Role of carotid bodies in control of the neuroendocrine response to exercise

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The present study was designed to test the hypothesis that the carotid bodies, or receptors near this site, play a role in initiating the neuroendocrine response and maintaining arterial glucose homeostasis during exercise. To examine the role of the carotid bodies, or receptors anatomically near the site, carotid body-resected (CBR) conscious dogs or dogs having undergone a sham surgery (Sham) were studied in the basal state and during 150 min of moderate-intensity treadmill exercise. Isotope-dilution methods were used to calculate glucose kinetics.

MATERIALS AND METHODS

Animal maintenance and surgical procedures. Mongrel dogs (n = 12, 23.9 ± 0.6 kg body wt) of either gender that had been fed a standard diet (Pedigree Choice Cuts, Vernon, CA; LabDiet, PMI Nutrition International, St. Louis, MO) were studied. The dogs were housed in a facility that met American National Standards Institute (ANSI) and American Association for Accreditation of Laboratory Animal Care (AAALAC) guidelines. Isotopic methods were used to measure glucose production and utilization. Glucose turnover rate was determined by the isotope-dilution technique. Glucose production was calculated by determining the amount of glucose produced as glucose-6-phosphate (G6P) by hepatic and other tissues, and the amount of glucose utilized by these same tissues was calculated by determining the amount of glucose used as fuel for the production of G6P. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

THE EXERCISE-INDUCED INCREASE in muscle glucose uptake would result in hypoglycemia if it were not matched by a similar increase in hepatic glucose production. Hypoglycemia does not normally occur, since exercise initiates neural and hormonal responses that aggres-
can Association for the Accreditation of Laboratory Animal Care guidelines, and the protocols were approved by the Vanderbilt University Animal Care and Use Committee. At least 16 days before each experiment, a laparotomy was performed under general anesthesia (1–2% isoflurane). Silastic catheters (0.03 in. ID) were inserted into the vena cava for subsequent tracer (\(^{3-3H}\)glucose) and indocyanine green (ICG) infusion. Silastic catheters (0.04 in. ID) were also inserted into the portal vein, left common hepatic vein, and iliac artery for subsequent blood sampling. After insertion, all catheters were filled with saline containing heparin (200 U/ml; Abbott Laboratories, North Chicago, IL), and their free ends were knotted.

Ultrasound blood flow probes (Transonic Systems, Ithaca, NY) were used to measure portal vein and hepatic artery blood flow (19). The portal vein and hepatic artery were accessed from the abdominal incision and fitted with 6.0- and 3.0-mm-ID flow probe cuffs, which were then secured around the vessels. Catheters and the Doppler probe leads were placed under the skin at the incision sites.

A 3-cm-long midline incision was made 1 cm proximal to the mylohyoid muscle and extended 8 cm distally. Blunt dissection was used to expose the left and right common carotid arteries at the point of their bifurcation into the external and internal branches. The tissue at the carotid sinus in which the carotid bodies were thought to lie was identified and excised. However, because the carotid bodies are difficult to visualize, associated nerves supplying the skeletonized area were transected to ensure that if carotid body tissue remained, it would not be able to transmit signals to the brain. Segments (1 cm) of the common carotid and each branch were skeletonized and cleared of all tissue. Care was taken not to disrupt the occipital, cranial, laryngeal, or other arterial branches close to the site. To ensure disruption of all neural tissue, the skeletonized areas were swabbed with alcohol (19). After the closure of the incision sites, the effectiveness of carotid body removal was verified by the absence of a ventilatory response to NaCN (20–40 \(\mu\)g/kg).

Starting 1 wk after surgery, dogs were accustomed to running on a motorized treadmill regardless of whether they were used for sedentary or exercise experiments. Animals were not exercised during the 48-h preceding an experiment. Only animals that had 1) a leukocyte count \(<18,000/\text{mm}^3\), 2) a hematocrit \(>36\%, 3\) normal stools, and 4) a good appetite (consuming the entire daily ration) were used for experiments. Studies were conducted after an 18-h fast, because dogs are postabsorptive after this interval. When dogs were postabsorptive after this interval, they were not exercised during the 48 h preceding an experiment. Heart rate and blood pressure were determined using an ultrasonic blood flow probe (Transonic Systems, Inc., Ithaca, NY). Heart rate and blood pressure were recorded continuously from the frequency shifts of the pulsed sound signal emitted from the blood flow probes (19). Heart rate and blood pressure were monitored throughout all studies. Arterial blood gases were determined at 30, 50, and 120 min.

Processing of blood samples. Plasma glucose levels were determined by the glucose oxidase method using a glucose analyzer (Glucose Analyzer 2, Beckman Instruments, Fullerton, CA). For the determination of plasma \(^{3}H\)glucose radioactivity, samples were deproteinized with barium hydroxide (Sigma Diagnostics, St. Louis, MO) and zinc sulfate (Sigma Diagnostics) on the day of the study. Samples were centrifuged, and the supernatant was evaporated and reconstituted in 1 ml of water and 10 ml of Ecolyte (+ ICN, Irvine, CA). Radioactivity was then determined by liquid scintillation counting using a Beckman LS-5000TD instrument. ICG concentration was measured spectrophotometrically (805 nm) in arterial and hepatic vein plasma immediately after experiments. Plasma nonesterified fatty acids were measured spectrophotometrically using the kit made by Wako Chemicals (Richmond, VA). Whole blood lactate, alanine, and glycerol concentrations were determined in samples deproteinized with a 1:3 volume of 4% perchloric acid by enzymatic methods (12) on a Monarch 2000 centrifugal analyzer (Instrumentation Laboratories, Lexington, MA). An acid-base analyzer (model ABL30, Radiometer, Copenhagen, Denmark) was used for determination of arterial blood gases and pH. Corrections were made between the temperature setting of the analyzer and the body temperature of the dogs.

Immunoreactive insulin was measured using a double-antibody system (interassay coefficient of variation (CV) = 10%). Immunoreactive glucagon was measured in plasma samples containing 50 \(\mu\)l of 500 kallikrein-inactivating units of Trasylol per milliliter (Bayer, Kankakee, IL) using a double-antibody system (interassay CV = 7%) modified from the method developed for insulin. Plasma norepinephrine and epinephrine levels were determined using a high-performance liquid chromatography technique (interassay CV = 11 and 13%, respectively). Plasma cortisol was measured using the Coat-A-Count cortisol radioimmunoassay kit (Diagnostic Products, Los Angeles, CA; interassay CV = 6%). The methods used for hormone analyses by this laboratory have been described previously (5).

Materials. High-performance liquid chromatography-purified \(^{3}H\)glucose was obtained from New England Nuclear (Boston, MA). ICG was purchased from Sigma Chemical (St. Louis, MO). Standard glucagon, \(^{125}\)I-glucagon, glucagon, insulin antisera, standard insulin, and \(^{125}\)I-insulin were obtained from Linco Research (St. Louis, MO). Enzymes used in chemical analyses were obtained from Sigma Chemicals (St. Louis, MO) or Boehringer Mannheim Biochemicals.

Calculations. Total glucose appearance (Ra, mg\(\cdot\)kg\(^{-1}\)\cdot min\(^{-1}\)) and disappearance (Rd, mg\(\cdot\)kg\(^{-1}\)\cdot min\(^{-1}\)) were determined using the two-compartment model described by Mari (14) for non-steady state with \(^{3}H\)glucose as the tracer. The isotope infusion was increased with exercise. This minimized the change in specific activity caused by the increased release of glucose from the liver and, thereby, the model dependency of the Ra calculation.

Net hepatic substrate balance (presented as \(\mu\)mol\(\cdot\)kg\(^{-1}\)\cdot min\(^{-1}\) or mg\(\cdot\)kg\(^{-1}\)\cdot min\(^{-1}\)) was determined by the following formula: HAF \(\times [(A) - (H)] + PVF \times [(P) - (H)]\), where [A], [P], and [H] represent arterial, portal venous, and hepatic venous concentrations, respectively.
[\text{P}], and [H] are the arterial, portal, and hepatic vein substrate concentrations and HAF and PVF are the hepatic artery and portal vein blood (or plasma) flows. In the calculations of lactate and glucose, the sign (+/−) was reversed so that net output would be a positive number. Net hepatic fractional substrate extraction equaled net substrate uptake by the liver divided by the substrate load reaching the liver, where the load equals HAF \times [A] + PVF \times [P]. Doppler-determined blood flows were used to calculate balances, except in cases where probes did not elicit a clear signal. In these instances, the ICG extraction method was used to determine total hepatic flow (6), with the assumption that 80% of the flow was via the portal vein.

Statistics were performed using StatView and SuperANOVA (Abacus Concepts, Berkeley, CA) on a Macintosh computer. Statistical comparisons between groups and over time were made using analysis of variance designed to account for repeated measures. Specific time points were examined for significance using contrasts solved by univariate repeated measures. Values for exercise time periods (Table 1) were calculated as the mean of three samples taken 20 min apart within the indicated time interval. This grouping was intended to provide values that reflected the response to initial stages of exercise, the transition from early to prolonged exercise, and the response to prolonged exercise. Differences were considered significant when \( P \leq 0.05 \). Values are means ± SE.

**RESULTS**

**Basal arterial blood gases, blood pressures, and hematocrit.** \( P_{\text{CO}} \) was significantly elevated in CBR (41 ± 3 mmHg) compared with Sham (33 ± 1 mmHg), while \( P_{\text{O}} \) was reduced (82 ± 9 and 103 ± 6 mmHg in CBR and Sham, respectively). Renal compensation for the hypercapnia was effective, inasmuch as pH was equivalent in the two groups (7.39 ± 0.01 and 7.38 ± 0.02 in CBR and Sham, respectively). Systolic and diastolic blood pressures were 164 ± 13 and 85 ± 7 mmHg in CBR and 145 ± 10 and 84 ± 3 mmHg in Sham. Heart rate was 90 ± 6 and 91 ± 6 beats/min in CBR and Sham, respectively. Hematocrit was 0.38 ± 0.01 and 0.38 ± 0.01 at rest in CBR and Sham, respectively, and 0.39 ± 0.02 and 0.41 ± 0.01 during exercise. There were no significant differences in blood pressure, heart rate, or hematocrit between the two groups.

**Arterial plasma glucagon and insulin.** Figure 1 shows changes in arterial plasma glucagon and insulin from basal. Insulin was equal in the basal period in Sham (8 ± 1 μU/mL) and CBR (7 ± 1 μU/mL), and concentrations decreased similarly during exercise. Basal arterial glucagon was reduced in CBR compared with Sham (29 ± 3 vs. 47 ± 3 pg/mL). During exercise, the glucagon increase was greater in Sham than in CBR (increase of 47 ± 9 vs. 15 ± 2 pg/mL).

**Arterial plasma cortisol and catecholamine responses.** Figure 2 shows arterial plasma cortisol. Basal cortisol was not significantly different in Sham and CBR. Arterial cortisol tended to increase higher in Sham than in CBR after 60 min of exercise, but differences were not significant. Figure 3 shows arterial plasma norepinephrine and epinephrine concentra-

**Table 1. Effect of exercise on arterial concentrations and hepatic balances of alanine, glycerol, lactate, and FFA in sham and CBR 18-h fasted dogs**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>10–50 min</th>
<th>60–100 min</th>
<th>110–150 min</th>
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</thead>
<tbody>
<tr>
<td><strong>Arterial alanine, μM</strong></td>
<td></td>
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<tr>
<td>Sham</td>
<td>289 ± 30</td>
<td>290 ± 38</td>
<td>245 ± 31</td>
<td>196 ± 23</td>
</tr>
<tr>
<td>CBR</td>
<td>232 ± 16</td>
<td>240 ± 22</td>
<td>206 ± 20</td>
<td>171 ± 22</td>
</tr>
<tr>
<td><strong>Net hepatic alanine uptake, μmol·kg⁻¹·min⁻¹</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>1.64 ± 0.4</td>
<td>1.79 ± 0.34</td>
<td>2.35 ± 0.54</td>
<td>2.31 ± 0.87</td>
</tr>
<tr>
<td>CBR</td>
<td>1.38 ± 0.25</td>
<td>1.7 ± 0.34</td>
<td>2.21 ± 0.37</td>
<td>2.11 ± 0.38</td>
</tr>
<tr>
<td><strong>Arterial glycerol, μM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>73 ± 65</td>
<td>216 ± 33</td>
<td>328 ± 69</td>
<td>390 ± 86</td>
</tr>
<tr>
<td>CBR</td>
<td>68 ± 5</td>
<td>200 ± 18</td>
<td>274 ± 15</td>
<td>287 ± 11</td>
</tr>
<tr>
<td><strong>Net hepatic glycerol uptake, μmol·kg⁻¹·min⁻¹</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sham</td>
<td>1.17 ± 0.16</td>
<td>3.04 ± 0.59</td>
<td>4.27 ± 1.07</td>
<td>4.59 ± 1.57</td>
</tr>
<tr>
<td>CBR</td>
<td>1.10 ± 0.10</td>
<td>2.57 ± 0.37</td>
<td>4.02 ± 0.53</td>
<td>4.55 ± 0.7</td>
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<tr>
<td><strong>Arterial lactate, μM</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sham</td>
<td>403 ± 46</td>
<td>708 ± 132</td>
<td>942 ± 194</td>
<td>829 ± 186</td>
</tr>
<tr>
<td>CBR</td>
<td>309 ± 38</td>
<td>693 ± 136</td>
<td>863 ± 208</td>
<td>792 ± 247</td>
</tr>
<tr>
<td><strong>Net hepatic lactate output, μmol·kg⁻¹·min⁻¹</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>1.51 ± 1.38</td>
<td>10.21 ± 4.07</td>
<td>0.12 ± 2.71</td>
<td>−4.94 ± 2.71</td>
</tr>
<tr>
<td>CBR</td>
<td>−0.23 ± 1.64</td>
<td>2.03 ± 1.87</td>
<td>−3.44 ± 1.67</td>
<td>−6.1 ± 1.21</td>
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<tr>
<td><strong>Arterial FFA, μM</strong></td>
<td></td>
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<tr>
<td>Sham</td>
<td>788 ± 84</td>
<td>844 ± 109</td>
<td>1,355 ± 227</td>
<td>1,633 ± 259</td>
</tr>
<tr>
<td>CBR</td>
<td>783 ± 96</td>
<td>832 ± 151</td>
<td>1,202 ± 172</td>
<td>1,424 ± 143</td>
</tr>
<tr>
<td><strong>Net hepatic FFA uptake, μmol·kg⁻¹·min⁻¹</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>2.42 ± 0.29</td>
<td>3.09 ± 0.42</td>
<td>3.90 ± 0.54</td>
<td>5.18 ± 0.67</td>
</tr>
<tr>
<td>CBR</td>
<td>2.08 ± 0.47</td>
<td>2.58 ± 0.64</td>
<td>3.54 ± 0.76</td>
<td>4.18 ± 0.67</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 6 \). CBR, carotid body resection; Sham, sham resection; FFA, free fatty acid.

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tions. Basal norepinephrine and epinephrine were similar in CBR and Sham. During exercise, norepinephrine increased by $432 \pm 6124$ pg/ml in Sham, but by only $201 \pm 28$ pg/ml in CBR ($P < 0.05$). Arterial epinephrine responses to exercise were similar in Sham and CBR.

**Arterial plasma glucose and glucose kinetics.** Arterial plasma glucose was similar in the basal period in Sham and CBR (105 $\pm 2$ and 108 $\pm 2$ mg/dl, respectively). Figure 4 shows exercise-induced changes in arterial plasma glucose from basal. Arterial glucose was not significantly changed in Sham (decreased by $3 \pm 2$ mg/dl) but dropped by $10 \pm 3$ mg/dl at the onset of exercise in CBR. The difference in arterial glucose was sustained for the first 100 min of exercise.

Basal glucose kinetics were equal in Sham and CBR (Fig. 5). At the onset of exercise, $R_a$ and $R_d$ were transiently uncoupled in CBR (i.e., $R_d > R_a$) but were closely matched in Sham. In steady-state exercise, $R_a$ and $R_d$ were closely matched in both groups. Net hepatic glucose output (NHGO) was $1.7 \pm 0.3$ mg·kg$^{-1}$·min$^{-1}$ in the basal state in Sham and 6.4 $\pm 1.0$, 7.9 $\pm 1.7$, and 8.3 $\pm 2.2$ mg·kg$^{-1}$·min$^{-1}$ at 10–50, 60–100, and 110–150 min, respectively. Basal NHGO was $1.7 \pm 0.2$ mg·kg$^{-1}$·min$^{-1}$ in CBR and $5.2 \pm 1.7$.
cannot rule out that the impairment in the increases in sympathetic activity and arterial glucagon is linked, so that an impaired sympathetic nervous response leads to decreased pancreatic α-cell glucagon release. We recently showed that the increase in net splanchnic release of glucagon with exercise occurs even after the pancreas has been denervated (7). Of course, this finding may be specific to pancreata that have been denervated chronically and may not apply to animals with an intact nerve supply to the pancreas. Another possibility is that it is the increment in circulating norepinephrine that is controlling the glucagon response, and it is the reduction in this variable that results in the attenuated glucagon response to exercise. The results of the present studies are consistent with the demonstration that the response to hypoxia, which is mediated by the carotid bodies, is characterized by activation of the neuroendocrine system (27). Moreover, they are consistent with the demonstration that inhalation of 100% O_2, which diminishes the electrical activity of carotid body afferents (15), attenuates the exercise-induced increase in norepinephrine (8).

It is conceivable that the impaired hypoglycemia- (11) and exercise-induced glucagon levels occur not as a result of impaired sensing of a blood signal due to the absence of the carotid bodies or receptors nearby, but as a result of an impaired capacity of the α-cell to produce or secrete the hormone. Although we could find no direct evidence in the literature to indicate that this should be expected, the presence of the chronic reduction in basal glucagon would be consistent with an adaptation of the α-cell that resulted in impaired glucagon synthesis or secretion. The possibility exists that the procedure alters a neural or chemical signal to the α-cell that chronically alters its function. The same possibility also exists for the exercise-impaired norepinephrine response. It should be noted, however, that basal concentrations and the capacity to increase norepinephrine in response to hypoglycemia are normal after CBR (11).

We recently showed that CBR dogs have an impaired glucoregulatory response to insulin-induced hypoglycemia. Although $R_a$ rose by $-2$ mg·kg$^{-1}$·min$^{-1}$ in response to moderate hypoglycemia ($-65$ mg/dl) in Sham dogs, it did not respond to hypoglycemia in CBR dogs. Compared with the response to hypoglycemia, the effect of CBR on glucoregulation during exercise was much more subtle. Arterial plasma glucose fell by $-10$ mg/dl at the onset of exercise in CBR (first sample was 10 min after exercise onset), while it was essentially unchanged in Sham. The arterial glucose was reduced for the remainder of the exercise period with respect to basal values. Interestingly, the effect of CBR on regulation of arterial glucose is essentially the same as it is with regulation of arterial $P_{CO_2}$. Human subjects treated for asthma by surgical removal of their carotid bodies exhibit dissociation between $CO_2$ production and ventilation, which results in a larger excursion in arterial $P_{CO_2}$ than in healthy controls at the onset of exercise (26). The resulting hypercapnia was sustained in CBR subjects for the remainder of the exercise period.
period. So with the regulation of arterial glucose and arterial \( PCO_2 \), there is mismatching of release and removal of these compounds, which results in a small deviation from resting values. Other mechanisms or compensation for the absence of carotid bodies become important during steady-state exercise as the mismatching is corrected, and there is no further deviation in these variables.

CBR resulted in only a small transient deviation in arterial glucose. Even very small, essentially undetectable changes in arterial glucose can elicit compensation that may mask a primary deficit in glucoregulation (5, 9, 10, 22, 23). This was exemplified by an experiment in which a reduction in arterial plasma glucose of 6 mg/dl due to a low-dose intraportal insulin infusion resulted in a peak compensatory \( Ra \) response of \( 4 \) mg·kg\(^{-1}\)·min\(^{-1}\) in the exercising dog (22). In a second study, it was shown that cessation of a glucose infusion that completely prevented the exercise-induced rise in \( Ra \) resulted in a small drop in arterial plasma glucose of \( 5 \) mg/dl, which led to a compensatory increase in \( Ra \) of \( 4 \) mg·kg\(^{-1}\)·min\(^{-1}\) (5). One remarkable result of the latter study was that full compensation was essentially present 2.5 min after cessation of the glucose infusion. The glucoregulatory system is sufficiently sensitive and responds with enough rapidity to a decrement in blood glucose during exercise to prevent a more pronounced drop in blood glucose. Clearly, however, if compensation were present here, it would have to be due to sensing at a site other than the carotid bodies (e.g., liver or brain).

Our previous work showed that the increase in glucagon is a major determinant of the increment in \( Ra \) during exercise (20). For this reason, it was surprising that the impaired glucagon response did not result in a greater deficit in \( Ra \) and NHGO. There was a tendency for reduced \( Ra \) and NHGO in CBR compared with Sham; however, differences were not significant. Thus even the reduced glucagon response seen in CBR appears to be largely adequate for the stimulation of \( Ra \) during exercise. It is possible that the small decrease in glucose heightens the responsiveness of the liver to glucagon. Perhaps the tonic reduction in glucagon that resulted from the resection procedure resulted in up-regulation of hepatic glucagon receptors (1, 17) or signaling molecules.

If, in fact, carotid body function is necessary for the full neuroendocrine response to exercise, the issue then becomes the signal or signals that they are sensing. It is well known that the carotid bodies are sensitive to pH, \( PO_2 \), and \( PCO_2 \). More recently, it has been shown that they are sensitive to glucose (3, 4, 11). The signal sensed by the carotid bodies that stimulates the neuroendocrine response to exercise is impossible to elucidate from these studies. It is important to recognize that if it is responding to blood gases or glucose, the signal can be transmitted without a measurable error signal, inasmuch as these variables are generally unchanged during moderate exercise. It is important to appreciate that although the experimental sampling frequency is finite and varies, the body samples arterial blood continuously and is considerably more apt to detect oscillations or rapid changes over time.

Sympathetic nerve stimulation is the primary means of increasing lipolysis during exercise (21). Despite the attenuation of the exercise-induced increase in arterial norepinephrine by CBR, and presumably sympathetic nerve activity, arterial glycerol and nonesterified fatty acid levels were not significantly blunted. Apparently, the attenuated increase in sympathetic drive was still adequate, sympathetic drive to adipose tissue was not affected, or compensation for the deficit in sympathetic activity was present.

The carotid bodies are difficult to visualize in the dog. Therefore, we took the precaution of denervating the region immediately surrounding the tissue where the carotid bodies were presumed to lie as added insurance that no signal from the carotid bodies was transmitted to the central nervous system. The absence of a pulmonary response to intravenous NaCN injection in CBR confirmed that the procedure was successful. A consequence of the surgical procedures in CBR is the likelihood that all or some of the innervation to baroreceptors in the carotid sinus, as well as in the carotid bodies, was removed. Resting arterial systemic and diastolic blood pressures were similar in CBR and Sham, suggesting that compensation for the removal of any baroreceptors was effective. It is also important to note that, because of the difficulty of aortic chemoreceptors, the aortic bodies, which are believed to play a minor role in regulation of blood gases, at least, were left intact. One cannot rule out that aortic chemoreceptors play a role in neuroendocrine regulation.

Arterial \( PO_2 \) and \( PCO_2 \) were 82 and 41 mmHg, respectively, in CBR. The reduced \( PO_2 \) and elevated \( PCO_2 \) are added confirmation that the carotid bodies were no longer effective (13). Arterial pH was similar in CBR and Sham, indicating that renal compensation for the greater retention of \( CO_2 \) was complete. It is unlikely that changes in blood gas concentration affected the neuroendocrine or glucoregulatory responses to exercise. In a previous study, we examined the effects of decreasing arterial \( PO_2 \) on liver and muscle glucose metabolism and whole body glucose fluxes in the dog (27). Arterial \( PO_2 \) had no effect on glucose metabolism until it was <60 mmHg. Moreover, decreased arterial \( PO_2 \) tends to increase glucagon and norepinephrine levels and not diminish the response, as seen during exercise in CBR (27).

In summary, these studies suggest that input from the carotid bodies, or receptors anatomically close to them, 1) play a role in the neuroendocrine response to exercise and 2) participate in the non-steady-state coupling of \( Ra \) to \( R_d \) but 3) are not essential to glucoregulation during sustained exercise. These results support the notion that carotid body function is not restricted to blood gas regulation but may also play a role in neuroendocrine function.

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