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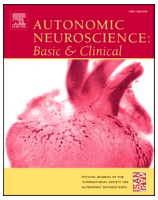

Carotid body interoception in health and disease

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ABSTRACT

Interoception entails perceiving or being aware of the internal state of the body, playing a pivotal role in regulating processes such as heartbeat, digestion, glucose metabolism, and respiration. The carotid body (CB) serves as an interoceptive organ, transmitting information to the brain via its sensitive nerve, the carotid sinus nerve, to maintain homeostasis. While traditionally known for sensing oxygen, carbon dioxide, and pH levels, the CB is now recognized to possess additional interoceptive properties, detecting various mediators involved in blood pressure regulation, inflammation, and glucose homeostasis, among other physiological functions. Furthermore, in the last decades CB dysfunction has been linked to diseases like sleep apnea, essential hypertension, and diabetes.

In this review manuscript, we make a concise overview of the traditional interoceptive functions of the CB, acting as a sensor for oxygen levels, carbon dioxide levels, and pH, and introduce the novel interoceptive properties of the CB related to vascular, glucose and energy regulation. Additionally, we revise the contribution of the CB to the onset and progression of metabolic diseases, delving into the potential dysfunction of its interoceptive metabolic functions as a contributing factor to pathophysiology. Finally, we postulate the use of therapeutic interventions targeting the metabolic interoceptive properties of the CB as a potential avenue for addressing metabolic diseases.

1. Introduction

The concept of interoception refers to the sense of the internal state of the body, including sensations related to physiological processes such as heartbeat, respiration, hunger, thirst, and other bodily functions (Berntson and Khalsa, 2021). In physiology, interoception plays a crucial role in maintaining homeostasis, which is the body's ability to regulate and maintain a stable internal environment despite external changes. Also, interoception and modulation of interoceptive signals are crucial in various states of physiopathology and are increasingly recognized in the context of different diseases, varying from psychiatric, eating, cardiovascular, neurological disorders, among many others.

The carotid bodies (CB) are known to play a crucial role in interoception, meaning in sensing the physiological state of the body, in both health and disease. CB interoception in health involves not only monitoring and regulating factors such as oxygen (O_2), carbon dioxide (CO_2), and pH levels in the blood, but also monitoring the function of many metabolic factors such as insulin, leptin, glucagon-like peptide-1 (GLP-1), among others that are crucial to maintain glucose and energy homeostasis.

In the context of metabolic diseases, disruptions in the interoceptive functions of the CB can have implications for the regulation of the above-mentioned metabolic factors and the autonomic nervous system. Dysregulation of these processes can contribute to conditions like metabolic syndrome, obesity, and diabetes. The interplay between the CB, the peripheral nervous system, and the central nervous system in the context of metabolic diseases is an active area of research, and a better understanding of these interactions may lead to novel therapeutic approaches for managing these conditions.

2. Physiology of the carotid body

The CB is a paired organ located in the bifurcation of the common carotid artery in the neck. These small organs are multimodal sensors capable of detecting biochemical substances in arterial blood. Their strategic location enables them to serve as primary sensors in regulating the chemical composition of blood before it reaches the brain. The information detected by the CBs is integrated in the nucleus solitary tract

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(NTS), through the carotid sinus nerve (CSN), the CB sensitive nerve. This sensory input leads to reflex adjustments in the functional activity of efferent organs (Fig. 1). The classical stimulus for CB activation is hypoxia, leading to an increase in CSN activity that is integrated in the NTS inducing reflex respiratory, autonomic and cardiovascular adjustments that aim to normalize the altered blood gasses via hyperventilation (Gonzalez et al., 1994) and to regulate blood pressure and cardiac performance through an augment in sympathetic nervous system (SNS) activity (Marshall, 1994).

The CB is organized into glomeruli, clusters of cells surrounded by an abundant network of capillaries, connective tissue and afferent and efferent sensory fibers (Gonzalez et al., 2010b). Each glomerulus contains chemoreceptor cells or type I cells, that derived from the neural crest and received afferent innervation from the CSN (Gonzalez et al., 1994). These cells are surrounded by type II or sustentacular cells and are filled with numerous clear and dense-core synaptic vesicles containing various neurotransmitters, including catecholamines (dopamine and norepinephrine), ATP, adenosine, acetylcholine, GABA, serotonin, neuropeptides, among others (Conde et al., 2014; Gonzalez et al., 1994; Nurse, 2010; Nurse and Piskuric, 2013; Wang et al., 1992; Conde et al., 2012). Type II cells have been identified as multipotent stem cells, that contribute to both neurogenesis and angiogenesis by proliferating and differentiating into type I cells and vascular cells, respectively, in response to hypoxia (Annese et al., 2017; Pardal et al., 2007). Additionally, type II cells also contribute to the paracrine signaling and purinergic catabolic pathways that integrate sensory output of the CB during chemotransduction in response to hypoxia and probably in response to other stimuli (Nurse et al., 2018; Nurse and Piskuric, 2013).

2.1. Carotid body chemotransduction mechanisms

It is generally accepted that the transduction cascade in the CB involves several steps. These include: 1) the closure of K^+ channels, 2) type I cell membrane depolarization, 3) activation of voltage dependent Ca^{2+} channels, 4) increase in intracellular Ca^{2+}, 5) release of neurotransmitters, 6) increase in the frequency of action potentials of the CSN that are integrated in the brainstem (Gonzalez et al., 2010a, 2010b; López-Barneo et al., 2016) (Fig. 2). Several neurotransmitters have been postulated to be involved in the synaptic process between CB type I cells and the CSN (for a review (Gonzalez et al., 1994; Kumar and Prabhakar, 2012)). More recently, the concept of a tripartite synapse, where CB type II cells contribute to modulate CB sensitivity and CSN discharge has emerged (Leonard et al., 2018; Nurse, 2014). Among the neurotransmitters contained in chemoreceptor cells are catecholamines (dopamine and norepinephrine), serotonin, acetylcholine, GABA, neuropeptides (substance P and enkephalins), adenosine and ATP (Buttigieg and Nurse, 2004; Conde and Monteiro, 2004; Fearon et al., 2003; Gonzalez et al., 1994). All these substances, their agonists and antagonists are capable of modifying CSN activity. Among the several hypotheses generated through several decades to explain CB-CSN transmission, are the cholinergic hypothesis and the dopaminergic hypothesis, being catecholamines the most well characterized neurotransmitters at the CB (for a review see Gonzalez et al., 1994; Kumar and Prabhakar, 2012), however the most consensual hypothesis is the recent purinergic hypothesis (Conde et al., 2017a; Nurse, 2014). The first study on the effects of ATP on CSN activity, by McQueen and Ribeiro (McQueen and Ribeiro, 1983), observed that this nucleotide increased CSN activity in a dose-dependent manner. Additional experiments led them to conclude that the excitatory action of ATP was due to the adenosine formed by its extracellular degradation. However, Zhang and co-workers (Zhang et al., 2000)

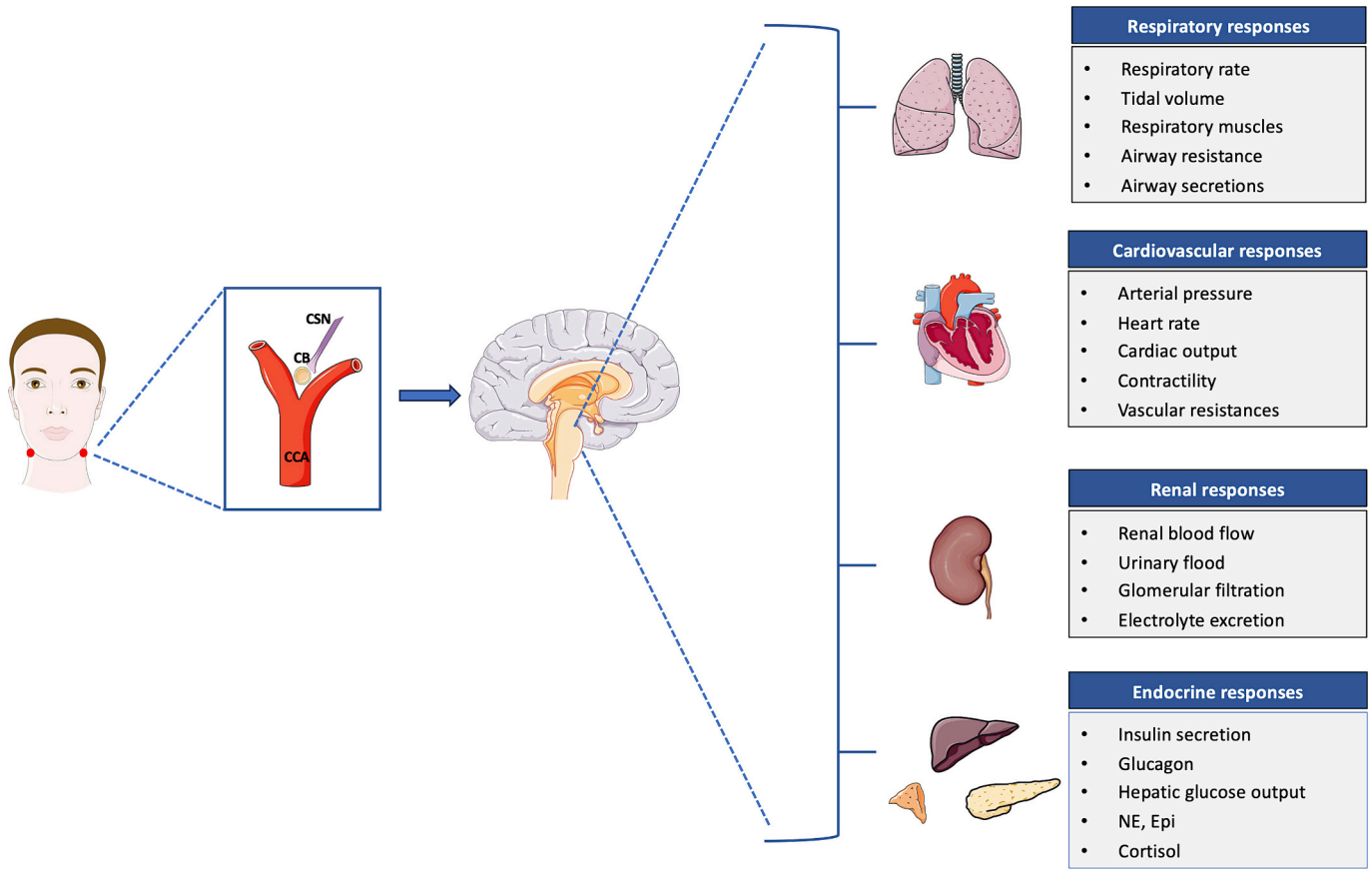

Fig. 1. Schematic representation of the carotid body (CB) location and the physiological responses elicited by their stimulation. Note that the activity of the organ is integrated via carotid sinus nerve (CSN) into the central nervous system to elicit respiratory, cardiovascular, renal and endocrine responses.

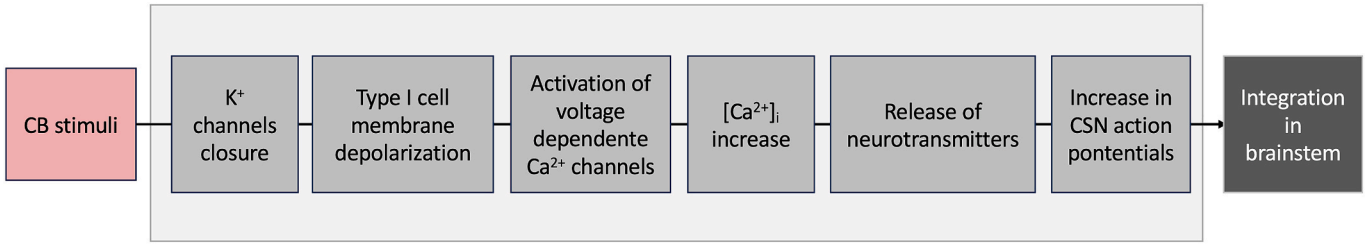

Fig. 2. Chemotransduction cascade in the carotid body (CB) – carotid sinus nerve (CSN) transmission and its integration in the brainstem.

showed that the application of blockers of P2X receptors decreased the hypoxia-evoked excitatory postsynaptic responses, an effect that was sustained by the finding that $P2X_2$ receptor knockout mice showed a markedly attenuated ventilatory response to hypoxia (Rong et al., 2003), and by the finding that ATP is released from rat CB in hypoxia (Buttigieg and Nurse, 2004; Conde et al., 2012; Conde et al., 2006). Thus, in response to hypoxia, chemoreceptor cells will depolarize and release ATP which would act postsynaptically in $P2X_{2/3}$ receptors on afferent nerve terminals. However, the complete blockade of P2 receptors in the CB by suramin was insufficient to fully promote inhibition of ventilation and the CSN chemosensory response to hypoxia (Niane et al., 2011; Reyes et al., 2007; Zhang et al., 2000) suggesting the involvement of other excitatory co-transmitters. Several authors proposed the co-release of ATP and acetylcholine, as demonstrated by studies where the application of a mixture of nicotinic and purinergic antagonists completely suppressed the CSN response to hypoxia (Varas et al., 2003; Zhang et al., 2000). However, this hypothesis is not universally accepted, as applying nicotinic and P2X blockers did not completely suppress CSN chemosensory activity in vivo in cats (Reyes et al., 2007). In 2012, Conde's group proposed that both adenosine and ATP are the main players of the hypoxic chemotransmission in the CB sensory synapse, the contribution of each neurotransmitter depending on the intensity of hypoxia (Conde et al., 2012). It was demonstrated that a simultaneous release of adenosine and ATP occurs in the CB in response to hypoxia, with the release of ATP and its extracellular catabolism to adenosine being the main origin of extracellular adenosine at high-intensity hypoxia, whereas at mild hypoxia adenosine is also released by the equilibrative nucleoside transporter (Conde et al., 2012; Conde and Monteiro, 2004). Also, it was found that the blockade of A2 adenosine receptors decreased more profoundly CSN discharges evoked by moderate hypoxia than intense hypoxia and conversely the blockade of P2 receptors decreased more profoundly CSN discharges evoked by intense hypoxia (Conde et al., 2012). The simultaneous application of both antagonists strongly inhibited CSN discharges elicited by both hypoxic intensities (Conde et al., 2012) meaning that the excitatory effects of adenosine on the CB via $A2_A$ and $A2_B$ receptors (Conde et al., 2006) together with the activation of P2X ATP receptors will be primordial in the genesis of CSN chemoresponses to hypoxia. More recently, a role for ATP as a modulator via $P2Y_2$ receptors present in CB type II cells, which may enhance the ATP signal through the opening of pannexin-1 channels, has been suggested (Nurse, 2014).

While much of the research on chemotransmission and chemotransduction processes has focused on responses to the classical interoceptive properties of the CB – such as hypoxia and hypercapnia/acidosis – the CB is known to sense and respond to a wide range of stimuli. These "new" CB interoceptive stimuli likely involve the same neurotransmitters used for communication at the CB-CSN synapse. However, further research is needed to elucidate these mechanisms.

2.2. Cardiorespiratory responses elicited by the carotid body

The CB is mainly known for its role in the control of ventilation, with the respiratory response to CB stimulation being the most expected. In fact, this organ is pivotal in the ventilatory changes associated with exercise, pregnancy, and adaptation to high altitude (Kumar and Prabhakar, 2012). However, CB stimulation also produces cardiovascular, endocrine, and renal responses (Fig. 1). While the ventilatory and cardiovascular responses have been the most extensively CB evoked responses studied (see Sections 2.2.1 and 2.2.2.), more recently the role of CB in evoking metabolic (Alvarez-Buylla and de Alvarez-Buylla, 1988, 1994; Conde et al., 2014, 2018; Koyama et al., 2000; Koyama et al., 2001; Ribeiro et al., 2013; Sacramento et al., 2018a), renal (Kious et al., 2022) and anti-inflammatory (Fernandez et al., 2014; Iturriaga et al., 2022; Sacramento et al., 2020) responses have emerged. In Section 5 we will explore in more detail the role of CB in metabolic and energy homeostasis, highlighting the CB dysfunction as a major factor contributing to dysmetabolic states.

2.2.1. Respiratory responses

The role of CB in the ventilatory control has been extensively described. The CB is important in the maintenance of resting ventilation, since CB denervation induced changes in resting ventilatory parameters, such as a decrease in minute ventilation and an increase in the partial arterial pressure of CO2 (Bisgard et al., 1976; Feustel et al., 1981; Ribeiro et al., 2013). Additionally, CB activation by hypoxia and hypercapnia induced an increase in respiratory rate and tidal volume (see Gonzalez et al., 1994) as well as in airway secretions and airway resistance (Fitzgerald and Shirahata, 1997). In human and animal studies, CB removal or denervation abolished the respiratory response to acute hypoxia (Honda, 1985; Melo et al., 2022; Timmers et al., 2003). Moreover, the bilateral denervation or removal of the CB may also promote a small residual response to acute hypoxia that may be present during simultaneous hypercapnia and induced a decrease in CO_2 sensitivity by 20–30 % (Timmers et al., 2003). These effects are more severe after bilateral than unilateral CB resection (Honda et al., 1979), suggesting a compensation of the remaining CB.

In hypercapnic or respiratory acidosis, that occur with the elevation of CO_2 levels in blood and the consequent decrease in the extracellular pH (acidemia), the CB contributes to approximately 30 % of the respiratory drive, being this contribution greater than the contribution of CB to the hyperventilation that occur in metabolic acidosis (Gonzalez et al., 1994; Irsigler et al., 1980). In metabolic acidosis, the PCO_2 is normal but the pH and bicarbonate are reduced (Rausch et al., 1991). The rest 70 % of the respiratory drive produced by hypercapnic acidosis is mediated by the central chemoreceptors (Gonzalez et al., 1994). The CB is also important in the ventilatory alterations associated with exercise. In subjects with CB resection the exercise hyperpnea was depressed, when compared with subjects with intact CB (Honda, 1985). In high-intensity exercise, the CB is essential for the ventilatory adjustments to exercise, as seen in ponies submitted to CB denervation (Pan et al., 1983). In fact, bilateral CB denervation in humans induced a decrease in pulmonary ventilation during high-intensity exercise (Jeyaranjan et al., 1987). Recently, Spiller et al. (2020) showed that the CBs are important in the inspiratory and expiratory responses to high-intensity exercise, but not low-intensity exercise, being involved in the respiratory compensation against metabolic acidosis promoted by high-intensity exercise in rats (Spiller et al., 2020). This finding aligns with previously observations in ponies, where intracranial and aortic chemoreceptors were sufficient to

address ventilatory-metabolic matching during low-intensity exercise (Pan et al., 1983). Furthermore, CB hyperexcitability is proposed to be the primary cause of heat-induced hyperventilation during exercise (Gibbons et al., 2022).

2.2.2. Cardiovascular responses

CB stimulation is also involved in cardiovascular regulation, directly and primarily by influencing the heart and regional circulations and promoting bradycardia, decreased cardiac output and peripheral vasoconstriction (Kumar and Bin-Jaliah, 2007; Marshall, 1994), but also secondarily in the consequent of the CB-evoked central ventilatory responses (Marshall, 1994). Moreover, it is also known that CB stimulation may evoke the release of several mediators, including norepinephrine, epinephrine (see Marshall, 1994) as well as several vascular factors, like endothelin-1, angiotensin II and others, (see Section 4) that can contribute to cardiovascular regulation.

In contrast to the respiratory responses, the cardiovascular responses to CB stimulation were controversial for several decades due to multiple confounding factors, such as hyperventilation, hypocapnia, pulmonary stretch/vagal activation, central respiratory drive, baroreceptor involvement, circulating catecholamines, and variations in study preparation (e.g., species, awake or anesthetized animals) (Marshall, 1994). However, it is generally agreed that CB stimulation modulates both cardiac vagal activity and sympathetic activity. The pivotal role of the CB in cardiovascular regulation has been more recently emphasized by the involvement of these organs in the pathophysiology of several cardiovascular diseases, including chronic heart failure (Del Rio et al., 2013; Schultz et al., 2013) and various forms of hypertension (Abdala et al., 2012; Paton et al., 2013; Prabhakar and Peng, 2004), contributing fundamentally to the onset and progression of these conditions. For example, the contribution from the CB is critical for the onset and maintenance of hypertension in spontaneously hypertensive rats (Abdala et al., 2012; McBryde et al., 2013) and in obesity-associated hypertensive mice (Shin et al., 2019). Also, it was shown, that rats with chronic heart failure develop increased CB chemoreflex drive and chronic central presympathetic neuronal activation, increased sympathetic outflow, increased breathing variability, and apnea incidence as well as desensitization of the baroreflex, these effects being reduced by CB ablation (Del Rio et al., 2013). These preclinical data are consistent with human studies demonstrating that unilateral CB removal reduced blood pressure in eight drug-resistant hypertensive patients, accompanied by decreases in sympathetic activity, effects attenuated 12 months post-surgery (Narkiewicz et al., 2016). Similarly, the impact of CB resection in heart failure was associated with a notable decrease in both muscle sympathetic activity and peripheral chemosensitivity, resulting also in improved exercise tolerance (Niewinski et al., 2017). Together, these results confirm the role of the CB in regulating blood pressure and cardiac performance via SNS activation.

3. Classical interoceptive properties of the carotid body

3.1. Oxygen

The CB is considered the main O_2 sensor in the body, being essential to survive in conditions of low oxygen levels (hypoxia). Type I cells are extremely sensitive to O_2 and the chemotransduction cascade in response to hypoxia is activated rapidly at PO_2 between 20 and 40 mmHg (Biscoe et al., 1990; Buckler and Vaughan-Jones, 1994a). While most steps of O_2 CB chemotransduction cascade have been widely accepted for several decades (Fig. 2), the molecular identity of the specific O_2 sensor in type I cells remains controversial and several hypotheses have been proposed. One of the first hypotheses to be postulated was the membrane hypothesis that suggested that the electrophysiological events, as K^+ channels opening and the subsequent type I cell depolarization that occur in the plasma membrane of CB type I cells, are fundamental for the O_2 CB chemotransduction (Gonzalez et al., 1994). Additionally, other CB O_2-sensing mechanisms have been proposed including: 1) the mitochondrial ATP production or metabolic hypothesis that states that mitochondria is the O_2 sensor and the decrease in ATP levels mediate O_2 sensing; 2) the AMP-activated protein kinase hypothesis saying that a change in the energy status of the cell by 5′AMP-activated protein kinase (AMPK) is the O_2 sensor; 3) the hydrogen sulphide (H_2S) hypothesis that says that gasotransmitters carbon monoxide and H_2S mediate O_2 sensing; 4) the mitochondrial complex I signaling hypothesis saying that reactive oxygen species (ROS) are key drivers in O_2 signaling; 5) the Lactate–Olfr 78 hypothesis saying that activation of a lactate-sensitive atypical olfactory receptor 78 (Olfr78) expressed in CB type I cells is the O_2 sensor (for a review see (Gonzalez et al., 2010b; López-Barneo et al., 2016; Rakoczy et al., 2018b). Below we present some information supporting or contradicting these hypotheses.

In the last decades, studies performed in mice with ablation of genes for the receptors or enzymes relevant for the oxygen sensing transduction contradicted the *in vitro* studies, questioning the validity of the oxygen sensing hypothesis that have been proposed. NADPH oxidase was proposed to be the O_2 sensor, however knockout mice for the gp91phox subunit of NADPH oxidase enzyme complex, exhibited a preserved hypoxic ventilatory response (HVR) and preserved intracellular Ca^{2+} responses to hypoxia in CB type I cells (He et al., 2002; Roy et al., 2000). In mice with conditional deletion of AMPK-α1 and/or AMPK-α2 genes in catecholaminergic cells the HVR was reduced but the CSN responses to hypoxia were not altered when compared to the control animals, suggesting that the effect on ventilation is not mediated by the O_2 sensing ability of the CB (Mahmoud et al., 2016). Furthermore, H_2S has been proposed as the CB gasotransmitter mediating O_2 sensing, as evidenced by studies showing that mice lacking cystathionine γ-lyase (CSE), an enzyme involved in H_2S production, exhibited impaired CB and ventilatory responses to hypoxia (Peng et al., 2010). However, knockout mice lacking heme oxygenase-2 (HO-2), an enzyme that generates carbon monoxide and contributes to H_2S production via CSE, showed normal CB responsiveness to hypoxia (Ortega-Sáenz et al., 2006). Moreover, Wang et al. (2017) described that the deletion of CSE has no effect on the acute CB response to hypoxia. These recent studies have contradicted the proposed role of H_2S in acute O_2 sensing by the CB and further studies are needed to clarify its role. Additionally, it cannot be ruled out that compensatory mechanisms may occur in knockout models, given the complexity of the CB system. Due to the importance of the response to hypoxia throughout life, it is expected that if one mechanism fails, others will compensate.

In 2015, Chang et al. proposed that the Olfr78 receptor activated by lactate serves as the O_2 sensor in the CB (Chang et al., 2015). The authors observed expression of Olfr78 in CB type I cells, with activation occurring at low millimolar concentrations of lactate. Furthermore, knockout mice lacking Olfr78 showed a decreased HVR, while their response to hypercapnia remained intact (Chang et al., 2015). However, the work developed by Torres-Torrelo et al. (2018) contradicted these results questioning the role of Olfr78-lactate signaling in CB acute O_2 sensing. The authors described that the knockout mice for Olfr78 had a normal response to hypoxia and a similar release of catecholamines from type I cells promoted by hypoxia and lactate than the wild-type mice (Torres-Torrelo et al., 2018). In addition, recent studies from Prabhakar and collaborators described that Olfr78 is involved in the CSN and type I cell responses to moderate hypoxia, but not severe hypoxia, an effect that is not mediated by lactate or any other short-chain fatty acids as acetate, propionate and butyrate (Peng et al., 2020).

More recently, a model combining the membrane and mitochondrial hypothesis have been proposed (Ortega-Sáenz and López-Barneo, 2019; Moreno-Domínguez et al., 2020) suggesting that O_2 sensing might occur as a result of the integration of different postulated mechanisms. Moreno-Domínguez et al. (2020) suggested that the mitochondrial complex IV is the O_2 sensor, the mitochondrial complex I is the effector and NADPH and ROS are the signaling molecules that modulate ion channels

in the CB type I cells. Moreover, it has been suggested that hypoxia-inducible factor 2 alpha (HIF-2α) induces the expression of CB genes for the atypical cytochrome oxidase subunits in mitochondria (Moreno-Domínguez et al., 2020). Despite the hypothesis proposed by López-Barneo group that integrate the CB membrane and the mitochondrial hypothesis for acute oxygen sensing, it cannot be ruled out the contribution of the other mechanisms previously described or the integration of other novel hypothesis to be discovered.

3.2. Carbon dioxide and pH

Carbon dioxide (CO_2) is another stimulus sensed by the CB. As for low O_2, the transduction mechanisms for hypercapnia and acidic stimuli involve membrane depolarization of type I cells (Buckler and Vaughan-Jones, 1994a, 1994b; Zhang and Nurse, 2004) (Fig. 2). The majority of the studies agree that the activation of type I cells by hypercapnia is due to a reduction in intracellular pH, a process catalyzed by carbonic anhydrase (Buckler and Vaughan-Jones, 1994a, 1994b; Iturriaga et al., 1991; Iturriaga et al., 1993). This enzyme is located in the type I cells (Nurse, 1990) and its pharmacological inhibition by acetazolamide or methazolamide inhibited the chemoexcitatory responses to hypercapnia (Iturriaga et al., 1993; Zhang and Nurse, 2004). However, Summers et al. reported that CO_2 might also increase L-type Ca^{2+} currents in rabbit type I cells independently of changes in internal pH, but the mechanisms are still unknown (Summers et al., 2002).

It is generally accepted that a decrease in pH inhibits CB voltage-dependent K^+ channels, the tandem pore domain acid-sensitive K^+ channel (TASK) (Buckler et al., 1991; Buckler and Vaughan-Jones, 1994a, 1994b). Additionally, it has been reported that TASK channels play a role in the control of breathing (Buckler, 2015). TASK-1 knockout mice exhibited a decrease in ventilatory response to hypercapnia and hypoxia, whereas this effect was not observed in TASK-3 knockout mice (Trapp et al., 2008). Moreover, in vitro superfused CB/CSN preparations from TASK-1 knockout mice, but not from TASK-3 knockout mice, showed a decrease in hypercapnia- evoked increases in CSN activity (Trapp et al., 2008). Furthermore, mice lacking both TASK-1 and TASK-3 channels exhibited an increase in basal CSN chemosensory activity without a decrease in CB chemosensory responses (Trapp et al., 2008). Altogether these results suggested that TASK-1 channels are involved in the CB response to hypercapnia. However, Ortega-Sáenz et al. (2010) suggested that TASK-3 channels contribute to the background K+ current in CB type I cells and to the sensitivity of these cells to external pH (Ortega-Sáenz et al., 2010). Patch-clamp experiments performed in type I cells from TASK-1/3 knockout mice showed that these cells had a higher membrane resistance and cell depolarization, without any alterations in the electrical properties of CB type I cells from mice lacking TASK-1 (Ortega-Sáenz et al., 2010). However, the response to hypercapnia and hypoxia, measured by the amperometric recording of the catecholamine release, was not modified in type I cells from TASK-1 and TASK-1/3 knockout mice (Ortega-Sáenz et al., 2010). The discrepant results between the studies could be related to the type of preparation used, in vitro whole CB- CSN preparation (Trapp et al., 2008) vs type I cells/CB slices (Ortega-Sáenz et al., 2010). Moreover, apart from TASK channels, the CB transduction mechanism to external pH also involves the inhibition maxi-K^+ (Peers and Green, 1991) and voltage-gated K^+ channels (López-López et al., 1989), as well as the activation of acid-sensing ion channel (ASIC) (Lu et al., 2013; Tan et al., 2007, 2010) and an inwardly rectifying chloride current (Petheo et al., 2001).

Regarding the transduction cascade, the hypercapnic and acidic stimuli in the CB promoted the release of catecholamines from type I cells (Ramirez et al., 2012; Rocher et al., 2009). In the cat CB, a decrease in pH is associated with an increase in the synthesis of dopamine and norepinephrine, and the release of dopamine is proportional to the increase in the CSN chemosensory activity (Rigual et al., 1984). Interestingly, in isohydric and acidic hypercapnia the rat CB releases acetylcholine and ATP (Zhang and Nurse, 2004). Adenosine is also involved in CB chemotransduction in response to hypercapnia (Sacramento et al., 2018b), as this stimulus increases the release of adenosine from the CB and CSN activity. These effects are mediated by $A2_A$ and $A2_B$ adenosine receptors (Sacramento et al., 2018b).

4. Novel interoceptive properties of the carotid body

The novel interoceptive properties of the CB are demonstrated both by the beneficial effects of resecting the CSN in several CB-associated diseases and its properties as a metabolic sensor. These properties enable it to respond to variations in the levels of metabolic, vascular and inflammatory mediators circulating in the body, such as insulin, leptin, GLP-1, and pro- inflammatory cytokines (Baby et al., 2023; Lataro et al., 2024; Pauza et al., 2022; Ribeiro et al., 2018; Sacramento et al., 2020).

4.1. Hormones

Insulin and leptin are potent sympathetic activators (Marino et al., 2011), and their activity in the central nervous system has been highlighted as one of the primary determinants in metabolism, particularly regulating peripheral glucose levels, insulin response, and lipid metabolism (Kimura et al., 2016). However, scientific evidence has long indicated that these two hormones also act at the peripheral level to modulate the SNS and to control metabolism. GLP-1, an incretin, released by the gut, maintains glucose homeostasis by augmenting insulin and inhibiting glucagon secretion (Kimura et al., 2016). More recently, attention has been focused on the role of GLP-1 in the brain regulating metabolism through its effects on satiety and energy regulation (Flint et al., 1998), and its effects on the CB by regulating SNS activity (Pauza et al., 2022).

4.1.1. Insulin

Pereda et al., 60 years ago, observed that the administration of insulin into the carotid artery of anesthetized dogs induced a greater increase in sympathetic activity than systemic administration, suggesting a role of the peripheral nervous system in the insulin-mediated increase in SNS activity (Pereda et al., 1962). Conde's postulated that insulin might be acting on the CB (Ribeiro et al., 2013; Sacramento et al., 2017) based on early findings showing that insulin-induced hypoglycemia increased ventilation (Bin-Jaliah et al., 2004; Ward et al., 2007) but that low glucose per se did not increase CSN activity (Bin-Jaliah et al., 2004). The effect of insulin on ventilation independently of glucose was later confirmed in rats (Ribeiro et al., 2013) and humans (Barbosa et al., 2018) (Table 1). Moreover, the effect of insulin on ventilation was mediated by the CB, as evidenced by its absence in animals with CSN resection (Ribeiro et al., 2013). The CB mediated effects of insulin on ventilation were consistent with the presence of insulin receptors in the CB (Pauza et al., 2022; Ribeiro et al., 2013) and their phosphorylation in response to this hormone (Table 1, Ribeiro et al., 2013). Physiological concentrations of insulin are also capable of triggering a neurosecretory response in the CB, measured as an increase in intracellular Ca^{2+} concentration and the release of ATP and dopamine (Ribeiro et al., 2013). *In vivo* administration of insulin in rats and dogs also increased the electrophysiological activity of the CSN (Baby et al., 2023; Cracchiolo et al., 2019a, 2019b), the SNS in the upper cervical chain (Cracchiolo et al., 2019a, 2019b) and lead to changes in heart rate, arterial blood pressure and minute ventilation in dogs (Baby et al., 2023) (Table 1). The effects of insulin on SNS activity were abolished by bilateral denervation of the CSN (Cracchiolo et al., 2019a, 2019b), indicating that the CB mediates the effect of insulin on SNS activity. These findings together with the fact that insulin mediated effects on ventilation are mediated by the CB, clearly supports the idea that insulin itself can stimulate the CB and lead to important reflex changes in cardiovascular and respiratory function. Moreover, recent findings by Lemus Vidal et al., showed that the administration of insulin on the isolated carotid sinus, thereby acting primarily acting on the CB increase the suprahepatic and arterial glucose

Table 1
Summary of the effects of exogenously applied insulin on the carotid body (CB) and the responses elicited by CB activation in rats, dogs, and humans submitted to control diets and hypercaloric diets (High-fat high-sucrose diet, HFHSu) with and without carotid sinus nerve (CSN) denervation.

				
Increased basal ventilation independently of glucose	Sham	✓	✓	✓
	CSN resection	Abolished	–	–
Increased basal CSN activity	Sham	✓	✓✓	–
	HFHSu	✓✓	–	–
CB Insulin Receptors	Sham	✓	–	–
	HFHSu	✓	–	–
	HFHSu resection	↓	–	–
CB Insulin Receptor Phosphorilation	Sham	✓	–	–
CB Neurosecretory response	Sham	✓	–	–
References		Ribeiro et al., 2013; Cracchiolo et al., 2019a, 2019b; Melo et al., 2022; Pauza et al., 2022	Baby et al., 2023	Barbosa et al., 2018

levels suggesting a role for the CB on glucose homeostasis (Lemus Vidal et al., 2019).

4.1.2. Leptin

Leptin is another hormone that activates the CB (Caballero-Eraso et al., 2019; Ribeiro et al., 2018). The first description of leptin receptors (*Ob-Rb*) in the CB dates to 2011 (Porzionato et al., 2011). Afterwards, several groups described that these receptors are present in type I cells of the CB in mice, rats, and humans (Caballero-Eraso et al., 2019; Messenger et al., 2012; Porzionato et al., 2011; Ribeiro et al., 2018) (Table 2). In human CBs, approximately 40 % of type I cells are immunoreactive to leptin, with 57 % of type I cells being immunoreactive to all leptin receptor isoforms and approximately 30 % to the *Ob-Rb* isoforms (Porzionato et al., 2011). The first description that leptin activates the CB dates from 2012, when it was demonstrated that systemic leptin administration induces pSTAT3 and Fos/Fra-1 in CB type I cells, suggesting that leptin could exert modulatory actions in this organ (Messenger et al., 2012) (Table 2). Subsequently, substantial evidence supported the notion that leptin activates the CB, inducing CB-mediated reflex responses. Acute exogenous administration of leptin increases basal ventilation and ventilatory responses to ischemic and hypoxic conditions in mice and rats, effects that were mediated by the CB as were attenuated by CSN denervation (Caballero-Eraso et al., 2019; Olea et al., 2015; Ribeiro et al., 2018; Sacramento et al., 2020) (Table 2). In addition, intra-carotid injections of leptin increased the discharges of single units of nucleus tractus solitarius regions, suggesting that leptin could act as a mediator of the chemosensory circuit that potentiates the sympatho-excitatory responses by activating the CB and consequently the peripheral chemoreflex (Ciriello and Moreau, 2013; Porzionato et al., 2013). In line with these excitatory effects of leptin on CB-mediated reflexes, exogenous leptin administration increased the electrophysiological activity of the CSN measured *ex vivo* and *in vivo* (Caballero-Eraso et al., 2019; Ribeiro et al., 2018; Shirahata et al., 2015). When investigating the mechanism by which leptin receptors activate CB type I cells, Shirahata et al. (2015) discovered that leptin-CB type I cells activation is mediated through transient receptor potential channels (TRP) channels as they observed that leptin-induced CSN activity was inhibited by nonselective blockers of TRP channels (Shirahata et al., 2015) (Table 2). More recently, TRPM7 channels, a member of the family of TRP channels, were implicated. These channels colocalize with leptin receptors in CB type I cells and leptin was found to increase an outwardly rectifying cation current, which was reversed by two small molecule antagonists of TRPM7 channels (Shin et al., 2019). This CB-TRMP7 channels effect was further confirmed by CSN resection (Shin et al., 2019). When exploring CB-CSN transmission, it was found that leptin induces the release of adenosine from isolated CB (Ribeiro et al., 2018), contrasting with the absence of catecholamine release (Olea et al., 2015) (Table 2), suggesting that adenosine might be one of the players mediating leptin CB-CSN transmission. This hypothesis is plausible considering that adenosine is recognized as a key player in response to hypoxia (Conde et al., 2012). However, further research is needed to establish the connection between CB TRPM7 channel activation by leptin, the adenosine release, and subsequent CSN activation leading to reflex responses.

4.1.3. Glucagon-like peptide 1

Glucagon-like peptide 1 (GLP-1) is a hormone that plays a significant role in regulating glucose homeostasis and appetite. It is primarily

Table 2
Summary of the effects of leptin administration on the carotid body (CB) and the CB-evoked responses in mice, rats and humans in control conditions and in mice lacking leptin receptors (db/db mice) and rats under high-fat diet. Ado – adenosine, CAs – catecholamines, CSN – carotid sinus nerve.

		Control			db/db	High-fat diet
						
Increased basal ventilation	Sham	✓	✓	–	✓	Abolished
	CSN resection	Abolished	Abolished	–	–	=
Ventilation in response to hypoxia	Sham	✓	✓		✓	✓
	CSN resection	Abolished	Abolished	—	–	–
Increased basal CSN activity	Sham	✓	✓	–	–	No
CSN in response to hypoxia	Sham	✓	No	–	–	No
Leptin Receptors	Sham	✓	✓	✓	–	✓
Activation of TRP channels	Sham	✓	–	–	–	–
Activation of signaling pathways	Sham	–	✓	–	–	–
CAs release	Sham	–	No	–	–	–
Ado release	Sham	–	✓	–	–	No
References		Shirahata et al., 2015; Caballero-Eraso et al., 2019; Shin et al., 2019	Porzionato et al., 2011; Messenger et al., 2012; Ribeiro et al., 2018	Porzionato et al., 2011	Caballero-Eraso et al., 2019	Ribeiro et al., 2018

produced in the gut and released in response to the ingestion of food, particularly carbohydrates. GLP-1 has effects on multiple organs, including the pancreas, where it stimulates insulin secretion and decreases glucagon secretion, and the brain, where it affects appetite and satiety (Flint et al., 1998). While GLP-1 is primarily known for its role in glucose regulation and metabolic control, there is ongoing research exploring its potential influence on various physiological systems, including interoception and the CB. Moreover, GLP-1 and its analogs have been investigated for their potential effects on blood pressure regulation, which could be linked to CB function, as these structures play a role in blood pressure control.

GLP-1 receptors (GLP-1R) were found in the CB type I cells, in rodents and humans, and co localizes with tyrosine hydroxylase (Melo et al., 2022; Pauza et al., 2022). The recent findings by Pauza et al. (2022) also showed that exendin-4, a GLP-1R agonist, reduces sympathetic activity measured at the thoracic nerves but increased systolic blood pressure and heart rate in spontaneous hypertensive rats (Pauza et al., 2022). Interestingly, Pauza also showed that exendin-4 administrated near the CB reduced sympathetic activation and systolic blood pressure in response to acute hyperglycemia or sodium cyanide in Wistar and spontaneous hypertensive rats (Pauza et al., 2022), suggesting that GLP-1 action on the CB could be responsible for the cardioprotective role of GLP-1R agonists (Fox et al., 2015). The authors also suggested that GLP-1R at the CB might be a novel therapeutic target for controlling aberrant sympathetic activity in diabetes and hypertension. However, to completely prove that the exendin-4 effect observed by Pauza and collaborators is due to an effect on the CB, experiments should be performed in the same conditions in CSN resected animals.

4.2. Proinflammatory cytokines

In the last decade, several experimental pieces of evidence suggest that the CB also has the ability to sense inflammation, detecting and responding to both pro-inflammatory and anti- inflammatory cytokines (Sacramento et al., 2020). The first piece of evidence is the presence of receptors for tumor necrosis factor alpha (TNF-α) and for the interleukins IL-1, IL-6, and IL- 10 in human CBs, as well as in mouse and rat CBs (for a review, see Sacramento et al., 2020; Kåhlin et al., 2014; Katayama et al., 2022; Mkrtchian et al., 2012) (Table 3). Additionally, it is known that the CB expresses pro-inflammatory cytokines such as IL-1, IL-6 and anti-inflammatory cytokines such as IL-10 (Del Rio et al., 2011; Falvey et al., 2020; Katayama et al., 2022). In addition, pro- and anti-inflammatory cytokines can modulate the excitability of CB type I cells – by modulating K^+ currents, altering intracellular concentrations of Ca^{2+}, modulating the release of neurotransmitters from this organ, such as ATP and acetylcholine, and the neuronal activity of the CSN (Kåhlin et al., 2014; Katayama et al., 2022; Porzionato et al., 2013; Zapata et al., 2011) (Table 3), this suggesting that circulating cytokines can modulate the inflammatory response and the anti-inflammatory reflex by targeting the CB. More recently, it has been observed that both IL6 and TNF-α can promote an increase in spontaneous ventilation, which is respectively attenuated or completely abolished when the CSN is resected (Sacramento et al., 2020) (Table 3), suggesting a modulatory effect of pro- inflammatory cytokines on CB mediated-ventilatory control.

The importance of CB in sensing and regulating inflammation is reflected in some studies where it is shown that CSN electrical stimulation in conscious rats, modulates the innate immune response to lipopolysaccharides (LPS) by attenuating the plasma levels of TNF-α, IL-1β and IL-6 as well as by increasing the anti-inflammatory cytokine IL-10 (Falvey et al., 2020; Santos-Almeida et al., 2017) (Table 3). Furthermore, this chemoreflex anti-inflammatory pathway was found to be diminished by bilateral carotid chemoreceptor denervation and using propranolol and methylatropine, which are blockers of sympathetic and parasympathetic pathways, respectively (Santos-Almeida et al., 2017). Recent studies have demonstrated that electrical stimulation of the CSN triggers the anti-inflammatory reflex under different conditions (Soares et al., 2023) highlighting therefore the importance of the inflammatory sensing by the CB.

4.3. Vascular factors

4.3.1. Nitric oxide

Nitric oxide (NO) is a signaling molecule that plays a crucial role in various physiological processes, including vascular function and oxygen sensing. The interaction between NO and the CB is an area of research that has implications for understanding cardiovascular and respiratory regulation. The relationship between NO and the CB appears of extreme importance in the regulation of vasodilation and blood flow, modulation of chemoreceptor activity, influence on respiratory control, neurotransmission of the CB and cardiovascular regulation (Mosqueira and Iturriaga, 2002).

Table 3
Summary of the effects of pro-inflammatory cytokines on the carotid body (CB) and the CB-evoked responses in mice, rats and humans. CAs – catecholamines, CSN-carotid sinus nerve, HF – high-fat diet, HFHSu – high-fat high-sucrose diet.

					
		TNF-α	IL1	IL6	Hypoxia
Increased basal ventilation	CTL Sham	✓	–	✓	–
	CTL CSN resection	Abolished	–	Abolished	–
Increased basal CSN activity	CTL Sham	–	✓	–	–
Cytokine Receptors	CTL Sham	✓	✓	✓	↑
	HF Sham	↑	↑	No	–
	HFHSu sham	↑	=↑	No	–
CAs release	CTL Sham	–	No	✓	–
	HF Sham	–	No	–	–
K^+ currents	CTL Sham	–	✓	–	–
$[Ca^{2+}]i$	CTL Sham	✓	✓	✓	–
Cytokines release	CTL	–	–	–	↑
CSN electrostimulation	Colitis model and LPS-induced inflammation	↓	↓	–	–
References		Wang et al. (2002); Lam et al. (2008); Fernández et al. (2011); Sacramento et al. (2020); Falvey et al. (2020)	Shu et al. (2007); Zhang et al. (2007); Lam et al. (2008); Sacramento et al. (2020); Soares et al. (2023)	Wang et al. (2002); Lam et al. (2008); Fan et al. (2009); Sacramento et al. (2020)	Kåhlin et al. (2014); Kåhlin et al. (2015)

NO at physiological concentrations is a tonic inhibitor of CB chemosensory activity by many different mechanisms (Mosqueira and Iturriaga, 2002). However, the role of NO on CB function depends not only on NO levels but also on the PO_2 level: in hypoxia, high levels of NO increase the chemosensory discharges, while in normoxia, high levels of NO reduce the CB discharge (Mosqueira and Iturriaga, 2002). In the CB, NO role might be associated with inflammation sensing (Lataro et al., 2024). In fact, NO, through activation of inducible NO synthase by immune cells, is highly released in conditions of inflammation (Cook and Cattell, 1996; Moncada and Higgs, 1991). Together with anti-inflammatory reflex described in the previous section, NO might contribute to host defenses. Therefore, NO action might be particularly relevant to modulation of chemoreceptor afferent activity of the CB, contributing to its overactivation described in inflammatory diseases and associated with high sympathetic activity and heart function deregulation.

4.3.2. Vasopressin

Vasopressin (AVP), also known as antidiuretic hormone, is a neurohormone critically involved in maintaining body homeostasis. After being synthesized in the hypothalamus will be released from the pituitary gland in response to increase of extracellular fluid osmolality (Proczka et al., 2021). Other stimuli for AVP release are hypovolemia, hypotension, hypoxia, hypoglycemia, angiotensin II, among others (Szczepanska-Sadowska et al., 2017). AVP plays numerous functions in the body: renal, circulatory, nervous, endocrine, metabolic, behavioral, respiratory, among others (Japundžić-Žigon et al., 2019).

Recently, Żera et al. (2018) showed the presence of V1aR AVP receptors in the chemosensitive CBs type I cells in the rat (Żera et al., 2018) which is consistent with the findings by Zhou et al. (2016) that described the presence of key intracellular components of the V1aR signaling in the CB type I cells by single-cell transcriptomics in mouse (Zhou et al., 2016). These findings indicate that AVP may modulate the activity of the CB. It is already known that by modulating CB activity, AVP controls the respiratory system namely the pulmonary ventilation, however further studies are needed to understand if AVP directly activates the chemosensitive CB cells that express V1aRs or if the AVP-mediated decrease in the CB blood flow is responsible for the sensitization of the chemoreceptors (Brognara et al., 2021). One indication of an indirect action of AVP on the function of CB is the fact that the blockade of V1aRs in the NTS is able to attenuate increase in plasma glucose concentration induced by activation of CB chemoreflex (Montero et al., 2006).

So, AVP as neurohormone present in the circulation influences the respiratory activity via neuronal modulation of various regions and via the chemoreceptors located in the CB. In fact, Żera et al. (2018) also demonstrated that local stimulation of the CB with AVP increases ventilation, which is contrary to systemic effects of AVP that are manifested by a decrease in ventilation leading to the hypothesis that excitatory effects of AVP within the CB provide a counterbalancing mechanism for the inhibitory effects of systemically acting AVP on the respiration (Żera et al., 2018).

4.3.3. Endothelin-1

Endothelin-1 (ET-1) play an important role as modulator of the CB O_2 chemosensory process being an important regulator of the response to acute and chronic hypoxia (Mosqueira and Iturriaga, 2019). ET-1 is expressed in the CB vasculature and in CB type I cells enhancing CSN chemosensory discharge by reducing CB blood flow or by increasing intracellular Ca^{2+} concentration in type I cells, leading to the increase of excitatory transmitters release (Mosqueira and Iturriaga, 2019). Even though both ETA and ETB receptors are present in the CB type I cells, there are evidence that the excitatory effect of ET-1 on CB is mainly mediated by ETA (Chen et al., 2002). Additionally, Li et al. confirmed the previous data in the literature showing that local increase in ET-1 expression in the CB might contribute to hypertonicity of the CB in chronic intermittent hypoxia (Prabhakar et al., 2015) and demonstrated that ETA receptor mediates the increase in CSN activity through phospholipase C (PLC), protein kinase C (PKC) and p38 Mitogen-activated protein kinase (MAPK) signaling pathways in chronic intermittent hypoxia (Li et al., 2019).

Moreover, it is also known that NO and ET-1 signaling pathways interact in the CB since the activation of ETB induces the synthesis of NO (Rossi et al., 2001) and NO may inhibit ET-1 transcription (Vanhoutte, 2000). Therefore, ET-1 is clearly important for the modulation of CB and for the effect of NO on this organ.

4.3.4. Prostaglandins

The initial evidence for the effect of prostaglandins on CB activity dates to the 1960s. Carlson and Orö (1966) provided the first descriptions, demonstrating that prostaglandin E1 (PGE1) has direct actions on the carotid artery or its associated structures, eliciting reflex vascular changes in dogs (Carlson and Orö, 1966). Additionally, Kaplan et al. showed that the hypotensive response to PGE1 administration is attributable to its actions on the carotid sinus-body structures (Kaplan et al., 1969). These results were rebutted by McQueen and Belmonte (1974) that tested several prostaglandins in vascular and respiratory responses of the cat showing that is unlikely that chemoreceptors are directly involved in the responses to those molecules (McQueen and Belmonte, 1974). In fact, McQueen stated that the effect of PGE1 on the increase in CSN activity seemed to be secondary to vascular effects (McQueen and Belmonte, 1974). The following studies performed in rabbits by Gómez-Niño et al. showed that hypoxia, acidic-hypercapnic or high K^+-containing solutions increase the basal release of PGE2 (Gómez-Niño, et al., 1994). They also showed that PGE2 inhibits the release of catecholamines induced by hypoxic or high K^+ containing solutions, not affecting catecholamine release in basal conditions or hypercapnic– acidic solution (Gómez-Niño et al., 1994a, 1994b). These studies mainly describe the role of PGE2, but the possible role of other prostaglandins has also been suggested (Gómez-Niño et al., 1994a, 1994b). Taken together, some controversy exists in what concerns to the role of prostaglandins in the modulation of chemoreception of CB, possibly based on the diverse effect of different types of prostaglandins, therefore more work must be done.

4.3.5. Angiotensin II

Angiotensin II is a vasoconstrictor peptide that is part of the renin–angiotensin–aldosterone system (RAS) and, together with catecholamines and vasopressin, is involved in the maintenance of blood pressure and fluid homeostasis (Bellomo et al., 2024). In addition, angiotensin II also augments ventilation (Ohtake and Jennings, 1993; Potter and McCloskey, 1979) an effect that was in part mediated by the CB (Allen, 1998). In the CB, type I cells express angiotensin- converting enzyme and angiotensinogen, the precursor of angiotensin II (Lam et al., 2014; Lam and Leung, 2002). Additionally, angiotensin II promotes a short inhibition followed by an increase in the CSN chemosensory activity, an effect that was mediated by AT1 receptors, since the infusion of losartan, an AT1 receptor antagonist, blocked this effect (Allen, 1998). Indeed, angiotensin II also promotes the increase in intracellular Ca^{2+} in type I cells in a dose- dependent manner, an effect that was mediated by the AT1 receptors, but not by the AT2 receptors (Fung et al., 2001). Furthermore, angiotensin II when applied repetitively promotes sensory long-term facilitation of the CB, an effect that occur through the activation of NADPH oxidase 2 (Nox2) by AT1 receptors (Peng et al., 2011).

Besides the expression of AT1 receptors in the CB type I cells (Fung et al., 2001; Lam and Leung, 2002), Murali and collaborators (Murali et al., 2014) described that AT1 receptors were also present in CB type II cells. The authors observed that in dissociated CB cultures angiotensin II promotes the release of intracellular Ca^{2+} in CB type II cells, an effect abolished by the AT1 receptors antagonist losartan (Murali et al., 2014). Moreover, angiotensin II was also able to activate pannexin-1 currents, that are known to release ATP when activated. Therefore, these results

lead the authors to propose that type II cells also contribute to the excitatory effect of angiotensin II in the CB, an effect that could be mediated by $P2Y_2$ receptors stimulation of pannexin-1, which induced the release of ATP specially in pathophysiological conditions, as sleep apnea and chronic heart failure (Murali et al., 2014). In chronic hypoxia and chronic intermittent hypoxia, a condition associated with sleep-disordered breathing, and in chronic heart failure the expression of AT1 receptors is upregulated (Lam et al., 2014; Leung et al., 2000; Li et al., 2006). Besides the upregulation of AT1 receptors, in chronic intermittent hypoxia, it was also described the upregulation of angiotensinogen and angiotensin-converting enzyme (Lam et al., 2014). Additionally, in chronic intermittent hypoxia rats the daily treatment with losartan abolished the release of intracellular Ca^{2+} induced by angiotensin II and attenuated the levels of oxidative stress, macrophage infiltration and NADPH oxidase subunit gp91phox expression in the CB (Lam et al., 2014). Altogether, these results suggested that RAS could be involved in the increase of CB chemosensory activity in chronic intermittent hypoxia, and therefore, sleep-breathing disorders, as well as local inflammation through the activation of AT1 receptors in the CB. Furthermore, the increase in sympathetic nervous system activity that occur with acute intermittent hypoxia was prevented by the pre-treatment with losartan or the inhibition of renin activity (Kim et al., 2018), suggesting that the effects of acute intermittent hypoxia on sympathetic activity is in part mediated by the activation of CB by RAS.

4.4. Lactate

In mammals, there is strong evidence that lactate is sensed by CB type I cells (Torres-Torrelo et al., 2021). In 2015, Chang et al. (2015) documented the discovery of a new acute hypoxia sensor in CB type I cells, an olfactory receptor activated by lactate, the Olfr78 (Chang et al., 2015). By interacting with this receptor lactate increased intracellular Ca^{2+} and induced exocytosis in isolated CB type I cells in mice (Chang et al., 2015). The hypothesis that lactate can depolarize type 1 cells has been challenged by additional data showing that lactate sensing is preserved in Olf78r- deficient glomus cells tested in several sources of mice (Torres-Torrelo et al., 2018, 2021). However, Peng et al. (2020) described that Olfr78 receptor is involved in CB sensory nerve and type I cells response depending on the intensity of hypoxia, since Olfr78 null mice exhibit impaired responses to moderate hypoxia but not to severe hypoxia (Peng et al., 2020). Moreover, the authors found that lactate produced modest stimulation of the CSN activity compared to moderate hypoxia, effects that were no different between wild-type and Olfr78 null mice, indicating that the lactate effects on CB and CSN were not mediated by Olfr78 receptors (Peng et al., 2020).

Recently, when rats were submitted to high-intensity treadmill exercise (until exhaustion) presented significant increases in the lactate concentration and the bilateral removal of CBs significantly reduced the active inspiratory and expiratory responses to that exercise and worsened the exercise-induced metabolic acidosis (Spiller et al., 2021). These results suggest that lactate can activate the CBs and consequently the respiratory response to exercise, but the exact mechanisms involved are still unknown. The same group showed in another manuscript that different lactate concentrations were incapable of modulating neither the excitability of isolated CB type I cells from Wistar rats nor the respiratory autonomic and vascular functions, suggesting that this molecule is not involved in the Wistar rats' glomus cells' sensitivity to hypoxia and supporting the last hypothesis that lactate is not a direct modulator of CB chemoreception (Spiller et al., 2021). Therefore, we can conclude that further research on lactate effects on the CB, as well as in its mechanism of action and its role on chemotransduction are needed to clarify its role on CB chemoreception.

5. Contribution of the carotid body to the onset and progression of metabolic diseases

The initial evidence linking CB function as a metabolic sensor to its role in the development and progression of metabolic diseases was based on the observations that CB stimulation can increase insulin secretion (Petropavlovskaya, 1953) and the recognition that CB overactivation is associated with various sympathetic-mediated conditions such as essential hypertension, hypertension linked with obstructive sleep apnea (OSA), and chronic heart failure (Abdala et al., 2012; Del Rio et al., 2013, 2014; Iturriaga et al., 2005; Peng and Prabhakar, 2003; Prabhakar and Kumar, 2010; Siński et al., 2012). In 2013, Conde's research group hypothesized that CB dysfunction caused by high-caloric diets leads to overactivation of the SNS, resulting in metabolic dysregulation. Aiming to prove this hypothesis, they first described that chronic resection of CSN could prevent the development of insulin resistance and hypertension in animal models of prediabetes and metabolic syndrome induced by exposure to two different diets: a high-fat diet for 3 weeks and a high-sucrose diet for 4 weeks (Ribeiro et al., 2013). This suggested that the CB was involved in the onset of metabolic disease. Additional experiments were performed in animals with induced metabolic dysregulation after CSN resection. They found in either models that induce glucose dysregulation 1) obesity induced by exposure to high-fat diet for 19 week (Melo et al., 2022)s, or 2) type 2 diabetes induced by exposure to high-fat and high-sucrose diet for 25 (Sacramento et al., 2018a, 2018b; Sacramento et al., 2017) and 45 weeks (Melo et al., 2022), that CSN resection was able to reverse features of dysmetabolism, including weigh gain, insulin resistance and glucose intolerance. Furthermore, CSN resection in these animal models with metabolic pathology normalized sympathetic overactivation, as evidenced the restoration of the increased plasma and adrenal medulla catecholamine levels, as well as the normalization of the increased low-frequency heart rate variability and low frequency/high frequency ratio in heart rate variability analysis, which are characteristic of metabolic diseases (Melo et al., 2023; Ribeiro et al., 2013; Sacramento et al., 2017). This sympathetic overactivation in metabolic pathology models was further confirmed through electrophysiological recordings in the upper cervical chain, with this increase in SNS activity disappearing with CSN resection (Cracchiolo et al., 2019a, 2019b). Together, these findings demonstrate that CB dysfunction contributes to the onset and development of metabolic diseases through SNS overactivation.

Consistent with this hypothesis, animals exposed to hypercaloric diets and patients with metabolic disease exhibited altered CB chemosensitivity. Cunha-Guimaraes et al. (2020) showed that prediabetic patients exhibited higher CB activity, assessed through the Dejour test, that correlated with waist circumference and insulin resistance, but not with fasting or 2-h glucose levels (Cunha-Guimaraes et al., 2020). More recently, it was shown that prediabetes and type 2 diabetes patients demonstrated an exaggerated peripheral chemoreflex sensitivity, measured by the hypoxic ventilatory response, that was associated with the severity of the disease (Lis et al., 2022). Furthermore, rodent models exposed to hypercaloric diets, representing prediabetes, early type 2 diabetes, and metabolic syndrome, consistently exhibit heightened ventilatory responses to ischemic and hypoxic hypoxia (Melo et al., 2022; Ribeiro et al., 2013) and increased carotid sinus nerve activity (Cracchiolo et al., 2019b; Ribeiro et al., 2018), indicating a significant dysfunction in the arterial chemoreflex. This observed increase in peripheral chemosensitivity in prediabetes and type 2 diabetes was also associated with increased CB size, percentage of type I cells, tyrosine hydroxylase levels, and catecholamine release by the CB in dysmetabolic rodents (Dos Santos et al., 2018; Ribeiro et al., 2013). Furthermore, consistent with the hypothesis that CB dysfunction is associated with dysmetabolism, Paleczny et al. (2016) described in men that overweight/obesity is accompanied by an increased pressor response from peripheral chemoreceptors, although respiratory and heart rate responses remain unchanged. They also demonstrated that

hyperinsulinemia and insulin resistance (but not hyperleptinemia) were associated with these increased pressor responses mediated by the CB (Paleczny et al., 2016).

Building on preclinical and clinical data showing that CB dysfunction is involved in the development of metabolic diseases, it has been observed that hyperbaric oxygen therapy, an intervention that drastically reduces CB activity, improves fasting glucose and postprandial glucose control in patients with type 2 diabetes (Vera-Cruz et al., 2015).

In conclusion, the CB plays a crucial role in metabolic homeostasis, and its dysfunction is pivotal in the onset and progression of metabolic diseases. One contributing factor to its pathophysiology could be the dysfunction/disruption of its metabolic interoceptive functions.

5.1. Hyperinsulinemia, carotid body and dysmetabolism

Hyperinsulinemia is an early feature of dysmetabolic states, being associated with insulin resistance, a characteristic of metabolic syndrome, prediabetes and type 2 diabetes. Building on this evidence and on the observation that insulin is detected and stimulates the CB (Baby et al., 2023; Ribeiro et al., 2013), Conde's group hypothesized that hyperinsulinemia could be a significant factor driving CB dysfunction, thereby contributing to the onset and progression of metabolic diseases (Conde et al., 2014; Conde et al., 2017b). Consistent with this hypothesis, animals fed hypercaloric diets present high levels of circulating C-peptide and insulin, indicating increased insulin secretion that are normalized upon CSN bilateral resection (Melo et al., 2022; Ribeiro et al., 2013; Sacramento et al., 2017). This together with the fact that CBs from animals submitted to a high-fat high-sucrose diet exhibited increased positive staining for insulin receptors in the CB (Melo et al., 2022) and that insulin administration induce a neural activity with a stronger power spectral density in the range [550 to 1100] Hz in high-fat high-sucrose animals than in controls (Cracchiolo et al., 2019a) suggest that hyperinsulinemia acting on the CB drives CB dysfunction with consequent overactivation of the SNS. In fact, the effect of insulin promoting a stronger neural activity of the SNS in high- fat high-sucrose diet animals were absent in CSN-resected animals (Cracchiolo et al., 2019a) confirms this hypothesis. The link between hyperinsulinemia and CB dysfunction was observed not only in dysmetabolic animals but also in patients with prediabetes. These patients showed increased CB chemosensitivity, assessed through the Dejour test, which correlates with elevated circulating insulin levels and insulin resistance (Cunha-Guimaraes et al., 2020). Interestingly, this study not only provides evidence in humans linking hyperinsulinemia to increased CB activity and dysmetabolic states, but also offers the opportunity for early screening and diagnosis of metabolic diseases through non-invasive evaluation of CB activity, which has the potential to be a game-changer. This approach allows for the identification of individuals who, despite lacking clinical signs of metabolic disease, are silently developing dysmetabolism due to CB overactivation, making them potential candidates for therapeutic CB-specific modulation.

5.2. Hyperleptinemia, carotid body and dysmetabolism

The idea that leptin could contribute to CB dysfunction and increased SNS activity observed in obesity and obesity-related syndromes, such as prediabetes and type 2 diabetes, stemmed from the observation that CB activity was more elevated in obese, insulin-resistant animal models than in lean, insulin-resistant models (Ribeiro et al., 2013). Obese insulin-resistant animals exhibited a more pronounced increase in spontaneous ventilation, hypoxia- induced hyperventilation, CB weight, and on CB protein levels of tyrosine hydroxylase (the limiting enzyme of catecholamine synthesis) compared to lean insulin-resistant animals, despite having similar insulin levels (Ribeiro et al., 2013). These data suggested the existence of an obesity-related factor that would contribute to CB stimulation in a metabolic dysfunction context.

Given that obesity is a pathological condition associated with hyperleptinemia, an increase in CB and CSN activity in these conditions would be expected. Indeed, insulin-resistant obese rats fed with a high-fat diet for 3 weeks had augmented CB activation compared with animals under normal chow diet (Ribeiro et al., 2013, 2018). However, in accordance with the presence of increased CB hypertonicity (increased CB basal activity), hyperleptinemia and leptin resistance (a decrease in the action of leptin due to its elevated concentrations) in dysmetabolic states, high-fat diet rats fed for 3 weeks show increased spontaneous ventilation but a blunted effect of exogenous leptin on increasing CSN baseline activity and ventilation (Ribeiro et al., 2018; Sacramento et al., 2018a, 2018b; Sacramento et al., 2020). The effects on ventilation were not altered by CSN resection (Sacramento et al., 2020). Furthermore, in contrast with what happens in control animals, the exogenous administration of leptin in hypercaloric diet fed animals did modify the ventilatory responses to ischemic hypoxia (Ribeiro et al., 2018). In agreement with the action of leptin on the CB, and with the development of leptin resistance in the CB, rats fed with high-caloric diets for more extended periods (8 weeks, 16 weeks, or 25 weeks) exhibit decreased spontaneous baseline ventilation and reduced ventilatory responses to hypoxia (Rakoczy et al., 2018a; Sacramento et al., 2018a; Yuan et al., 2018). Similar results were observed in the obese Zucker rat, a model lacking the gene encoding the leptin receptor Ob-R (Yuan et al., 2018).

One of the important mechanisms involved in regulation of breathing in obesity-related syndromes, as sleep disorder breathing (Kim et al., 2022) and on the action of leptin in obesity-related hypertension (Shin et al., 2019), is the activation of TRPM7 channels in the CB. Indeed, exogenous administration of leptin to levels like the ones founded in obesity induced hypertension in C57BL/6J mice, an effect abolished by CB denervation, TRPM7blockers, and TRPM7 small hairpin RNA applied to CBs. Moreover, *Ob-Rb* overexpression in CB of *Ob-Rb*- deficient *db/db* mice demethylated the TRPM7 promoter, increased Trpm7 gene expression, and induced hypertension (Shin et al., 2019). While these results show a new mechanism for the development of hypertension, in which leptin activation of TRPM7 channels in CB glomus cells contributes to leptin-induced hypertension, it remains to be established the mechanisms by which leptin could activate the CB and contribute to dysmetabolic states. Moreover, the precise signaling pathway by which leptin activates TRPM7 channels remains uncertain and probably other mechanisms must be also involved in the effect of leptin on CB in conditions of dysmetabolism.

5.3. GLP-1, the carotid body and dysmetabolism

GLP-1 is an incretin hormone whose significance in metabolism has greatly increased, largely driven by the widespread use and impact of GLP-1R agonists in the treatment of type 2 diabetes and obesity. Apart from targeting insulin and glucagon secretion and promote satiety, GLP-1 analogs were shown to reduce blood pressure, improve lipid profile and have direct effects on the heart and vascular endothelium (Marx et al., 2022; Ussher and Drucker, 2023), having therefore high benefits in managing cardiovascular disease and risk in patients with metabolic diseases. Knowing that cardiometabolic diseases are associated with increased sympathetic activity (Grassi et al., 2015) and that the CB contributes to that sympathetic overactivation (see e.g. Conde et al., 2017b), Pauza et al. (2022) showed that upon activation by exenedin-4, GLP-1R in the CB, inhibit peripheral chemosensitivity and chemoreflex-evoked sympathetic activation, suppressing the blood pressure response of CB-peripheral chemoreflex to hyperglycemic stimulation in a spontaneously hypertensive rat model along with a downregulation in the expression of GLP-1R in the CB (Pauza et al., 2022). These results suggested that the CBs could be potential targets for ameliorating excessive sympathetic activity using GLP-1R agonists in the cardiometabolic dysfunctional states. However, no alterations were found in GLP-1R levels in the CBs of animals submitted to hypercaloric diets, suggesting that this mediator may not be involved in CBs and metabolic dysfunction promoted by hypercaloric diets (Melo et al., 2022) or that

the change might be on the GLP-1 downstream signaling pathways. Although any of these hypotheses could be true, this leads to the idea that further research is needed to understand the contribution of GLP-1 and GLP-1R to dysmetabolic states induced by hypercaloric diets, those that better mimic human metabolic diseases, such as obesity and type 2 diabetes.

5.4. Inflammation, carotid body and dysmetabolism

Given the close connection between insulin resistance, leptin resistance, and metabolic states with low chronic inflammation, Conde's group (Conde et al., 2017b; Sacramento et al., 2020) postulated that pro-inflammatory cytokines could be contributing to CB dysfunction in metabolic disorders. The authors found in a prediabetes model that induces insulin resistance, obesity, and hypertension after exposure to high-fat diet for 3 weeks, that IL-1 receptor and TNF-α receptor levels in the CB were increased while IL-6 receptor were not affected (Sacramento et al., 2020). On the other hand, in animals exposed to high-fat diet and with sucrose for 25 weeks, TNF-α receptor levels were increased with no changes in IL-6Rα and IL-1R levels (Sacramento et al., 2020). While the upregulation of inflammatory cytokines receptors maybe be related with altered levels and action of these mediators that are known to be high and present in animals submitted to hypercaloric diets, so far we can only suggest that changes in IL-1β and TNF-α signaling and the inflammatory reflex mediated by the CB may contribute to the increased activity of this organ and to alterations in the immune- metabolism-nervous system connection observed in metabolic diseases (Cracchiolo et al., 2019a, 2019b; Cunha-Guimaraes et al., 2020; Ribeiro et al., 2013, 2018).

6. Conclusions and future perspectives

In conclusion, the CB is an interoceptive organ, sensing multiple alterations in blood composition and transmitting the information to the brain to maintain homeostasis. While the classical sensitive properties of the organ include the detection of alterations in blood O_2, CO_2 and pH, in the last decades, the CB was found to also detect blood hormones, cytokines, vascular factors among other substances. Moreover, the CB was shown to be involved several sympathetic-mediated diseases, including metabolic diseases, as an increased CB hypertonicity and hypereflexivity promotes and increase SNS activity (Sections 2.2 and 5). Knowing that hormones like insulin, leptin and GLP-1, as well as pro-inflammatory cytokines (see Sections 4.1 and 4.2), are detected by the CB, and recognizing that these mediators, along with changes in their levels and actions, contribute to metabolic diseases, it is reasonable to hypothesize that altered interactions of these substances with the CB could lead to CB dysfunction and consequently dysmetabolic conditions. Although studies have shown that CSN denervation (Sacramento et al., 2017) and CSN bioelectronic neuromodulation (Sacramento et al., 2018a) are able to reverse insulin resistance and glucose intolerance, no one tested, so far, the specific targeting of the receptors and or the downstream signaling pathways of these substances on the CB for the treatment of dysmetabolic states. In support of this notion, Del Rio et al. (2012) showed that ibuprofen treatment prevented CB cytokine over-expression and the enhanced HVR and hypertension induced by chronic intermittent hypoxia, but failed to avoid CB overactivation, suggesting that the management of CB inflammation may prevent excessive CB responsiveness (Del Rio et al., 2012). Moreover, Shin et al. (2019) tested the abolishment of Trmp7 signaling in the CB for the treatment of obesity-induced hypertension (Shin et al., 2019). Consequently, further exploration into blocking the effects of insulin, leptin, GLP-1, and pro-inflammatory cytokines within the CB during dysmetabolic conditions, as well as elucidating the signaling pathways of these mediators, could offer new strategies to target CB dysfunction and improve metabolic diseases.

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CRediT authorship contribution statement

Silvia V. Conde: Writing – review & editing, Writing – original draft, Conceptualization. **Fatima O. Martins:** Writing – review & editing, Writing – original draft. **Joana F. Sacramento:** Writing – review & editing, Writing – original draft.

Data availability

No data was used for the research described in the article.

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