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MINI-REVIEW: NEURO FORUM

Neurophysiology of Exposure to Extreme Environments — Pressure, Temperature, & Microgravity

Peripheral chemoreceptor, a new player in metabolic sensing during physical exertion: a hypothetical scenario

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Abstract

The cardiorespiratory and metabolic response to exercise has been associated with meeting the organism's metabolic demands during physical exertion. Of note, an incremental exercise is characterized by *1*) cardiodynamic phase related to cardiac output enhancement mainly determined by a positive chronotropic response, *2*) ventilatory threshold one, associated with a significant contribution of cardiovascular and pulmonary ventilation, and *3*) ventilatory threshold two, correlated with a tremendous increase in breathing and metabolic responses to exercise. Notably, it has been shown that the ventilatory response to exercise increases concomitantly with the release and accumulation of metabolites (i.e., lactate released from skeletal muscle). The principal peripheral chemoreceptors are the carotid bodies (CBs), allocated into the carotid bifurcation and demonstrated to respond to several stimuli, triggering autonomic and ventilatory responses. Indeed, in past and recent years, it has been shown that CB could respond to lactate in in vitro and in vivo preparations, eliciting an increase in CB activity and ventilation. However, not all evidence indicates that peripheral chemoreceptors respond to lactate. Thus, considering that CB chemoreceptors' role in lactate-dependent breathing response is not completely clear and their potential preponderance as metabolic sensors during exercise has not been thoroughly explored, the present review was focused on the possible role of CB chemoreceptors as metabolic sensors during physical exertion in a physiological context, proposing it as a new actor in exercise physiology.

carotid body; exercise; hypoxia; lactate; maximal oxygen uptake

INTRODUCTION

Daily physical activities usually take place at lower metabolic rates (3.5–7.0 mL/min/kg) relative to the maximum aerobic capacity (35–50 mL/min/kg); however, during dynamic nonsteady state exercise, oxygen (O_2) uptake and carbon dioxide (CO_2) clearance increases more than 20-fold to cope with the metabolic demand during physical activity (1). It has been well-known for nearly a century that the gas exchange rate relies on the respiratory and circulatory capacity and muscle bioenergetics to respond appropriately to exercise load (2, 3). The cardiopulmonary exercise test (CPET or CPEX) has been classically used to assess the maximal O_2 consumed during exercise ($\dot{V}O_{2max}$) (1, 4). Accordingly, relative to O_2 consumption and CO_2 production, three events characterize a maximum incremental exercise test: *1*) cardiodynamic response, related to increases in cardiac output (CO) mainly determined by an increase in heart rate (HR) (5–8), *2*) ventilatory threshold one (VT1), associated to a slight increase of O_2 uptake, CO_2 clearance, and lactate production (~2–4 mM in venous blood), but with a significant contribution of cardiovascular response (i.e., increases in HR) and pulmonary ventilation; and *3*) ventilatory threshold two (VT2) or anaerobic threshold, associated with a more considerable increase in cardiopulmonary response (i.e., HR and O_2 uptake) and lactate accumulation (>10 mM in venous blood) (9). Notably, during all these short-term responses (at normoxia), the cardiorespiratory adjustments are essential to managing O_2 demands from several cells, tissues, and organs (10–13). However, in a hypoxic environment, where the O_2 availability is decreased, the $\dot{V}O_{2max}$ and endurance performance are markedly reduced (14–21); nevertheless, the evidence is not completely clear, showing the precise mechanism that explains the exercise performance deterioration in this environment (22). Although physical performance deterioration

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during hypoxia is undeniable, the mechanisms explaining this phenomenon are not fully described, leading to various hypothetical scenarios.

Interestingly, recent evidence suggests that the carotid body (CB), primary arterial O_2 sensor (i.e., hypoxia) involved in the regulation of breathing and hemodynamic response to chemical alterations in the arterial blood, may serve as metabolic sensors due to their ability to respond to several metabolic-related signaling molecules such as insulin, glucose, histamine, lactate, among others (23–26). Therefore, metabolic signals released/accumulated during exercise may activate the CB, activating neural mechanisms, and initiating the cardiopulmonary response. In this sense, lactate could be a CB-dependent relevant actor during physical exertion, considering it is released and accumulated during exercise; however, the evidence is not entirely robust. Indeed, contrary to this hypothetical scenario, it has been shown that glomus cells, principal CB cells related to O_2 sensing derived from Wistar rats, and ventilation from the same animals did not respond to exogenous lactate (20 mM) (27). However, active inspiration and expiration apparently could be CB-dependent (28), suggesting that CB is relevant but not through a lactate-dependent mechanism. Notwithstanding, it has been shown that Wistar rats displayed a tremendous breathing response to 2-M lactate infusion (29), which suggests that the mechanism could be concentration-dependent. Therefore, considering the limited and controversial evidence, the present review proposes a hypothetical scenario where the CB could be relevant during exercise through a metabolic signal and neural circuit activation.

Cardiopulmonary Response to an Incremental Exercise: A Classical View

According to the oxygen Fick equation, the O_2 consumption is $\dot{V}O_2 = CO \cdot (CaO_2 - CvO_2)$, where CO is cardiac output, determined by the product between stroke volume (SV) and HR, CaO_2 is the arterial O_2 content, and CvO_2 is the venous O_2 content (30). The CO and $CaO_2 - CvO_2$ represent perfusion and diffusion, respectively, at rest and during exercise (31). The SV is the difference between end-diastolic volume and end-systolic volume, which is affected by the pre- and after-heart loads and the autonomic nervous system (venous return) (32). Along with this, the HR is also determined by the sympathetic and parasympathetic outflow to the heart. The other determinant of O_2 uptake is diffusion, represented by the difference between the arterial and venous O_2 contents, determined by the arterial O_2-carrying capacity and tissue delivered, and by the ability of the respiratory system to load O_2 in the pulmonary capillaries (31).

One of the principal determinants of $\dot{V}O_{2max}$ is the CO. Indeed, a linear relationship between $\dot{V}O_{2max}$ and HR has been observed. The HR increase, as well as the rise of SV during exercise (increase the venous return), have been attributed to sympathoexcitation and parasympathetic withdrawal (32, 33). However, exceptional exercise performance has been associated with an exacerbated vagal outflow (34–36). Along with this, studies in rats have shown that activation of parasympathetic neurons through optogenetic and chemogenetic approaches can improve exercise performance, mimicking the effects of a training regimen, while silencing cardiovagal neurons can impair exercise capacity (37). Furthermore, it has been shown that parasympathetic drive is crucial to exercise-mediated increases in coronary artery blood flow through vasoactive intestinal peptide (vasodilator) in sheep (38) (Fig. 1). Notably, severe deterioration of parasympathetic drive is associated with a parallel decline in exercise performance during hypoxia in both humans and rodents have been observed (39–41).

Thus, during exercise, the sympathoexcitation contributes to venous contraction, and together, active muscles, which can function as a pump, promote an increase in the cardiac preload; on the other hand, the exercise-dependent parasympathetic overactivation could contribute to facilitated O_2 uptake of heart muscle during physical exertion. Notably, during a reduction of O_2 availability, the aerobic capacity is markedly reduced (14–21). Nevertheless, there are no severe changes in the left ventricle chamber diameter during hypoxia. Still, in contrast, the internal diameter of the right ventricle is slightly decreased due to elevated pulmonary pressure after short-term hypoxic exposure (42), which could suggest that CO is reduced; nevertheless, as the HR increases, the CO is preserved during hypoxia. Consequently, cardiac perfusion is maintained during hypoxia, suggesting that the adverse effects of hypoxia on $\dot{V}O_{2max}$ are more related to diffusion than increased perfusion.

Potential Role of Neural Control on the Cardiorespiratory and Metabolic Response during Incremental Exercise

Further to the classical view of physiological response during an incremental exercise, the neural control of autonomic functions could be more involved than was initially proposed. Thus, in this section, we described and explored some potential contributions of sensors, which have yet to be considered, from an exercise phase-dependent manner during an incremental physical exertion.

Cardiodynamic response.

It is well known that there is an increase in energy demand during physical activity and, consequently, an increase in cardiopulmonary and metabolic responses to meet the new energy requirements (2). During the initial phase of physical activity, there is a cardiodynamic response, led by an increase in HR and SV, with a secondary contribution from ventilation (10–13). It has been proposed that the cardiodynamic phase is related to the exercise pressor reflex (EPR) and not necessarily to the chemoreflex, activating brainstem cardiovascular regulatory centers (43–45). The EPR is a feedback mechanism associated with group III/IV muscle afferent sensory neurons, which are anatomically connected with the brainstem cardiovascular control areas. These fibers are activated by intramuscular mechanical and chemical stimuli, triggering increased discharge, which promotes an activation of the cardiovascular system (46). Notably, the activation of the EPR activates the nucleus tractus solitarii (NTS) and the rostral ventrolateral medulla (RVLM), eliciting a sympathoexcitation promoting an increase of blood pressure and CO, coping with the exercise-dependent metabolic demand (46–48). Interestingly, metabolic signals, such as lactate, released by the skeletal

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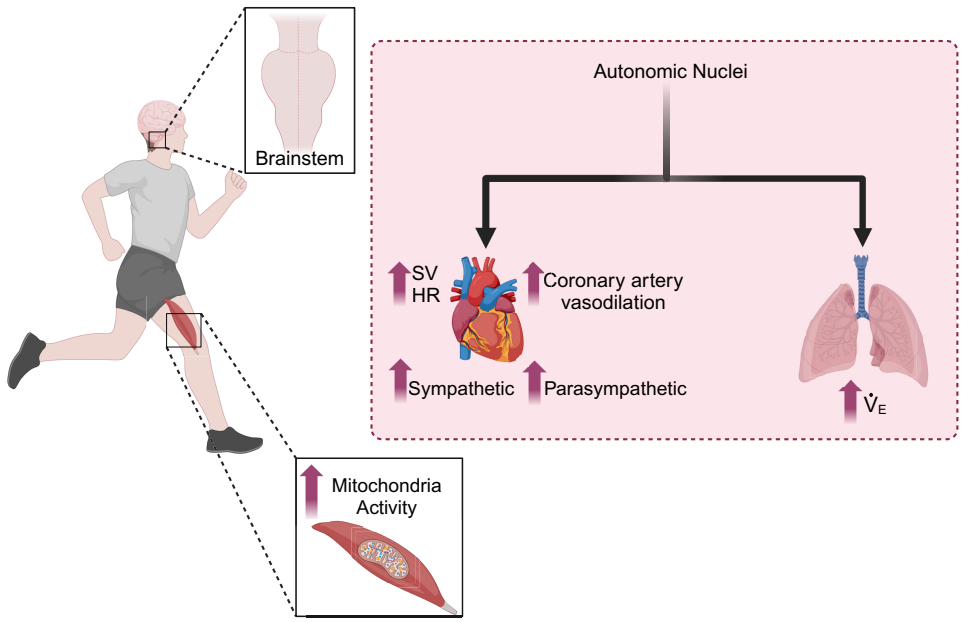


Figure 1. Classical physiological response to an incremental physical exercise. During incremental physical effort, there is a significant increase in cardiac output (CO), which is determined by an increase in stroke volume (SV) and heart rate (HR) (perfusion). It has been proposed that the enhancements in HR and SV are sympathetic-mediated through norepinephrine release and increased venous return. In addition, the cardiovascular parasympathetic-mediated effects are related to coronary arterial vasodilatation, promoting increased cardiac O_2 uptake during exercise. Furthermore, concomitant with the cardiovascular response, there is a substantial increase in minute ventilation ($\dot{V}_E$) during exercise, which is ventilatory threshold dependent. Regarding diffusion, the exercise-dependent increase in arterial O_2 content promotes a rise in O_2 in mitochondria, facilitating ATP formation and compensating for metabolic needs during exercise. Figure was created with a licensed version of BioRender.com.

muscle during the cardiodynamic phase may impact cardiopulmonary regulation. However, this is still a matter of debate, even considering the lower accumulation during low-intensity exercise (8, 49).

Ventilatory threshold 1.

As the exercise intensity increases, the VT1 phase appears, characterized by a significant increase in pulmonary ventilation. Nevertheless, there is still no significant accumulation of lactate (~5% compared with the baseline circulating concentration) without relevant changes in arterial gases (9, 49–51). Therefore, a metabolic signal regarding eliciting a ventilatory drive could be discarded. Interestingly, it has been demonstrated that breathing rate during locomotion (i.e., similar to low-intensity exercise) is related to the mesencephalic locomotor region and spinal cord through activation of preBötzinger complex and central chemoreceptors (52). Indeed, the cuneiform nucleus from the mesencephalic locomotor region directly projects and activates the preBötzinger complex through glutamatergic neurons (52); therefore, the locomotion itself elicited a breathing response to exercise. Furthermore, the breathing-dependent locomotion elicited by activation of L2 through N-methyl-D-aspartate (NMDA)/5-HT receptors also required central chemoreceptor cell integrity allocated into the retrotrapezoid nucleus (RTN) in brainstem-spinal cord neonatal preparation (52). Central chemoreceptor neurons in the RTN are critical players in the regulation of CO_2-mediated central ventilatory drive (53) through activation of the center pattern generator (54). Nevertheless, it is well known that the arterial gases are not modified by breathing compensation until the anaerobic threshold (VT2).

Ventilatory threshold 2.

At VT2 or anaerobic threshold and $\dot{V}O_{2max}$, there is an abrupt increase in pulmonary ventilation, a massive increase in systemic lactate concentration (>10 mM), CO_2 retention, and metabolic and respiratory acidosis (9, 49, 51, 55). As previously mentioned, the RTN neurons play a pivotal role in CO_2-mediated central hyperventilation (53) by activating the center pattern generator (54). Both RTN neurons and astrocytes contributed to elicited CO_2/H^+-dependent hyperventilation through G-protein receptor 4 (GPR4) and TWIK-related acid-sensitive K^+ channel 2 (TASK2) receptor in the neuron and sodium-bicarbonate exchanger (NBCe) and sodium-calcium (Na/Ca) exchange in the astrocyte (53, 54). Briefly, neuronal depolarization is caused by the acid-induced closure of TASK-2 and by the closure of an unidentified leak potassium channel operated by GPR4. Concomitant acidification depolarizes astrocytes and activates an NBCe, eliciting the activation of Na/Ca exchange by a rise of intracellular Na^+, increasing intracellular Ca^{2+}, causing the vesicular release of ATP, finally activating RTN neurons via P2Y receptors (53, 54). Thus, it is possible that during physical exertion, like VT2 or $\dot{V}O_{2max}$, the RTN neurons/astrocytes could be activated by CO_2 retention and metabolic acidosis, promoting a considerable increase in ventilation during the physical effort. However, this mechanism was not described during the exercise, generating another hypothetical scenario; nevertheless, in the current review, we described the possible role of peripheral chemoreceptors as metabolic sensors and not the role of central chemoreceptors, although we do not discount their relevance.

Along with the previous mechanism, it has been shown that the CB, the main peripheral chemoreceptors located at the carotid artery bifurcation, constitutively express all the molecular machinery to respond to blood-borne metabolic stimuli such as changes in systemic lactate (24–26, 46). It is well known that during physical exercise, there is a phase-related release and accumulation of several metabolic signals, including, but not restricted to, lactate (i.e., adrenaline and cortisol) (8). However, the CB does not sense the cortisol (56) but is released during CB activation (57). In

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addition, the adrenaline activates the carotid body (58) and is released during exercise; however, the peak of adrenaline during exercise is closely associated with the phase where the greatest exhaustion is perceived (59) when lactate could have already acted to modulate the cardiorespiratory response to exercise. Therefore, considering that the CB peripheral chemoreceptors are "sensing" the arterial blood on a beat-to-beat basis, they might serve as a metabolic sensor during exercise; then, the CB may regulate the cardiopulmonary adaptation to exercise, modulating the sympathetic/parasympathetic balance and respiratory outflows through the chemoreflex arch. Interestingly, it has been proposed that peripheral chemoreceptors serve as sensing support to the central chemoreceptors, which could be relevant to breathing response during exercise, generating new physiological mechanisms that govern breathing responses to physical exertion.

Peripheral Chemoreceptors and Their Metabolic Role

Classical CB activation model.

The CBs are located in the carotid bifurcation, which responds to several blood-borne stimuli, including changes in O_2, CO_2, H^+, flow, glucose, temperature, osmolarity, insulin, histamine, and lactate (22–24, 60–64). Upon activation, the CB elicits a chemoreflex response characterized by a marked increase in pulmonary ventilation, sympathetic outflow, cardiac output, and blood pressure (65). The CB comprises two cell types: the primary chemoreceptor cells are the glomus cells (type I cells), and the other is the sustentacular clusters of type II cells (60, 63). The current chemoreception model convergence proposes that upon stimulation, CB type I cells get depolarized by inhibiting O_2-sensitive K^+ channels, then Ca^{2+}-dependent release of several neurotransmitters such as acetylcholine (Ach) and adenosine triphosphate (ATP) takes place, to finally interact with receptors in the nerve terminal of petrosal sensory neurons, increasing the neural activity from the CBs (60, 63, 66). The increased CB activity elicited activation of the NTS at the brainstem, which projects into the respiratory pattern generator and cardiovascular nuclei (i.e., rostral aspect of the medulla) to increase ventilation and sympathetic activity, respectively (60, 63, 66) (Fig. 2, *left*). Notwithstanding the convergence of the chemoreception model on close K^+ channels to activate CB glomus cells, various activation mechanisms are present. However, for the intent of the present manuscript, our focus is directed toward CB metabolic sensing.

Metabolic CB activation.

Several endogenous signals, such as lactate, are effective in activating the CB-mediated chemoreflex response (24, 27, 67, 68). Accordingly, Chang et al. (24) proposed the CB as an organ lactate receptor as it expresses the G-coupled olfactory receptor (Olfr78), which lactate activates. They showed that olfactory receptor Olfr78$^{-/-}$-deficient mice had a blunted isolated CB activity response to 10% hypoxia and lactate, implying that Olfr78 could be pivotal in respiratory sensitivity to these metabolic stimuli. Likewise, Peng et al. (67, 68) showed that Olfr78/BL6$^{-/-}$ mice showed a reduced ventilatory chemoreflex response to 12% O_2, as well as CB sensory response to hypoxia compared with wild-type animals. Contrarily, Lopez-Borneo's group found that when Olfr78$^{-/-}$ mice were assessed for their response to hypoxia and lactate, Olfr78 deletion led to a diminished response to hypoxia; however, it did not impair their lactate response, suggesting that the Olfr78 receptor could serve as a hypoxic but not a lactate sensor. The activation mechanism of Olfr78 involves the increase of adenylyl cyclase, cAMP, and activation of cyclic nucleotide-gated channel alpha 2 (Cnga2), promoting the increase of intracellular Ca^{2+} and neurotransmitter release (69). In addition, Colinas et al. (70) showed that in TH-Olfr78$^{-/-}$ mice, this receptor is irrelevant to eliciting breathing response during hypoxia; however, they participate in the glomus cell maturation from CB neuroblast to mature glomus cell. Another mechanism proposed to explain lactate-dependent CB activity is related to monocarboxylate transport (MCT). Torres-Torrelo et al. (25) confirmed that exogenous lactate applications into isolated CB type I cells were sufficient to elicit a CB type I cell depolarization through MCT. Then, these authors proposed that during metabolic stress (i.e., exercise or hypoxia), the lactate enters the cells through MCT, and the lactate dehydrogenase enzyme converts lactate to pyruvate with the subsequent production of NADH, which activates NADH-dependent membrane cation channels to promotes cell depolarization. Thus, the evidence suggests that independent of the mechanism (Olfr78 or MCT), the CB could serve as a metabolic sensor during physiological stress. However, unlike previous research, a blunted lactate (20 mM)-dependent respiratory response in situ hemisected Wistar rats and from isolated CB glomus cells has been shown (27). Nevertheless, the author did not confirm the arterial lactate concentrations during infusion in all animal experiments (27). Indeed, it has been shown that female and male Wistar rats displayed a huge breathing response to 2-M lactate infusion (29). Therefore, considering the ample lactate clearance metabolic rate, the infused lactate concentration is not the same concentration that CB can sense, evidencing an experimental limitation (71, 72) (Fig. 2, *right*).

All these pieces of evidence strongly suggest that CB could respond to lactate; however, no results showed their role during physical exertion, where the metabolic demand severely increases. Furthermore, considering that peripheral and central chemoreceptors can be found synergistically in concert with other reflexes (EPR), it is possible that during exercise, there is an orchestrated physiological mechanism where CB peripheral chemoreceptors could serve as support in other reflexes, as well as a metabolic sensor; however, this is only a hypothetical scenario until now.

Possible Role of Peripheral Chemoreceptors during Exercise

The precise contribution of peripheral chemoreceptors to exercise physiology has been a question that has generated significant interest among respiratory and exercise physiologists; however, it remains largely unknown. One of the first published works was from Masuda et al. (73), who studied the effects of acute transient depressions of CB-mediated chemoreflex drive on the ventilatory response to exercise.

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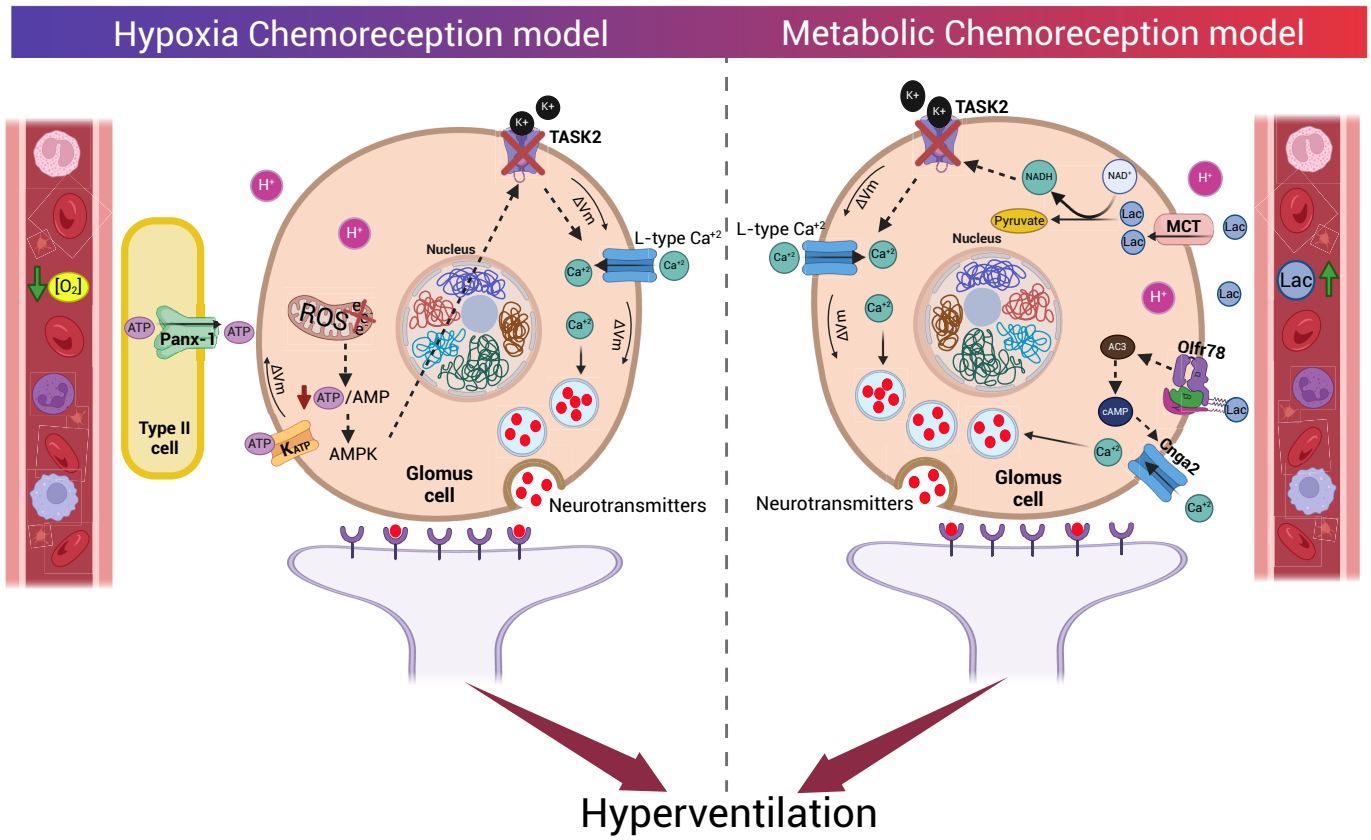


Figure 2. Hypoxic and metabolic chemoreception models. Glomus cells are the principal carotid body chemoreceptor cells. *Left*: the hypoxic chemoreception model proposes that upon stimulation, CB glomus cells get depolarized by inhibiting O_2-sensitive K^+ channels and TWIK-related acid-sensitive K^+ channel 2 (TASK2) by AMPK, promoting Ca^{2+} entry and the release of several neurotransmitters such as acetylcholine (Ach) and adenosine triphosphate (ATP). On the other hand, (*right*) the metabolic chemoreception model proposes that G-coupled olfactory receptor (Olfr78) involves the increase of adenylyl cyclase, cAMP, and activation of cyclic nucleotide-gated channel α 2 (Cnga2), promoting the increase of intracellular Ca^{2+} and neurotransmitter release. Parallelly, the monocarboxylate transport (MCT) has also been shown to be involved. Mechanistically, the lactate enters the cells through MCT, and the lactate dehydrogenase enzyme converts lactate to pyruvate with the subsequent production of NADH, which activates NADH-dependent membrane cation channels to promote cell depolarization. Figure was created with a licensed version of BioRender.com.

Human patients were subjected to hyperoxic gas during VT2, and the authors found that pulmonary ventilation decreases during CB unloading, suggesting that the CB contributes at least in part to increased ventilation at VT2 during exercise exertion (73). Although hyperoxic gas has several side effects during physical exercise (i.e., acidosis, norepinephrine release, and potassium) (74), the impact of transient hyperoxia on silencing the CB activity is well-known (75). In another even older work, Honda et al. (76) showed that resection of CBs in patients with asthma decreases the kinetic of the respiratory response in all phases of a CPET compared with patients with intact CBs (76). More recently, we found that CB resection severely decreases exercise running capacity in rats with heart failure (77). Contrary to the previous description, ponies subjected to CB denervation showed a greater hyperventilatory response during exercise (78). However, ponies develop hypoventilation at rest with CO_2 retention after CB denervation, which may sensitize central chemoreceptors. This partially explains the enhanced ventilatory response during exercise in ponies (i.e., metabolic acidosis). Nevertheless, it is worth mentioning that CO_2 retention was not determined in human experiments performed before (73, 76), which is a gap in the experimental evidence.

On the other hand, it has been proposed that CB is essential to sympathetic-mediated blood flow redistribution during exercise (79–81). In this sense, dopamine-dependent CB inhibition (5–10 μg/kg) elicited vasodilatation during exercise in dogs with heart failure, which probably was sympathetic-mediated (80). Expanding on this evidence, Stickland et al. (79) showed that the CB chemoreceptor contributes to skeletal muscle blood flow regulation during exercise at normoxia in healthy humans. Indeed, a low dose of dopamine (CB inhibition) did not affect steady-state blood flow at rest but increased femoral blood flow and conductance during exercise (79), suggesting that CB chemoreceptors could play an essential role in regulating blood flow during exercise. In support of this notion, a hyperoxic gas during steady-state exercise significantly reduced the sympathoexcitation elicited by exercise in healthy humans, probably associated with CB unloading (81). Recently, Sayegh et al. (82) showed that dopamine-dependent CB inhibition augmented the brachial artery blood flow and vascular conductance responses to rhythmic handgrip, indicating that the peripheral chemoreflex is tonically actively at rest and can restrain the blood flow and vascular conductance during exercise (82). Thus, these results suggest that the CB contributes, at least in part, to regulating

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breathing and cardiovascular response during exercise; however, the precise role of peripheral chemoreceptors has yet to be wholly described.

Hypothetical Statement: CB Metabolic Role during Exercise

As previously mentioned, during exercise, O_2 consumption and CO_2 production are constant relative to minute ventilation ($\dot{V}_E$). Therefore, arterial pO_2, pCO_2, and pH levels remain mostly constant during pulmonary ventilation until the maximum O_2 uptake is reached (83). Hence, if CBs contribute to ventilatory regulation and, therefore, $\dot{V}O_2$ uptake during exercise, their contribution is probably not related to pO_2 and pCO_2 sensing but rather to the ability of other exercise-related released molecules to change CB activity. Accordingly, the CB may serve as a mismatched metabolic sensor rather than a constant sensor during exercise, probably associated with lactate release and accumulation from skeletal muscles (83).

It is well known that lactate is formed from pyruvate through lactate dehydrogenase (LDH) at the end of glycolysis (84). A family of membrane-bound MCT facilitates transport across cellular membranes, whose flux rate and direction depend upon the diffusion gradients (71, 85). Notably, it has been shown that the CB expresses MCT (70), and exogenous lactate applications into isolated CB type I cells elicited cell depolarization through MCT activity. Therefore, it is possible that during exercise, the lactate enters the CB cells through MCT, activating NADH-dependent membrane cation channels and promoting cell depolarization (25), which facilitates a considerable increase in ventilation during physical exertion. LDH activity (86) and MCT expression (87) changes have been observed following long-term exercise training. Therefore, it is possible that an exercise regimen could impact MCT expression in the CB, which could modify the hypoxic or metabolic ventilatory response; however, it has not been described yet.

Another proposed mechanism that could explain the CB lactate sensing is related to Olfr78, which lactate activates, promoting an increase in chemosensory discharge. In support of this notion, Olfr78$^{-/-}$-deficient mice had a blunted isolated CB activity response to 10% hypoxia and lactate (24). Other manuscripts also showed that Olfr78/BL6$^{-/-}$ mice experienced a reduced ventilatory chemoreflex response to 12% O_2 (67, 68). Although this new mechanism was promising, other groups showed that CB Olfr78 deletion led to a diminished response to hypoxia; however, it did not impair their lactate response (67, 68). Interestingly, it has been demonstrated that Olfr78 is also expressed in blood vessels, participating in blood pressure and flow regulation (88, 89). Indeed, transgenic mice coexpressing β-galactosidase with Olfr78 markedly express Olfr78 in blood vessels from skeletal muscle (89). Interestingly, the CB is able to sense blood flow (90, 91), eliciting peripheral chemoreceptor activation (90). Therefore, it is possible that the lactate release and accumulation elicited a CB activation through an Olfr78-dependent blood flow regulation in the CB during exercise; however, it has not been determined whether CB blood vessels and/or closed blood vessels express Olfr78.

Unlike previous research, not all papers showed that lactate elicited hyperventilation. Indeed, a blunted lactate (20 mM)-dependent respiratory response in situ hemisected Wistar rats and from isolated CB glomus cells have been shown (27). Of note is that the authors used a lactate bolus and not a continuous infusion, an essential experimental limitation associated

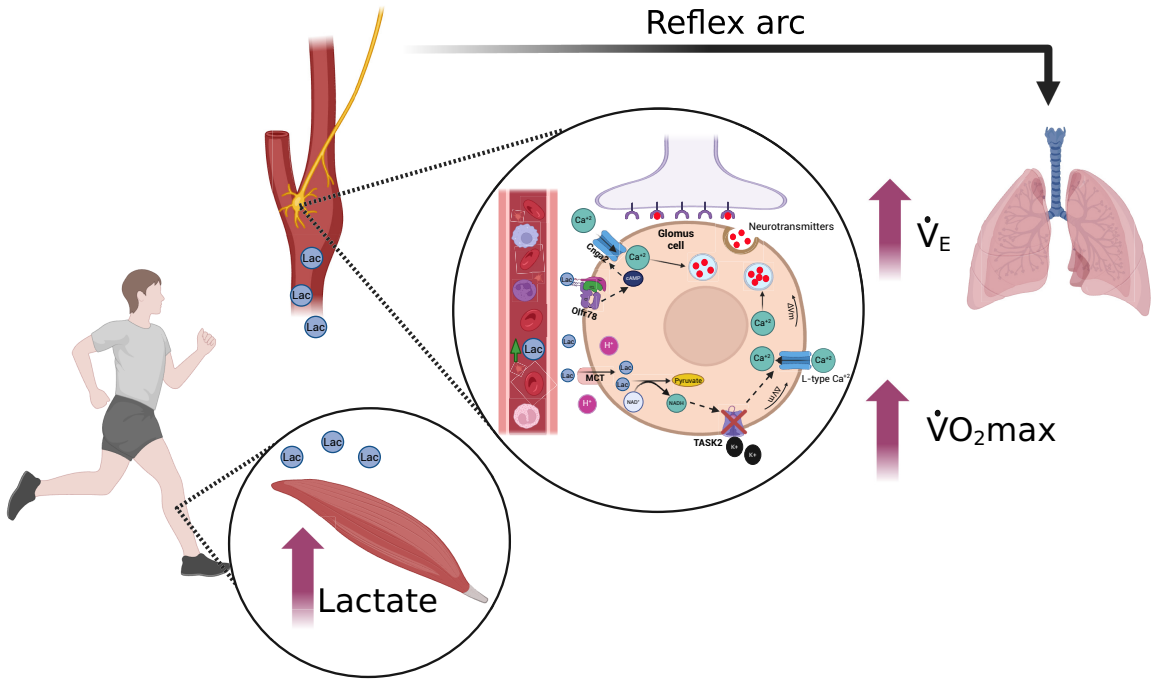


Figure 3. Hypothetical role of the carotid body's peripheral chemoreceptor as a sensor during exercise. During exercise, there is a massive release and accumulation of lactate, which initiates CB activation through G-coupled olfactory receptors (Olfr78) and/or monocarboxylate transporters (MCT), activating the chemoreflex arc, which in turn enhances the ventilatory drive, contributing to an increase in maximal O_2 uptake. Figure was created with a licensed version of BioRender.com.

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with the vast lactate clearance metabolic rate. The shuttling of lactate is undistinguishably linked to metabolic activity and demands (92–94), as well as the action of the liver and kidneys in capturing this metabolite (95); therefore, it depends on local blood flow, facilitated diffusion across cellular membranes, and mitochondrial oxidative capacity (71, 85, 96). Thus, considering the ample lactate clearance metabolic rate, the infused lactate concentration is not the same concentration that CB can sense (71, 72). Indeed, the same author did not confirm the arterial lactate concentrations during the bolus (27) across in situ hemisected preparation ventilatory experiments, which evidenced an experimental limitation. Thus, the manuscript of Spiller et al. (27) did not discount the role of CB as a metabolic sensor. Indeed, there is evidence that female and male Wistar rats displayed a tremendous breathing response to 2-M lactate infusion, supporting the notion that lactate needs to be accumulated to be sensed by the peripheral chemoreceptors. Thus, hypothetically, if CB functions as a metabolic sensor during exercise, it is possible that the exercise-dependent accumulated lactate activates molecular signaling in the CB (MCT- and/or Olfr78-dependent mechanism), facilitating an increase of ventilation and, therefore, $\dot{V}O_{2max}$ during physical exertion (Fig. 3).

Perspectives

The goal standard for determining aerobic capacity and performance is the $\dot{V}O_{2max}$ through a CPET. Although the physiological response to physical exertion is known, the mechanisms governing hyperventilation during exercise do not wholly underpin them (97). In the past, the CB peripheral chemoreceptors were considered relevant during exercise due to their pivotal role in cardiorespiratory physiology, which has gained greater relevance in recent years by their role as lactate sensors (24, 25, 68). Lactate is one of the more abundant metabolites released and accumulated during high-intensity exercise; accordingly, it is reasonable to propose that CB could be a sensor during physical exertion. Until now, there are several limitations regarding specifically targeting CB during exercise. Nevertheless, the chemogenetic and optogenetic approaches are now available to study the role of specific type I and II CB cells on $\dot{V}O_{2max}$ (52, 98–100). Thus, it is possible to study if the organ is sufficient or necessary for $\dot{V}O_{2max}$ at high-intensity exercise. Therefore, future researchers need to be focused on determining the precise role of CB cell-type dependent on metabolic response to physical exertion. Furthermore, from a translational view, it is important to move the basic knowledge to a human setting, moreover, considering that animal experiments are not completely reliable.

CONCLUSIONS

The current review summarizes and proposes a hypothetical scenario where the CB peripheral chemoreceptors could be considered metabolic sensors during physical exertion. Although evidence suggests that CB could be essential for maintaining hyperpnea during incremental exercise through several molecular entities, no compelling evidence demonstrates their role in this phenomenon. Notably, during physical exertion, there is a massive release and accumulation of lactate, and it has been shown that CB can sense it; therefore, our review proposes that lactate could be the principal signal triggering hyperpnea during high-intensity exercise. Nevertheless, this is only a hypothetical scenario that needs clarification in the future.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.C.A. conceived and designed research; prepared figures; drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

REFERENCES

1. **Rossiter HB.** Exercise: kinetic considerations for gas exchange. *Compr Physiol* 1: 203–244, 2011. doi:10.1002/cphy.c090010.
2. **Hill AV**, **Lupton H.** Muscular exercise, lactic acid, and the supply and utilization of oxygen. *QJM* 16: 135–171, 1923. doi:10.1093/qjmed/os-16.62.135.
3. **Meakins J**, **Long CN.** Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *J Clin Invest* 4: 273–293, 1927. doi:10.1172/JCI100123.
4. **Lee J**, **Zhang XL.** Physiological determinants of VO_{2max} and the methods to evaluate it: a critical review. *Science & Sports* 36: 259–271, 2021. doi:10.1016/j.scispo.2020.11.006.
5. **Anrep GV**, **Barsoum GS.** Appearance of histamine in the venous blood during muscular contraction. *J Physiol* 85: 409–420, 1935. doi:10.1113/jphysiol.1935.sp003328.
6. **Lee TH**, **Brown MJ**, **Nagy L**, **Causon R**, **Walport MJ**, **Kay AB.** Exercise-induced release of histamine and neutrophil chemotactic factor in atopic asthmatics. *J Allergy Clin Immunol* 70: 73–81, 1982. doi:10.1016/0091-6749(82)90232-9.
7. **Romero S**, **Ely M**, **Sieck D**, **Buck T**, **MacLean D**, **Halliwill J.** Is sustained post-exercise vasodilation associated with an exercise-induced mast cell activation? *FASEB J* 28, Suppl 1: 1106.19, 2014. doi:10.1096/fasebj.28.1_supplement.1106.19.
8. **Luttrell MJ**, **Halliwill JR.** The intriguing role of histamine in exercise responses. *Exerc Sport Sci Rev* 45: 16–23, 2017. doi:10.1249/JES.0000000000000093.
9. **Hofmann P**, **Tschakert G.** Intensity- and duration-based options to regulate endurance training. *Front Physiol* 8: 337, 2017. doi:10.3389/fphys.2017.00337.
10. **Whipp BJ**, **Ward SA**, **Rossiter HB.** Pulmonary O2 uptake during exercise: conflating muscular and cardiovascular responses. *Med Sci Sports Exerc* 37: 1574–1585, 2005. doi:10.1249/01.mss.0000177476.63356.22.
11. **Housh TJ**, **Devries HA**, **Housh DJ**, **Tichy MW**, **Smyth KD**, **Tichy AM.** The relationship between critical power and the onset of blood lactate accumulation. *J Sports Med Phys Fitness* 31: 31–36, 1991.
12. **McLellan TM**, **Cheung KS.** A comparative evaluation of the individual anaerobic threshold and the critical power. *Med Sci Sports Exerc* 24: 543–550, 1992.

Downloaded from journals.physiology.org/journal/jn (146.083.153.245) on June 5, 2025.

13. **Pringle JS**, **Jones AM.** Maximal lactate steady state, critical power and EMG during cycling. *Eur J Appl Physiol* 88: 214–226, 2002. doi:10.1007/s00421-002-0703-4.
14. **Maher JT**, **Jones LG**, **Hartley LH.** Effects of high-altitude exposure on submaximal endurance capacity of men. *J Appl Physiol* 37: 895–898, 1974. doi:10.1152/jappl.1974.37.6.895.
15. **Young AJ**, **Sawka MN**, **Muza SR**, **Boushel R**, **Lyons T**, **Rock PB**, **Freund BJ**, **Waters R**, **Cymerman A**, **Pandolf KB**, **Valeri CR.** Effects of erythrocyte infusion on VO_{2max} at high altitude. *J Appl Physiol (1985)* 81: 252–259, 1996. doi:10.1152/jappl.1996.81.1.252.
16. **Bassett DR Jr**, **Howley ET.** Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc* 32: 70–84, 2000. doi:10.1097/00005768-200001000-00012.
17. **Fulco CS**, **Rock PB**, **Cymerman A.** Maximal and submaximal exercise performance at altitude. *Aviat Space Environ Med* 69: 793–801, 1998.
18. **Andrade DC**, **Arce-Alvarez A**, **Toledo C**, **Díaz HS**, **Lucero C**, **Quintanilla RA**, **Schultz HD**, **Marcus NJ**, **Amann M**, **Del Rio R.** Revisiting the physiological effects of exercise training on autonomic regulation and chemoreflex control in heart failure: does ejection fraction matter? *Am J Physiol Heart Circ Physiol* 314: H464–H474, 2018. doi:10.1152/ajpheart.00407.2017.
19. **Millet GP**, **Roels B**, **Schmitt L**, **Woorons X**, **Richalet JP.** Combining hypoxic methods for peak performance. *Sports Med* 40: 1–25, 2010. doi:10.2165/11317920-000000000-00000.
20. **Dempsey JA**, **Forster HV**, **Birnbaum ML**, **Reddan WG**, **Thoden J**, **Grover RF**, **Rankin J.** Control of exercise hyperpnea under varying durations of exposure to moderate hypoxia. *Respir Physiol* 16: 213–231, 1972. doi:10.1016/0034-5687(72)90052-7.
21. **Burtscher M**, **Niedermeier M**, **Burtscher J**, **Pesta D**, **Suchy J**, **Strasser B.** Preparation for endurance competitions at altitude: physiological, psychological, dietary and coaching aspects. A narrative review. *Front Physiol* 9: 1504, 2018. doi:10.3389/fphys.2018.01504.
22. **Alvarez-Araos P**, **Jiménez S**, **Salazar-Ardiles C**, **Núñez-Espinosa C**, **Paez V**, **Rodriguez-Fernandez M**, **Raberin A**, **Millet GP**, **Iturriaga R**, **Andrade DC.** Baroreflex and chemoreflex interaction in high-altitude exposure: possible role on exercise performance. *Front Physiol* 15: 1422927, 2024. doi:10.3389/fphys.2024.1422927.
23. **Del Rio R**, **Moya EA**, **Koenig CS**, **Fujiwara K**, **Alcayaga J**, **Iturriaga R.** Modulatory effects of histamine on cat carotid body chemoreception. *Respir Physiol Neurobiol* 164: 401–410, 2008. doi:10.1016/j.resp.2008.09.005.
24. **Chang AJ**, **Ortega FE**, **Riegler J**, **Madison DV**, **Krasnow MA.** Oxygen regulation of breathing through an olfactory receptor activated by lactate. *Nature* 527: 240–244, 2015. doi:10.1038/nature15721.
25. **Torres Torrelo H**, **Ortega-Sáenz P**, **Gao L**, **López-Barneo J.** Lactate sensing mechanisms in arterial chemoreceptor cells. *Nat Commun* 12: 4166, 2021. doi:10.1038/s41467-021-24444-7.
26. **Peng YJ**, **Su X**, **Wang B**, **Matthews T**, **Nanduri J**, **Prabhakar N.** Role of olfactory receptor78 in carotid body-dependent sympathetic activation and hypertension in murine models of chronic intermittent hypoxia. *J Neurophysiol* 125: 2054–2067, 2021. doi:10.1152/jn.00067.2021.
27. **Spiller PF**, **da Silva MP**, **Moraes DJA.** Lactate does not activate the carotid body of Wistar rat. *Respir Physiol Neurobiol* 285: 103593, 2021. doi:10.1016/j.resp.2020.103593.
28. **Spiller PF**, **da Silva CAA**, **Francescato HDC**, **Moraes DJA.** The role of carotid bodies in the generation of active inspiratory and expiratory responses to exercise in rats. *Exp Physiol* 105: 1349–1359, 2020. doi:10.1113/EP088203.
29. **Olsson M**, **Ho HP**, **Annerbrink K**, **Thylefors J**, **Eriksson E.** Respiratory responses to intravenous infusion of sodium lactate in male and female Wistar rats. *Neuropsychopharmacology* 27: 85–91, 2002. doi:10.1016/S0893-133X(02)00296-8.
30. **Omote K**, **Reddy YNV**, **Borlaug BA.** Chapter 35 - Invasive hemodynamic assessments during exercise: normal patterns and clinical value. In: *Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease*, edited by Chirinos JA. USA: Academic Press, 2022, p. 545–563.
31. **Ferretti G**, **Fagoni N**, **Taboni A**, **Vinetti G**, **di Prampero PE.** A century of exercise physiology: key concepts on coupling respiratory oxygen flow to muscle energy demand during exercise. *Eur J Appl Physiol* 122: 1317–1365, 2022. doi:10.1007/s00421-022-04901-x.
32. **Buckwalter JB**, **Mueller PJ**, **Clifford PS.** Sympathetic vasoconstriction in active skeletal muscles during dynamic exercise. *J Appl Physiol (1985)* 83: 1575–1580, 1997. doi:10.1152/jappl.1997.83.5.1575.
33. **Almeida MB**, **Araújo CGS.** Effects of aerobic training on heart rate. *Rev Bras Med Esporte* 9: 113–120, 2003. doi:10.1590/S1517-86922003000200006.
34. **Carter JB**, **Banister EW**, **Blaber AP.** Effect of endurance exercise on autonomic control of heart rate. *Sports Med* 33: 33–46, 2003. doi:10.2165/00007256-200333010-00003.
35. **Sacknoff DM**, **Gleim GW**, **Stachenfeld N**, **Coplan NL.** Effect of athletic training on heart rate variability. *Am Heart J* 127: 1275–1278, 1994. doi:10.1016/0002-8703(94)90046-9.
36. **Swain DP**, **Leutholtz BC**, **King ME**, **Haas LA**, **Branch JD.** Relationship between % heart rate reserve and % VO2 reserve in treadmill exercise. *Med Sci Sports Exerc* 30: 318–321, 1998. doi:10.1097/00005768-199802000-00022.
37. **Machhada A**, **Trapp S**, **Marina N**, **Stephens RCM**, **Whittle J**, **Lythgoe MF**, **Kasparov S**, **Ackland GL**, **Gourine AV.** Vagal determinants of exercise capacity. *Nat Commun* 8: 15097, 2017. doi:10.1038/ncomms15097.
38. **Shanks J**, **Pachen M**, **Chang JW**, **George B**, **Ramchandra R.** Cardiac vagal nerve activity increases during exercise to enhance coronary blood flow. *Circ Res* 133: 559–571, 2023. doi:10.1161/CIRCRESAHA.123.323017.
39. **Beltrán AR**, **Arce-Álvarez A**, **Ramirez-Campillo R**, **Vásquez-Muñoz M**, **von Igel M**, **Ramírez MA**, **Del Rio R**, **Andrade DC.** Baroreflex modulation during acute high-altitude exposure in rats. *Front Physiol* 11: 1049, 2020. doi:10.3389/fphys.2020.01049.
40. **Andrade DC**, **Beltrán AR**, **Labarca-Valenzuela C**, **Manzo-Botarelli O**, **Trujillo E**, **Otero-Farias P**, **Álvarez C**, **Garcia-Hermoso A**, **Toledo C**, **Del Rio R**, **Silva-Urra J**, **Ramírez-Campillo R.** Effects of plyometric training on explosive and endurance performance at sea level and at high altitude. *Front Physiol* 9: 1415, 2018. doi:10.3389/fphys.2018.01415.
41. **Hainsworth R**, **Drinkhill M**, **Rivera-Chir M.** The autonomic nervous system at high altitude. *Clin Auton Res* 17: 13–19, 2007. doi:10.1007/s10286-006-0395-7.
42. **Williams AM**, **Levine BD**, **Stembridge M.** A change of heart: mechanisms of cardiac adaptation to acute and chronic hypoxia. *J Physiol* 600: 4089–4104, 2022. doi:10.1113/JP281724.
43. **McCloskey DI**, **Mitchell JH.** Reflex cardiovascular and respiratory responses originating in exercising muscle. *J Physiol* 224: 173–186, 1972. doi:10.1113/jphysiol.1972.sp009887.
44. **Amann M**, **Blain GM**, **Proctor LT**, **Sebranek JJ**, **Pegelow DF**, **Dempsey JA.** Group III and IV muscle afferents contribute to ventilatory and cardiovascular response to rhythmic exercise in humans. *J Appl Physiol (1985)* 109: 966–976, 2010. doi:10.1152/japplphysiol.00462.2010.
45. **Tocco F**, **Crisafulli A**, **Milia R**, **Marongiu E**, **Mura R**, **Roberto S**, **Todde F**, **Concu D**, **Melis S**, **Velluzzi F**, **Loviselli A**, **Concu A**, **Melis F.** Nervous facilitation in cardiodynamic response of exercising athletes to superimposed mental tasks: implications in depressive disorder. *Clin Pract Epidemiol Ment Health* 11: 166–173, 2015. doi:10.2174/1745017901511010166.
46. **Wan HY**, **Bunsawat K**, **Amann M.** Autonomic cardiovascular control during exercise. *Am J Physiol Heart Circ Physiol* 325: H675–H686, 2023. doi:10.1152/ajpheart.00303.2023.
47. **Kaufman MP**, **Waldrop TG**, **Rybicki KJ**, **Ordway GA**, **Mitchell JH.** Effects of static and rhythmic twitch contractions on the discharge of group III and IV muscle afferents. *Cardiovasc Res* 18: 663–668, 1984. doi:10.1093/cvr/18.11.663.
48. **Adreani CM**, **Hill JM**, **Kaufman MP.** Responses of group III and IV muscle afferents to dynamic exercise. *J Appl Physiol (1985)* 82: 1811–1817, 1997. doi:10.1152/jappl.1997.82.6.1811.
49. **Wasserman K**, **Whipp BJ**, **Koyl SN**, **Beaver WL.** Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 35: 236–243, 1973. doi:10.1152/jappl.1973.35.2.236.
50. **Jones AM**, **Wilkerson DP**, **DiMenna F**, **Fulford J**, **Poole DC.** Muscle metabolic responses to exercise above and below the "critical power" assessed using 31P-MRS. *Am J Physiol Regul Integr Comp Physiol* 294: R585–R593, 2008. doi:10.1152/ajpregu.00731.2007.
51. **Cerezuela Espejo V**, **Courel Ibáñez J**, **Morán-Navarro R**, **Martínez Cava A**, **Pallarés J.** The relationship between lactate and ventilatory thresholds in runners: validity and reliability of exercise test performance parameters. *Front Physiol* 9: 1320, 2018. doi:10.3389/fphys.2018.01320.

Downloaded from journals.physiology.org/journal/jn (146.083.153.245) on June 5, 2025.

52. **Hérent C**, **Diem S**, **Usseglio G**, **Fortin G**, **Bouvier J.** Upregulation of breathing rate during running exercise by central locomotor circuits in mice. *Nat Commun* 14: 2939, 2023. doi:10.1038/s41467-023-38583-6.
53. **Guyenet PG**, **Stornetta RL**, **Souza GMPR**, **Abbott SBG**, **Shi Y**, **Bayliss DA.** The retrotrapezoid nucleus: central chemoreceptor and regulator of breathing automaticity. *Trends Neurosci* 42: 807–824, 2019. doi:10.1016/j.tins.2019.09.002.
54. **Moreira TS**, **Sobrinho CR**, **Falquetto B**, **Oliveira LM**, **Lima JD**, **Mulkey DK**, **Takakura AC.** The retrotrapezoid nucleus and the neuromodulation of breathing. *J Neurophysiol* 125: 699–719, 2021. doi:10.1152/jn.00497.2020.
55. **Del Coso J**, **Hamouti N**, **Aguado-Jimenez R**, **Mora-Rodriguez R.** Respiratory compensation and blood pH regulation during variable intensity exercise in trained versus untrained subjects. *Eur J Appl Physiol* 107: 83–93, 2009. doi:10.1007/s00421-009-1101-y.
56. **Raff H**, **Tzankoff SP**, **Fitzgerald RS.** Chemoreceptor involvement in cortisol responses to hypoxia in ventilated dogs. *J Appl Physiol Respir Environ Exerc Physiol* 52: 1092–1096, 1982. doi:10.1152/jappl.1982.52.4.1092.
57. **Fernandez R**, **Nardocci G**, **Navarro C**, **Reyes EP**, **Acuña-Castillo C**, **Cortes PP.** Neural reflex regulation of systemic inflammation: potential new targets for sepsis therapy. *Front Physiol* 5: 489, 2014. doi:10.3389/fphys.2014.00489.
58. **Holmes AP**, **Ray CJ**, **Thompson EL**, **Alshehri Z**, **Coney AM**, **Kumar P.** Adrenaline activation of the carotid body: Key to CO_2 and pH homeostasis in hypoglycaemia and potential pathological implications in cardiovascular disease. *Respir Physiol Neurobiol* 265: 92–99, 2019. doi:10.1016/j.resp.2018.05.008.
59. **Warren JB**, **Dalton N**, **Turner C**, **Clark TJ**, **Toseland PA.** Adrenaline secretion during exercise. *Clin Sci (Lond)* 66: 87–90, 1984. doi:10.1042/cs0660087.
60. **Iturriaga R**, **Alcayaga J.** Neurotransmission in the carotid body: transmitters and modulators between glomus cells and petrosal ganglion nerve terminals. *Brain Res Brain Res Rev* 47: 46–53, 2004. doi:10.1016/j.brainresrev.2004.05.007.
61. **Atanasova D**, **Iliev M**, **Lazarov N.** Morphology of the rat carotid body. *Biomedical Reviews* 22: 41–55, 2011. doi:10.14748/bmr.v22.34.
62. **Gonzalez C**, **Almaraz L**, **Obeso A**, **Rigual R.** Carotid body chemoreceptors: from natural stimuli to sensory discharges. *Physiol Rev* 74: 829–898, 1994. doi:10.1152/physrev.1994.74.4.829.
63. **Iturriaga R**, **Alcayaga J**, **Chapleau MW**, **Somers VK.** Carotid body chemoreceptors: physiology, pathology, and implications for health and disease. *Physiol Rev* 101: 1177–1235, 2021. doi:10.1152/physrev.00039.2019.
64. **Arce-Álvarez A**, **Salazar-Ardiles C**, **Cornejo C**, **Paez V**, **Vásquez-Muñoz M**, **Stillner-Vilches K**, **Jara CR**, **Ramirez-Campillo R**, **Izquierdo M**, **Andrade DC.** Chemoreflex control as the cornerstone in immersion water sports: possible role on breath-hold. *Front Physiol* 13: 894921, 2022. doi:10.3389/fphys.2022.894921.
65. **Prabhakar NR**, **Peng YJ.** Peripheral chemoreceptors in health and disease. *J Appl Physiol (1985)* 96: 359–366, 2004. doi:10.1152/japplphysiol.00809.2003.
66. **Iturriaga R**, **Varas R**, **Alcayaga J.** Electrical and pharmacological properties of petrosal ganglion neurons that innervate the carotid body. *Respir Physiol Neurobiol* 157: 130–139, 2007. doi:10.1016/j.resp.2006.12.006.
67. **Torres-Torrelo H**, **Ortega-Sáenz P**, **Macías D**, **Omura M**, **Zhou T**, **Matsunami H**, **Johnson RS**, **Mombaerts P**, **López-Barneo J.** The role of Olfr78 in the breathing circuit of mice. *Nature* 561: E33–E40, 2018. doi:10.1038/s41586-018-0545-9.
68. **Peng YJ**, **Gridina A**, **Wang B**, **Nanduri J**, **Fox AP**, **Prabhakar NR.** Olfactory receptor 78 participates in carotid body response to a wide range of low O_2 levels but not severe hypoxia. *J Neurophysiol* 123: 1886–1895, 2020. doi:10.1152/jn.00075.2020.
69. **Peng YJ**, **Nanduri J**, **Wang N**, **Kumar GK**, **Bindokas V**, **Paul BD**, **Chen X**, **Fox AP**, **Vignane T**, **Filipovic MR**, **Prabhakar NR.** Hypoxia sensing requires H_2S-dependent persulfidation of olfactory receptor 78. *Sci Adv* 9: eadf3026, 2023. doi:10.1126/sciadv.adf3026.
70. **Colinas O**, **Mombaerts P**, **López-Barneo J**, **Ortega-Sáenz P.** Carotid body function in tyrosine hydroxylase conditional olfr78 knockout mice. *Function (Oxf)* 5: zqae010, 2024. doi:10.1093/function/zqae010.
71. **Juel C.** Lactate-proton cotransport in skeletal muscle. *Physiol Rev* 77: 321–358, 1997. doi:10.1152/physrev.1997.77.2.321.
72. **Emhoff CW**, **Messonnier LA.** Concepts of lactate metabolic clearance rate and lactate clamp for metabolic inquiry: a mini-review. *Nutrients* 15: 3213, 2023. doi:10.3390/nu15143213.
73. **Masuda A**, **Paulev PE**, **Sakakibara Y**, **Ahn B**, **Takaishi S**, **Pokorski M**, **Nishibayashi Y**, **Honda Y.** Estimation of peripheral chemoreceptor contribution to exercise hyperpnea in man. *Jpn J Physiol* 38: 607–618, 1988. doi:10.2170/jjphysiol.38.607.
74. **Dempsey JA**, **Smith CA.** Do carotid chemoreceptors inhibit the hyperventilatory response to heavy exercise? *Can J Appl Physiol* 19: 350–359, 1994. doi:10.1139/h94-028.
75. **Dejours P.** Chemoreflexes in breathing. *Physiol Rev* 42: 335–358, 1962. doi:10.1152/physrev.1962.42.3.335.
76. **Honda Y**, **Watanabe S**, **Hashizume I**, **Satomura Y**, **Hata N**, **Sakakibara Y**, **Severinghaus JW.** Hypoxic chemosensitivity in asthmatic patients two decades after carotid body resection. *J Appl Physiol Respir Environ Exerc Physiol* 46: 632–638, 1979. doi:10.1152/jappl.1979.46.4.632.
77. **Andrade DC**, **Díaz-Jara E**, **Toledo C**, **Schwarz KG**, **Pereyra KV**, **Díaz HS**, **Marcus NJ**, **Ortiz FC**, **Ríos-Gallardo AP**, **Ortolani D**, **Del Rio R.** Exercise intolerance in volume overload heart failure is associated with low carotid body mediated chemoreflex drive. *Sci Rep* 11: 14458, 2021. doi:10.1038/s41598-021-93791-8.
78. **Pan LG**, **Forster HV**, **Bisgard GE**, **Murphy CL**, **Lowry TF.** Independence of exercise hyperpnea and acidosis during high-intensity exercise in ponies. *J Appl Physiol (1985)* 60: 1016–1024, 1986. doi:10.1152/jappl.1986.60.3.1016.
79. **Stickland MK**, **Fuhr DP**, **Haykowsky MJ**, **Jones KE**, **Paterson DI**, **Ezekowitz JA**, **McMurtry MS.** Carotid chemoreceptor modulation of blood flow during exercise in healthy humans. *J Physiol* 589: 6219–6230, 2011. doi:10.1113/jphysiol.2011.218099.
80. **Stickland MK**, **Miller JD**, **Smith CA**, **Dempsey JA.** Carotid chemoreceptor modulation of regional blood flow distribution during exercise in health and chronic heart failure. *Circ Res* 100: 1371–1378, 2007. doi:10.1161/01.RES.0000266974.84590.d2.
81. **Stickland MK**, **Morgan BJ**, **Dempsey JA.** Carotid chemoreceptor modulation of sympathetic vasoconstrictor outflow during exercise in healthy humans. *J Physiol* 586: 1743–1754, 2008. doi:10.1113/jphysiol.2007.147421.
82. **Sayegh ALC**, **Plunkett MJ**, **Babbage T**, **Dawes M**, **Paton JFR**, **Fisher JP.** Peripheral chemoreflex restrains skeletal muscle blood flow during exercise in participants with treated hypertension. *J Physiol*, 2024. doi:10.1113/JP286998.
83. **Parkes MJ.** Evaluating the importance of the carotid chemoreceptors in controlling breathing during exercise in man. *Biomed Res Int* 2013: 893506, 2013 [Erratum in *Biomed Res Int* 2015: 969257, 2015]. doi:10.1155/2013/893506.
84. **Rogatzki MJ**, **Ferguson BS**, **Goodwin ML**, **Gladden LB.** Lactate is always the end product of glycolysis. *Front Neurosci* 9: 22, 2015. doi:10.3389/fnins.2015.00022.
85. **Brooks GA**, **Dubouchaud H**, **Brown M**, **Sicurello JP**, **Butz CE.** Role of mitochondrial lactate dehydrogenase and lactate oxidation in the intracellular lactate shuttle. *Proc Natl Acad Sci USA* 96: 1129–1134, 1999. doi:10.1073/pnas.96.3.1129.
86. **Messonnier L**, **Freund H**, **Féasson L**, **Prieur F**, **Castells J**, **Denis C**, **Linossier MT**, **Geyssant A**, **Lacour JR.** Blood lactate exchange and removal abilities after relative high-intensity exercise: effects of training in normoxia and hypoxia. *Eur J Appl Physiol* 84: 403–412, 2001. doi:10.1007/s004210000378.
87. **Dubouchaud H**, **Butterfield GE**, **Wolfel EE**, **Bergman BC**, **Brooks GA.** Endurance training, expression, and physiology of LDH, MCT1, and MCT4 in human skeletal muscle. *Am J Physiol Endocrinol Physiol* 278: E571–E579, 2000. doi:10.1152/ajpendo.2000.278.4.E571.
88. **Pluznick JL**, **Protzko RJ**, **Gevorgyan H**, **Peterlin Z**, **Sipos A**, **Han J**, **Brunet I**, **Wan LX**, **Rey F**, **Wang T**, **Firestein SJ**, **Yanagisawa M**, **Gordon JI**, **Eichmann A**, **Peti-Peterdi J**, **Caplan MJ.** Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. *Proc Natl Acad Sci USA* 110: 4410–4415, 2013. doi:10.1073/pnas.1215927110.
89. **Mermer P**, **Strotmann J**, **Kummer W**, **Paddenberg R.** Olfactory receptor Olfr78 (prostate-specific G protein-coupled receptor PSGR) expression in arterioles supplying skeletal and cardiac muscles and in arterioles feeding some murine organs. *Histochem Cell Biol* 156: 539–553, 2021. doi:10.1007/s00418-021-02032-6.

Downloaded from journals.physiology.org/journal/jn (146.083.153.245) on June 5, 2025.

90. **Ding Y**, **Li YL**, **Schultz HD.** Role of blood flow in carotid body chemoreflex function in heart failure. *J Physiol* 589: 245–258, 2011. doi:10.1113/jphysiol.2010.200584.
91. **Del Rio R**, **Andrade DC**, **Toledo C**, **Diaz HS**, **Lucero C**, **Arce-Alvarez A**, **Marcus NJ**, **Schultz HD.** Carotid body-mediated chemoreflex drive in the setting of low and high output heart failure. *Sci Rep* 7: 8035, 2017. doi:10.1038/s41598-017-08142-3.
92. **Stainsby WN**, **Welch HG.** Lactate metabolism of contracting dog skeletal muscle in situ. *Am J Physiol* 211: 177–183, 1966. doi:10.1152/ajplegacy.1966.211.1.177.
93. **Johnson ML**, **Emhoff CA**, **Horning MA**, **Brooks GA.** Transpulmonary lactate shuttle. *Am J Physiol Regul Integr Comp Physiol* 302: R143–R149, 2012. doi:10.1152/ajpregu.00402.2011.
94. **Brooks GA.** The science and translation of lactate shuttle theory. *Cell Metab* 27: 757–785, 2018. doi:10.1016/j.cmet.2018.03.008.
95. **Bellomo R.** Bench-to-bedside review: lactate and the kidney. *Crit Care* 6: 322–326, 2002. doi:10.1186/cc1518.
96. **Hashimoto T**, **Hussien R**, **Brooks GA.** Colocalization of MCT1, CD147, and LDH in mitochondrial inner membrane of L6 muscle cells: evidence of a mitochondrial lactate oxidation complex. *Am J Physiol Endocrinol Physiol* 290: E1237–E1244, 2006. doi:10.1152/ajpendo.00594.2005.
97. **Welch JF**, **Mitchell GS.** Inaugural review prize 2023: the exercise hyperpnoea dilemma: a 21st-century perspective. *Exp Physiol* 109: 1217–1237, 2024. doi:10.1113/EP091506.
98. **Korsak A**, **Sheikhbahaei S**, **Machhada A**, **Gourine AV**, **Huckstepp RTR.** The role of parafacial neurons in the control of breathing during exercise. *Sci Rep* 8: 400, 2018. doi:10.1038/s41598-017-17412-z.
99. **Toledo C**, **Andrade DC**, **Diaz-Jara E**, **Ortolani D**, **Bernal-Santander I**, **Schwarz KG**, **Ortiz FC**, **Marcus NJ**, **Oliveira LM**, **Takakura AC**, **Moreira TS**, **Del Rio R.** Cardiorespiratory alterations following intermittent photostimulation of RVLM C1 neurons: implications for long-term blood pressure, breathing and sleep regulation in freely moving rats. *Acta Physiol (Oxf)* 236: e13864, 2022. doi:10.1111/apha.13864.
100. **Toledo C**, **Díaz-Jara E**, **Diaz HS**, **Schwarz KG**, **Pereyra KV**, **Las Heras A**, **Rios-Gallardo A**, **Andrade DC**, **Moreira T**, **Takakura A**, **Marcus NJ**, **Del Rio R.** Medullary astrocytes mediate irregular breathing patterns generation in chronic heart failure through purinergic P2X7 receptor signalling. *EBioMedicine* 80: 104044, 2022. doi:10.1016/j.ebiom.2022.104044.

Downloaded from journals.physiology.org/journal/jn (146.083.153.245) on June 5, 2025.