Mid), and an increased amplitude of EMG bursts. Vertical cal = 50 μV.

stereotaxically placed bilaterally into the dorsal hippocampus and the central nucleus of the amygdala (16), and stainless-steel screws were placed into the bone overlying the sensorimotor cortex. A thermistor was placed over the parietal cortex, and another thermistor was placed in muscle between the scapulae to record brain and core body temperature, respectively. Stainless-steel cannulae, temporarily occluded at 1 end, were placed within the lateral cerebral ventricle. Electrocardiographic (ECG) activity was recorded from the same respiratory leads placed in the diaphragm; this activity was acquired to provide an indication of pulse rate. Electrodes were led subcutaneously to a 20-pin connector which was attached to the surface of the skull using stainless steel screws and dental acrylic.

After 2 weeks of surgical recovery, the animals were placed in a sound-attenuated 1 m^3 recording chamber kept at room temperature, (approximately 22°C). Electrodes were attached from the head connector to a Grass 78 polygraph, and signals were band pass filtered (cortical and hippocampal EEG, 1–30 Hz; ECG, 1–100 Hz; diaphragmatic and laryngeal EMG, 10 Hz–1 kHz; temperature, DC coupled) and simultaneously written on polygraph paper, digitized at appropriate rates as dictated by the Nyquist frequency (8), and stored on digital media as well as on analog tape. After a control recording of 1 sleep and waking cycle, the subjects were administered 1 of 3 doses of cocaine HCl in 25 mg/ml solution intravenously (5.0, 7.5, or 10.0 mg/kg or an equivalent volume of saline) over a time course of 10 s or, in the case of ventricular administration, 0.625, 1.25, or 2.5 mg or an equivalent volume of artificial cerebrospinal fluid (CSF) for control studies. Cocaine HCl in 25 mg/ml solution in artificial CSF was delivered into the indwelling ventricular cannulae via a Hamilton syringe over a time course of 10 s. Venous blood samples (0.4 cc) were drawn at 5 points in the test cycle in a subset of animals.

Analysis

All portions of the recording session, including predrug baseline, cocaine or placebo administration period, and 2 h of recording post administration were continuously digitized and were thus available for analysis. The EMG signals were rectified and then smoothed by a 31-point moving average digital filter using a correction for mathematically-induced phase shift. The onsets of inspiratory efforts of these traces were then determined, and intervals between onsets calculated as interbreath intervals (T_{tot}). Timed samples (minimum 3 min) were taken in the waking baseline period immediately prior to cocaine administration, and 10, 20, 90, and 120 min postcocaine administration for summary statistics. Analysis of variance procedures, using the BMDP series (4), were used to examine drug effects and drug-time interactions.

RESULTS

Rates

An immediate and sustained tachypnea resulted from either intravenously or intraventricularly administered cocaine (Fig. 1) at all doses; the respiratory rates occasionally reached levels 6 times higher than basal quiet waking rates. Respiratory rates after intravenous administration were significantly elevated over rates in the quiet, waking state at all of the time intervals measured, i.e., 10, 20, 60, 90 and 120 min postinjection ($p<0.0001$). There was no difference between the increased rates at any of the doses ($p=0.35$, ns), and no time effects over these intervals ($p=0.77$, ns), i.e., rates remained elevated over the entire 120 min postcocaine administration. Respiratory rates following ventricular administration were also significantly elevated ($p=0.006$). There were no significant differences between the effect of different drug doses on rate ($p=0.49$, ns), but a significant time effect ($p<0.001$), and no interaction between dose and time ($p=0.79$, ns). The time course of tachypnea was dependent on route of administration; with intravenous doses, the increases in rate peaked at 20 min ($p<0.0001$) and extended as long as 3 h, while intraventricular administration resulted in increased respiratory rates that peaked at 10 min ($p<0.0001$) and returned to baseline after 2 h

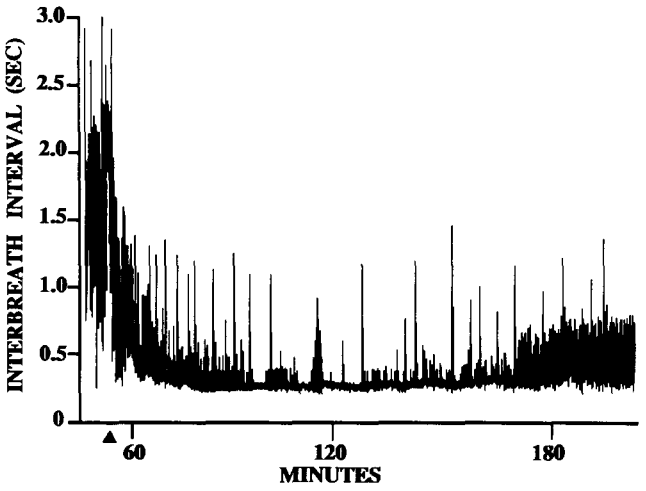

FIG. 2. Plot of successive breath to breath intervals (measured as inspiratory onset to inspiratory onset times), with interval time on the y axis, and successive intervals on the x axis prior to and following 10 mg/kg intravenous cocaine administration (triangle). Note that the x axis time tics will vary in length along that axis, since short, successive intervals will sum to shorter "times" than longer intervals. Thus shorter intervals indicate faster rates, and administration of cocaine at 20 min leads to extremely short intervals; these intervals gradually lengthen over the 60–120 min period. The tall "spikes" in the record are not artifacts, but exceptionally long (for the condition) interbreath intervals; in the cocaine period, these long breaths are typically long inspiratory efforts.

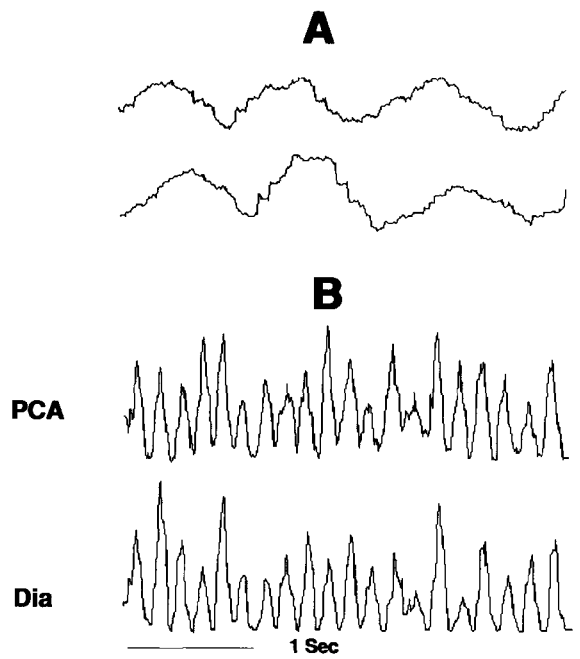

FIG. 3. Rectified and filtered laryngeal dilator (PCA) and diaphragmatic (Dia) traces during precocaine waking periods (A) and 48 min postcocaine (B). Both the upper airway and diaphragmatic phasic patterning increased in rate following cocaine administration. Laryngeal dilator activity phase-led diaphragmatic activity slightly in the baseline period; that phase lead disappeared in the postcocaine period.

($p=0.12$, ns). Similar response curves were exhibited across all intraventricular doses ($p=0.56$, ns). There were no significant differences between pre- and postvehicle-only respiratory rates when the state of alertness was controlled ($p=0.18$, ns).

Mean peak respiratory rates were comparable between routes of administration (5 mg/kg IV mean = 148.3 breaths/min ± 26.2; 7.5 mg/kg mean = 155.3 breaths/min ± 23.3; 10 mg/kg mean = 187.1 breaths/min ± 37.6) (no dose effect, $p=0.11$, ns); (0.625 mg intraventricular mean = 130.3 breaths/min ± 52.5; 1.25 mg mean = 154.3 breaths/min ± 49.4; 2.5 mg mean = 162.7 breaths/min ± 36.2) (no dose effect, $p=0.75$, ns). A plot of all breath to breath intervals pre and post 10 mg/kg IV cocaine administration, derived from diaphragmatic EMG activity in 1 cat, is shown in Fig. 2. The figure shows the marked decline in inspiratory intervals (i.e., faster rates) following cocaine administration; occasional long inspiratory intervals occur, but tachypnea immediately follows these long inspiratory efforts.

Upper Airway vs. Diaphragmatic Activity

The time between inspiratory onsets of the posterior cricoarytenoid and diaphragmatic muscles was diminished following cocaine administration (Fig. 3). The mean difference between diaphragm and PCA inspiratory onsets precocaine was 264.0 ms (± 101.5); approximately 1 h postcocaine, the mean onset difference had decreased to 17.3 ms (± 16.2). There were no significant overall differences between EMG burst rates measured from the PCA and from the diaphragm postcocaine injection (20-min values mean Dia = 164.6 breaths/min ± 51.3 breaths/min, mean PCA = 171.6 breaths/min ± 42.1 breaths/min, $p=0.82$, ns).

Activity During Phasic Motor Events

The highest intravenous and intraventricular doses of cocaine were accompanied by extreme extension of the limbs, including claw extension, together with extension of the head and neck. This extension was interrupted by phasic flexor movements, occuring typically at intervals of 3 s slowing to 30 s after 8–10 min postinjection, following an intravenous dose level of 7.5 mg/kg or higher. Pronounced and sustained diaphragmatic and PCA inspiratory efforts accompanied these phasic movements, but tachypnea immediately resumed following the phasic efforts, i.e., apneustic efforts were not maintained in the intervening periods (Fig. 4). Blood CO_2 values rose substantially, and O_2 values declined during these phasic efforts; CO_2 values then declined with tachypnea.

Although extreme hypertonicity accompanied the highest ventricular doses, the extensive phasic movements did not occur. However, isolated spike discharges were observed in hippocampal traces, and occasional apneustic efforts occurred following ventricular administration (Fig. 5). These efforts were immediately followed by tachypnea.

Relationship to Temperature

Both core and brain temperature increased following cocaine administration. The elevation following 5 mg/kg and 7.5 mg/kg intravenous doses ranged from 0.57 to 1.30°C, mean = 0.94°C; 10 mg/kg elevations ranged from 1.06 to 1.32°C, mean = 1.19°C. After intravenous administration, temperature rapidly increased (mean = 0.85°C increase in 30 min). A gradual increase then followed, with a maximum temperature reached within 1½–2 h postinjection; temperature then declined slowly, returning to baseline typically 2½ to 3 h following cocaine administration. A temperature curve following 2.5 mg intraventricular administration is shown in Fig. 6, with an overlapping respiratory rate curve. Both brain and core temperature increased following ventricular ad-

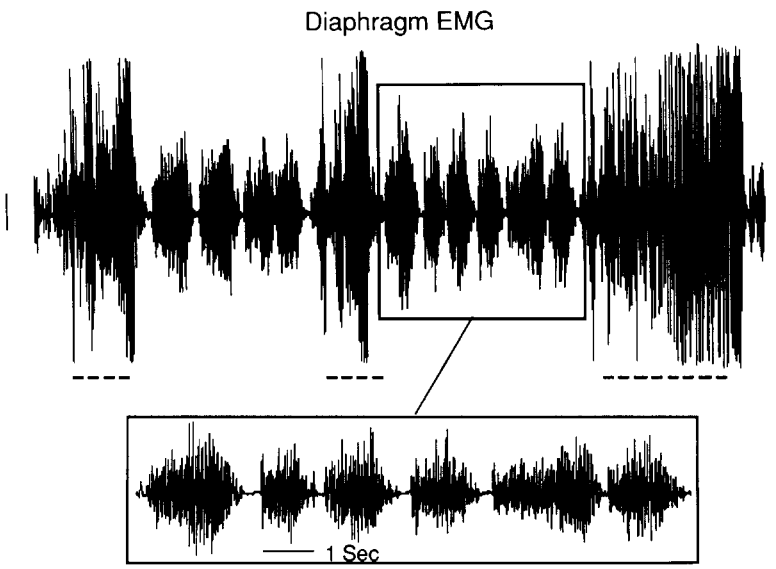

FIG. 4. Diaphragmatic EMG tracings following 10 mg/kg intravenous administration which resulted in extreme hypertonicity with phasic flexor movements (dashed lines) superimposed on tonic extensor rigidity. Phasic diaphragmatic patterning continued (inset) immediately following each flexion effort.

ministration, but the temperature rise was smaller than that found for intravenous administration (1.07°C intravenous vs. 0.81°C intraventricular). Intraventricular administration resulted in a sharp rise in temperature, reaching a maximum 8–15 min postinjection (range = 0.49 to 1.0°C, mean = 0.81°C), regardless of dose level. Temperature declined thereafter and returned to normal baseline within 30 min. Although temperature increased following cocaine administration, the temperature/respiratory relationships were only loosely correlated, as indicated in Fig. 6. Cocaine administration also elicited gasping, characterized by enhanced upper airway activity, e.g., enhanced genioglossal activity, as manifested by tongue protrusion.

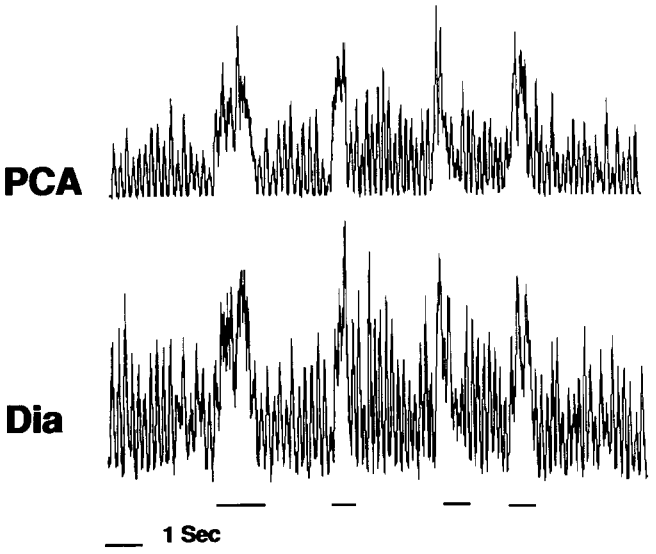

FIG. 5. Rectified and filtered laryngeal dilator (PCA) and diaphragmatic activity (Dia) activity 50 min following 2.5 mg cocaine delivered intraventricularly. Long inspiratory efforts (underscores) occur in a loose periodic sequence, interspersed with tachypnea. The tachypneic and larger inspiratory patterns are present in both the upper airway and diaphragmatic musculature.

Tonic Activity in PCA and Diaphragmatic Muscles

Both the PCA and the diaphragm exhibited an increase in extent of EMG activity with each breath, and an increase in tonic background activity, as shown in Figs. 1 and 3. This increase continued over the 2-h monitoring period postcocaine.

DISCUSSION

The most profound effect of cocaine on respiratory patterning was an extreme tachypnea which was largely independent of the

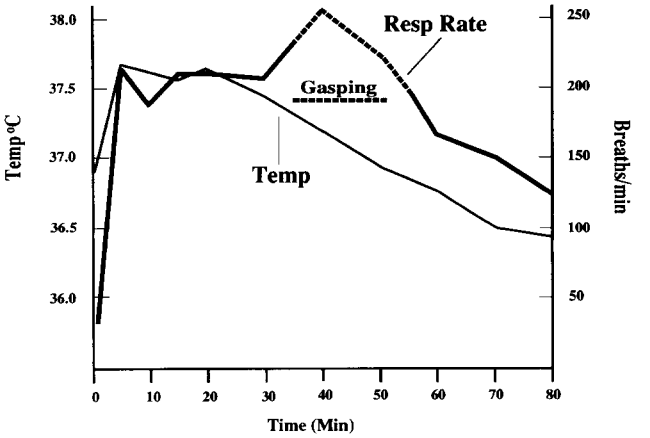

FIG. 6. Respiratory rates and brain temperature curves prior to and following 2.5 mg intraventricular cocaine administration. Note that, although brain temperature and respiratory rates rise in near coincidence, brain temperature decline more rapidly than respiratory rate.

route of administration. With the dose levels used, cocaine appeared to elicit maximal respiratory rates, since no differences in peak rates were found between either intravenous or intraventricular doses, or dose amounts. The increased rates occurred in both upper airway dilators and the diaphragm. No evidence of tonic suppression or passive relaxation of upper airway dilators was found following cocaine administration. On the contrary, excessive activation of upper airway musculature, e.g., genioglossal activation, as manifested by tongue protrusion, was frequently observed, especially in conjunction with gasping. Enhanced background EMG of PCA musculature following cocaine typically accompanied the rapid breathing. The similarity in effects from both intravenous and intracerebral administration suggest a primary cocaine action on respiratory patterning through central mechanisms.

The magnitude of upper airway muscle tone, the marked genioglossal efforts, and the absence of diaphragmatic activity indicative of inspiratory loading suggest that upper airway obstruction of the type that characterizes obstructive sleep apnea does not underlie respiratory disturbance following cocaine administration. Atonia of the upper airway, together with repetitive deep diaphragmatic efforts, are characteristic of obstructive sleep apnea (7). Extreme inspiratory efforts occurred following cocaine administration, especially in relation to convulsive movements, but these efforts were normally immediately followed by resumption of extremely rapid rates. Such rapid diaphragmatic cycling would be unlikely to provide sufficient negative pressure to maintain an upper airway collapse in an obstructive apnea scenario.

Both core and brain temperature increased following cocaine administration, and this temperature rise followed either intravenous or intraventricular administration. Tachypnea loosely paralleled the increase in core and brain temperature, but the temperature and respiratory curves were not coincident. The tachypnea persevered long after the decline in temperature, and momentary increases in an otherwise declining temperature curve, elicited by handling-induced movement, for example, resulted in a transient phasic rise in temperature, but little change in an already-high respiratory rate. Although intraventricular cocaine administration induced only modest core and brain temperature increases, excessive respiratory rates, comparable to those found for intravenous administration, accompanied cocaine delivery directly to the cerebrospinal fluid. These findings do not preclude a direct action of cocaine on hypothalamic structures mediating temperature-related respiratory patterning changes, but suggest that other neural structures primarily mediate the tachypnea. We speculate that a portion of the rise in respiratory rate may depend on the cocaine-induced temperature elevation, but that the respiratory timing changes partially result from direct cocaine effects on phasic timing mechanisms.

High-dose cocaine did induce gasping in some animals (4 of 8), occurring on occasion after the peak brain temperature rise, a finding confirmed in an associated set of studies. Such activation recruited both diaphragmatic and upper airway musculature, and primarily occurred following the higher intravenous cocaine doses; gasping was observed in 1 animal administered the 0.625 mg ventricular dose.

We found only hyperthermia following cocaine administration in these cats, with studies performed at room temperature (22°C). Lomax and Daniel (11) also found core temperature increases in the rat following cocaine administration, but ambient temperatures had to be raised to the thermoneutral zone for that preparation before a core temperature rise occurred; a lowering of core temperature was found in the rat if cocaine was administered with ambient temperatures at conventional room temperatures. Thermoneutral values for the cat (24–27°C) are lower than for the rat (29–30°C) (5); thus the mechanisms underlying temperature increases observed in the cat may be in accord with those described for the rat. A direct examination of the question of temperature changes following cocaine administration and the partitioning of temperature-induced respiratory effects should directly consider the role of ambient temperature; perhaps placing the cat in a cold environment following cocaine administration, or combining local hypothalamic cooling with cocaine delivery might address this issue.

A major cocaine effect exerted on both the laryngeal dilators and the diaphragm was an increase in EMG activity with each breath. The extent of the increase was pronounced, and can be observed in the traces of Figs. 1 and 3. A parallel increase occurred in tonic extensor activation of other skeletal musculature, including both fore- and hindlimbs and the longitudinal back muscles; at high cocaine doses, the animals adopted an exaggerated extensor position reminiscent of decerebrate rigidity (15), similar to that described in the lamb (18) and the cat (6). Cocaine thus appears to exert motor effects on skeletal musculature. However, much of the skeletal musculature, particularly the longitudinal back muscles and the abdominal muscles, exert prominent roles in ventilatory activity, especially in the expiratory phase of the respiratory cycle. The increased activation of laryngeal and diaphragmatic muscles suggests that a cocaine influence can be exerted on most, if not all, respiratory muscles. The activation of upper airway musculature did not proceed to "active obstruction." There was no indication of stridor or inspiratory loading; instead, tachypnea was characteristic.

Cocaine may directly or indirectly act on brain stem respiratory switching mechanisms (3). However, the role of peripheral influences on phase switching should not be excluded. For example, cocaine may activate thoracic wall afferents indirectly by increasing skeletal muscle tone. Similar increased activation of Group III and IV limb afferents might also enhance rates (12). The enhanced muscle activation likely generates excessive CO_2, thus promoting enhanced respiratory rates.

The purpose of this study was not to induce respiratory failure in these animals by lethal cocaine doses, but to examine influences of high levels of cocaine on respiratory musculature, and thus determine potential paths for respiratory distress. We found tachypnea and isolated apneusis, but not apnea. Of the possible mechanisms for respiratory distress, sustained convulsive activity from extremely high cocaine doses carries the potential to induce apnea. We did not examine activity at doses sufficient to elicit sustained convulsions which might elicit such apnea; our highest doses elicited convulsive-like phasic motor activity which was not sustained, and elicited only apneusis. The most deleterious blood gas values were found with this phasic activity. With the dose levels used in this study, rapid respiratory cycling continued between the prolonged inspiratory efforts associated with the phasic action, i.e., the periods between efforts were not apneic or apneustic; instead, respiratory efforts continued, although at excessive rates perhaps incompatible with adequate ventilation. If dose levels were extended, we speculate that convulsive effects would be prominent, and that apneustic efforts or apnea associated with the convulsions would further compromise ventilation.

These findings pose major questions about the action of cocaine on respiratory and thermoregulatory brain structures. The major respiratory influence of high dose cocaine in the cat appears to be not atonic upper airway-mediated obstructive apnea, but tachypnea, with extreme hypertonicity combined with phasic motor activity adding a potential for sustained inspiration. The increases in both laryngeal and diaphragmatic rates are so substantial that they compromise ventilation. A portion of that respiratory response may result indirectly from core or brain hyper-

thermic influences on respiratory patterning. A major effect, however, appears to result from a broad influence of cocaine on motor control, of which the respiratory musculature comprises a part. The mechanisms of action of cocaine on these neural structures controlling movement, and particularly on neural structures mediating respiratory phase switching should be the object of examination.

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