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Lateral parabrachial nucleus mediates shortening of expiration and increase of inspiratory drive during hypercapnia

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ABSTRACT

We have previously shown that unilateral or bilateral lesions of the lateral parabrachial nucleus (LPBN) in anesthetized, vagotomized rats markedly and selectively attenuate the shortening of expiratory duration (T_E) during hypoxia without appreciably affecting all other hypoxic response components. Here, we report that unilateral LPBN lesion by kainic acid in the same group of animals not only abolished normal T_E-shortening during central chemoreceptors activation by hyperoxic hypercapnia, but led to paradoxical T_E-prolongation and corresponding decrease of respiratory frequency. Furthermore, LPBN lesion significantly attenuated the increase in phrenic activity during hyperoxic hypercapnia, without appreciably affecting the corresponding shortening of inspiratory duration (T_I). These findings provide the first evidence indicating that central chemoafferent inputs are organized in parallel and segregated pathways that separately modulate inspiratory drive, T_I, and T_E in conjunction with similar parallel and segregated central processing of peripheral chemoafferent inputs reported previously [Young, D.L., Eldridge, F.L., Poon, C.S., 2003. Integration-differentiation and gating of carotid afferent traffic that shapes the respiratory pattern. J. Appl. Physiol. 94, 1213–1229].

1. Introduction

The hypercapnic ventilatory response in humans is highly stereotyped (Cunningham et al., 1986) and is comprised of increases of inspiratory drive and tidal volume, increases of respiratory frequency (f), and decreases in inspiratory and expiratory durations (T_I, and T_E) (Gardner, 1980; Poon, 1989a; Poon, 1989b; Jubran et al., 1997). In adult animals hypercapnia typically elicits increases in inspiratory drive and tidal volume, but corresponding responses in f, T_I and T_E may vary depending on experimental conditions and animal species. In anesthetized or awake dogs, cats and rats with intact or severed vagi, hypercapnia generally causes increases of f and shortening of T_E, with slight decrease or no change in T_I (Clark and von Euler, 1972; Gautier, 1976; Ledlie et al., 1981; Oliven et al., 1985; Coles et al., 2002). However, hypercapnia reportedly may also lead to a paradoxical prolongation of T_E in decerebrate cats (St John, 1979; Clanton and Lipscomb, 1984) and similar post-hypercapnia prolongation of T_E in awake rats (Coles et al., 2002). The central pathways mediating these varied effects during central and/or peripheral chemoreceptors activation by hypercapnia are unclear.

In a companion report (Song and Poon, 2009) we have shown that unilateral or bilateral lesions of the lateral parabrachial nucleus (LPBN) in anesthetized, vagotomized rats markedly and selectively attenuate the decrease of T_E during hypoxia without appreciably affecting all other hypoxic response components (such as short-term potentiation and depression), suggesting an important role of this dorsolateral pontine structure in modulating the peripheral chemoafferent-mediated shortening of T_E. In addition, baseline T_E under hyperoxia is significantly increased after bilateral LPBN lesions without appreciable changes in baseline T_I, indicating that the LPBN also mediates the shortening of T_E by some tonic inputs. In the present study, we used a similar preparation to test the hypothesis that the LPBN also mediated T_E-shortening during hyperoxic hypercapnia, a stimulus that preferentially activates the central but not peripheral chemoreceptors (Fitzgerald and Parks, 1971; Lahiri and DeLaney, 1975). To our surprise, we found that central chemoreceptor inputs not only promoted T_E-shortening but also an increase of inspiratory drive via the LPBN, as well as a paradoxical T_E-prolongation effect via other pathways.

2. Methods

Experiments were performed on 6 urethane-anesthetized, pancuronium-paralyzed, vagotomized and ventilated adult Sprague–Dawley rats (330–380 g, Charles River Laboratories). All

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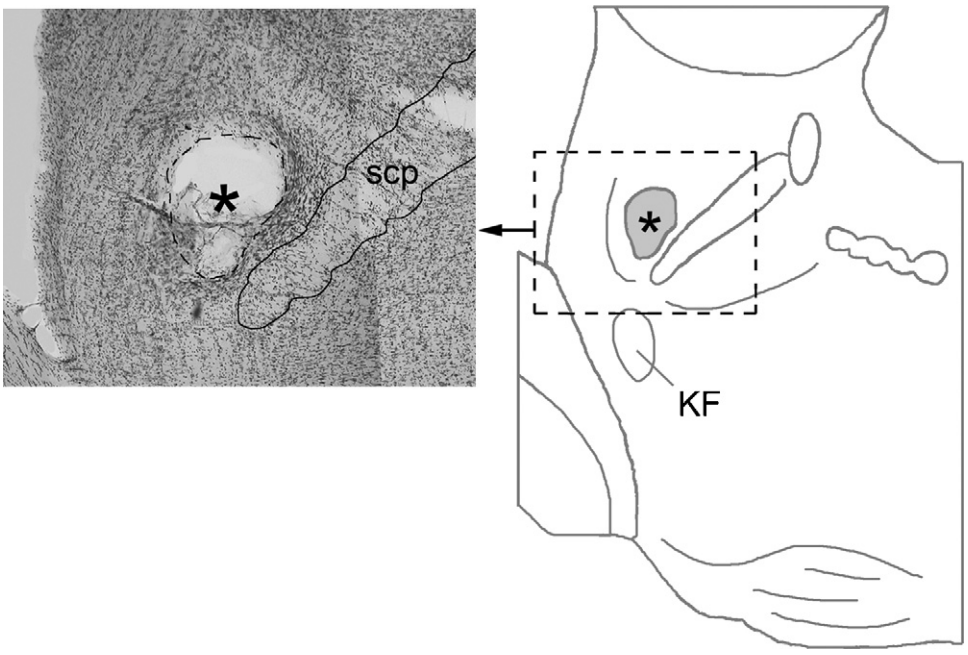

Fig. 1. Histological section showing LPBN lesion in a representative animal. *Left panel*: Montage photomicrograph showing the kainic acid injection site. The center of injection (*) was at the central LPBN. *Right panel*: Camera-lucida drawing of the histological section (rectangle with broken lines) on standard plate (plate 52) of Paxinos rat brain atlas (Paxinos and Watson, 1986). KF, Kölliker–Fuse nucleus; scp, superior cerebellum peduncle. See also (Song and Poon, 2009).

experimental protocols had been reviewed and approved by the M.I.T. Committee on Animal Care in accordance with published guidelines. Experimental methods and materials are as described in (Song and Poon, 2009) except as follows. Hyperoxic hypercapnia (O_2CO_2) was applied by abruptly switching the hyperoxic ventilation gas (40% O_2 balance N_2 medical-grade) to carbogen (5% CO_2 balance O_2) for 1 min. Thirty minutes after unilateral microinjection of kainic acid (KA, concentration at 1 μg/μl in ACSF) into the LPBN, another O_2CO_2 test was performed. In this group of animals a hypoxia test was also performed (see Song and Poon, 2009) at 15 min after each O_2CO_2 test, when the animal's end-tidal PCO_2 and PO_2 and blood pressure had returned to corresponding pre-test baseline levels. T_I, T_E, and f were measured for each respiratory cycle from recorded phrenic activity (Phr). Amplitude of inspiratory motor output ($\int$Phr) was measured as the peak of the integrated Phr signal. Inspiratory drive was measured as the ratio $\int Phr/T_I$. These values were normalized against their corresponding average pre-test baseline values in control or lesioned conditions. Data are expressed as means ± SE. Each animal served as its own control for all statistical analyses.

3. Results

In the six animals that received unilateral KA injection, the injection sites as marked by post-injection electrolytic lesions were verified to lie at the central or external-lateral subnucleus of the LPBN (Fig. 1). Baseline respiratory rhythm variables (f, T_E, T_I) under hyperoxia were not significantly different before and after lesion (Table 1, see also Song and Poon, 2009).

Before LPBN lesion, O_2CO_2 caused progressive shortening of T_E and increase in f (Fig. 2). The shortening of T_E reached maximum (−9.7 ± 2.2% below baseline; $P < 0.01$, two-tailed paired t-test) at ~30 s into O_2CO_2 before gradually relaxing toward baseline, resulting in an apparent decrementing-incrementing response pattern (although the incremental component was not found statistically significant during the relatively short test period). The increase in f also reached maximum (8.4 ± 1.5% above baseline; $P < 0.01$) at ~30 s into O_2CO_2 but remained relatively stable afterward. Following the O_2CO_2 test both variables gradually recovered.

After LPBN lesion, O_2CO_2 paradoxically caused progressive prolongation of T_E and decrease of f (Fig. 2), in opposite to the control effects. The maximal prolongation of T_E (8.6 ± 1.8% above baseline; $P < 0.01$, two-tailed paired t-test) and decrease in f (−3.9 ± 1.6%) occurred ~40 s into O_2CO_2. Following the O_2CO_2 test both variables gradually returned to baselines. The response curves in both variables were significantly different after lesion compared with control ($P < 0.01$, two-way ANOVA with repeated measures).

In contrast to T_E, T_I showed similar progressive shortening during O_2CO_2 as well as similar recovery before and after lesion (Fig. 3). In two animals the shortening of T_I appeared to develop more rapidly after lesion compared with control. However, two-way ANOVA (with repeated measures) for the group as a whole showed no significant differences in the response curves before and after lesion ($P > 0.1$).

In both control and lesioned conditions, $\int$Phr and $\int Phr/T_I$ showed progressive increases during O_2CO_2 and gradual return during recovery (Fig. 3). However, in both cases the increases were significantly smaller after lesion compared with control ($P < 0.01$, two-way ANOVA with repeated measures). For example, the maximal increase in $\int$Phr and $\int Phr/T_I$ were 36.1 ± 6.4% and 54.6 ± 4.8% above baseline in control condition, but only 20.6 ± 3.6% and 32·5 ± 3.6% respectively after lesion ($P < 0.01$, two-tailed paired t-test).

Table 1
Effects of unilateral LPBN lesion on baseline respiratory patterns.

		Before	After
Unilateral lesion ($n = 6$)	f (min^{-1})	39.2 ± 1.8	43.0 ± 3.3
	T_E (s)	1.15 ± 0.06	1.05 ± 0.12
	T_I (s)	0.40 ± 0.03	0.42 ± 0.03

Data are means ± S.E. of 1-min baseline recordings before or after LPBN lesion. f, respiratory frequency; T_E and T_I, expiratory and inspiratory durations. The differences in all variables before and after lesion were statistically insignificant ($P > 0.1$, two-tailed paired t-test). See also (Song and Poon, 2009).