Hypoxic Inhibition of Respiratory Neural Regulation in Anesthetized Rats

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Abstract To determine the neural mechanism of hypoxic respiratory inhibition, discharge patterns of efferent phrenic (Phr), vagal superior laryngeal (Xsl), and vagal pharyngeal (Xphar) nerves were analyzed during systemic hypoxia in the urethane-anesthetized, vagotomized and artificially ventilated rat. In the carotid sinus nerve (CSN) intact rat, moderate hypoxia (end-tidal P_{O_2} , 40–50 mmHg) caused an initial increase in respiratory activity which was followed by inhibition due to reduction in respiratory frequency (f). The decrease in f was associated with prologation of decremental Xphar expiratory (E) activity and retardation of the onset of inspiratory (I) activity. Integrated peak Phr or Xsl I and Xphar E activities remained augmented during respiratory inhibition. After bilateral CSN section, moderate hypoxia produced an extreme reduction in f due to delayed onset of I activity and a strong reduction in the Xphar E activity. Phr and Xsl I activities were little affected, and changes in inspiratory time were small. These results suggest that hypoxia centrally inhibits the process of initiating the onset of rhythmic I activity and the activity of decremental Xphar E motoneurons. Carotid chemoreceptor stimulation was inadequate to offset the central inhibitory effect of hypoxia on the onset of I activity.

Key words: hypoxia, respiratory regulation, central inhibition, onset of inspiration, peripheral chemoreceptor afferents.

Systemic hypoxia has dual effects on respiration. Respiratory stimulation is initiated mainly by peripheral chemoreceptor activation. Central hypoxia, on the other hand, produces inhibition of respiration (CHERNIACK *et al.*, 1970, 1971; LAHIRI and GELFAND, 1981; BERKENBOSCH *et al.*, 1983; SANTIAGO and EDELMAN, 1986). Respiratory response to systemic hypoxia is thus the net result of these dual opposing effects, and respiratory depression appears when inhibition predominates over stimulation (ST. JOHN and WANG, 1977; LAHIRI and GELFAND,

1981). Since hypoxic respiratory depression is a fundamental response process against exposure to hypoxia, its underlying mechanism has been extensively studied (MORRILL *et al.*, 1975; WEISKOPF and GABEL, 1975; BERKENBOSCH *et al.*, 1983; BROWN and LAWSON, 1988; NEUBAUER *et al.*, 1990). Involvement of neurochemicals such as adenosine, GABA, or opioids has been suggested to mediate hypoxic respiratory depression (GRUNSTEIN *et al.*, 1981; CHIANG *et al.*, 1984; MILLHORN *et al.*, 1984; EASTON and ANTHONISEN, 1988). However, the functional site of respiratory inhibition during hypoxia has not been clarified. In previous reports on the anesthetized spontaneously breathing or artificially ventilated rat (FUKUDA and HONDA, 1988; MARUYAMA *et al.*, 1989) we found that the decrease in respiratory frequency was the main cause of respiratory inhibition during acute hypoxia. Deteriorations of frequency control during hypoxia were also found in human neonate, cat and other animals (RIGATTO, 1984; GAUTIER and BORONA, 1979; BLANCO *et al.*, 1984). Since these results were obtained mainly from observations of ventilatory pattern, the neural mechanism of reduction in respiratory frequency during hypoxia has not been determined. The present experiment was addressed to clarifying the inhibitory effect of hypoxia on central mechanism of controlling respiratory timing by analyzing the discharge pattern of phrenic and cranial nerve inspiratory or expiratory activities in anesthetized rats. We have previously demonstrated that the discharge pattern of cranial nerve motoneurons rather than that of phrenic nerve provided important information concerning the intramedullary process of the onset of inspiratory activity during altered chemical stimuli (FUKUDA and HONDA, 1988). Roles of peripheral chemoreceptor stimulation in the generation of hypoxic respiratory inhibition were also studied.

MATERIALS AND METHODS

General. Male Wistar rats (body weight, 300–400 g) were anesthetized with halothane (induction, 2.5%; maintenance during operation, 1.2%). The animal was tracheotomized and breathed spontaneously through a tracheal cannula during operation. The femoral artery and vein were cannulated for blood pressure measurement and for drug injection, respectively. After exposure of the phrenic, superior laryngeal and vagal pharyngeal nerves, the animal was bilaterally vagotomized, immobilized with pancuronium bromide (Myoblock[®], 0.2 mg/h, i.v.), and artificially ventilated. Halothane was discontinued and the anesthesia was switched to urethane (1.0 g/kg, i.v.). A small additional dose of urethane was injected (0.2–0.3 g/kg, i.v.) repeatedly to maintain a constant level of anesthesia. This was judged by a stable blood pressure, heart rate, respiratory frequency and inspiratory or expiratory discharges. End-tidal P_{O_2} and P_{CO_2} (PET_{O_2} and PET_{CO_2}) were continuously monitored via sampling the tracheal gas with an expiratory gas analyzer (1H21, NEC San-Ei Instruments, Tokyo) (FUKUDA *et al.*, 1982; TOJIMA *et al.*, 1988). Since the level of CO_2 stimulus affected respiratory nerve discharges and the

threshold $P_{ET_{O_2}}$ for ventilatory depression (MARUYAMA *et al.*, 1989), $P_{ET_{CO_2}}$ was maintained constant at 45–50 mmHg throughout the experiment by adjusting the rate and depth of artificial ventilation. Previous study showed that systemic hypoxia initiated hypotension in the halothane-anesthetized, vagi intact and spontaneously breathing rat (MARUYAMA *et al.*, 1989). In the present experiment on the urethane-anesthetized, vagotomized, artificially ventilated animal, however, the reduction in blood pressure was small and systolic pressure was always maintained above 80–90 mmHg even during hypoxia.

Recording of nerve activity. The phrenic (Phr), vagal superior laryngeal (Xsl), and vagal pharyngeal (Xphar) nerves were sectioned unilaterally and desheathed. Efferent respiratory neural activities were recorded from central cut end of whole nerves by bipolar platinum-iridium electrodes. Activities were fed into a band-pass filter amplifier (0.1–5 kHz), a half-wave rectifier, and then a leaky integrator (time constant, 0.05 s). Original activities were stored on a magnetic tape for later replay. The height of peak integrated E or I activities were measured (Fig. 1B). Inspiratory time (T_i) was defined as the interval between the onset of Phr I activity and peak integrated I activity. The total cycle duration (T_{tot}) was the interval between the onset to the next onset of Phr I activity. Expiratory time (T_e) was obtained by subtracting T_i from T_{tot} . Since the gradual onset of Xsl I activity preceded the abrupt start of Phr I activity, the time delay between the onset of Xsl and Phr was measured (T_d) (FUKUDA and HONDA, 1982a, b, 1988). These are presented in Fig. 1B. In some experiments, unilateral carotid sinus nerve (CSN) was exposed and sectioned. Afferent mass discharges from the carotid chemoreceptor were recorded from cut central end of the CSN (FUKUDA *et al.*, 1987).

Experimental protocol. Efferent respiratory nerve activities were recorded during ventilation with hyperoxic gas (control hyperoxia, $P_{ET_{O_2}}$ above 200 mmHg). The $P_{ET_{O_2}}$ was suddenly reduced to about 70–80 mmHg (mild hypoxia) or to 40–50 mmHg (moderate hypoxia) by injecting hypoxic gas into a respirator for a period of about 120 s, and then elevated quickly to hyperoxic condition. These two levels of $P_{ET_{O_2}}$ were set to observe responses both to mild hypoxia where hypoxic depression was not significant and to moderate hypoxia by which reversible respiratory depression was consistently produced. T_i , T_e , T_d , respiratory frequency (f), peak integrated Phr, Xsl, and Xphar nerve activities were measured every 10 s. The height of the peak integrated inspiratory (I) or expiratory (E) activities during the hypoxia test were expressed as percent of activity in control hyperoxia. Respiratory nerve activity responses to hypoxia were compared before and after bilateral CSN section.

Statistical analysis. Measured variables were compared between control hyperoxic and hypoxic conditions and also before and after bilateral CSN section. Differences were considered significant when p value was less than 0.05 (t -test).

Fig. 1. Respiratory activity in cranial and phrenic nerves of the anesthetized rat in hyperoxia. A, original traces. Xphar (E), expiratory activity of vagal pharyngeal nerve; Xsl (I), inspiratory activity of vagal superior laryngeal nerve; Phr (I), inspiratory activity of phrenic nerve. B, integrated E and I activities. Measurements of inspiratory time (T_l), expiratory time (T_e), time delay (T_d) from the onset of Xsl I activity to the start of Phr are shown. Abbreviations are the same in the following figures.

RESULTS

Respiratory nerve activities in hyperoxic condition

The Phr I discharge began suddenly, gradually augmented and ceased abruptly (Fig. 1). Post-inspiratory activities were small and were seen only occasionally. The Xsl I activity started slowly at the terminal phase of Xphar E activity but much

Table 1. Changes in respiratory timing, inspiratory and expiratory activities by hypoxia.

	CSN intact		CSN denervated	
	Hyperoxia	Hypoxia	Hyperoxia	Hypoxia
Respiratory frequency (f , min ⁻¹)	44.3±1.4	27.7±2.3*	46.4±1.5	16.2±2.2*†
Inspiratory time (T_i , s)	0.332±0.016	0.296±0.016	0.328±0.017	0.424±0.046†
Expiratory time (T_e , s)	1.061±0.040	1.964±0.168*	0.976±0.028	3.647±0.618*†
Time delay: Xsl-Phr (T_d , s)	0.199±0.028	0.216±0.038	0.260±0.031	0.104±0.027*†
Peak integ. Phr I (%)	100	142.8±5.5	100	89.0±4.3†
Peak integ. Xsl I (%)	100	141.2±3.8	100	93.7±1.8†
Peak integ. Xphar E (%)	100	225.7±33.3	100	17.3±11.3†
Phr× f (%)	100	95.3±10.3	100	32.3±5.0†

Values are mean±S.E. CSN, carotid sinus nerve; hyperoxia, $P_{ET_{O_2}} > 200$ mmHg; hypoxia, $P_{ET_{O_2}}$ 40–50 mmHg (100 s after start of hypoxia); Phr, phrenic nerve; Xsl, vagal superior laryngeal nerve; Xphar, vagal pharyngeal nerve; I, inspiratory activity; E, expiratory activity. Statistically significant difference between hyperoxia and hypoxia (*), and between CSN intact and denervated rats (†), $p < 0.05$ or less (t -test). Number of observations, 8.

earlier than the onset of Phr discharges. The T_d from the start of Xsl I activity to the Phr onset was about 200 ms (Table 1). The Xsl discharges increased greatly when the Phr I activity started, and disappeared synchronously with the offset of Phr activity. The decremental Xphar E activity started immediately following the termination of Xsl and Phr I activity. In some preparations small I activity was seen in the Xphar discharges.

Carotid sinus nerve activity during hypoxia test

Afferent mass discharges of the rat CSN are composed mostly of activities from the carotid body chemoreceptor with quantitatively only minor fraction of the activity from carotid sinus baroreceptors (FUKUDA *et al.*, 1987). The CSN afferent discharge increased with reduction in $P_{ET_{O_2}}$, and was maintained high level during exposure to hypoxia (about 120 s) (Fig. 2). The activity returned completely to control level when $P_{ET_{O_2}}$ was elevated.

Respiratory nerve activity during hypoxia test with intact CSN

A stepwise reduction in $P_{ET_{O_2}}$ from above 200 mmHg down to 70–80 mmHg (mild hypoxia) for about 120 s initiated an increase in f and augmented I or E activities in three respiratory nerves (Fig. 3, left). The increase in the Xphar E activity was much larger than those of Phr or Xsl I activities. An increase in f was

Fig. 2. Afferent discharge of the carotid sinus nerve (CSN) during hypoxia test. Integrated Phr nerve I activity is also shown.

Fig. 3. Respiratory nerve activity responses to two levels of hypoxia (PET_{O_2} : left 80 mmHg, right 42 mmHg) in the CSN intact rat.

transient and was followed by a decrease to control level. A reduction of PET_{O_2} to 40–50 mmHg produced a more significant initial increase in f , which was followed by a profound decrease due to prolongation of T_e (Fig. 3, right; Figs. 4, 7). Values

Fig. 4. Expiratory and inspiratory nerve discharges during hypoxia test in the CSN intact rat. Voltage calibration: Xphar and Xsl, $100\mu\text{V}$; Phr, $200\mu\text{V}$. Time (s) presented in the figure indicates the time after the start of hypoxia.

of respiratory timing and the height of integrated I or E activity in control hyperoxia and at 100 s exposure to moderate hypoxia are compared in Table 1. The initial increase in f was associated with a shortening of T_e and with prolonged T_d (350–370 ms at 20–70 s of hypoxia). The onset of Xsl and Phr I discharges was, however, delayed with an extremely augmented Xphar E activity in the later phase of hypoxia test (60–120 s). In some cases there was a partial breaking of prolonged E activity associated with small early Xsl I discharge but without synchronized large Xsl and Phr discharges. Such partial interruption of the genesis of synchronized Phr and Xsl discharges was transient and was followed by a much longer prolongation of T_e . The duration of T_i was shortened slightly throughout the hypoxia test. The integrated E and I activities remained augmented even in the later phase of hypoxia test (Figs. 3, 7). Recovery of prolonged T_e , reduced f , and augmented peak I or E activity took a relatively long time after elevating $P_{\text{ET}_{\text{O}_2}}$ to hyperoxic level (20–40 min).

Responses to hypoxia after CSN section

Bilateral section of the CSN did not alter the respiratory nerve activity and timing in control hyperoxia with the same $P_{\text{ET}_{\text{CO}_2}}$ range (45–50 mmHg) (Table 1, Figs. 5, 6). A mild hypoxia ($P_{\text{ET}_{\text{O}_2}}$ 70–80 mmHg) produced a reduction in the height of Xphar E discharges only (Fig. 5, left). Respiratory timing and Phr and Xsl I activities were unaffected. However, when $P_{\text{ET}_{\text{O}_2}}$ was lowered to 40–50 mmHg, there was a strong reduction in f and Xphar E activity (Figs. 5–7). The reduction in f started at 30–40 s exposure to hypoxia and reached a steady state at

Fig. 5. Respiratory nerve activity responses to two levels of hypoxia (P_{ETO_2} : left 80 mmHg, right 42 mmHg) in the CSN denervated rat.

Fig. 6. Expiratory and inspiratory nerve discharges during hypoxia test in the CSN denervated rat. Voltage calibration: Xphar and Xsl, $100\mu\text{V}$; Phr, $200\mu\text{V}$. Time (s) presented in the figure indicates the time after the start of hypoxia.

Fig. 7. Summary of respiratory nerve activity responses to moderate hypoxia (PET_{O_2} , 40–50 mmHg) in the CSN intact and denervated rats. Values are mean $\pm$ S.E. ($n=8$). Calculated minute Phr activity (peak Phr $\times f$) is also shown. f , respiratory frequency. *Statistically significant difference between CSN intact and denervated animals ($p < 0.05$, t -test).

about 90–100s. In some cases, reduction in f was preceded by a slight increase as seen in Fig. 5 (right). T_l increased slightly during hypoxia test but did not differ from that in control hyperoxia. T_d shortened with extreme prolongation of T_e . The height of integrated Xsl and Xsl I discharges did not alter during the hypoxia test. The decremental E activity was prolonged initially but became extremely suppressed in the following period of hypoxia test. In contrast to the CSN intact rat, decreased f and prolonged T_e recovered within several minutes after elevating PET_{O_2} to hyperoxic condition.

Changes in respiratory timing and the magnitude of E and I activities in steady state condition during moderate hypoxia (PET_{O_2} , 40–50 mmHg) are summarized in Fig. 7. A common finding in both the CSN intact and denervated animals was that respiratory inhibition was produced by the prolongation of T_e due to delayed onset of I activity. In the CSN intact animals, the reduction in f was less marked and was compensated by an increase in the peak Phr I activity, which resulted in much smaller reduction of minute Phr activity (Phr $\times f$) in the steady state condition of hypoxia test.

DISCUSSION

The Phr, Xsl, and Xphar efferent mass discharges represent overall states of neuronal activity in the spinal Phr motoneurons (or Phr driving medullary premotor neurons) and vagal I and E motoneurons in the ambiguus and/or retrofacial nuclei, respectively (FELDMAN, 1986; EZURE *et al.*, 1988; ISCOE, 1988). These respiratory output neurons are synaptically driven by inputs from a rhythm-generating neuronal network in the medulla oblongata (COHEN, 1975; EULER, 1983; FELDMAN, 1986). The early onset of the laryngeal nerve I discharges is due to that firing threshold of these motoneurons to I drive inputs is lower than that of Phr (or Phr driving) motoneurons (COHEN, 1975, 1979; ST. JOHN *et al.*, 1981). It is generally accepted that the time delay between the Xsl and Phr I onset occurs in the medulla oblongata (COHEN, 1975; EULER, 1983; FELDMAN, 1986). The Xsl and Xphar nerves innervate the cricothyroid muscle (ANDREW, 1955, 1956; SHERREY and MEGIRIAN, 1977) and pharyngeal constrictor muscles (MURAKAMI and KIRCHNER, 1974; SHERREY and MEGIRIAN, 1975), respectively. The Xphar E motoneurons as well as the laryngeal E motoneurons innervating the thyroarytenoid muscle probably receive a burst of EPSP's at the beginning of the E phase and then fire in a decremental pattern (FELDMAN and COHEN, 1978; MATHEW and REMMERS, 1984; FELDMAN, 1986; ZHOU *et al.*, 1989). Because the onset of I discharge during asphyxia differed significantly between the Phr and cranial nerves, observation of Phr activity alone would not be adequate to evaluate the intramedullary process of respiratory timing during altered chemical stimuli (FUKUDA and HONDA, 1988).

Systemic hypoxia initiates various responses such as chemoreceptor stimulation, inhibition of medullary respiratory neurons, changes in cerebral blood flow or autonomic nervous activity. Although the net result of these responses determines the respiratory neuron activity, the most important factors are the peripheral chemoreceptor activity and the direct or indirect inhibition of respiratory neuron activity due to reduced brain oxygenation (SANTIAGO and EDELMAN, 1986; MARUYAMA *et al.*, 1989). Since the CSN afferent activity remained augmented during hypoxia test, respiratory inhibition was likely to have resulted not from accommodation of peripheral chemoreceptors but from central inhibition. The inhibitory effect of hypoxia on respiratory neural activity was best shown in the CSN denervated animals in which major peripheral chemoreceptor afferents were eliminated. An extreme prolongation of T_e with slightly shortened T_d and reduction in Xphar E activity indicated that the onset of medullary I activity and the activation of vagal E motoneurons were suppressed by hypoxia. Since these changes started at 30–40 s after the start of hypoxia, some time-consuming process(es), such as accumulations of inhibitory substances (GRUNSTEIN *et al.*, 1981; CHIANG *et al.*, 1984; MILLHORN *et al.*, 1984; EASTON and ANTHONISEN, 1988; NEUBAUER *et al.*, 1990), might be involved. There was a slight prolongation of T_i

but it was much less than that of T_e . The height of Phr and Xsl I activity were little affected. These indicated that the neural mechanism(s) for I offswitch and for synchronization of I discharges among various I motoneurons (or premotor neurons) were not largely inhibited at the examined level of hypoxia.

In the CSN intact animals, afferent signals from the carotid body chemoreceptor modified the inhibitory effect of hypoxia described above. Due to a smaller decrease in f and augmented Phr I activity, the reduction in minute Phr activity during moderate hypoxia was much less than that in CSN denervated animals (Table 1 and Fig. 7). However, the reduction in f following an initial increase was produced by prolongation of T_e . Since T_d was not prolonged when f was decreased, respiratory inhibition in the CSN intact animal was also caused by a delayed onset of I activity. An interesting observation was that during initial stimulatory phase the onset of slow Xsl I started extremely earlier than the Phr onset resulting in an increase in T_d . Furthermore, smooth transition from the early onset of slow Xsl I activity to the synchronized large bursts was interrupted in the later phase of hypoxia. This was accompanied by an incomplete breaking of augmented Xphar E activity. These observations indicated a possibility that rhythmic generation of medullary I activity includes the following two sequential processes: 1) a slow but early onset of I activity in the late E phase which appears in the Xsl (and probably in other cranial nerve) motoneurons, and 2) following synchronized bursting mechanism which initiates coordinated large I discharges in both the Phr and Xsl motoneurons. The result suggested that the former was facilitated by hypoxia via activation of peripheral chemoreceptors, whereas it was suppressed by central hypoxia. The balance between this facilitation and inhibition determines the actual onset of I activity in the CSN intact animals. The duration of T_d may represent the time required from the start of the former to the generation of the latter. The transition between the two processes would be smooth in hyperoxic condition. Prolongation of T_d and a lack of synchronized large I large discharges observed temporarily in the CSN intact animals might be due to interruption of transition from the former to the latter. An extreme increase in medullary E activity may inhibit the initiation of synchronized I discharges. It was, however, difficult to determine whether changes in T_d were due to alteration of firing threshold of cranial nerve motoneurons by hypoxia. In contrast, termination of I activity (I offswitch) occurred synchronously in the Phr and Xsl motoneurons, and T_i was not influenced by hypoxia. Therefore I offswitch or I to E phase switch mechanism was not suppressed by hypoxia. Functional roles of an extreme increase in decremental Xphar E activity by hypoxia have not been evaluated. However, prolonged and augmented Xphar E activities interrupt the E flow by pharyngeal constriction (BARTLETT, 1986; ISCOE, 1988) and may increase the functional residual capacity of the lung, by which O_2 is preserved in the lung. This response depends completely upon the peripheral chemoreceptor afferent. There is a possibility that these changes in breathing pattern during hypoxic respiratory inhibition may represent important acute physiologic responses in a condition where the increase in ventila-

tion can no longer take up enough amount of O_2 from the lung rather than signs of hypoxic deterioration of respiratory control. Changes in the discharge pattern of respiratory nerves correlated well with ventilatory pattern change observed in halothane-anesthetized, vagi intact, and spontaneously breathing rats, i.e., decreased f with prolongation of T_c and large tidal volume (MARUYAMA *et al.*, 1989).

The time course of the recovery of hypoxic reduction in f with elevating PET_{O_2} differed between the CSN intact and denervated rats, i.e., the former showed a more prolonged inhibition than the latter. Since the carotid chemoreceptor afferent activity returned quickly to the control level in the post hypoxic period, prolonged inhibition was not due to a greater reduction of afferent chemoreceptor discharges. A long continued increase in E activity in the post hypoxic period may suppress the initiation of synchronized I activity resulting in a prolonged reduction in f . On the contrary, the inhibitory effect of central hypoxia seen in the CSN denervated animal would fade easily when restoring the brain oxygenation.

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