Is Brain ECF [H+] an Important Drive to Breathe in Man?*

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The importance of brain extracellular fluid [H+] in the control of breathing has been amply emphasized for more than two decades. The input from these medullary chemoreceptors is believed to represent a critical drive to eupneic ventilation in health at sea-level and has been implicated as the key mediator of time-dependent ventilatory acclimatization to a variety of chronic conditions—including all acid-base disturbances and high altitude sojourn. These claims are based essentially on 2 premises: that these chemoreceptors have an extremely high gain as estimated from ventricular-cisternal perfusion experiments in awake goats and CO2 breathing in man, to approximate 5 L/min Δ V̇A per Δ 0.1 CSF pH (in man); that [H+] in the brain ECF environment of these chemoreceptors is very precisely and quickly regulated, with respect to plasma, during various acid-base disturbances. We have examined the role of brain ECF [H+] in the control of ventilation in man during acclimatization to high altitudes and progesterone therapy and during "de-acclimatization" from long-term hypocapnia and hypoxia. Our data fail to support either of the 2 premises outlined above and are consistent with the postulate that brain ECF [H+] is a function rather than a cause of ventilatory control in these physiologic (air-breathing) states. Our evidence is summarized according to 3 possible environments for these medullary chemoreceptors in brain ECF.

1. **Role of [H+] in the bulk CSF.** A key finding here is that in long-term hypocapnia—unlike primary metabolic acid-base disturbances or shorter-term hypercapnia (see Kazemi, this issue)—compensatory reductions in [HCO₃⁻] are equivalent in CSF and plasma (Fig 1). The result is a progressive, sustained alkalosis in CSF during ventilatory ac-

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**FIGURE 1.** HCO₃⁻ vs PCO₂ and [H+] vs PCO₂ in CSF or arterial plasma in healthy humans in long-term hypocapnia (2-3 weeks' oral medroxyprogesterone and 26 hours' voluntary hyperventilation) and hypoxic hypcapnia (5 days to 3 weeks at 3100-4300 m). The regression lines ± 95% confidence intervals are: plasma [HCO₃⁻] = 0.41 (PCO₂) + 7.97 ± 0.8 meq/L; and CSF [HCO₃⁻] = 0.34 (PCO₂) + 7.52 ± 0.8 meq/L. Percent [H+] compensation at any given level of chronic hypocapnia was identical (and incomplete) in plasma and CSF.
climatization—as shown at high altitudes in Figure 2. CSF [H+] is not the only variable changing in a direction incompatible with the accompanying ventilatory changes, i.e., from acute through 1-2 weeks of hypoxia, arterial PO₂ and pH both rise. Accordingly, if these potential chemoreceptor stimuli represent the only change in drive during acclimatization, clearly the sojourner would experience a severe progressive hypoventilation and CO₂ retention.

2. Role of [H+] in brain interstitial fluid—may be a more appropriate question if—contrary to published data—bulk CSF and chemoreceptor ECF [H+] do not change equally in the chronic steady-state. This interstitial fluid cannot be measured directly but may be determined, or at least influenced by, the [HCO₃⁻] gradient between bulk CSF and capillary plasma. First we exposed 10 sojourners to 3200 m while maintaining plasma [HCO₃⁻] ≥ sea-level control values for 4-6 days (by NaHCO₃ ingestion). [HCO₃⁻] and pH in plasma and their gradients between CSF and plasma were markedly elevated above those in the normal sojourner, but ventilatory acclimatization proceeded in a normal fashion. Secondly, we had 8 subjects maintain PaCO₂ ≈ 30 mm Hg for 26 hours by voluntary hyperventilation in normoxia and mild hypoxia—and observed a spontaneous hyperventilation in normoxia which persisted following these 26 hour periods. Although this spontaneous hyperventilation was much greater following hypoxic than normoxic voluntary hyperventilation, plasma and CSF [HCO₃⁻] and [H+] were identical in the two conditions. These two studies demonstrate that neither plasma nor CSF [HCO₃⁻] or [H+] or their gradients determined ventilatory acclimatization to hypoxia.

3. Role of [H+] at any ECF site in brain—(i.e., those unaffected by bulk CSF or plasma [H+] or their differences). This hypothesis is of course more difficult to test, but we present 3 types of negative evidence based on the premise that molecular CO₂ diffuses readily to most ECF sites in brain.

a. We have shown that man’s ventilatory response to doxapram hydrochloride infusion is unchanged by acute respiratory or chronic metabolic acidosis but is enhanced fourfold during sojourn at high altitude.

b. Following acclimatization to high altitude, acute induction of normoxia is accompanied by continued hyperventilation which slowly decreases to sea-level normal values over the ensuing 24 hours. CSF pH became progressively more acid—down to values < 7.28—as ventilation fell toward normal. These negative CSF [H+]-ventilation relationships during de-acclimatization from hypoxia are a mirror image of those during acclimatization to hypoxia.

c. Six patients with mild to severe airway obstruction and chronic CO₂ retention and hypoxemia showed an acid CSF pH (≤ 7.29). The question of why they don’t respond to this apparently strong ventilatory drive may be traditionally explained by a failing ventilatory pump. However, these same patients corrected their CO₂ retention after 4-5 weeks of oral medroxyprogesterone treatment—a finding which we believe seriously questions the relative gain of the “central” [H+] stimulus.

In summary, we believe these data permit 3 main conclusions:

- That CSF [H+] is imperfectly regulated in chronic respiratory acid-base disturbances in man.
- That ventilatory acclimatization and de-acclimatization proceed despite the accompanying changes in brain ECF [H+].
- That the actual sensitivity of medullary [H+] chemoreceptors as a drive to ventilation in man is 252 20TH ASPEN LUNG CONFERENCE
substantially less than commonly claimed.

These findings also warrant the further question of whether brain ECF [H\(^+\)] really contributes to human ventilatory drive in truly physiologic situations, i.e., those conditions which do not involve CO\(_2\) breathing or ventricular perfusion with acid solutions. While further evidence is certainly needed on this important point, we believe the available negative evidence sufficient to warrant serious investigation of alternative mediators to ventilation in the CNS. Dr. Forster will elaborate on these alternatives in the following paper.

ACKNOWLEDGMENTS: This work was supported in part by National Heart, Lung and Blood Institute Grant No. 15469, U.S. Army Contract No. DAMD 17-77-C-7006 and National Heart, Lung and Blood Institute Career Development Award No. 00149.

REFERENCES
1 Leusen I: Regulation of cerebrospinal fluid composition with reference to breathing. Physiol Rev 52:1-56, 1972

Role of Intracranial [H\(^+\)] Receptor in Physiologic Regulation of Ventilation in Ponies*


Numerous studies have demonstrated the existence of an intracranial [H\(^+\)] chemoreceptor mechanism capable of stimulating ventilation.\(^1\) Supposedly, this chemoreceptor is located 0.2 mm below the surface of the ventrolateral side of the medulla and is responsive to [H\(^+\)] in the surrounding cerebral extracellular fluid (ECF). During chronic conditions, ECF [H\(^+\)] is supposedly in equilibrium with CSF [H\(^+\)]; hence, stimulus level can be established through sampling and analysis of CSF. In this presentation, we summarize data from studies on spontaneously breathing, unanesthetized ponies which suggests this [H\(^+\)] receptor may not contribute significantly to physiologic regulation of ventilation. We also provide evidence in support of one postulated CNS mechanism modulating ventilatory responsiveness.

Role of Intracranial [H\(^+\)] Receptor in Ventilatory Control

The mechanism underlying the hyperpnea of muscular exercise is as yet unknown. However, the relationship between ventilation (\(\dot{V}\)\(_A\)) and metabolic rate (\(\dot{V}\)\(_O_2\)) suggests exercise hyperpnea reflects merely an intensification of stimuli driving \(\dot{V}\)\(_A\) during euepnic conditions. Accordingly, ascertaining the role of a given stimulus in the hyperpnea of exercise also is informative regarding the role of this stimulus in euepnic \(\dot{V}\)\(_A\). We therefore felt it would be informative to study CSF [H\(^+\)] during treadmill exercise in ponies.

Normal ponies’ \(\dot{V}\)\(_A\) response to exercise is virtually identical to man’s (Table 1).\(^2\) \(\dot{V}\)\(_A\) and \(\dot{V}\)\(_O_2\) increase proportionately through approximately an eightfold increase in \(\dot{V}\)\(_O_2\), to maintain homeostasis of alveolar and arterial blood gases. At more intense exercise, that is, above the so-called anaerobic threshold, arterial lactacdois is evident and is accompanied by hyperventilation. Below the anaerobic threshold, CSF pH is unchanged from rest, but it increases during respiratory compensation of the metabolic acidosis in plasma during intense muscular exercise. Although CSF and ECF [H\(^+\)] may not be in equilibrium during dynamic conditions such as muscular exercise, we calculate ECF [H\(^+\)] would change qualitatively as the \(\dot{V}\)\(_O_2\) induced changes in CSF [H\(^+\)]. Accordingly, we conclude the intracranial [H\(^+\)] receptor does not contribute to the hyperpnea at any intensity of muscular exercise, and we question whether it contributes appreciably to euepnic breathing.

Data obtained from two conditions of chronic CSF acidosis support the above conclusions. In 3 afebrile healthy ponies with local inflammatory reaction at the site of a chronic cisternal CSF catheter, repeated CSF sampling during rest and exercise revealed an approximate 0.1 acidosis in CSF coupled with normal \(\dot{V}\)\(_A\) and arterial blood gases (Table 1). Our second example of chronic CSF acidosis is in hyperventilating, hypacapnic ponies following surgical removal of the peripheral chemoreceptors.\(^3\)\(^4\) Three weeks after surgery, \(\dot{V}\)\(_A\) was 20-25 percent below normal, while cisternal CSF pH was 0.028 to 0.045 acid. Accordingly, if the intracranial [H\(^+\)] receptor has a major role in normal regulation of ventilation, then it would seem the changes in [H\(^+\)] of

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CHEST, 73: 2, FEBRUARY, 1978 SUPPLEMENT

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