Advancements in Health Research

Advancements in Health Research 2026; 3:135
doi:10.4081/ahr.2026.135

Therapeutic target for reversal of overdose-induced respiratory depression: BK channels in the carotid body

Robert B. Raffa[1,2,3]

[1]Temple University (Emeritus), Philadelphia, PA; [2]University of Arizona (Adjunct), Tucson, AZ; [3]Enalare Therapeutics, Mullica Hill, NJ, USA

Abstract

Opioid-overdose has morphed from a mainly single-entity problem (e.g., heroin, or fentanyl, or some other opioid) to a predominantly polysubstance combination of opioid + non-opioid problem. Reversal of opioid-alone respiratory depression is straightforward (albeit not always easy) using an opioid receptor antagonist such as naloxone. Unfortunately, combinations containing non-opioid contributors to respiratory depression are not so pharmacologically straightforward. Given that the non-opioid component is often not known, a reversal agent that would work independently of the combination components ('agnostic') is highly desired. A promising target for such a drug is the peripherally-located carotid body, the primary peripheral arterial chemoreceptor that detects arterial hypoxia and responds with compensatory signals. Large-conductance Ca^{2+}- and voltage-activated potassium channels (BK, Maxi-K, KCa1.1) within the glomus cells regulate the response of the carotid body to hypoxia, and the gain and stability of the respiratory feedback loop. Hypoxia inhibits BK channels via direct and indirect mechanisms, enhancing the gain of signaling from the carotid body to brainstem respiratory nuclei. Although initially proposed to be intrinsic oxygen sensors, current evidence supports a more integrative role in modulatory control of carotid body activity. This minireview gives a succinct overview of the molecular biology and structural diversity of BK channels and their accessory β/γ subunits, the physiological mechanisms linking BK channel activity to hypoxia chemotransduction, and systems-level roles in negative-feedback drive of ventilatory responsiveness. Also included are future directions and a proposed control system model of carotid body BK feedback.

Key words: overdose, respiratory depression, carotid body, BK (Maxi-K, KCa1.1) channel, control system.

Correspondence to: Robert B. Raffa, PhD, 3825 E. Diablo Canyon Pl, Tucson, AZ, USA. E- mail: robert.raffa@gmail.com

Introduction

Current challenges and knowledge gaps

The treatment for reversal of opioid overdose has historically lagged behind the evolving challenges. For example, despite the fact that the μ-opioid receptor (MOR) antagonist naloxone had been known to reverse the respiratory depressant effects of opioids since the 1960s[1] and a nasal formulation was FDA-approved for that use in 1971, naloxone did not become generally acceptable until decades later.[2] But already by that time, there was a trend toward more potent and complex opioids such as fentanyl and its analogs.[3] Now that naloxone is more widely available, the characteristics – and challenges – of 'opioid' overdose have shifted again. Now the most common situation is not a single opioid, with straightforward mechanism of action and straightforward and effective pharmacologic treatment strategy, viz., antagonism of MOR, but instead involves combinations of opioids and non-opioids ('poly-substance' overdose).[4,5] Although the opioid component is sensitive to a MOR antagonist, the non-opioid component is not.[6] Therefore, a therapeutic agent that is 'agnostic' to the respiratory depressants in the combinations is desirable.[7]

Centrally-acting respiratory stimulants have some efficacy, but they suffer from a host of central nervous system adverse effects.[8] In contrast, a peripherally-acting agent would not have this problem. In this regard, since the major peripheral organ involved in the detection and regulation of respiration is the carotid body (CB),[9-11] the CB is a logical target for an 'agnostic' respiratory-depression reversal therapeutic. A selective, peripherally-acting CB-targeted agent would have rapid onset of action (due to easy access to the CB and lack of need to cross the blood-brain barrier), be 'agnostic' to the mechanism(s) of action of the causative drugs, and lack central nervous system adverse effects.[8]

The carotid body as poly-substance overdose drug-discovery target

The carotid body,[12-14] located within the carotid sinus, is the major peripheral chemosensory organ.[10,15-18] It monitors and responds to decreases in arterial oxygen PaO_2 (hypoxemia),[19-24] and amplifies adaptive physiologic countermeasures.[25,26] The glomus (type I) cells in the CB transduce detected hypoxia into transmitter release (including acetylcholine, ATP, dopamine, and neuropeptides) and enhance carotid sinus nerve (CSN)[27,28] activity via coordinated changes in ion channels and other mechanisms of sig-

naling that initiate compensatory adjustments to re-establish adequate PaO_2 (Table 1).[9,29-31]

Among the responsive elements involved in the transduction, the large-conductance Ca^{2+}- and voltage-activated BK (big potassium, Maxi-K, $K_{Ca}1.1$) channel plays a central role in modulating membrane potential, action-potential waveform, and downstream synaptic output via the carotid sinus nerve,[32-35] which activates brainstem respiratory-control centers, such as the nucleus tractus solitarius (NTS) and the pre-Bötzinger complex (preBötC).[36,37] BK channels are of particular interest in CB function because of their dual sensitivity to membrane voltage and intracellular Ca^{2+}, positioning them as dynamic regulators of the response to hypoxia. Early studies proposed that BK channels themselves are direct O_2 sensors; subsequent work suggests they act more as downstream effectors of mitochondrial and metabolic sensors.[38,39] More recent research indicates that BK channels participate not only in acute hypoxic signaling, but also in long-term plasticity, redox biology, and feedback control of ventilatory drive. They can be localized to plasma membranes (primary role in excitability), mitochondria inner membrane (mitoBK), and endoplasmic reticulum (Ca^{2+} stores). Specific trafficking depends on splice variants. Hypoxia tends to increase variants more Ca^{2+}-sensitive, potentially enhancing glomus-cell gain.

This review provides a concise overview of BK channels in the CB, integrating molecular biology, electrophysiology, systems physiology, and feedback-control theory, situating BK channels within a multi-tiered chemotransductive system.

Composition of bk channels in the carotid body

The pore-forming a subunit combines voltage- and Ca^{2+}-sensing domains. Accessory b (*KCNMB1-4*) and g (*LRRC26*) subunits tune gating kinetics, Ca^{2+} sensitivity, and pharmacology.[15] *KCNMA1* transcription is modulated by hypoxia-inducible factors, oxidative stress, and inflammatory cytokines, linking BK expression to CB plasticity in chronic hypoxia and disease.[34,40]

KCNMA1 (on human chromosome 10q22) encodes a ~125-kDa a subunit with seven transmembrane segments (designated S0-S6), a large cytosolic *C*-terminal gating ring containing Ca^{2+}-sensitive RCK1/RCK2 domains, with the S1-S4 region forming the voltage-sensor domain and S5-S6 forming a pore and selectivity filter. The S0 segment allows association with b subunits.[41] The large cytostolic *C*-terminus contains two domains that assemble into a gating ring, forming ion binding sites. Four a subunits co-assemble to form a functional tetrameric channel with notably large K^+-conductance capability. *KCNMA1* mRNA and protein are highly expressed In CB glomus cells.

Four β-subunits (β_1-β_4) modulate BK channel properties. Each β-subunit has two transmembrane segments and a large extracellular loop that interacts with the a-subunit's S0-S1 region. Expression of these subunits is tissue-specific and confers specific properties:[34,40] β1 (KCNMB1) is principally located in vascular and smooth muscle, where it increases Ca^{2+} sensitivity and slows deactivation, and in some CB preparations; β2 (KCNMB2) is principally located in CB glomus, and endocrine and chromaffin cells, where it produces fast inactivation and may contribute to rapid repolarization in neuronal cells; β3 (KCNMB3) is principally located in testis and brain, with multiple splice variants having complex gating effects; and β4 (KCNMB4) is principally located in CB glomus cells and neurons, where it confers resistance to classical BK channel blockers (*e.g.*, iberiotoxin, charybdotoxin) and reduces Ca^{2+} sensitivity.

KCNMA1 expression undergoes extensive alternative splicing,[42] producing variants that differ in Ca^{2+} sensitivity, trafficking, and redox modulation. Hypoxia itself modulates the expression of splice variants in some tissues.[43] Whether CB-specific splice patterns modulate hypoxic responsiveness remains under investigation. The β_2 and β_4 subunits dominate in CB glomus cells. β_2 confers fast inactivation and high Ca^{2+} sensitivity, whereas β_4 provides slow gating and resistance to IbTX and charybdotoxin. The co-expression of β_2 and β_4 creates a composite phenotype: BK channel currents that inactivate partially, yet remain modulated during sustained depolarization - properties ideal for hypoxia-evoked signaling. The g-subunits (LRRC26, LRRC38, LRRC52, LRRC55) further modify BK gating.[44] These single-pass transmembrane proteins can shift BK voltage-activation, permitting BK opening at near-resting potentials, influencing baseline CSN discharge.

BK-channel gene expression is dynamically regulated by several factors. For example, hypoxia-inducible factors (HIF-1a, HIF-2a) bind regulatory elements of the *KCNMA1* promoter, and transcriptomic profiling suggests HIF-dependent tuning of BK channel expression in the CB.[45,46] Chronic hypoxia decreases expression of BK channels, consistent with increased sensitivity of glomus cells under prolonged low PaO_2. Because CB inflammation is a feature of sleep apnea, heart failure, and metabolic disease [47], inflammatory repression of *KCNMA1* may contribute to pathological CB hyperexcitability. BK channels also undergo phosphorylation (*via*, *e.g.*, PKA, PKC, CaMKII) and redox modifications that modulate their activity.[48] In glomus cells, PKC activation mimics hypoxia by inhibiting BK, whereas PKA activation restores BK current. Reactive oxygen species (ROS) can also oxidize cysteine residues on the gating ring, which modifies Ca^{2+} sensitivity. These mechanisms provide a biochemical interface between cellular metabolism and electrophysiological output.

Table 1. The role of BK channels during detection of deviations from normal arterial oxygen (and carbon dioxide) levels, and reestablishment of normal levels.

Phase	BK-channel status	Effect	Functional role
Normoxia	Open (active)	Stabilizes membrane potential	Basal negative feedback (prevents 'false' activation)
Hypoxia onset	Inhibited	Depolarization, Ca^{2+} influx, neurotransmitter release	Initiates neurotransmitter release (feed-forward activation)
Sustained hypoxia	Reactivated by the rising Ca^{2+} level	Hyperpolarization, reduced Ca^{2+} influx, repolarization	Local feedback control (limits excitation)
Normoxia restoration	Fully activated	Restoration of baseline resting potential	System reset

Expression of BK channels in the carotid body

Immunocytochemical and in-situ hybridization studies demonstrate *KCNMA1* mRNA and BK channel protein in type I glomus cells, but not in type II sustentacular cells or vascular endothelium. The channel localizes mainly to the plasma membrane of glomus cells, often in proximity to voltage-gated Ca^{2+} channels (CaV2.1, CaV3.2) and mitochondria – suggesting that Ca^{2+} transients can rapidly affect BK channel current. Electrophysiological recordings from isolated glomus cells[49] reveal a large Ca^{2+}-dependent outward K^+ current, that is blocked by IbTX or paxilline and activates between −20 mV and +10 mV.

BK channel expression and oxygen sensitivity vary[50] among species[51] and even among mouse strains[52]: in rats, BK current is inhibited by moderate hypoxia; in mice (DBA/2J *vs* A/J), only DBA/2J show hypoxia-induced BK channel inhibition, correlating with higher β_2 expression; in cats and rabbits, there is a smaller BK channel component, larger TASK (TWIK-related acid-sensitive K^+) channel contribution; and in humans, immunolabeling confirms BK in CB tissue.[53] Such diversity implies that the BK channel's contribution to chemosensitivity is species- and genotype-dependent, reflecting adaptation to metabolic and respiratory physiology. β_2 and β_4 transcripts have been identified in both DBA/2J and A/J mouse CBs, with $\beta_2 > \beta_4$ in DBA/2J. Functionally, mild hypoxia inhibits BK currents only in DBA/2J glomus cells; A/J cells, with less β_2, show little inhibition. Moreover, IbTX mimics hypoxia only in DBA/2J, suggesting that β_2 confers O_2 sensitivity to BK channels. β_4's role appears to be modulatory:[54] its expression in both DBA/2J and A/J mouse strains correlates with IbTX resistance in a subset of cells. This heterogeneity may allow parallel populations of glomus cells -some rapidly inactivated, others sustained- to encode different phases of hypoxic signaling. BK channels in vascular smooth muscle typically contain β_1, not β_2, and are insensitive to hypoxia in the physiological range.[9] Neuronal BK channels express β_4, producing slow gating and toxin resistance, but they do not respond directly to PaO_2 tension. Thus, the CB configuration ($\alpha + \beta_2/\beta_4$) is unique, enabling both high Ca^{2+} sensitivity and hypoxic inhibition.

The β_2 subunit introduces an *N*-terminal inactivation domain, yielding transient BK channel currents that contribute to the initial depolarization during hypoxia.[55] As intracellular Ca^{2+} rises, the β_4-containing non-inactivating channels reopen, providing negative feedback that limits Ca^{2+} influx and further neurotransmitter release. This dual behavior mirrors the CB's requirement for rapid activation followed by stabilization – properties seldom required of BK channels elsewhere. In the CB, BK channels are functionally coupled to heme oxygenase-2 (HO-2) and cystathionine-g-lyase (CSE), which generate CO and H_2S, respectively. HO-2-derived CO activates BK, while H_2S inhibits BK through sulfhydration of cysteine residues on the α-subunit. During hypoxia, reduced HO-2 activity decreases CO production, and increases CSE activity elevates H_2S, both of which suppress BK activity and depolarize the glomus cell.[56-60]

Electrophysiology and hypoxic modulation in the carotid body

In glomus cells, BK channel coupling to L-type Ca^{2+} channels helps shape spike repolarization and limits Ca^{2+} entry. An example is that in acute hypoxia this coupling disinhibits BK negative feedback, thereby preventing excess response to hypoxia, *i.e.*, overshoot (by increasing depolarization, Ca^{2+} influx, and transmitter release).[61,62] In isolated glomus cells, perforated-patch recordings show outward K^+ currents with characteristics consistent with BK channels.[63] At rest, BK channels contribute modestly to membrane potential due to requirement for elevated Ca^{2+}. However, localized Ca^{2+} concentration near voltage-gated Ca^{2+} channels (VGCCs)[64] allow BK channels to be active during action-potential depolarization even at baseline.

BK channels contribute ~20-40% of the hypoxia-sensitive K^+ conductance depending on species.[65] Blockade of BK channels prolongs spike duration by 30-70%, increases afterdepolarization amplitude, enhances repetitive firing, increases intracellular Ca^{2+} transients, and shifts firing mode from tonic to burst-like patterns. These changes are transmitted to the CSN and then to central respiratory networks.

The tight coupling of BK channels to L-type Ca^{2+} channels (CaV1 family)[66] provides a fast negative feedback loop. Channel blockers such as paxilline or iberiotoxin prolong action-potential duration and enhance Ca^{2+} influx.[65]

A defining feature of glomus-cell BK channels is their inhibition by hypoxia.[38,67-70] Hypoxic inhibition decreases outward K^+ current, contributing to depolarization, activation of VGCCs, and transmitter release. The proposed mechanism(s) include: channel-intrinsic direct O_2 sensing, as suggested in early studies[67]; metabolic-mitochondrial coupling, wherein hypoxia reduces mitochondrial ATP production, ROS generation, or heme-based signaling, ultimately inhibiting BK channels;[71-73] and accessory subunit-dependent modulation, wherein β2/β4 subunits alter hypoxic responses. BK blockers (*e.g.*, iberiotoxin, charybdotoxin, and paxilline) blunt hypoxia-induced depolarization[49] and openers (*e.g.*, NS1619, NS11021, and newer benzimidazolone derivatives) mimic hypoxic responses – supporting a causal role in chemostimulus-evoked depolarization.

BK channels in acute oxygen sensing

Mitochondrial depolarization, changes in ROS generation, and reduced HO-2-dependent CO production converge on BK gating.[74] These mechanisms integrate with other O_2-sensitive channels (*e.g.*, TASK, Kv) to influence overall glomus-cell excitability.[26,75,76] Early work proposed that BK channels were themselves O_2 sensors, inhibited by low PaO_2 via an intrinsic heme-binding or redox mechanism.[67] However, later studies produced mixed results, with some failing to observe intrinsic O_2 sensitivity in cell-free patches.[77] Subsequent models suggest that BK channel inhibition results from mitochondrial signals rather than direct O_2 binding.[11,78,79] Proposed mediators include: reduced ROS generation in hypoxia, altering redox-sensitive cysteines on BK;[80] changes in ATP/ADP ratio, influencing nearby Ca^{2+} signaling or metabolic coupling; and modulation by HO-2 and its by-products CO and biliverdin[77,81], having an O_2-binding heme whose catalytic activity is O_2-dependent, making them plausible O_2 sensors.

Hypoxia inhibits multiple K^+ channels in glomus cells: Kv channels,[82] TASK background K^+ channels,[83] and SK (small-conductance calcium-activated) channels.[84] BK channels bind heme, which confers gas-neurotransmitter sensitivity.[85] Thus, BK channels are one of several converging conductance channels. Genetic

ablation of BK channels reduces, but does not abolish, hypoxic responses,[82] indicating redundancy.

The current consensus is that BK channels are regulated by O_2-dependent metabolic signals, not by direct O_2 binding. According to a reasonable scheme: Low O_2 → ↓HO-2 → ↓CO → BK inhibition → CB excitation, which provides a biochemical negative-feedback pathway with PaO_2 as the controlled variable.

Mitochondrial oxidative phosphorylation decreases with low PaO_2, which alters NADH/NAD^+, ROS (superoxide, H_2O_2), ATP/ADP, and mitochondrial membrane potential.[71] These signals modulate BK channels via redox-sensitive cysteines, metabolic enzymes (PKC, PKA), Ca^{2+} concentration changes, and direct mitoBK (mitochondrial BK) activity. If mitoBK channels exist in CB glomus cells, they may directly participate in the PaO_2-sensing pathway, modulating metabolic signals upstream of plasma-membrane BK channels. Pharmacological evidence includes findings that: complex-I inhibitors mimic the effect of hypoxia on BK channels,[80] mitochondrial uncouplers depress BK channels and depolarize glomus cells, and ROS donors restore BK channel activity during hypoxia.

In sum, BK channels participate in a larger O_2-sensing network including: AMPK (AMP-activated protein kinase),[86,87] NADPH oxidases, NOX2(NADPH oxidase 2)-dependent ROS, HIF pathways, and TASK/Kv channels.[88] Thus, BK channels are best understood as principal effectors within a distributed sensing architecture.

BK channels, neurotransmitter release, and CSN discharge

Hypoxic conditions lead to increase in Ca^{2+} mediated by the activity of voltage-gated Ca^{2+} channels (Cav), mechanosensitive channels, or ionotropic or metabotropic receptors (*e.g.*, ACh).[89] BK channels prevent excess response. Their inhibition has the opposite effect, *i.e.*, increased CSN discharge frequency.

Dopamine D2 receptors inhibit Ca^{2+} channels and activate K^+ channels. BK channel facilitation by dopamine may contribute to presynaptic autoinhibition.[90] ATP is an excitatory transmitter from glomus cells. P2X(purinoreceptor)-mediated Ca^{2+} influx may secondarily activate BK channels, shaping burst patterns. Nicotinic acetylcholine receptors produce rapid depolarization and Ca^{2+} entry. BK channels limit the resulting excitation. Endothelin(ET)-1, angiotensin II, and inflammatory cytokines all influence BK activity via second-messenger pathways. ET-1, released by CB sustentacular (type II) cells, activates ET-A receptors, elevates intracellular Ca^{2+}, suppresses BK channels, and enhances glomus-cell excitability.[91] In chronic hypoxia, ET-1 levels increase significantly. IL-1β and TNF-a suppress BK channels in many cell types. In the CB, IL-1β increases hypoxic neurotransmitter release and cytokine-induced BK channel suppression contributes to pathological hyperresponsiveness. Pharmacological inhibition of BK channels increases the release of dopamine, ATP (via pannexin channels), and acetylcholine. In rat CB slices, paxilline increases hypoxia-evoked dopamine release by 40-70%.[65] BK channels thus set the gain on quantal transmitter output.

In vivo recordings show that BK channel blockers increase baseline CSN firing, BK openers (*e.g.*, NS1619) dampen hypoxic responses,[49] and BK channels contribute to phase resetting of respiratory rhythm during hypoxia.[65] In *KCNMA1* knockout mice, CSN responses to hypoxia are enhanced, but not abolished, and breathing is more unstable. Dysfunction of BK channels contributes to deleterious effects on breathing and cardiovascular conditions.[92-95]

BK channels as part of closed-loop feedback control systems

At the cellular level, BK channels provide a fast negative feedback loop: depolarization → Ca^{2+} influx → BK channel activation → repolarization. At the systems level, BK channels influence the slope of the PaO_2-CSN response curve, and thus the gain and stability of the ventilatory control loop. At the molecular level BK channels integrate: voltage sensing domains, Ca^{2+} (RCK1/RCK2 domains), b/g subunit modulation, redox state (*e.g.*, cysteine oxidation, *S*-nitrosylation), heme/HO-2 and CO, and phosphorylation by, *e.g.*, PKA, PKC, PKG, CaMKII. This makes BK channels a multi-input, multi-output node where diverse signals converge. O_2-sensitive pathways influence one or more of the inputs. At the organ level: BK channel activity in one glomus cell affects neurotransmitter output, which acts on neighboring cells and CSN, and autocrine and paracrine signaling feedback modulates BK and other K^+ channels. Thus, BK channels are part of a network of glomus-glomus and glomus-nerve interactions that shape population-level responses of the CB. At the systems level, ventilation is governed by feedback and feed-forward loops[96] modeled as:

Sensor: carotid bodies that detect PaO_2, $PaCO_2$, and pH
Controller: brainstem respiratory centers that integrate input
Effector: respiratory muscles that adjust ventilation
Plant: factors that influence PaO_2
Feedback: updated PaO_2 information fed back to the sensor

Within this loop, BK channels act at the sensor stage, influencing the transfer function from PaO_2 → CSN firing, tempering fast fluctuations in response. BK channel activation flattens the CSN-PaO_2 curve, stabilizing the system at homeostasis. Conversely, inhibition of BK channels steepens the curve (effectively increasing loop gain), counteracting excessive deviations due to hypoxia.

At the cellular level, BK channels form a fast negative-feedback loop: hypoxia depolarizes glomus cells → opens Ca^{2+} channels → raises Ca^{2+} → activates BK → opposes depolarization (Table 2). This sequence restrains excitability, preventing runaway transmitter release.

In system control-theory terms, BK channels provide stabiliz-

Table 2. Three levels of feedback control in which carotid BK channels are involved.

Level	Function	Control type	Timescale
Cellular (glomus)	Limit depolarization and Ca^{2+} entry	Negative feedback	msecs to secs
Organ (CB-CSN)	Adjust gain of chemosensory response	Adaptive/dynamic feedback	secs to mins
Systemic (CB -respiratory)	Maintain PaO_2	Global negative feedback	secs to mins

ing derivative-like control by shortening action potentials and opposing excessive depolarization, BK channels reduce loop gain, and inhibition of BK channels influence shifts the sensor toward higher gain.

Excess BK inhibition or genetic disruption results in exaggerated ventilatory responses and increased oscillatory breathing tendencies.[82]

In chronic hypoxia, glomus type I cells proliferate, CB size increases, transmitter stores enlarge and channel expression changes,[19] and BK function displays plasticity:[96] reduced BK expression increases hypoxic sensitivity and changes in β subunit composition alter gating and PaO_2 responsiveness. These adjustments tune the sensor for chronic low-O_2 environments, re-balancing feedback loop gain. The role of BK channels in ventilatory control involves at least three nested feedback loops.

Several publications discuss the CB as part of a feedback ventilatory loop,[97-103] but the author is unaware of a prior publication that provides a model of the CB as an explicit control element using control-system formalisms. A simple conceptual control-system block diagram is presented in Figure 1.

In the time-domain, the input (controlled variables) are:

$$x(t) = f\{PaO_2(t), PaCO_2(t), pH(t)\}, \quad \text{(Eq. 1)}$$

and the output is:

$$y(t) = f\{PaO_2(t), PaCO_2(t), pH(t)\}. \quad \text{(Eq. 2)}$$

The CSN firing rate would be:

$$F_{CSN}(t) = f\{PaO_2(t), PaCO_2(t), pH(t), gBK, Ca^{2+}\}, \quad \text{(Eq. 3)}$$

where g*BK* = BK channel conductance; *d*(g*BK*)/*dt* incorporates hypoxic inhibition, redox modulation, and β/γ subunit composition. The transfer function of the system in the s-domain (Laplace transform of the time-domain input and output) is:

$$\frac{y(s)}{x(s)} = \frac{P(s)G(s)}{1+P(s)G(s)} \quad \text{(Eq. 4)}$$

Since BK channels are also modulated by dopamine autoinhibition, nitric oxide (NO) production, and peptide neuromodulators (*e.g.*, endothelin),[104] these provide additional slow feedback loops, adapting gain over seconds to minutes.

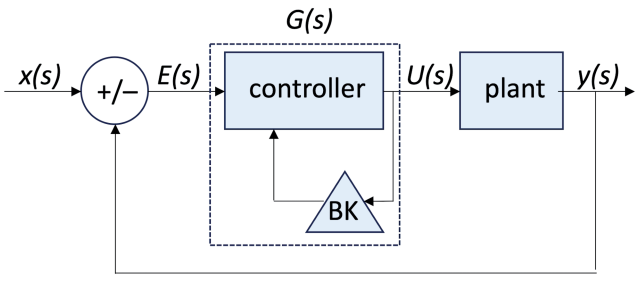

Figure 1. Postulated generalized schematic control-system representation of the role of BK channels within the carotid body feedback response to changes in arterial blood gases. This is a conceptual framework, currently not a quantitatively validated formal model.

Influences on, and plasticity of, BK channels

ROS such as H_2O_2 and superoxide can modulate BK channels through Cysteine oxidation[105] and interaction with accessory subunits. Hypoxia decreases mitochondrial ROS generation, likely shifting BK channel gating via redox signaling.[80] HO-2 produces CO in an O_2-dependent manner. CO directly activates BK channels.[77] Thus, in hypoxia the sequence of events is: HO-2 activity falls → CO production decreases → BK activity decreases → glomus-cell depolarization increases. This provides an additional biochemical feedback mechanism linking local O_2 concentration to BK activity. Local ATP depletion during hypoxia reduces Na^+/K^+-pump activity and influences Ca^{2+} levels.

BK channels respond to: *S*-glutathionylation (increases PaO_2), *S*-nitrosylation (varies by species), *S*-oxidation (of Cys911, Cys430)[105], and CO modulation via a heme-binding domain.[77] Chronic oxidative stress, as in chronic intermittent hypoxia (CIH), reduces the expression of BK channels[106,107], contributing to heightened CB sensitivity. AMPK phosphorylates ion channels, including BK channels, in some neurons.[86] Hypoxia-driven AMPK activation could inhibit BK directly, alter Ca^{2+} handling, or shift mitochondrial Ca^{2+} uptake, indirectly affecting BK channels.

Chronic intermittent hypoxia (CIH), obstructive sleep apnea (OSA), heart failure, and hypertension are associated with enhanced CB activity, oxidative stress, and inflammation.[46,108-110] In these states, BK channel expression and function are reduced. Aging and developmental transitions also remodel K^+ channel expression, including BK and TASK channels, thereby altering CB chemosensory properties.[76,111-113] Neonatal animals exhibit lower BK channel expression and greater hypoxic sensitivity than do adults.[114] Maturation increases BK channel contributions to excitability.[115] Aged CBs show reduced BK channel levels, impaired Ca^{2+} clearance, and decreased ventilatory adaptation.[116] BK channel alterations may contribute to reduced hypoxic ventilatory response in the elderly. Rodents exposed to chronic intermittent hypoxia exhibit reduced BK channel current density, upregulation of HIF-1a, increased ROS, and exaggerated CB responses. Chronic hypoxia also induces changes in β subunit expression (β2 → β4 shifts), and altered splice variant abundance. These changes enhance CB sensitivity in low-O_2 environments.[117] CIH is a hallmark of OSA and produces a characteristic phenotype of CB hypersensitivity, sympatho-excitation, and hypertension[57,117,118] CIH enhances CB sensory discharge to acute hypoxia, increases baseline CSN activity, and promotes sensory long-term facilitation, a persistent augmentation of chemoreceptor output following episodic hypoxia.[19,117]

Recent reviews emphasize that BK channels are a part of a network linking ROS, HIF-1a, inflammatory mediators, and Ca^{2+} signaling, especially in cardiorespiratory disease including OSA-associated hypertension.[40] CB overactivity contributes to sympathetic overdrive and poor prognosis in heart failure and systemic hypertension.[119,120] Animal models show enlarged CBs, enhanced hypoxic responses, and increased expression of pro-inflammatory and renin-angiotensin components. Although most studies of CB has focused on TASK and Kv channels[121-123], BK channel down-regulation fits well with the heightened gain and oscillatory behavior seen in CIH models.

Aging is associated with a reduced hypoxic ventilatory response and impaired CB plasticity.[116,124] With age, BK channel expression often declines in neurons and smooth muscle, Ca^{2+} homeostasis becomes dysregulated, and mitochondrial dysfunction

and chronic oxidative stress accumulate. During postnatal development, CB sensitivity to hypoxia is initially low, but increases over the first weeks of life; developmentally regulated changes in K^+ channels (including BK and TASK) are key to this maturation.[124-126] Although direct measurements in aged CB are scarce, a scenario in which BK channel expression decreases while other depolarizing influences increase could distort the dynamic range of the sensor, contributing to blunted hypoxic responsiveness, yet increased variability in breathing.

Pharmacological modulation of BK channels in the carotid body

BK channel openers such as NS1619 hyperpolarize glomus cells and blunt hypoxic responses, suggesting a potential approach to damp pathological CB hyperactivity. However, systemic BK channel activation carries risks if the ligands are not highly selective for CB, due to widespread expression of BK channels in vasculature and central nervous system. Pharmacological BK channel openers (*e.g.* NS1619, NS11021, benzimidazolone derivatives)[127,128] increase K^+ efflux. In the context of feedback control, such drugs reduce sensor gain and might be beneficial to damp excessive chemoreflex activity in conditions like OSA, heart failure, or hypertension. However, systemic application of low-selectivity compounds risks off-target effects in vascular smooth muscle and CNS, potentially causing hypotension or impairing protective hypoxic responses. A theoretical strategy, therefore, is targeted delivery (*e.g.* local intra-carotid or nanoparticle-based approaches) to selectively modulate BK channels in CB while bypassing other tissues.

BK channel blockers (*e.g.*, iberiotoxin, charybdotoxin, paxilline) are experimental tools that mimic hypoxia, enhancing glomus-cell depolarization and CSN discharge. *In vivo*, this would increase ventilatory drive and sympathetic outflow, which might be useful in the rare conditions of CB hypoactivity.

Discussion

BK channels located in the carotid body are molecularly specialized hypoxia-sensing transducers.[32,34,61,63] Their unique combination of β_2/β_4 subunits, STREX(stress axis-regulated exon)-containing a-isoforms, and gasotransmitter regulation allows them to operate near the physiological resting potential of glomus cells, respond dynamically to PaO_2 fluctuations, and engage in both excitatory and inhibitory feedback. In contrast, BK channels in vascular and neuronal tissues serve primarily as effectors that couple Ca^{2+} signals to hyperpolarization or spike shaping without direct PaO_2 sensitivity.

The relative importance of BK *vs* other PaO_2-sensitive channels is species dependent. For example, rat CB glomus cells display robust BK channel currents that contribute significantly to resting potential and hypoxic depolarization; charybdotoxin and other BK channel blockers strongly depolarize these cells and mimic hypoxia.[52,129] In mice, TASK and other Kv channels appear to dominate PaO_2 sensing (genetic ablation of TASK1/3 greatly attenuates hypoxic responses), whereas HO-2 and BK manipulations have more modest effects.[121,122] Recent reviews emphasize that the role of BK channels as a PaO_2 sensor is robust in some contexts (pulmonary vasculature, neonatal adrenal chromaffin cells), but less universal than initially thought.[76]

An unresolved issue is whether hypoxia directly inhibits BK channels via a membrane-delimited mechanism or acts indirectly via mitochondrial and metabolic signals. Some studies using recombinant human BK channels report membrane-delimited Ca^{2+}-sensitive inhibition by hypoxia, even in excised patches, consistent with direct O_2 sensing.[130] Others find that O_2 sensitivity disappears upon patch excision or requires cytosolic factors, pointing to upstream signals. The mitochondrial hypothesis is supported by pharmacological mimicry of hypoxia with mitochondrial poisons and by the requirement for mitochondrial integrity.[131,132] A plausible reconciliation is that multiple mechanisms converge on BK channel responsiveness: O_2-dependent heme/HO-2, ROS/redox modulation, and changes in Ca^{2+} microdomains, which all influence gating. This is consistent with the findings that relative dominance likely varies among species, developmental stages, and disease states.

Conclusions

BK channels are modulators of carotid-body chemotransduction. Although not the sole PaO_2 sensor, they integrate metabolic, Ca^{2+}, redox, and transmitter signals to shape excitability. They operate within multilevel feedback loops that stabilize cellular and whole-organism responses to hypoxia. Their dynamic regulation in chronic hypoxia, disease, and developmental transitions highlights their importance in respiratory homeostasis. Future work will refine understanding of the breadth and precise roles of BK channels in health and disease, and their potential as therapeutic targets.

BK channels in the carotid body are best understood as multifunctional regulators rather than simple 'on/off' PaO_2 sensors:

- At baseline, BK channels provide a Ca^{2+}-dependent brake on excitability, stabilizing glomus-cell membrane potential, and an influence on the dynamic range of stimulus-response relationships.
- During acute hypoxia, BK channel inhibition – whether direct or via mitochondrial, HO-2/CO, or other pathways – amplifies depolarization and transmitter release, contributing to the rapid rise in CSN discharge that drives reflex counteraction.
- Within the CB, BK channels participate in fast negative feedback at the level of the action potential and in slower modulation through transmitter-mediated signaling, assisting in shaping patterning of CSN activity and preventing runaway excitation.
- Over longer timescales, BK channel expression and modulation adapt to chronic hypoxia, inflammation, and disease. Excess downregulation of BK channels or shifts in accessory subunits can exaggerate CB gain, contributing to the maladaptive hypersensitivity seen in CIH, OSA, heart failure, and hypertension.
- At the systems level, BK channels influence the stability of the respiratory control loop. Too little BK channel activity predisposes to unstable, oscillatory breathing; too much may blunt life-saving responses to hypoxia.

From a conceptual standpoint, BK channels are positioned anatomically and physiologically such that they mediate not only the immediate electrical response of a sensory cell, but also the long-term stability of a vital homeostatic loop.

From a therapeutic standpoint, BK-channels are an attractive target for tuning CB activity. The challenge is achieving sufficient selectivity to avoid widespread off-target and CNS side-effects. ENA-001 (previously GAL-021), *N*-(4,6-*bis*-*n*-propylamino-[1,3,5]-triazin-2-yl)-*N*,*O*-dimethylhydroxylamine, is being studied as a potential such compound. It is a selective BK-channel antagonist in the CB,[133,134] that stimulates ventilation in animals and human volunteers,[135] and it reduces the respiratory depression

induced by opioids, including morphine, fentanyl, and alfentanil,l[133,136-138] and non-opioids, including barbiturates (midazolam), propofol, and isoflurane,[139] and the respiratory depression induced by the combination of fentanyl plus xylazine.[138] It is currently in clinical development.[140]

Future directions

Interpretation of BK channel function in CB is complicated by certain methodological issues. These limitations underscore the need for selective tool drugs and standardized protocols. Key open questions include:

- Are BK channels direct PaO_2 sensors, or downstream effectors?
- What is the precise molecular mechanism of hypoxic inhibition?
- What is the *in vivo* relevance of mitochondrial BK in glomus cells?
- How do b and g subunits modulate hypoxic responses?
- How do BK channels contribute to disease-related CB hyperexcitability?
- Can BK channel modulators serve as therapeutics for breathing disorders?
- Novel techniques, such as glomus-cell single-cell transcriptomics, CRISPR knock-ins of specific splice variants, mitochondrial-targeted reporters, closed-loop optogenetic-chemodenervation techniques, and computational models that integrate O_2 sensing, metabolism, and ion channels seem potentially informative.

Abbreviations

BK – big potassium channel (also Maxi-K, $K_{Ca}1.1$)
CaMKII – Ca^{2+}/calmodulin-dependent protein kinase II
CaV – voltage-gated Ca^{2+} channel
CB – carotid body
CIH – chronic intermittent hypoxia
CSE – cystathione-g-lyase
CSN – carotid sinus nerve
ET – endothelin
HO-2 – heme oxygenase-2
IbTX – IberiotoxinHIF – hypoxia-inducible factors
mitoBK – mitochondrial BK
NADPH – nicotinamide adenine dinucleotide phosphate
NO – nitric oxide
Nox2 – NADPH oxidase 2
OSA – obstructive sleep apnea
P2X – purinoreceptor
PKA (PKC, PKG) – protein kinase subtypes
preBötC – pre-Bötzinger complex
ROS – reactive oxygen species
STREX – stress axis-regulated exon
TASK – TWIK-related acid-sensitive K^+ channel
VGCC – voltage-gated Ca^{2+} channel

References

1. Martin WR. Opioid antagonists. Pharmacol Rev 1967;19:463-521.
2. Kolbe L, Fins JJ. The birth of naloxone: an intellectual history of an ambivalent opioid. Camb Q Healthc Ethics 2021;30:637-50.
3. Raffa RB, Pergolizzi JV Jr, LeQuang JA, et al. The fentanyl family: a distinguished medical history tainted by abuse. J Clin Pharm Ther 2018;43:154-8.
4. Pergolizzi JV Jr, Dahan A, LeQuang JA, Raffa RB. The conundrum of polysubstance overdose. J Clin Pharm Ther 2021;46:1189-93.
5. Peppin JF, Raffa RB, Schatman ME. The polysubstance overdose-death crisis. J Pain Res 2020;13:3405-8.
6. Dahan A, Franko TS, Carroll JW, et al. Fact vs. fiction: naloxone in the treatment of opioid-induced respiratory depression in the current era of synthetic opioids. Front Public Health 2024;12:1346109.
7. van Lemmen M, van der Schrier R, Dahan A, van Velzen M, Sarton E, Niesters M. Pharmacology of viable mechanism agnostic respiratory stimulants for the reversal of drug-induced respiratory depression in humans. Expert Opin Drug Metab Toxicol 2023;19:671-9.
8. Peppin JF, Pergolizzi JV Jr, Fudin J, Meyer TA, Raffa RB. History of respiratory stimulants. J Pain Res 2021;14:1043-9.
9. Bee D, Howard P. The carotid body: a review of its anatomy, physiology and clinical importance. Monaldi Arch Chest Dis 1993;48:48-53.
10. Biscoe TJ. Carotid body: structure and function. Physiol Rev 1971;51:437-95.
11. Chang AJ. Acute oxygen sensing by the carotid body: from mitochondria to plasma membrane. J Appl Physiol (1985) 2017;123:1335-43.
12. Verna A. Ultrastructure of the carotid body in the mammals. Int Rev Cytol 1979;60:271-330.
13. Lopez-Barneo J. Neurobiology of the carotid body. Handb Clin Neurol 2022;188:73-102.
14. Ortega-Sáenz P, Lopez-Barneo J. Physiology of the carotid body: from molecules to disease. Annu Rev Physiol 2020;82:127-49.
15. Iturriaga R, Alcayaga J, Chapleau MW, Somers VK. Carotid body chemoreceptors: physiology, pathology, and implications for health and disease. Physiol Rev 2021;101:1177-235.
16. Kay JM, Laidler P. Hypoxia and the carotid body. J Clin Pathol Suppl (R Coll Pathol) 1977;11:30-44.
17. Prabhakar NR, Peng YJ. Oxygen sensing by the carotid body: past and present. Adv Exp Med Biol.2017;977:3-8.
18. Guyenet PG. Regulation of breathing and autonomic outflows by chemoreceptors. Compr Physiol 2014;4:1511-62.
19. Prabhakar NR. Oxygen sensing by the carotid body chemoreceptors. J Appl Physiol (1985) 2000;88:2287-95.
20. Gronblad M. Function and structure of the carotid body. Med Biol 1983;61:229-48.
21. Gao L, Moreno-Dominguez A, Ortega-Saenz P, Lopez-Barneo J. The carotid body oxygen sensor. Curr Opin Neurobiol 2025;92:103022.
22. Zoccal DB, Vieira BN, Mendes LR, Evangelista AB, Leirao IP. Hypoxia sensing in the body: an update on the peripheral and central mechanisms. Exp Physiol 2024;109:461-9.
23. Prabhakar NR, Peng YJ, Nanduri J. Recent advances in understanding the physiology of hypoxic sensing by the carotid body. F1000Res 2018;7:1900.
24. Prabhakar NR, Semenza GL. Regulation of carotid body oxygen sensing by hypoxia-inducible factors. Pflugers Arch 2016;468:71-5.
25. Olson LG, Saunders NA. Structure and function of the carotid body. Aust N Z J Med 1985;15:775-81.
26. Yang H, Zhang G, Cui J. BK channels: multiple sensors, one activation gate. Front Physiol 2015;6:29.
27. Porzionato A, Macchi V, Stecco C, De Caro R. The carotid sinus nerve — structure, function, and clinical implications. Anat Rec (Hoboken).2019;302:575-87.
28. Piskuric NA, Nurse CA. Expanding role of ATP as a versatile

messenger at carotid and aortic body chemoreceptors. J Physiol 2013;591:415-22.
29. Gonzalez C, Almaraz L, Obeso A, Rigual R. Oxygen and acid chemoreception in the carotid body chemoreceptors. Trends Neurosci 1992;15:146-53.
30. Peers C. Ionic channels in type I carotid body cells. Adv Exp Med Biol 1994;360:29-40.
31. Conde SV, Monteiro EC, Sacramento JF. Purines and carotid body: new roles in pathological conditions. Front Pharmacol 2017;8:913.
32. Wang J, Kim D. Activation of voltage-dependent K(+) channels strongly limits hypoxia-induced elevation of [Ca(2+)]i in rat carotid body glomus cells. J Physiol.2018;596:3119-36.
33. Pichard LE, Crainiceanu CM, Pashai P, et al. Role of BK channels in murine carotid body neural responses in vivo. Adv Exp Med Biol 2015;860:325-33.
34. Gomez-Nino A, Obeso A, Baranda JA, et al. MaxiK potassium channels in the function of chemoreceptor cells of the rat carotid body. Am J Physiol Cell Physiol 2009;297:C715-22.
35. Donnelly DF, Kim I, Yang D, Carroll JL. Role of MaxiK-type calcium dependent K+ channels in rat carotid body hypoxia transduction during postnatal development. Respir Physiol Neurobiol 2011;177:1-8.
36. Zoccal DB, Furuya WI, Bassi M, et al. The nucleus of the solitary tract and the coordination of respiratory and sympathetic activities. Front Physiol. 2014;5:238.
37. Munoz-Ortiz J, Munoz-Ortiz E, Lopez-Meraz ML, et al. Pre-Bötzinger complex: generation and modulation of respiratory rhythm. Neurologia (Engl Ed) 2019;34:461-8.
38. Buckler KJ, Vaughan-Jones RD. Role of intracellular pH and [Ca2+]i in acid chemoreception in type-I cells of the carotid body. Adv Exp Med Biol 1994;360:41-55.
39. Rakoczy RJ, Schiebrel CM, Wyatt CN. Acute oxygen-sensing via mitochondria-generated temperature transients in rat carotid body type I cells. Front Physiol.2022;13:874039.
40. Ochoa SV, Otero L, Aristizabal-Pachon AF, et al. Hypoxic regulation of the large-conductance, calcium and voltage-activated potassium channel, BK. Front Physiol 2021;12:780206.
41. Liu G, Zakharov SI, Yang L, et al. Position and role of the BK channel alpha subunit S0 helix inferred from disulfide crosslinking. J Gen Physiol 2008;131:537-48.
42. Shipston MJ. Alternative splicing of potassium channels: a dynamic switch of cellular excitability. Trends Cell Biol 2001;11:353-8.
43. Chen L, Shipston MJ. Cloning of potassium channel splice variants from tissues and cells. Methods Mol Biol 2008;491: 35-60.
44. Zhang J, Yan J. Regulation of BK channels by auxiliary gamma subunits. Front Physiol 2014;5:401.
45. Macias D, Cowburn AS, Torres-Torrelo H, et al. HIF-2alpha is essential for carotid body development and function. Elife 2018;7:e34681.
46. Ortega-Sáenz P, Moreno-Dominguez A, Gao L, Lopez-Barneo J. Molecular mechanisms of acute oxygen sensing by arterial chemoreceptor cells. Role of HIF2alpha. Front Physiol 2020; 11:614893.
47. Fung ML. Pathogenic roles of the carotid body inflammation in sleep apnea. Mediators Inflamm 2014;2014:354279.
48. Ross FA, Rafferty JN, Dallas ML, et al. Selective expression in carotid body type I cells of a single splice variant of the large conductance calcium- and voltage-activated potassium channel confers regulation by AMP-activated protein kinase. J Biol Chem 2011;286:11929-36.
49. Pardal R, López-Barneo J. Carotid body thin slices: responses of glomus cells to hypoxia and K(+)-channel blockers. Respir Physiol Neurobiol 2002;132:69-79.
50. Latorre R, Castillo K, Carrasquel-Ursulaez W, et al. Molecular determinants of BK channel functional diversity and functioning. Physiol Rev.2017;97:39-87.
51. Ecaterina S, Hodor D, Sall IM, et al. Comparative exploration of the carotid body in domestic animals: morphology, physiology, histology, and pathology. Front Vet Sci 2024;11:1409701.
52. Otsubo T, Kostuk EW, Balbir A, et al. Differential expression of large-conductance Ca-activated K channels in the carotid body between DBA/2J and A/J strains of mice. Front Cell Neurosci 2011;5:19.
53. Hartness ME, Brazier SP, Peers C, et al. Post-transcriptional control of human maxiK potassium channel activity and acute oxygen sensitivity by chronic hypoxia. J Biol Chem 2003;278: 51422-32.
54. Wang B, Rothberg BS, Brenner R. Mechanism of beta4 subunit modulation of BK channels. J Gen Physiol 2006;127: 449-65.
55. Gonzalez-Perez V, Lingle CJ. Regulation of BK channels by beta and gamma subunits. Annu Rev Physiol 2019;81:113-37.
56. Prabhakar NR, Peers C. Gasotransmitter regulation of ion channels: a key step in O2 sensing by the carotid body. Physiology (Bethesda) 2014;29:49-57.
57. Prabhakar NR. Hydrogen sulfide (H(2)S): a physiologic mediator of carotid body response to hypoxia. Adv Exp Med Biol 2012;758:109-13.
58. Olson KR. A case for hydrogen sulfide metabolism as an oxygen sensing mechanism. Antioxidants (Basel) 2021;10:1650.
59. Prieto-Lloret J, Aaronson PI. Hydrogen sulfide as an O(2) sensor: a critical analysis. Adv Exp Med Biol 2017;967:261-76.
60. Olson KR. Hydrogen sulfide as an oxygen sensor. Antioxid Redox Signal 2015;22:377-97.
61. Peers C, Wyatt CN. The role of maxiK channels in carotid body chemotransduction. Respir Physiol Neurobiol 2007;157:75-82.
62. Riesco-Fagundo AM, Perez-Garcia MT, Gonzalez C, Lopez-Lopez JR. O(2) modulates large-conductance Ca(2+)-dependent K(+) channels of rat chemoreceptor cells by a membrane-restricted and CO-sensitive mechanism. Circ Res 2001; 89:430-6.
63. Lopez-Lopez JR, Gonzalez C, Perez-Garcia MT. Properties of ionic currents from isolated adult rat carotid body chemoreceptor cells: effect of hypoxia. J Physiol.1997;499:429-41.
64. Barak P, Parekh AB. Signaling through Ca(2+) microdomains from store-operated CRAC channels. Cold Spring Harb Perspect Biol 2020;12:a035097.
65. Peña F, Ramirez JM. Hypoxia-induced changes in neuronal network properties. Mol Neurobiol 2005;32:251-83.
66. Marcantoni A, Vandael DH, Mahapatra S, et al. Loss of Cav1.3 channels reveals the critical role of L-type and BK channel coupling in pacemaking mouse adrenal chromaffin cells. J Neurosci 2010;30:491-504.
67. Lopez-Lopez J, Gonzalez C, Urena J, Lopez-Barneo J. Low pO2 selectively inhibits K channel activity in chemoreceptor cells of the mammalian carotid body. J Gen Physiol 1989;93:1001-15.
68. Buckler KJ. A novel oxygen-sensitive potassium current in rat carotid body type I cells. J Physiol 1997;498:649-62.
69. Buckler KJ, Vaughan-Jones RD. Effects of hypercapnia on membrane potential and intracellular calcium in rat carotid body type I cells. J Physiol 1994;478:157-71.
70. Buckler KJ, Vaughan-Jones RD. Effects of hypoxia on mem-

brane potential and intracellular calcium in rat neonatal carotid body type I cells. J Physiol.1994;476:423-8.
71. Holmes AP, Ray CJ, Coney AM, Kumar P. Is carotid body physiological O(2) sensitivity determined by a unique mitochondrial phenotype? Front Physiol.2018;9:562.
72. Papreck JR, Martin EA, Lazzarini P, et al. Modulation of K2P3.1 (TASK-1), K2P9.1 (TASK-3), and TASK-1/3 heteromer by reactive oxygen species. Pflugers Arch 2012;464:471-80.
73. Prabhakar NR, Peng YJ, Yuan G, Nanduri J. Reactive oxygen radicals and gaseous transmitters in carotid body activation by intermittent hypoxia. Cell Tissue Res 2018;372:427-31.
74. Iturriaga R, Diaz HS. Reactive oxidative species in carotid body chemoreception: their role in oxygen sensing and cardiorespiratory alterations induced by chronic intermittent hypoxia. Antioxidants (Basel) 2025;14:675.
75. Fernandez-Aguera MC, Gao L, Gonzalez-Rodriguez P, et al. Oxygen sensing by arterial chemoreceptors depends on mitochondrial complex I signaling. Cell Metab 2015;22:825-37.
76. Lopez-Barneo J, Ortega-Saenz P, Gonzalez-Rodriguez P, et al. Oxygen-sensing by arterial chemoreceptors: mechanisms and medical translation. Mol Aspects Med 2016;47-48:90-108.
77. Williams SE, Wootton P, Mason HS, et al. Hemoxygenase-2 is an oxygen sensor for a calcium-sensitive potassium channel. Science. 2004;306:2093-7.
78. Holmes AP, Swiderska A, Nathanael D, et al. Are multiple mitochondrial related signalling pathways involved in carotid body oxygen sensing? Front Physiol 2022;13:908617.
79. Rakoczy RJ, Wyatt CN. Acute oxygen sensing by the carotid body: a rattlebag of molecular mechanisms. J Physiol 2018; 596:2969-76.
80. Waypa GB, Chandel NS, Schumacker PT. Model for hypoxic pulmonary vasoconstriction involving mitochondrial oxygen sensing. Circ Res 2001;88:1259-66.
81. Kemp PJ, Williams SE, Mason HS, et al. Functional proteomics of BK potassium channels: defining the acute oxygen sensor. Novartis Found Symp 2006;272:141-56.
82. Perez-Garcia MT, Colinas O, Miguel-Velado E, et al. Characterization of the Kv channels of mouse carotid body chemoreceptor cells and their role in oxygen sensing. J Physiol 2004;557:457-71.
83. Buckler KJ. TASK-like potassium channels and oxygen sensing in the carotid body. Respir Physiol Neurobiol 2007;157:55-64.
84. Bond CT, Maylie J, Adelman JP. Small-conductance calcium-activated potassium channels. Ann N Y Acad Sci 1999;868: 370-8.
85. Tang XD, Xu R, Reynolds MF, et al. Haem can bind to and inhibit mammalian calcium-dependent Slo1 BK channels. Nature 2003;425:531-5.
86. Evans AM, Mahmoud AD, Moral-Sanz J, Hartmann S. The emerging role of AMPK in the regulation of breathing and oxygen supply. Biochem J. 2016;473:2561-72.
87. Evans AM. AMPK breathing and oxygen supply. Respir Physiol Neurobiol 2019;265:112-20.
88. Lin AY, Turnbull CD, Pandit JJ. The "TASK" of breathing: anesthetic relevance of background two-pore domain potassium channels as therapeutic targets for respiratory control. Anesth Analg 2025;140:1414-25.
89. Duchen MR, Biscoe TJ. Relative mitochondrial membrane potential and [Ca2+]i in type I cells isolated from the rabbit carotid body. J Physiol 1992;450:33-61.
90. Jackson A, Nurse C. Dopaminergic properties of cultured rat carotid body chemoreceptors grown in normoxic and hypoxic environments. J Neurochem 1997;69:645-54.
91. Rey S, Corthorn J, Chacon C, Iturriaga R. Expression and immunolocalization of endothelin peptides and its receptors, ETA and ETB, in the carotid body exposed to chronic intermittent hypoxia. J Histochem Cytochem 2007;55:167-74.
92. Prabhakar NR, Peng YJ, Nanduri J. Carotid body hypersensitivity in intermittent hypoxia and obstructive sleep apnoea. J Physiol 2023;601:5481-94.
93. Tafil-Klawe M, Trzebski A, Klawe J, Palko T. Augmented chemoreceptor reflex tonic drive in early human hypertension and in normotensive subjects with family background of hypertension. Acta Physiol Pol 1985;36:51-8.
94. Trzebski A, Tafil M, Zoltowski M, Przybylski J. Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension. Cardiovasc Res 1982;16:163-72.
95. Schultz HD, Marcus NJ, Del Rio R. Role of the carotid body in the pathophysiology of heart failure. Curr Hypertens Rep 2013;15:356-62.
96. Dahan A, Nieuwenhuijs D, Teppema L. Plasticity of central chemoreceptors: effect of bilateral carotid body resection on central CO2 sensitivity. PLoS Med 2007;4:e239.
97. Grodins FS, Gray JS, Schroeder KR, et al. Respiratory responses to CO2 inhalation; a theoretical study of a nonlinear biological regulator. J Appl Physiol 1954;7:283-308.
98. Cheng L, Ivanova O, Fan HH, Khoo MC. An integrative model of respiratory and cardiovascular control in sleep-disordered breathing. Respir Physiol Neurobiol 2010;174:4-28.
99. Duffin J. A mathematical model of the chemoreflex control of ventilation. Respir Physiol 1972;15:277-301.
100. Middendorf T, Loeschcke HH. [Mathematical simulation of the respiratory system (author's transl)].[Article in German]. J Math Biol 1976;3:149-77.
101. Milhorn HT Jr, Benton R, Ross R, Guyton AC. A mathematical model of the human respiratory control system. Biophys J 1965;5:27-46.
102. Ursino M, Magosso E, Avanzolini G. An integrated model of the human ventilatory control system: the response to hypoxia. Clin Physiol 2001;21:465-77.
103. Virkki A, Polo O, Gyllenberg M, Aittokallio T. Can carotid body perfusion act as a respiratory controller? J Theor Biol 2007;249:737-48.
104. Silva JM, Lewis DL. Nitric oxide enhances Ca(2+)-dependent K(+) channel activity in rat carotid body cells. Pflugers Arch 2002;443:671-5.
105. DiChiara TJ, Reinhart PH. Redox modulation of hslo Ca2+-activated K+ channels. J Neurosci 1997;17:4942-55.
106. Moya EA, Arias P, Varela C, et al. Intermittent hypoxia-induced carotid body chemosensory potentiation and hypertension are critically dependent on peroxynitrite formation. Oxid Med Cell Longev 2016;2016:9802136.
107. Dallas ML, Scragg JL, Wyatt CN, et al. Modulation of O(2) sensitive K(+) channels by AMP-activated protein kinase. Adv Exp Med Biol 2009;648:57-63.
108. Conde SV, Sacramento JF, Martins FO. Immunity and the carotid body: implications for metabolic diseases. Bioelectron Med 2020;6:24.
109. Semenza GL, Prabhakar NR. The role of hypoxia-inducible factors in carotid body (patho)physiology. J Physiol 2018;596: 2977-83.
110. MacFarlane PM, Ribeiro AP, Martin RJ. Carotid chemoreceptor development and neonatal apnea. Respir Physiol Neurobiol 2013;185:170-6.
111. Di Giulio C. Ageing of the carotid body. J Physiol 2018; 596:3021-7.

112. Caravagna C, Seaborn T. Oxygen sensing in early life. Lung 2016;194:715-22.
113. Lopez-Barneo J, Macias D, Platero-Luengo A, et al. Carotid body oxygen sensing and adaptation to hypoxia. Pflugers Arch 2016;468:59-70.
114. Wasicko MJ, Breitwieser GE, Kim I, Carroll JL. Postnatal development of carotid body glomus cell response to hypoxia. Respir Physiol Neurobiol 2006;154:356-71.
115. Narang BJ, Manferdelli G, Millet GP, Debevec T. Respiratory responses to hypoxia during rest and exercise in individuals born pre-term: a state-of-the-art review. Eur J Appl Physiol 2022;122:1991-2003.
116. Pokorski M, Walski M, Dymecka A, Marczak M. The aging carotid body. J Physiol Pharmacol 2004;55:S107-13.
117. Peng YJ, Prabhakar NR. Effect of two paradigms of chronic intermittent hypoxia on carotid body sensory activity. J Appl Physiol (1985) 2004;96:1236-42.
118. Iturriaga R, Andrade DC, Del Rio R. Enhanced carotid body chemosensory activity and the cardiovascular alterations induced by intermittent hypoxia. Front Physiol 2014;5:468.
119. Felippe ISA, Rio RD, Schultz H, et al. Commonalities and differences in carotid body dysfunction in hypertension and heart failure. J Physiol 2023;601:5527-51.
120. Moraes DJ, Machado BH, Paton JF. Carotid body overactivity induces respiratory neurone channelopathy contributing to neurogenic hypertension. J Physiol 2015;593:3055-63.
121. Buckler KJ. TASK channels in arterial chemoreceptors and their role in oxygen and acid sensing. Pflugers Arch 2015;467:1013-25.
122. Ortega-Sáenz P, Levitsky KL, Marcos-Almaraz MT, et al. Carotid body chemosensory responses in mice deficient of TASK channels. J Gen Physiol.2010;135:379-92.
123. Kim D, Kim I, Papreck JR, et al. Characterization of an ATP-sensitive K(+) channel in rat carotid body glomus cells. Respir Physiol Neurobiol 2011;177:247-55.
124. Díaz-Jara E, Schwarz KG, Rios-Gallardo A, et al. Carotid body-mediated chemoreflex function in aging and the role of receptor-interacting protein kinase. Adv Exp Med Biol 2023;1427:195-201.
125. Kim D. K(+) channels in O(2) sensing and postnatal development of carotid body glomus cell response to hypoxia. Respir Physiol Neurobiol.2013;185:44-56.
126. Kameda Y. Molecular and cellular mechanisms of the organogenesis and development of the mammalian carotid body. Dev Dyn 2020;249:592-609.
127. Gessner G, Cui YM, Otani Y, et al. Molecular mechanism of pharmacological activation of BK channels. Proc Natl Acad Sci USA 2012;109:3552-7.
128. Olesen SP, Munch E, Watjen F, Drejer J. NS 004 — an activator of Ca(2+)-dependent K+ channels in cerebellar granule cells. Neuroreport 1994;5:1001-4.
129. Wyatt CN, Wright C, Bee D, Peers C. O2-sensitive K+ currents in carotid body chemoreceptor cells from normoxic and chronically hypoxic rats and their roles in hypoxic chemotransduction. Proc Natl Acad Sci USA 1995;92:295-9.
130. Lewis A, Peers C, Ashford ML, Kemp PJ. Hypoxia inhibits human recombinant large conductance, Ca(2+)-activated K(+) (maxi-K) channels by a mechanism which is membrane delimited and Ca(2+) sensitive. J Physiol 2002;540:771-80.
131. Lahiri S, Roy A, Baby SM, et al. Oxygen sensing in the body. Prog Biophys Mol Biol 2006;91:249-86.
132. Donnelly DF, Carroll JL. Mitochondrial function and carotid body transduction. High Alt Med Biol 2005;6:121-32.
133. Golder FJ, Dax S, Baby SM, et al. Identification and characterization of GAL-021 as a novel breathing control modulator. Anesthesiology 2015;123:1093-104.
134. Lu TL, Gao ZH, Li SW, Wu SN. High efficacy by GAL-021: a known intravenous peripheral chemoreceptor modulator that suppresses BK(Ca)-channel activity and inhibits I(K(M)) or I(h). Biomolecules 2020;10:188.
135. McLeod JF, Leempoels JM, Peng SX, et al. GAL-021, a new intravenous BKCa-channel blocker, is well tolerated and stimulates ventilation in healthy volunteers. Br J Anaesth 2014;113:875-83.
136. Roozekrans M, Olofsen E, van der Schrier R, et al. Reversal of opioid-induced respiratory depression by BK-channel blocker GAL021: a pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Clin Pharmacol Ther 2015;97:641-9.
137. Roozekrans M, van der Schrier R, Okkerse P, et al. Two studies on reversal of opioid-induced respiratory depression by BK-channel blocker GAL021 in human volunteers. Anesthesiology 2014;121:459-68.
138. Miller TL, Mathews J, Dungan GC, et al. ENA-001 reverses xylazine/fentanyl combination-induced respiratory depression in rats: a qualitative pilot study. Cureus 2024;16:e74826.
139. Jansen SC, van Lemmen M, Olofsen E, et al. Reversal of propofol-induced depression of the hypoxic ventilatory response by BK-channel blocker ENA-001: a randomized controlled trial. Anesthesiology 2024;140:1076-87.
140. Pergolizzi J Jr, Miller TL, Mathews J, et al. A single ascending-dose study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel respiratory stimulant ENA-001. Cureus 2024;16:e55057.

Received: 12 March 2026; Accepted: 11 May 2026.

Conflict of interests: the author is a co-founder of Enalare Therapeutics, which is developing a BK-channel antagonist. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of generative AI and AI-assisted technologies in the writing process: during the preparation of this manuscript, the author used the GenAI tool ChatGPT v5.2 for the purposes of assisting with identifying and summarizing literature sources and some content organization. The author reviewed and edited the output, and takes full responsibility for the content of this publication.

Data availability statement: the author declares that all the data supporting the findings of this study are contained within the paper.