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The Carotid Chemoreceptors are a Major Determinant of Ventilatory CO_2 Sensitivity and of $PaCO_2$ During Eupneic Breathing

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Abstract Both carotid and intracranial chemoreceptors are critical to a normal ventilatory CO_2-H^+ chemosensitivity. At low levels of hypercapnia, the carotid contribution is probably greater than the central contribution but, at high levels, the intracranial chemoreceptors are dominant. The carotid chemoreceptors are also critical to maintaining a stable and normal eupneic $PaCO_2$, but lesion-induced attenuation of intracranial CO_2-H^+ chemosensitivity does not consistently alter eupneic $PaCO_2$. A major unanswered question is why do intracranial chemoreceptors in carotid body denervation (CBD) animals tolerate an acidosis during eupnea which prior to CBD elicits a marked increase in breathing.

For years, views on ventilatory CO_2-H+ chemosensitivity were based primarily on elegant studies in awake goats (Fencl, Miller and Pappenheimer 1966). Under conditions of acute and chronic metabolic and respiratory acidosis and alkalosis, alveolar ventilation was a single function of cerebral interstitial fluid (ISF) [H+]. These data indicated that intracranial chemoreceptors were solely responsible for CO_2-H+ ventilatory responsiveness. Contributing to this view were studies showing only small changes in carotid sinus nerve activity of anesthetized mammals when arterial PCO_2 was altered, suggesting that carotid chemoreceptors contributed minimally to CO_2-H+ ventilatory responsiveness (Lahiri and DeLaney 1975).

However, views on CO_2-H^+ chemosensitivity have changed as a result of recent studies, which utilized different techniques such as transient CO_2 administration (Edelman, Epstein, Lahiri and Cherniack 1973), carotid body denervation (CBD) (Belleville, Whipp, Kaufman, Swanson, Aqleh and Wiberg 1979; Bisgard, Forster, Orr, Buss, Rawlings and Rasmussen 1976; Hodges, Opansky, Qian, Davis, Bonis, Krause, Pan and Forster 2005; Pan, Forster, Martino, Strecker, Beales, Serra, Lowry, Forster and Forster 1998; Rodman, Curran, Henderson, Dempsey and Smith 2001), mathematical modeling (Belleville, *et al*. 1979), and isolated perfusion of carotid and intracranial chemoreceptors (Heeringa, Berkenbosch, de Goede and Olievier 1979;

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Table 1 Intracranial and carotid chemoreceptors contribute to CO_2-H^+ sensitivity

Investigator	Central (%)	Peripheral (%)	Species	Technique
Edelman, *et al*. 1973	66	33	Awake human	Single breath
Heeringa, *et al*. 1979	66	33	Anesthetized cats	Isolated perfusion
Bellville, *et al*. 1979	66	34	Awake human	2 compartment model
Bellville, *et al*. 1979	35	—	CBD human	2 compartment model
Pan, *et al*. 1998	40	60	Awake goat	CBD
Rodman, *et al*. 2001	66	33	Awake dog	CBD
Smith, *et al*. 2006	63	37	Awake dog	Isolated perfusion

Smith, Rodman, Chenuel, Henderson and Dempsey 2006). The consistent finding has been that intracranial chemoreceptors contribute about two-thirds of the CO_2-H^+ ventilatory response while the carotid chemoreceptors contribute one third of the response (Table 1). However, as detailed later, it is likely that near the eupneic $PaCO_2$, the carotid contribution exceeds the intracranial contribution.

The carotid contribution seems large in spite of the small increase in sinus nerve activity during hypercapnia. This apparent discrepancy might be a result of carotid afferents having an effect beyond signaling the hypercapnia to medullary rhythm (RGN) and pattern (PGN) generating neurons. Indeed, studies on anesthetized rats indicate that carotid afferents modulate the activity of chemoreceptor neurons in the retrotrapezoid nucleus (Takakura, Moreira, Colombari, West, Stornetta and Guyenet 2006). Absence of this modulation might explain why in awake goats CBD accentuates the hypopnea induced by cooling the rostral ventrolateral medulla (Pan, Forster, Ohtake, Lowry, Korducki and Forster 1995). Also, carotid modulation of intracranial chemoreceptors may explain why CBD atttenuates the hyperpnea induced by focal acidosis in raphe nuclei (Hodges *et al*. 2005). Accordingly, it appears that carotid afferents affect the activity of intracranial chemoreceptor neurons and/or the response of the RGN and PGN to intracranial chemoreceptor activity.

The carotid CO_2-H^+ chemoreceptors are also determinants of eupneic breathing in the awake state. This conclusion is based on findings that hypocapnia specific to the carotid body reduced breathing (Daristotle, Berssenbrugge, Engwall and Bisgard 1990). Also, studies have found that CBD decreased eupneic breathing resulting in an increased $PaCO_2$ which, in awake dogs, goats and ponies reached 13.0, 13.3 and 18.1 mmHg above control respectively (Bisgard *et al*. 1976; Hodges *et al*. 2005; Pan *et al*. 1998; Rodman *et al*. 2001). This hypercapnia results in at least a 0.03 acidosis in cerebral ISF, which should increase activity of intracranial chemoreceptors (Bisgard *et al*. 1976). Accordingly, these data provide further evidence that absence of carotid chemoreceptor activity reduces sensitivity of intracranial chemoreceptors.

CBD also increases the minute-to-minute variation in eupneic $PaCO_2$ (Klein, Forster, Bisgard, Kaminski, Pan and Hamilton 1982). The increased variation likely

results from the slower response to changes in $PaCO_2$ of intracranial compared to carotid chemoreceptors; thus, after CBD, there is a relative delay in correction of $PaCO_2$ fluctuations resulting in more variability (Smith *et al*. 2006). Accordingly, it has been concluded "that the slower response of the central vs. the carotid chemoreceptors prevents the central chemoreceptors from contributing significantly to ventilatory responses to rapid, transient changes in arterial PCO_2" (Smith *et al*. 2006).

The contribution of the intracranial chemoreceptors to eupneic breathing in the awake state is unclear. Studies have found attenuated CO_2 sensitivity and decreased eupneic breathing after perturbations in the medulla (Forster, Ohtake, Pan, Lowry, Korducki, Aaron and Forster 1995; Gray, Janczewski, Mellen, McCrimmon and Feldman 2001). However, it is likely that these perturbations also affected RGN and PGN neurons; thus, these studies do not provide a clear indication of the contribution of intracranial chemoreceptors to eupneic breathing.

Many studies have found that lesions within known intracranial chemoreceptor areas result in a dissociation between effects on eupneic breathing and CO_2-H^+ ventilatory chemosensitivity. For example, in rats during wakefulness and NREM sleep, neurotoxic destruction of 58% to 79% of NK1R expressing neurons in the ventral medulla reduced CO_2 sensitivity by about 60%, but reduced eupneic breathing only 10% (Nattie and Li, in press). Similarly, in awake goats, lesions in the raphe, RTN, or cerebellar fastigial nucleus (CFN) reduced CO_2 sensitivity by 20% to 50% with no or minimal hypercapnia during eupnea (Forster, Pan, Lowry, Feroah, Gershan, Whaley, Forster and Sprtel 1998; Hodges, Opansky, Qian, Davis, Bonis, Bastasic, Leekley, Pan and Forster 2004; Martino, Davis, Opansky, Krause, Bonis, Pan, Qian and Forster, submitted). This dissociation differs markedly from the effects of CBD, after which there is always a close correspondence between changes in eupneic $PaCO_2$ and CO_2 sensitivity (Pan *et al*. 1998).

Data from lesioning the CFN suggest one contributing factor to the dissociation between eupneic $PaCO_2$ and CO_2-H^+ sensitivity (Martino *et al*., submitted). Specifically, after CFN lesioning, CO_2 sensitivity (pulmonary ventilation, $\dot{V}_1$ /$PaCO_2$) was reduced by a maximum of 43%, and the coefficient of variation (CV), assessed eight to ten times before and after lesioning, increased from 15% to 30%. In contrast, CFN lesioning only increased eupneic $PaCO_2$ by 0.3 ± 0.3 mmHg and the respective CVs were 4.0 ± 0.6 and 3.7 ± 0.4%. When $\dot{V}_1$ at elevated inspired CO_2 was expressed as a percent of the room air $\dot{V}_I$, the absolute values (Fig. 1A) and the CV at 3% and 5% inspired CO_2 did not differ between pre and post CFN lesion studies. However, the values at 7% inspired CO_2 were reduced ($p < 0.05$) by 14% and the CV was increased from 17 to 24% ($p < 0.05$). In contrast, in awake goats after CBD, all values were reduced ($p < 0.05$) after the first minute at 3% inspired CO_2 (Fig. 1B) (Hodges *et al*. 2005). It appears then that the CFN lesions did not affect the carotid contribution to CO_2 sensitivity. This unaltered carotid contribution could then at least partially explain the dissociation of CO_2 sensitivity and eupneic breathing following CFN lesioning. In essence, the tonic carotid input and the rapid response of carotid chemoreceptors to changes in $PaCO_2$ normally maintains a near normal and stable $PaCO_2$ in spite of changes in intracranial CO_2-H^+ chemosensitivity.

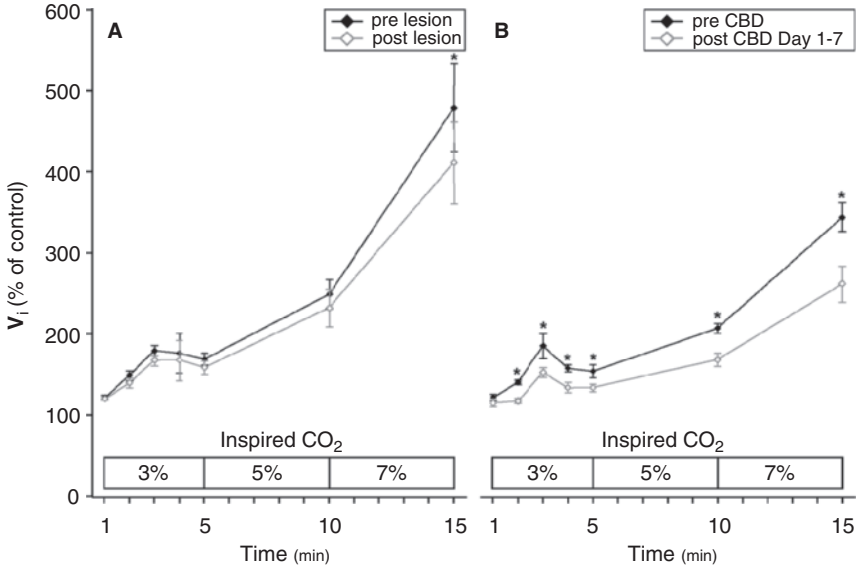

Fig. 1 Lesions within the CFN (n = 9) do not reduce CO_2 sensitivity until inspired CO_2 exceeds 5%, but CBD (n = 8) reduces sensitivity even at 3% inspired CO_2. Asterisks denote significant ($p < 0.05$) differences between pre and post CFN lesioning (A) and CBD (B)

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