Focal acidosis in the pre-Bötzing complex area of awake goats induces a mild tachypnea

K. L. Krause,1 H. V. Forster,1,2 S. E. Davis,1 T. Kiner,1 J. M. Bonis,1 L. G. Pan,3 and B. Qian1

1Department of Physiology, Medical College of Wisconsin, 2Veterans Affairs Medical Center, and 3Department of Physical Therapy, Marquette University, Milwaukee, Wisconsin

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CENTRAL RESPIRATORY CO2/H+ chemoreception has been traditionally attributed to sites at or near the ventrolateral medullary surface (16, 24, 27). However, studies over the last 15–20 yr indicate that the ventrolateral medullary surface is not the sole CO2/H+-sensitive area (1–3, 5, 15, 17, 21, 24, 31, 32). Electrophysiological recordings of in vitro preparations have shown that neurons in the retrotangential nucleus, nucleus of the solitary tract, the medullary raphe nucleus (MRN), locus coeruleus, and the pre-Bötzinger complex (preBötzC) increase discharge frequency when the pH in the bathing solution is reduced (3, 5, 8, 14, 22, 24). Studies in anesthetized preparations that either created a focal acidosis (FA) or assessed the effects of lesions on the hypercapnic ventilatory response also support the concept of widespread chemosensitivity in the medulla,pons, and cerebellum (11, 18, 32, 33, 36, 37).

While the in vivo data, under physiological conditions, suggest that chemoreceptors at multiple sites influence breathing; chemosensitivity

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dose-dependent manner, including bilateral responses greater than unilateral responses. Also, given the respiratory rhythm-generating role of the preBo\"tzC, and data from anesthetized cats showing that a FA in this nucleus increases f (12, 31, 32), we hypothesized that FA in this nucleus in awake goats would also increase f, and that the FA would not stimulate V\textsubscript{O}\textsubscript{2} and HR. Finally, we hypothesized that ECF pH in the preBo\"tzC will (as in the MRN) decrease less than plasma pH during whole body hypercapnia.

**Methods**

Physiological data were obtained on 10 adult female goats, weighing 43.3 ± 2.4 kg. Four additional goats were utilized for histological purposes only (44.1 ± 3.1 kg). Goats were housed and studied in an environmental chamber with a fixed ambient temperature and photoperiod. All goats were allowed free access to hay and water, except for periods of study. The goats were trained to stand comfortably in a stanchion during periods of study. All aspects of the study were reviewed and approved by the Medical College of Wisconsin Animal Care Committee before the studies were initiated.

**Surgical procedures.** Before all surgery, goats were anesthetized with a combination of ketamine and xylazine (15 and 1.25 mg/kg, respectively), intubated, and mechanically ventilated with 1.5% halothane in 100% O\textsubscript{2}. All surgeries were performed under sterile conditions. Each goat underwent an initial instrumentation surgery in which a 5-cm segment of each carotid artery was dissected from the vugus nerve and elevated subcutaneously for eventual insertion of a catheter. Electromyogram electrodes were implanted into the diaphragm to monitor muscle activity. Cefazolin sodium (Naxcel) (8 mg/kg) was administered (intramuscularly, every day) for 1 wk postoperatively to minimize infection.

After at least 2 wk of recovery, goats then underwent another surgery for the purpose of unilateral or bilaterally implanting 70-mm-long (1.27 mm outer diameter, 0.84 mm inner diameter) stainless steel microtubules (MTs) into the preBo\"tzC. An occipital craniotomy was created, and the dura mater was excised to expose the posterior cerebellum and the dorsal aspect of the medulla for visualization of obex. Using previously delineated coordinates of the preBo\"tzC in goats (36, 37), the MTs were implanted 2.5–3.5 mm rostral to obex, 4–5 mm lateral to the midline, and extending 5–7 mm from the dorsal surface of the medulla.

Experienced laboratory personnel continuously monitored the goat at least 24 h after brain surgery, or until the goat reached stable conditions. Buprenorphine hydrochloride (Buprenex) (0.005 mg/kg) was administered for pain, as needed. Each goat was also placed on a respirator for the purpose of unilaterally or bilaterally implanting 70-mm-long (1.27 mm outer diameter) compared with 1.27 mm (outer diameter) in our previous studies. We were only able to obtain a larger electrode. As a result, the MTs required for insertion of both the electrodes and dialysis probe were 1.7 mm (outer diameter) compared with 1.27 mm (outer diameter) in our previous studies. We implanted the larger MTs in the preBo\"tzC area of one goat, but the goat was sacrificed 2 days after surgery due to lack of recovery from severe postural, feeding, and respiratory defects. Histology revealed that destruction of the medulla was over nearly 3 mm surrounding the MT tract. Accordingly, because of these findings, we did not feel justified to attempt another goat, particularly since the ECF pH measurements during global brain acidosis change preBo\"tzC pH more than global acidosis in the medullary raphe. Thus we are confident that MD in the preBo\"tzC decreased ECF pH as much, or more than, MD in the raphe (10).

ECF pH measurements in the preBo\"tzC were also obtained during global acidosis (n = 5) for the purpose of comparing previous pH measurements of the MRN of awake goats (11). A custom-made metal-metal oxide pH electrode (70-mm shaft, 2-mm length-sensing tip, 0.5-mm inner diameter) (World Precision Instruments) was inserted unilaterally into a MT. A reference electrode was adhered to a
shaven area of skin. Both were then connected to a pH meter (Corning 315 pH/Ion), and millivolt (pH) readings were recorded every minute. After pH was measured in vivo, the electrode was calibrated in a heated water bath (39°C) using three different buffer solutions (pH 4, 7, and 10), and a linear calibration curve was calculated in millivolts/pH unit. This curve was then used to compute the change in ECF pH during the period when inspired CO2 was administered.

To determine whether the in vitro calibration accurately described pH in vivo, two holes were bored into the top of a 100-μl Eppendorf tube: an Ag-AgCl reference electrode (WPI) was inserted into one hole, and a pH electrode was inserted into a second hole. Another two holes were bored into the Eppendorf tube to allow for the flow of mCSF into and out of the tube. The tube was then filled with mCSF equilibrated with 6.4% CO2. mCSF equilibrated with either 6.4 or 50% CO2 was first analyzed for pH using a blood-gas analyzer and then flowed through the Eppendorf tube (50 μl/min) for 30 min. The pH in the tube was recorded at 1-min intervals. At the completion of the in vitro study, the pH electrode was calibrated as described above.

The change in pH of mCSF between 6.4 and 50% CO2 was 0.810, as determined by the blood-gas analyzer, and 0.767 as determined by the in vitro calibrated pH electrode. This close agreement indicates that an accurate estimate of the changes in ECF pH was obtained in vivo.

Glutamate receptor agonist injections. A glutamate receptor agonist applied to the preBo¨tzC elicits a classic physiological response, manifested as an increase in f (19, 30, 37). Weeks after the completion of the FA studies, the neurotoxin ibotenic acid (IA), an irreversible glutamate receptor agonist, was injected into the preBo¨tzC of the present group of goats to examine the plasticity of respiratory rhyth- mogenesis. The experimental design consisted of injecting a series of incremental, sequential volumes of IA (50 mM) that started with 500 nl and increased to 10 μl. Each injection was separated by 1 wk. After a 15-min eupneic control period, a unilateral injection of IA was made into the preBo¨tzC through the MT. Physiological variables were monitored for 1 h, and then an identical injection was made into the contralateral MT, except that, for the 10-μl volume, the contralateral injection was made 1 wk later.

Histological studies. After completion of all experimental protocols, the animals were euthanized (Beuthanasia), and the brain was...
perfused with phosphate-buffered saline solution and fixed with 4% paraformaldehyde. The medulla was then excised and placed in a 4% paraformaldehyde solution for 24–48 h and then placed in a 30% sucrose solution. Subsequently, the medulla was frozen and serial sectioned (25 μm) in a transverse plane and adhered to chrome alum-coated slides. The tissue was Nissl stained or stained with hematoxylin and eosin, coverslipped, and examined microscopically. The MT implantation site was identified by visualization of an area of absent or disrupted tissue and was defined as being the tip of the ventral-most aspect and middle of the MT-induced tissue disruption.

Four additional (control) goats were utilized solely to obtain histological data on the medulla of goats. These goats were killed, and the medulla was harvested and processed as above, except, in addition to the hematoxylin and eosin and Nissl staining, a series of sections were used for neurokinin-1 receptor (NK1R) immunoreactivity. An anti-NK1R primary antibody was complexed with biotinylated anti-mouse secondary antibody. After the antibody antigen complex was incubated, it was localized by avidin (Vector ABC Elite) and developed with diaminobenzoate. Total and NK1R immunoreactive neurons were counted every 100 μm from 2 to 4.6 mm rostral to obex in a 1.5- by 1.5-mm area just ventral to nucleus ambiguous (NA) (see Fig. 1).

Data analysis. 

Ventilation (V̇I) during 3, 5, and 7% CO₂ did not change significantly 5 days after FA compared with preacidosis control (P > 0.05, n = 6, 12 trials).

RESULTS

Histology and placement of MTs. Figure 1A is from a transverse section 2.9 mm rostral to obex from a control goat's medulla. This figure illustrates a high density of NK1R-expressing neurons ventral to NA. Figure 1B agrees with our laboratory’s previously published finding (36) that, ventral to NA, between 2.5 and 3.5 mm rostral to obex and 4.0 to 5.0 mm lateral to the midline, there is an unique high density of NK1R-expressing neurons, which we presume is the preBötzC. Histology completed after the goats were killed indicated that the MTs were placed between 2.5 and 3.5 mm rostral to obex, 4.0 and 5.0 mm lateral to the midline, and extending 5.0–7.0 mm from the dorsal surface, such that they were within, or ended just dorsal to, the preBötzC (Fig. 2). This location of all of the MTs was consistent with the previously reported stereotaxic definition of the preBötzC in goats (36). Physiological confirmation of correct MT placement in the goats studied herein is provided by the characteristic tachypnea (Fig. 3) in the goats when IA was injected into the preBötzC weeks after the completion of the FA studies. This tachypneic hyperpnea was dose dependent, increasing from 25 to 250% above control as the volume of IA increased from 0.5 to 5 μl (12).

Physiological responses post-FA. Eupneic breathing, resting Paco₂, and CO₂ sensitivity (ΔV̇I/ΔPaco₂) were measured 5 days pre- and post-FA (n = 6, 12 trials). Five days post-FA, resting Paco₂ was significantly increased by 2.6 Torr (P < 0.005, Table 1), although still within normal limits (9–11, 17, 18, 36, 37). Total ventilation during eupneic breathing conditions did not differ between pre- and post-FA studies (P = 0.76), but, 5 days after FA, f was accentuated by 10.5% (P < 0.002, n = 7). Note that there was no increase in f when IA was injected in an area that was dorsal and lateral to the preBötzC (control). The time point of injection is indicated by the dashed lines.

Table 1. A focal acidosis within the pre-Bötzinger complex results in chronic respiratory effects

<table>
<thead>
<tr>
<th>Goat</th>
<th>V̇I l/min</th>
<th>f, breaths/min</th>
<th>V̇̇I liters</th>
<th>Paco₂ Torr</th>
<th>CO₂ Sensitivity (ΔV̇I/ΔPaco₂)</th>
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<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<td>Pre</td>
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<tr>
<td>Average</td>
<td>7.9±0.6</td>
<td>7.8±0.7</td>
<td>20.3±1.6</td>
<td>30.5±3.2*</td>
<td>0.4±0.05</td>
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| 6 animals and 12 trials. Within 5 days after focal acidosis (Post), respiratory frequency (f) and resting arterial PCO₂ (Paco₂) were significantly increased, and tidal volume (V̇I) was significantly decreased compared with the pre-focal acidosis (Pre) studies (P = 0.002, n = 7). V̇I, pulmonary ventilation; Δ, change.

Fig. 3. The glutamate receptor agonist, ibotenic acid (IA), elicited a tachypneic hyperpnea when injected into the preBötzC of awake goats. When 0.5 μl IA was injected bilaterally into the preBötzC, there was a significant increase in respiratory frequency (f) (P = 0.002, n = 7).
and VT was decreased by 7.5% (P < 0.03). FA had no significant effect on CO2 sensitivity (P > 0.56) (Table 1) conventionally expressed as ΔVt/ΔPaCO2. Total ventilation during 3, 5, or 7% inspired CO2 (Fig. 4) also were not significantly (P > 0.06) different pre- vs. post-FA, but there was a trend of a lower value at each inspired CO2 fraction post-FA.

Plasma and preBötC ECF pH measurements during whole body hypercapnia. There was a progressive decrease in both blood and preBötC ECF fluid pH during 3, 5, and 7% inspired CO2 (Fig. 5). There was a trend that the change in brain pH decreased more than blood pH at each level of hypercapnia; however, these differences were not significant (P > 0.05, n = 5, 12 trials).

Physiological response to MD-FA in the preBötC area. Unilateral MD of mCSF equilibrated with 6.4% CO2 (control) had no significant effect on Vt, f, or VT (Fig. 6). However, MD of both 25 and 50% CO2 both significantly increased Vt (P < 0.03 and 0.01, respectively) as a function of a significant increase in f (P < 0.01, and 0.04, respectively) maximally by 10%, most often during the last 10 min of the dialysis period (n = 10, 17 trials). Vt and f often remained elevated during the recovery period, although both began to return to baseline in the recovery period. This temporal pattern during the recovery has been observed in our laboratory’s previous studies on FA in the MRN (10, 11) and CFN (17), and we presume this pattern reflects the gradual restoration of brain pH to normal. VT was unaffected by FA (P > 0.05, Fig. 6).

Bilateral MD of mCSF equilibrated with 6.4, 25, or 50% CO2 did not have any consistent and significant effect on Vt, f, or VT (P > 0.05, n = 6, 6 trials, Fig. 7). However, as shown in Fig. 8, in some goats bilateral MD at some levels of FA did stimulate breathing. For the group of goats, there were nonsignificant (P > 0.05) 4–8% increases in Vt and f, but not VT, with MD of 6.4% CO2 during the dialysis period, as well as nonsignificant 4–6% increases in Vt and f with 50% CO2, mostly during the recovery period (Fig. 7). In one goat, a bilateral FA was created by dialyzing 80% CO2 (pH = 6.35). During dialysis, there was a prominent
increase in $V_I$ to a level that was 180% above control (Fig. 8). Moreover, the characteristic regular inspiratory flow and diaphragm activity became very irregular (Fig. 8). For 4 days thereafter during control conditions, $f$ continued to be 50–200% above normal, and a gasping pattern emerged. However, there were also periods of decreased $V_I$, indicating possible upper airway constriction. After the fourth day, however, breathing and muscle activation patterns were normal.

In a second goat, a unilateral FA created with 80% CO$_2$ increased $f$ by 13%, although $V_I$ was relatively unchanged. However, during the entire dialysis periods, and for the subsequent days after MD, there were disruptions in the airflow pattern. Then 2 days later, almost immediately after the start of bilateral MD of 6.4% CO$_2$, $V_I$ and $f$ increased to levels 180% above control, and the disruptions in airflow pattern, as indicated by both fractionated breathing and prolonged apneas, were so severe that MD was stopped after 5 min. Based on the disruptions in the flow pattern in these two goats with dialysis of 80% CO$_2$, unilateral and bilateral MD with 80% CO$_2$ was discontinued in subsequent animals.

A unilateral or bilateral FA at any level did not significantly affect MABP, HR (Figs. 9 and 10), $V_O$, or $P_{aCO_2}$ ($P > 0.05$) (Fig. 11).

**DISCUSSION**

**Major conclusions.** The present study shows that a FA in the preBo¨tzC area of the awake goat does increase ventilation through effects on respiratory $f$ but not $V_T$. However, the increase in breathing during FA is small compared with the increase during a global brain acidosis.

Functional and anatomical definition of the preBo¨tzC. Several studies have attempted to define the boundaries of the preBo¨tzC. Studies in adult rats found a distinct increase in NK1R-positive neurons ventral to NA (6, 7, 34, 35). Subsequently, data from other studies suggested that a high density of somatostatin immunoreactive neurons ventral to NA accurately defined the boundaries of the preBo¨tzC (34). To further explore “the necessary and sufficient boundaries for a functional preBo¨tzC,” studies have recently been completed on neonatal rat medullary slices of different thicknesses (25, 26). The data indicate there is a core of rhythmogenic neurons ~0.7 mm caudal to the facial nucleus essential for respiratory rhythmogenesis, with neurons caudal and rostral to the core that contribute to the eupneic and sigh rhythms, respectively. From these and other studies, the general consensus is that the exact boundary of the preBo¨tzC, or boundary of the medullary neurons responsible for the eupneic respiratory rhythm, has not been established, and there is no consensus on anatomic markers that accurately define the preBo¨tzC. However, it is generally accepted that the preBo¨tzC includes an area ventral to NA that has a high density of NK1R- and somatostatin receptor-expressing neurons.

Previously reported data from our laboratory (36), together with data shown in Fig. 1 of this paper, establish that, in goats, there is a high density of neurokinin-1-positive neurons in an area that is just ventral to NA and medial to the spinal
trigeminal nucleus, spanning a region that is 2.5–3.5 mm rostral from obex. Postmortem histology on the goats studied herein revealed that the MTs were placed within a range of 2.5–3.5 mm rostral from obex, just dorsal to the area of peak neurokinin-1-expressing neurons (Fig. 2). Since the dialysis probe was inserted 2.0 mm beyond the tip of the MT, we are confident that FA was created in the preBo¨tzC.

Physiologically, the preBo¨tzC can be defined by a distinct, unique tachypnic and dysrhythmic response to injection of a glutamate receptor agonist (19, 30, 37). Weeks after the completion of the FA studies, the glutamate agonist IA was injected into the preBo¨tzC in incremental volumes over a period of 4 wk. The smallest 0.5-μl dose of IA elicited a significant tachypnea (Fig. 3), which was accentuated in a dose-dependent manner with 1 and 5 μl of IA. These data corroborate the histological findings that the MTs were correctly placed within the preBo¨tzC. Since the MT was in the ventral portion of NA, the FA may also have occurred in a portion of NA. However, our laboratory has previously documented that, for at least dialysis within the MRN, MD, even up to 80% CO₂, only creates an acidosis at a distance <1.4 mm from the dialysis probe (10). Thus we are confident that the acidosis created in this study was restricted to a small area within and surrounding the preBo¨tzC area.

**Physiological responses of an MD-FA in the preBo¨tzC.** A FA created in the preBo¨tzC elicits ventilatory responses that are uniquely different from the responses of a FA in the MRN (10, 11) or CFN (17) of awake goats. First, FA in the preBo¨tzC increases breathing solely due to increases in f, and not V̇t, whereas a FA in the MRN and CFN alters breathing through
changes in \( V_r \). The present data are consistent with the effects of carbonic anhydrase inhibition-induced FA in the preBo\( \ddot{\text{C}} \) in anesthetized cats (31) and the effect of acidosis in the superfusate bathing a neonatal rat medullary slice containing the preBo\( \ddot{\text{C}} \) (12). In both of these reduced preparations, acidosis increased phrenic burst frequency. Second, a FA in the preBo\( \ddot{\text{C}} \) does not elicit nonrespiratory effects, whereas a FA in the MRN (10, 11) or CFN (17) results in significant changes in \( V_O^2 \), MAP, or HR. These first two unique effects seem consistent with the important role of the preBo\( \ddot{\text{C}} \) in respiratory rhythm generation (4, 19, 23, 29, 30, 37). Third, bilateral FA with 25 and 50% CO\( _2 \) in the preBo\( \ddot{\text{C}} \) does not elicit any consistent or significant ventilatory response, whereas bilateral FA in the MRN elicits a greater response than a unilateral FA (10, 11).

Fourth, as opposed to FA in the MRN, a FA in the preBo\( \ddot{\text{C}} \) with 25 and then 50% CO\( _2 \) does not elicit a significant dose-dependent increase in \( V_I \) and \( f \). However, in two of two goats, dialysis of 80% CO\( _2 \) increased \( f \) more than dialysis of 25 and 50% CO\( _2 \), which appears to suggest a dose-dependent response. It might be relevant though that, in these two goats, dialysis with 80% CO\( _2 \) also caused dysrhythmic and disrupted breathing (Fig. 8) that persisted for days after dialysis. This type of response never occurred during FA in the MRN (10, 11) or CFN (17), but these responses somewhat resemble previous findings of Solomon et al. (31) that FA in the preBo\( \ddot{\text{C}} \) of anesthetized cats resulted in augmented phrenic bursts (fictive sighs) or doublet/prefixed phrenic bursts. In any event, it is clear that the responses to increasing levels of FA at the preBo\( \ddot{\text{C}} \) differ from the responses to increasing levels of FA at the MRN and CFN. Finally, it is important to note that, days after completion of the FA studies, resting \( f \) and \( P_{CO_2} \) were slightly increased, and there was a trend toward reduced CO\( _2 \) sensitivity compared with pre-FA studies. In our previous work of FA in the MRN and CFN, we never studied the chronic effects of FA on breathing.

We are unaware of any definite explanation for the differences in effects of FA in the preBo\( \ddot{\text{C}} \) and the MRN or CFN. One potential explanation for the absence of a dose-dependent effect between 25 and 50% CO\( _2 \) and/or absence of a bilateral FA effect as in the MRN is that FA may not affect the preBo\( \ddot{\text{C}} \) chemosensitive neurons uniformly. This possibility is similar to the contrasting observations reported with acidifying different portions of the CFN in awake goats (17). Accordingly, FA with 25% CO\( _2 \) may activate primarily chemosensitive neurons that stimulate breathing, while 50% CO\( _2 \) may activate neurons that stimulate breathing and other neurons that depress breathing. Another possibility is that chemosensitive and/or rhythmogenic neurons in the preBo\( \ddot{\text{C}} \) are less capable of tolerating the process of dialysis and/or FA than neurons in the MRN and CFN; thus bilateral dialysis or the extreme FA with 80% CO\( _2 \) may have “injured” the neurons, resulting in the unusual findings. Finally, it is possible that absence of a hyperpnea with bilateral dialysis reflects deterioration of the rhythm generator rendered nonresponsive to CO\( _2 \) because of previous exposure to FA. The small differences in breathing pre- vs. post-FA may reflect tissue damage/deterioration of the rhythm generator as a result of the FA or dialysis process per se. It is also possible that compression of the preBo\( \ddot{\text{C}} \) neurons caused by implanting the MTs may have damaged the chemosensitive neurons and attenuated their response to the FA. In evaluating this potential effect, however,
it is important to consider that compression and damage also occurred when MTs were implanted into the MRN and the CSF, and these differences between responses to FA at various sites cannot categorically be attributed to tissue damage. Also, despite any damage to the preBotzC neurons, there was a brisk, dose-dependent response to the IA injections, after completing the FA studies. Also important to consider is that, as explained in the Fig. 2 legend, the tissue damage shown in Fig. 2 is due primarily to the IA injections. Overall, the differences between the past and present studies seem to indicate that chemosensitive neurons in the preBotzC are inherently different from those in the MRN and CFN, or that the input of these chemoreceptors contributes differently than other chemoreceptors to the neuronal network controlling breathing.

In a previous study on awake adult goats, it was found that, when inspired CO$_2$ was sequentially increased at 5-min intervals to 3, 5, and 7% CO$_2$, the change in pH of ECF in the MRN was ~50% of the change in plasma pH (10). It was speculated that the relatively lesser change in the MRN ECF pH was due to local H$^+$ buffering mechanisms, such as an increase in blood flow to this region. In the present study, however, we found that the same protocol for inducing an acute global respiratory acidosis reduces ECF pH in the preBotzC and plasma pH equally. Others have found that intracellular acidosis during global acidosis is also not uniform over different medullary regions (14). These findings suggest that local H$^+$ regulation is not uniform throughout the brain stem; thus, for all chemoreceptors that have equal sensitivity, the chemoreceptors at different sites in the brain stem would not contribute equally to the hyperpnea during a systemic, whole body hypercapnic acidosis. Thus the data indicate that the response to FA is indeed not uniform over many chemosensitive sites.

Past and the present studies provide insight into the issue of the need for chemoreceptors at widespread sites in the brain. Nattie et al. (4, 20, 21) have proposed that chemoreceptors at widespread sites are needed to serve different physiological functions. For example, data from their studies suggest the effect on breathing and other physiological functions is state dependent (4, 20, 21). The key findings from this study are as follows: 1) during global acidosis, ECF pH does not change the same in the preBotzC as previously found in the MRN; and 2) the ventilatory and overall physiological responses to FA in the preBotzC are not qualitatively or quantitatively the same as previously shown for other brain sites. Accordingly, the data suggest that not all chemoreceptors are specifically respiratory, and that some affect other physiological functions that are required to meet the multiple physiological needs imposed by global acidosis. Finally, it seems intuitive to have widespread chemoreceptor sites, with variable response characteristics, rather than a single site with powerful response characteristics because, with the latter scenario, a FA at a powerful site would create an alkalosis throughout the remainder of the brain.

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