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Dynamic Properties of Respiratory Timing Following Cocaine Administration

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RICHARD, C. A., H. NI, R. K. HARPER AND R. M. HARPER. *Dynamic properties of respiratory timing following cocaine administration.* PHARMACOL BIOCHEM BEHAV **39**(4) 941–946, 1991.—We assessed the timing and amplitude characteristics of diaphragmatic muscle activity following administration of intravenous cocaine HCl (10 mg/kg) to awake, unrestrained cats. Cocaine produced a pronounced tachypnea which was interrupted by deep inspiratory efforts coincident with tonic-clonic movements over the first 10 min following cocaine administration. Following that period, diaphragmatic cycle rates slowly increased for up to 1 h and were interrupted occasionally by longer inspiratory efforts which were not associated with other overt motor activities. As respiratory rate increased, breath-to-breath variability decreased, and the incidence of deep inspiratory efforts decreased. As total cycle time decreased, the ratio of inspiratory time to expiratory time remained the same between precocaine and early, intermediate and late intoxication periods. The amplitude of diaphragmatic EMG activity increased with the extreme tachypnea. A number of neural mechanisms may mediate the changes in diaphragmatic muscle activity, including hyperthermia and alteration of rostral brain influences on brainstem timing mechanisms.

Cocaine Respiratory control Tachypnea Seizure Cat

RESPIRATORY patterning following acute cocaine administration typically develops into extreme tachypnea (2, 3, 12–14). This rapid breathing can be intermixed with occasional more sustained inspiratory efforts. The extreme nature of the primary tachypneic response, the near total loss of short-term variability, together with the intermittent but unpredictable occurrence of deep inspiratory efforts, suggest that cocaine exerts prominent excitatory influences on inspiratory/expiratory phase-switching mechanisms which are interrupted by influences which transiently prolong inspiration. Respiratory and pulmonary effects of cocaine intoxication that often accompany the tachypnea include pulmonary edema and severe acidosis (2, 20, 29). Chronic reductions in forced expiratory volume, maximum ventilation, closing volume and an acute and chronic reduction in diffusing capacity have been reported; however, contradictory results have also been reported (17,28). Some pulmonary pathologies have been hypothesized to result from cocaine-induced pulmonary vasospasm (29). Regardless of the particular sequelae, respiratory arrest (usually associated with generalized seizures) has been implicated as a common cause of death in cocaine poisoning in both humans and animals (2, 20, 22, 26, 30).

Determining the nature of the influence on inspiratory and expiratory phase-switching mechanisms is an essential step in the description of cocaine effects on respiratory patterning. The effects that cocaine exerts on both diaphragmatic and upper airway musculature may be partially mediated by both hyperthermia and excessive extensor activity (12,13). Partitioning the relative effects of each of these influences requires an adequate summarized description of the characteristics of the total respiratory cycle and the inspiratory and expiratory phases, as well as an assessment of the instantaneous, i.e., cycle-to-cycle or phase-to-phase, change in timing. The latter assessment is required to demonstrate the nature of the sustained inspiratory efforts which occur periodically during the tachypnea which follows cocaine administration, and to determine the trends in respiratory control during the development and progression of intoxication. For these reasons, we assessed both summary and moment-to-moment characteristics in respiratory patterning prior to and following high-dose intravenous (IV) cocaine administration in unrestrained cats which were free of other pharmacologic agents.

METHOD

These studies were carried out on three female and three male adult cats 2.8 to 4.0 kg in weight. Under sodium pentobarbital anesthesia, four sets of insulated, multistranded, stainless steel wires (Cooner Wire, Chatsworth, CA) were placed into the lateral costal diaphragm to assess electromyographic (EMG) activity. Electocardiographic (ECG) activity was recorded from the same respiratory leads placed in the diaphragm; this activity was used 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 with stainless steel screws and dental acrylic.

After 2 weeks of surgical recovery, the animals were habituated to a sound-attenuated 1 m^3 recording chamber kept at room temperature (approximately 22°C). This chamber was designed

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to allow recording from unrestrained (i.e., relatively stress-free) animals. Electrodes were attached from the head connector to a Grass 78 polygraph, and signals were band-pass-filtered (ECG, 1–100 Hz; EMG, 10 Hz–1 kHz; temperature, DC coupled), and simultaneously written on polygraph paper and stored on analog tape. Signals were also digitized and stored on digital media at appropriate rates as dictated by the Nyquist frequency (15). After a control recording of one sleep and waking cycle, the subjects were administered a 10-mg/kg dose of cocaine HCl in 25 mg/ml solution IV over a time course of 10–15 s. Cocaine administration was accomplished through a cannula placed in a radial vein.

All portions of the recording session, lasting 2–4 h postadministration, were continuously digitized and thus available for analysis. The diaphragmatic EMG signal was processed by full-wave rectifying and smoothing with a moving-average digital filter using a correction for mathematically induced phase shift. The onsets of inspiratory and expiratory efforts of these traces were determined as the maximal and minimal value, respectively, of the rectified and smoothed diaphragmatic EMG signal. Inspiratory, expiratory, and total cycle times (T_I, T_E and T_{Tot}) were calculated as intervals between these onset times. Although particular analyses and data plots were calculated for all data over the entire recording period, timed samples (minimum 100 s) were taken in the waking baseline period immediately prior to cocaine administration, and at 10 min (early), 30–60 min (intermediate) and 120–180 min (late) postcocaine administration for scatter plots. Breath-to-breath intervals were plotted successively across the entire recording period and for the sampled epochs. Scatter plots of T_{Tot}^{n} vs. T_{Tot}^{n+1} [Poincaré plots, (1)] were calculated prior to, and at successive periods following, cocaine administration to examine dynamic aspects of breath-to-breath timing. Similarly, plots of $Ampl^{n}$ vs. $Ampl^{n+1}$, T_I^{n} vs. T_I^{n+1} and T_E^{n} vs. T_E^{n+1} were calculated prior to, and at particular times following, cocaine administration. Finally, the relationships of EMG amplitude to inspiratory time were evaluated with scatter plots and regression analyses.

ANOVA procedures from the BMDP statistical package (7) followed by the Newman-Keul's test as post hoc tests (21) were used for summary assessments. A significance level of $p<0.05$ was adopted.

RESULTS

Cocaine administration resulted in marked respiratory pattern alterations which changed progressively over the 2–3-hour recording period. An indication of the shortening of respiratory intervals over time is shown in Fig. 1, which is a plot of successive breath-to-breath intervals for four epochs, including baseline, early, intermediate and late cocaine intoxication. An extreme tachypnea rapidly developed and was maintained following IV cocaine delivery. In all cases, the cats immediately developed extensor rigidity interrupted by tonic-clonic seizure-like movements which occurred at a rate of approximately 0.3 Hz and lasted from 2 to 10 min. Tachypnea occurred between those phasic periods which were accompanied by pronounced inspiratory efforts. Sharp peaks in the early intoxication and late epochs of Fig. 1 indicate deep inspiratory efforts embedded within the tachypnea. In contrast to those pronounced inspiratory efforts which occurred during the period immediately following cocaine administration, these deep efforts were not associated with any evidence of tonic-clonic activity. The prolonged inspiratory efforts which punctuate the extreme tachypnea were rare during the intermediate phase of intoxication.

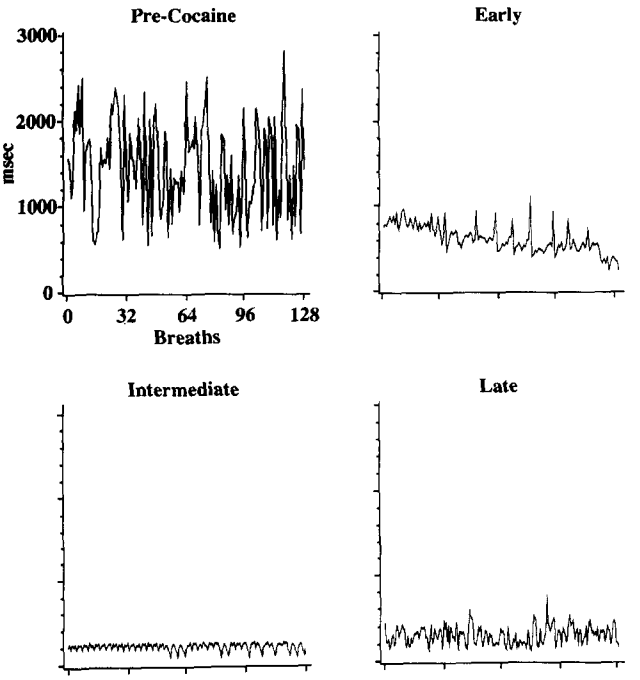

FIG. 1. Breath-to-breath intervals measured from inspiratory onsets in one cat. Interbreath intervals are represented on the y axis, and successive intervals are on the x axis. Thus a longer breath is represented by a higher y value. Each record contains 128 breaths (x axis) and therefore represents differing periods of time. Note the higher variation and longer intervals precocaine, and the extreme shortening and reduced variation in the intermediate record. In the late period, a portion of the variation returns, but rate remains high.

The short-term trends in breath-to-breath interval changes are reflected in the Poincaré plots of Fig. 2. Cocaine administration resulted in a gradual transition from a highly variable one breath-next breath distribution (Fig. 2, precocaine) to a distribution of intervals in which short interbreath intervals were followed by short intervals, and long interbreath intervals were followed by more variable intervals, forming a "V"-shaped pattern (Fig. 2, early). The pattern then changed to one of extremely rigid breath-to-breath intervals (Fig. 2, intermediate and late). The last pattern is associated with an extremely close clustering of values in the intermediate phase, with most points occurring within an exceptionally small region of variation. Because respiratory rates increased dramatically, the number of counts also increased from comparable recording periods.

Diaphragmatic EMG amplitude was used as an index of breath amplitude; this index also increased as a result of cocaine intoxication. Amplitude of EMG increased by an average of $56.1 \pm 40.12\%$ in the early intoxication period; by $89.43 \pm 36.73\%$ in the intermediate intoxication period; and $39.25 \pm 26.53\%$ in the late period. An analysis of precocaine vs. postcocaine amplitude changes indicated a significant increase from control ($p<0.01$). The amplitude changes were much more variable and exhibited a faster decline than those for the timing parameters. Figure 3 illustrates the overall trends in amplitude and timing changes and their variability between epochs. The decrease in respiratory period, and the contribution of inspiratory and expiratory times to that decrease, are evident in this figure. Decreases in total cycle length were found to be significantly

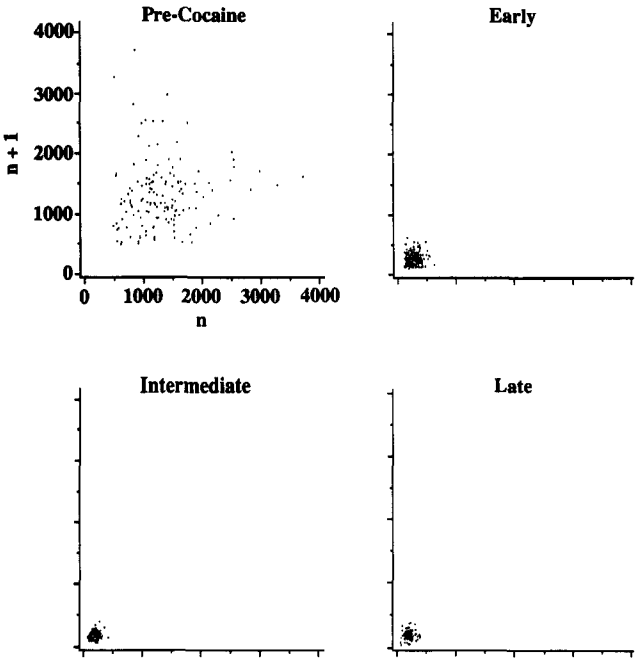

FIG. 2. Poincaré plots of T_{Tot} values for precocaine, early (~10 min) intermediate (30–60 min) and late (120–180 min) 3-min epochs from one representative recording. The interval lengths are on the x axis, while the next intervals (n+1) are on the y axis. N=149, Precocaine; 295, Early; 223, Intermediate; 215, Late.

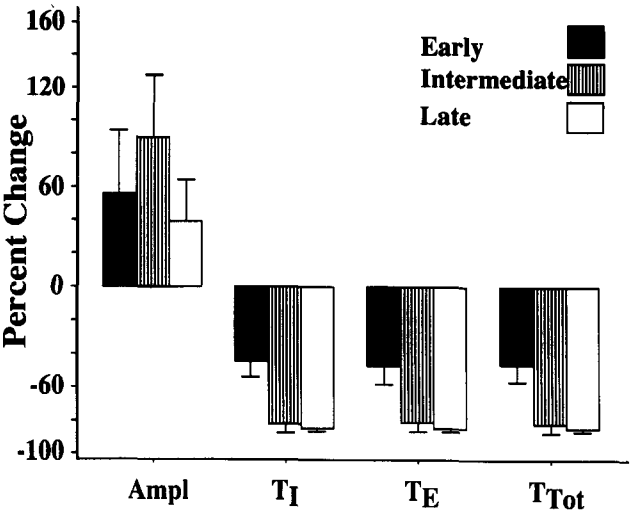

FIG. 3. Means and standard errors for all six cats showing the percent change from baseline in diaphragmatic EMG amplitude (Ampl), inspiratory duration (T_I), expiratory duration (T_E) and the total cycle time (T_{Tot}). Note the similarity in the magnitude of the changes in T_I and T_E and, subsequently, T_{Tot}. All measures were significantly ($p<0.05$) affected by cocaine.

different from baseline conditions at all postcocaine epochs, and the duration was also significantly less at intermediate periods (30–60 min) compared to early periods (~10 min) ($F>10$; $p<0.05$). Decreases in inspiratory and expiratory duration (T_I and T_E, respectively) were also significantly less than baseline at early, intermediate and late periods. In addition, intermediate and late periods had significantly shorter phase durations than the early period.

While cocaine exerted pronounced effects on respiratory rate and diaphragmatic EMG amplitude, the composition of the total cycle period was not significantly affected. When the relationship of the two phases of the cycle were evaluated on a breath-by-breath basis by plotting T_E against T_I, there was a consistent but not significant reduction in slope; in 3 of the 6 cats, the slope became negative in the intermediate phase of cocaine intoxication. When these data were summarized (Fig. 4), there were again no differences in the ratio of T_I to T_E from control or between phases of intoxication.

The relationships of diaphragmatic EMG amplitude to the duration of inspiration were assessed with scatter plots of these variables across all epochs. As can be seen in Fig. 5, in the precocaine epoch, most variability resided in T_I and was associated with relatively high T_I values. During the early intoxication periods, variability was comparable between the two measures, as were relative magnitude values. However, during the intermediate and late periods, a complete reversal of the precocaine condition occurred; during these late epochs, most of the variability was in the amplitude variable, with T_I showing very little variation in magnitude.

There were no consistent trends in the effect of cocaine on the short-term variability of T_I as compared to that of T_E, assessed by the amplitude of phase-to-phase plots (i.e., T_I^n vs. n, similar to the BBI plot of Fig. 1) and by comparison of T_I vs. Next T_I scatter plots with T_E vs. Next T_E plots.

DISCUSSION

Intravenously administered cocaine exerted a profound excitatory influence on respiratory phase-switching mechanisms and recruitment of diaphragmatic muscle activity at the dosage and delivery route used in this study. This excitatory influence developed rapidly (<1 min) and intensified over the first hour after administration. At periods of 2–3 h postcocaine, the tachypnea was still significantly faster than baseline respiratory rates. This

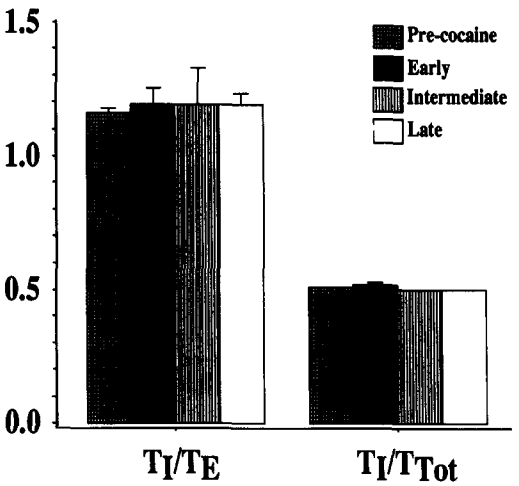

FIG. 4. Mean and standard error values from all six cats. Left—ratio of T_I to T_E (T_I/T_E) and right—duty cycle (T_I/T_{Tot}). None of the values are significantly different.

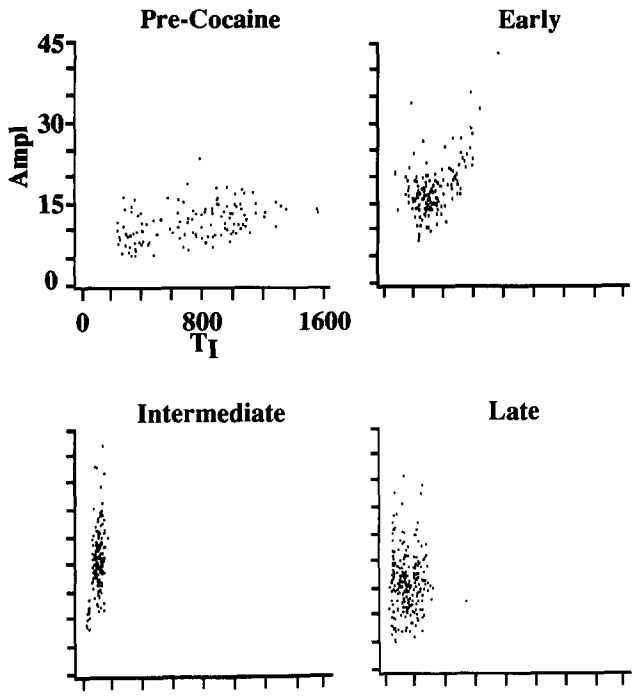

FIG. 5. Diaphragmatic EMG amplitude (Ampl) plotted against inspiratory time (T_I) for one cat. Note the change in scatter between measures from precocaine to the intermediate and late stages of intoxication.

long latency-to-peak effect underscores the need for detailed dynamic analysis of the evolving tachypnea. As respiratory rate increased, short-term variability decreased (i.e., adjacent interval lengths were very similar) except that occasional deep inspiratory efforts occurred in the early periods and appeared less frequently in the late intoxication periods. These relatively deep inspiratory efforts were represented by the vertical and horizontal scatter in the early and intermediate Poincaré plots. In the intermediate phase, long intervals occurred in almost total isolation, while in the early phase these long intervals were occasionally followed by long intervals. The reduction of variability was a hallmark of advanced cocaine intoxication.

The tachypnea that resulted from cocaine administration did not appear to result from peripherally derived drives resulting from the tonic-clonic activity or the tonic increases in skeletal muscle activity. The tonic-clonic activity continued for less than 10 minutes, and the muscular hypertonicity lasted for less than 20 minutes, whereas the increases in respiratory rate continued up to 60 minutes after cocaine delivery. The tachypnea was also unlikely to result from peripheral effects on the diaphragm since intraventricular (25) cocaine or local application of cocaine into the central nucleus of the amygdala (13) also results in a tachypnea.

Among other neurally related influences mediated by rostral brain structures, hyperthermia, a powerful influence on respiratory patterning, might play a role since both core and brain temperature increased in our cats following IV cocaine administration (16). The time course of the hyperthermia was approximately coincident with the tachypnea for this dose level and probably had some facilitatory effect on respiratory frequency. However, other evidence indicated that hyperthermia is not the main drive for cocaine-induced tachypnea. The extreme degree of tachypnea exceeded the level expected for the rather modest increases in temperature found in these studies [mean 1.19°C; (16)] as judged from previous reports (4). In addition, temperature changes induced by other dosages of cocaine declined to control levels much more rapidly than the changes in respiratory period (16). In addition, cocaine microinjected directly into the ACE, which also results in tachypnea, caused a fall in brain temperature (13).

As breath frequency increased, the relationship of inspiratory and expiratory times remained fairly constant. The increased regularity in respiratory patterning resulted from a similar reduction of both T_I and T_E to exceptionally short intervals. The lack of change in the T_I/T_E relationship is unusual, and is not normally associated with tachypnea. At least during hypercapnic tachypnea, T_E shortened more than T_I (6,10), probably due to recruitment of expiratory muscles and a decrease in upper airway resistance. Although breath frequency increased by over 700% (during the intermediate intoxication epoch), inspiratory and expiratory phase relationships were preserved; a mechanism which can account for such a tight coupling of phase durations is not obvious.

One additional factor that may be pertinent to the phase relationship results was the seemingly high T_I/T_E ratio in the control condition. Jennings and Szlyk (18) found that at low frequencies, T_I was much shorter than T_E, even though in half of their cats, at high frequencies (>30 breaths/min), T_E became slightly shorter than T_I. Gautier et al. (10) also reported a greater T_E than T_I in normocapnia. While Clanton and Lipscomb (6) reported a T_I/T_E relationship similar to those reported here, their cats were decerebrate. Our control data may differ from these previously published data because our cats were already experiencing some degree of increased respiratory drive from heightened behavioral arousal which shortened T_E relative to T_I.

The discrepancy in the control T_I/T_E ratios between the data reported here and those published elsewhere make comparisons tenuous. However, similar values in control mean T_I/T_E and T_I/T_{Tot} ratios have been reported to occur at particular levels of hypercapnic tachypnea (27). In contrast, Gautier et al. (10) reported that the reduction in T_{Tot} during hypercapnic tachypnea resulted mainly from decreases in T_E which translates into an increasing T_I/T_E ratio and an increasing T_I/T_{Tot} ratio over the course of the tachypnea.

In addition to significant increases in respiratory rate, diaphragmatic EMG amplitude also increased. Since the source of the enhanced respiratory drive is not known, it is impossible to evaluate whether this increase resulted directly from the influence of cocaine or whether the extreme rapidity of respiratory movements compromised gas exchange, resulting in an increased EMG amplitude as a compensatory response.

From an inspection of the amplitude vs. T_I plots, it is apparent, however, that a fundamental change in the control system operation has occurred. In the control condition, amplitudes remained relatively constant, while T_I varied widely [in agreement with Jennings and Szlyk (18)]; however, this characteristic was altered in early intoxication and reversed in intermediate and late epochs, where T_I became clamped and invariable, and EMG amplitude increased and varied widely.

Several factors are likely to influence respiratory patterning during cocaine intoxication. Metabolic or respiratory acidosis is one factor that would provide excitatory influences to respiratory timing mechanisms. These pH changes accompany cocaine use in humans (2,20) and have been associated with seizures and hypoventilation. Data from Catravas (5) indicate that the acidosis originated from central activation of skeletal muscle, since the fall in arterial pH could be prevented by pretreatment with the neuromuscular blocker pancuronium or with the sedative chlorpromazine. Acidosis can accentuate the cardiovascular effects of sympathomimetics such as cocaine (9), which could then further complicate respiratory control; for example, accentuated

hypertensive effects could initiate or exacerbate pulmonary edema.

Systemic hypertension and pulmonary edema are well-known pathologies associated with acute cocaine use (2,8). Pulmonary edema may itself represent an excitatory drive to the respiratory control system via compromised diffusion of blood gases or, more likely, by stimulation of pulmonary C-fibers (11). This possibility is especially intriguing in light of the high incidence of pulmonary edema as a concomitant of cocaine-related fatalities (23,30).

Jolly and Steinhaus (19) provide support for the concept that excitation of rostral brain areas provides an important drive for the tachypnea induced by cocaine. These investigators delivered cocaine intraarterially to the rostral brain by selective arterial cannulation and found a powerful excitation of the respiratory system, while selective delivery to the brainstem led to respiratory arrest. They hypothesized that death by cocaine-induced respiratory arrest (20, 25, 30) may be due to a predominance of brainstem effects related to dosage, while tachypneic effects resulted from a predominance of forebrain effects (lower dosage). This hypothesis is consistent with the progression of symptoms of cocaine intoxication leading to death from cardiopulmonary collapse.

Our own data also suggest a role for limbic regions of the rostral brain on the respiratory effects of cocaine (13). We found marked tachypnea following localized injections of cocaine into the central nucleus of the amygdala (ACE), a structure with major projections to brainstem regions associated with phase-switching functions. Ni et al. (24) found that half of ACE cells became silent following cocaine microinjection into that area, and Zhang et al. (32) found that nearly half of ACE respiratory-related cells altered that dependency following local ACE cocaine administration. Thus direct cocaine action on rostral brain structures may modify respiratory timing.

Cocaine may also exert a portion of its respiratory rate effects through the extreme extensor tone which develops immediately after cocaine delivery and persists for long periods of time. The excitatory effects on skeletal muscle may provide increased "respiratory drive" similar to the mechanisms proposed for exercise hyperpnea (31).

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