

Review Article

POTASSIUM CHANNELS AS MOLECULAR OXYGEN SENSORS- ITS PROGRESS THROUGH THE YEARS AND PERSISTENT PUZZLES IN THE CAROTID BODY AND PULMONARY VASCULATURE — A COMPREHENSIVE REVIEW

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ABSTRACT

Background: In 1988, a single electrophysiological observation, that a potassium current in carotid body glomus cells was directly inhibited by low oxygen tension, opened an entire field of research into how cells sense oxygen on a moment-to-moment basis. Thirty-five years on, the core observation has been reproduced many times over, yet the identity of the specific potassium channel responsible, and the biochemical mechanism linking hypoxia to channel closure, remain genuinely unresolved. **Objective:** This review synthesises the physiology, molecular biology, and ongoing controversies surrounding oxygen-sensitive potassium channels, with particular focus on carotid body chemoreceptor cells and pulmonary artery smooth muscle cells, the two tissues in which this mechanism has been studied most intensively.

Materials and Methods: A structured narrative synthesis was built from the foundational electrophysiological literature, the two principal mechanistic frameworks (the membrane model and the mitochondrial hypothesis), and the still-active redox controversy, using primary sources located through PubMed and cross-referenced against a 2024 anniversary review of the field.

Results: Voltage-gated (KV), calcium-activated (BKCa), and background TASK potassium channels have each been implicated as oxygen sensors, with substantial species and tissue variability complicating a unified account. Two competing mitochondrial models, the redox theory and the mitochondrial ROS theory, offer opposite predictions about whether hypoxia raises or lowers reactive oxygen species, and this disagreement has still not been definitively resolved despite two decades of investigation. Parallel signalling through AMP-activated protein kinase, carbon monoxide and hydrogen sulphide, and lactate-driven acidosis further complicate a single unifying mechanism.

Conclusion: Oxygen sensing by potassium channels is one of the best-documented yet least-settled stories in cellular physiology; resolving it further will matter directly for understanding pulmonary hypertension, high-altitude adaptation, and chemoreceptor pathology.

Keywords: AMPK; BKCa channel; Carotid body; Hydrogen sulphide; Hypoxia; Hypoxic pulmonary vasoconstriction; KV channel; Mitochondria; Oxygen sensing; Reactive oxygen species; TASK channel.

INTRODUCTION

1.1. Why a cell needs to know how much oxygen it has: Every cell in an aerobic organism depends on a

continuous supply of oxygen to keep mitochondrial oxidative phosphorylation running, and yet the amount of oxygen actually reaching any given tissue can swing considerably from one minute to the next

— climbing a flight of stairs, sleeping through an apnoeic pause, or simply travelling to altitude all shift the oxygen tension a cell experiences. For the organism to respond appropriately, something has to notice the change quickly, and something else has to notice it over a longer timescale and adjust gene expression accordingly. Nature appears to have settled on two rather different solutions to this problem, and it is worth being clear about the distinction before going any further, because much of the confusion in this field comes from conflating them.

1.2. Two different problems: acute sensing versus chronic adaptation

Chronic, sustained hypoxia is handled mainly through the hypoxia-inducible transcription factors, HIF-1 and its relatives, which are continuously synthesised and continuously degraded under normoxic conditions by oxygen-dependent prolyl hydroxylases; when oxygen falls, that degradation slows, HIF accumulates, and it goes on to switch on a broad programme of genes encoding erythropoietin, angiogenic growth factors, and glycolytic enzymes, reshaping the cell's metabolism over hours to days (Semenza, 2012). That system is elegant, well characterised, and, for the purposes of this review, not the main story. What concerns us here is the much faster, second system: acute, second-to-second oxygen sensing, which relies not on new gene expression but on the direct, physical modulation of ion channels already sitting in the plasma membrane. This is the system that lets the carotid body trigger a gasp within a single breath of falling arterial oxygen, and it is the system this review is devoted to.

1.3. Thirty-five years since the founding observation

The starting point for essentially everything discussed in this review is a 1988 paper from José López-Barneo and colleagues, who used the then still-new whole-cell patch-clamp technique on isolated rabbit carotid body type I cells and found something genuinely unexpected: a voltage-dependent outward potassium current in these cells was reversibly suppressed simply by lowering the oxygen tension of the bathing solution, with no other manipulation required (López-Barneo et al., 1988). It is difficult to overstate how strange this must have looked at the time. Ion channels were understood to respond to voltage, to ligands, to mechanical stretch — but a channel that responded directly to a dissolved gas, acting as its own oxygen sensor without any obvious intermediary, was a genuinely new category of biological sensing. That single finding launched a research programme that, thirty-five years later, has produced hundreds of papers, several competing mechanistic models, at least three candidate channel families, and, refreshingly, an honest and still-unresolved scientific argument about some of the most basic details (Rocher & Aaronson, 2024).

It is worth noting, too, that the carotid body was not actually the first place a hypoxia-sensing

phenomenon of this general kind had been observed physiologically, even if it was the first place its cellular and molecular basis was worked out. More than four decades earlier, Ulf von Euler and Göran Liljestrand had already shown, in anaesthetised cats, that ventilating the lungs with a hypoxic gas mixture caused a prompt and substantial rise in pulmonary arterial pressure, and had correctly inferred that this reflected local vasoconstriction rather than any change in cardiac output (von Euler & Liljestrand, 1946). What the 1988 patch-clamp finding eventually supplied, once its logic was extended from the carotid body to the pulmonary vasculature over the following decade, was a plausible cellular mechanism for the phenomenon von Euler and Liljestrand had already documented at the level of the whole organ. This review will return to that connection directly in Section 7.

1.4. Scope and aims of this review

This review does not attempt to catalogue every oxygen-sensitive ion channel ever described; calcium and sodium channels have also been shown to carry some oxygen sensitivity, but potassium channels remain both the best studied and the most physiologically important in the two tissues this review focuses on: carotid body chemoreceptor cells, which trigger the acute ventilatory response to hypoxia, and pulmonary artery smooth muscle cells, which mediate hypoxic pulmonary vasoconstriction, the reflex by which the lung redirects blood flow away from poorly ventilated regions. Following the lead of a recent and thorough anniversary review of the field (Rocher & Aaronson, 2024), this review first lays out the observations that have been reproduced across multiple independent laboratories and are, by the standards of this notoriously difficult field, close to settled, before turning to the specific mechanistic questions that remain genuinely contested. Readers should come away with a clear sense of both what modern physiology confidently knows about how a cell senses oxygen, and, just as importantly, what it still does not.

2. The Carotid Body: The Body's Primary Acute Oxygen Sensor

2.1. Anatomy and physiological role

The carotid bodies are a pair of minute, richly vascularised organs, each barely a few millimetres across, sitting at the bifurcation of the common carotid artery on either side of the neck. Despite their small size, they receive one of the highest blood flows per gram of tissue of any organ in the body, which makes physiological sense: their entire job is to sample arterial blood continuously and report back on its oxygen content, and a sluggish blood supply would defeat that purpose. Chemosensory function in this location was recognised nearly a century ago, well before anyone had any idea of the underlying cellular mechanism, and the organ's role in triggering reflex hyperventilation during hypoxemia has been textbook physiology for decades (López-Barneo et al., 2001).

2.2. Glomus (type I) cells as the chemosensory unit

Within the carotid body, the actual sensing is performed by clusters of neuron-like cells called glomus cells, or type I cells, which are electrically excitable, richly innervated by afferent sinus-nerve fibres, and packed with dense-core vesicles containing dopamine and other neurotransmitters. These cells are wrapped by glia-like sustentacular (type II) cells, whose precise functional contribution is still being worked out, but the type I glomus cell is where the oxygen-sensing machinery this review discusses actually resides. When arterial oxygen falls, glomus cells depolarise, open voltage-gated calcium channels, and release neurotransmitter onto the afferent nerve terminals that synapse with them, which in turn signal to the brainstem respiratory centres to drive hyperventilation and a rise in sympathetic tone (López-Barneo et al., 2008).

Glomus cells share a developmental origin with a rather more familiar structure: both arise embryologically from neural crest cells, placing them in the same broad lineage as the chromaffin cells of the adrenal medulla, with which they also share a good deal of their secretory machinery, including calcium-triggered dense-core vesicle exocytosis and, in many species, catecholamine synthesis. This shared ancestry is more than a developmental footnote; it likely explains why chromaffin cells themselves also display a degree of acute oxygen sensitivity, particularly around the time of birth, when the sudden transition from the relatively hypoxic intrauterine environment to room air appears to trigger chromaffin-cell catecholamine release through mechanisms with clear family resemblance to the carotid body pathway described here, even though the adrenal medulla is not usually thought of as a chemoreceptor organ in the adult.

2.3. The 1988 discovery and the birth of the membrane model

The specific finding that made all of this mechanistically tractable was that the depolarisation glomus cells undergo during hypoxia is driven, at least initially, by inhibition of a potassium conductance in the cell membrane itself, discovered directly in isolated cells using patch-clamp recording (López-Barneo et al., 1988). This gave rise to what has become known as the “membrane model” of chemotransduction: hypoxia closes an oxygen-sensitive potassium channel, reduced potassium efflux depolarises the membrane, depolarisation opens voltage-gated calcium channels, calcium influx triggers vesicle fusion, and neurotransmitter release activates the afferent nerve. Each step in that chain is now well supported experimentally and represents about as close to a consensus mechanism as this field offers. The genuinely contested part, as later sections make clear, is what actually causes the channel to close in the first place.



Figure 1: The classical “membrane model” of acute hypoxic chemotransduction in the carotid body

2.4. How we know what we know: methodological approaches in this field

Because so much of this review rests on claims about single-channel and whole-cell electrical behaviour, it is worth pausing briefly on the experimental tools that made this knowledge possible, not least because the strengths and limitations of these tools go a long way toward explaining why the field still disagrees on some fundamental points. The workhorse technique throughout has been patch-clamp electrophysiology in its various configurations: whole-cell recording, which reports the summed activity of all channels in a cell's membrane and was the configuration used in the original 1988 discovery; and excised patch recording, in which a small patch of membrane is physically pulled away from the rest of the cell, either right-side-out or inside-out, allowing experimenters to apply hypoxic solutions directly to one or the other face of the isolated membrane and ask whether the channel itself, stripped of its normal cytoplasmic context, still responds to oxygen.

Genetically modified animal models, particularly mice with global or tissue-specific deletion of individual candidate genes (specific KV pore-forming subunits, TASK channel genes, or components of the HO-2/CSE gasotransmitter pathway), have supplied much of the more recent evidence and represent a meaningful advance over the pharmacological channel blockers used in earlier decades, which were frequently criticised for incomplete selectivity. More recently still, genetically encoded fluorescent redox and calcium indicators, engineered to localise specifically to the mitochondrial matrix, the intermembrane space, or the cytosol, have allowed researchers to ask not just whether a hypoxic redox signal exists, but precisely where within the cell it originates, a level of subcellular resolution that was simply unavailable to the field's earlier chemiluminescence-based assays and that has itself become central to the redox controversy detailed in Section 6.

3. Potassium Channel Subtypes Implicated in O₂ Sensing

3.1. Voltage-gated K⁺ (KV) channels

Voltage-gated potassium (KV) channels were among the first candidates proposed, given that the original 1988 current was itself voltage-dependent, and various KV subtypes, particularly those in the KV3.3/KV4 and Shaker-related families depending on species and preparation, have since been shown to lose activity under hypoxic conditions in carotid body and pulmonary vascular tissue alike (Rocher & Aaronson, 2024). In pulmonary artery smooth muscle specifically, Kv2.1 (encoded by the gene KCNB1) has attracted particular attention as a redox-sensitive target, discussed further in Section 6, in part because its cytoplasmic regulatory domain contains cysteine residues whose oxidation state is plausibly altered by the very redox signals both competing theories propose, even though the two theories disagree about which direction that oxidation state moves.

3.2. Calcium-activated K⁺ (BKCa) channels

Large-conductance calcium-activated potassium (BKCa, encoded by KCNMA1) channels represent a second major candidate, and an early and influential study found that hypoxia selectively suppressed the calcium-activated potassium current in type I carotid body cells, while leaving other potassium currents comparatively unaffected in that particular preparation (Peers, 1990). BKCa channels are attractive candidates on more than purely electrophysiological grounds: because their gating is intrinsically sensitive to both membrane voltage and intracellular calcium, they sit at a natural convergence point for several of the signalling pathways discussed later in this review, making them a plausible common downstream effector even if the upstream hypoxia-sensing step differs between tissues. The alpha subunit encoded by KCNMA1 can also associate with a range of tissue-specific accessory beta and gamma subunits, and there is evidence that the particular accessory subunit complement expressed in a given tissue meaningfully shapes that tissue's oxygen sensitivity, offering one more plausible source of the species and tissue variability discussed in Section 3.4.

3.3. TASK (K2P background) channels

A third and mechanistically distinct family, the two-pore-domain “background” or “leak” channels,

particularly TASK-like currents, was identified somewhat later and behaves rather differently from the voltage-gated and calcium-activated channels discussed above. Because these channels conduct current across essentially the entire physiological voltage range rather than only upon depolarisation, their inhibition by hypoxia directly and continuously depolarises the resting membrane potential, rather than merely shaping the cell's response to an already-initiated depolarisation. A pH-and-oxygen-sensitive background potassium current with these characteristics was described directly in rat carotid body type I cells (Buckler, 1997), and TASK channels have since become a strong candidate for at least part of the resting oxygen sensitivity of these cells, with the additional appeal that they are also independently sensitive to the lactate-driven acidosis that accompanies hypoxic metabolism, discussed further in Section 5.4.

3.4. Species and preparation variability: why the field keeps disagreeing

One of the most persistent sources of confusion in this literature, and one the anniversary review under discussion is admirably candid about, is that the specific channel identified as “the” oxygen sensor varies considerably between species, between developmental stages of the same species, and even between different laboratories studying what is nominally the same preparation (Rocher & Aaronson, 2024). Rather than reflecting sloppy science, this variability probably reflects a genuine biological reality: several oxygen-sensitive channel types can coexist within the same chemoreceptor cell, and the full hypoxic response likely requires their combined, and somewhat redundant, action rather than depending on any single channel type acting alone. That is a scientifically satisfying resolution in principle, but it makes the job of definitively identifying “the” oxygen sensor considerably harder in practice, since a manipulation that only partially reduces the hypoxic response in one laboratory's preparation might fully abolish it in another's, depending on which channels that particular preparation happens to express.

Table 1: Major potassium channel families implicated in acute oxygen sensing

Channel family	Gating behaviour	Primary tissue evidence	Key supporting study
KV (voltage-gated)	Opens with depolarisation; hypoxia reduces current amplitude	Carotid body glomus cells; pulmonary artery smooth muscle (Kv2.1)	López-Barneo et al., 1988
BKCa (Ca ²⁺ -activated, large conductance)	Opens with depolarisation AND rising intracellular Ca ²⁺	Carotid body type I cells	Peers, 1990
TASK (two-pore K2P background)	Conducts across the full voltage range; sets resting potential	Carotid body type I cells	Buckler, 1997

4. The Membrane Model: Consensus and Its Limits

Taken together, the picture assembled across Sections 2 and 3 is genuinely well supported: hypoxia inhibits one or more potassium channel subtypes in the plasma membrane of the glomus cell, membrane

potential depolarises as a direct consequence, voltage-gated calcium channels open, and the resulting calcium influx triggers neurotransmitter release onto the afferent sinus nerve. This sequence has been demonstrated using excised membrane patches, meaning the channel itself, isolated from the

rest of the cell's cytoplasm and organelles, still responds to changes in oxygen tension applied directly to the patch — a finding that at first suggested the channel protein itself might be the primary oxygen sensor, requiring no intermediary signalling molecule at all.

It is worth dwelling for a moment on why the excised-patch result was, and remains, so influential. In a cell-attached or whole-cell recording, one can never entirely rule out the possibility that some diffusible cytoplasmic messenger, generated elsewhere in the cell, is what is actually reaching the channel and causing it to close; the channel's own behaviour is being observed, but its cellular context has not been removed. An inside-out excised patch changes this considerably: a small disc of membrane, together with whatever proteins happen to sit within a few nanometres of the channel itself, is physically pulled free of the rest of the cell and placed in a simple recording chamber, into which experimenters can perfuse solutions of precisely controlled and rapidly switchable oxygen tension. When channels in such patches still close in response to lowered oxygen, as they reproducibly have across multiple laboratories and multiple channel types, the most straightforward interpretation is that whatever machinery is required for oxygen sensing must be either intrinsic to the channel protein itself, or at most confined to a handful of very tightly and permanently associated accessory proteins that survive the excision process intact.

That finding, however, is also precisely where the trouble starts. If the channel senses oxygen directly, there ought to be a specific, identifiable oxygen-binding mechanism intrinsic to the channel protein, analogous to the way haemoglobin binds oxygen at a heme group. No such mechanism has been convincingly demonstrated for any of the candidate potassium channels despite considerable effort, and the fact that channel behaviour in excised patches can vary between preparations, and that the same channel type appears less oxygen-sensitive when studied in a different expression system, argues against a simple, universal, intrinsic oxygen-sensing mechanism residing in the channel protein itself. This observation is precisely what motivated the alternative family of models discussed in the next section: rather than the channel sensing oxygen directly, some upstream cellular process, most plausibly centred on the mitochondrion, might sense oxygen first and then relay that information to the channel through a diffusible intermediary.

One reasonable synthesis, and the position this review leans toward, is that the apparent contradiction between direct channel sensing and upstream mitochondrial sensing may be smaller than it first appears. A diffusible mitochondrial signal, provided it is small enough and generated close enough to the plasma membrane, could plausibly survive the patch-excision process well enough to still be present, at least transiently, within an inside-out patch, particularly if some of the relevant

signalling machinery, an associated enzyme or a tethered pool of a reactive small molecule, happens to remain physically attached to the excised membrane fragment. On this reading, excised-patch oxygen sensitivity would not necessarily prove the channel senses oxygen entirely on its own, only that whatever machinery it needs is unusually local and robust to physical excision, which is a considerably weaker and more easily reconciled claim than a channel possessing its own intrinsic oxygen-binding site.

5. The Mitochondrial Hypothesis: Oxygen Sensing Upstream of the Channel

5.1. The electron transport chain as a plausible oxygen sensor

Mitochondria are, in a sense, the most obvious place in the cell to look for an oxygen sensor, since the electron transport chain (ETC) is the one place where molecular oxygen is actually consumed as the terminal electron acceptor. The mitochondrial hypothesis proposes that falling oxygen tension slows electron flow through the ETC, and that this slowing itself generates one or more diffusible signals, changes in ATP production, in the NADH/NAD⁺ ratio, in lactate accumulation, and in reactive oxygen species (ROS) production, any or all of which could then act on the potassium channels described in Section 3 (Rocher & Aaronson, 2024). This reframes the central question of the field: instead of asking how a potassium channel senses oxygen, it asks how the mitochondrion senses oxygen, and then how that mitochondrial signal is relayed to the channel.

A genuinely striking recent piece of evidence in favour of the mitochondrion itself as the primary sensor comes from work showing that carotid body glomus cells express atypical, tissue-specific subunits of cytochrome c oxidase (Complex IV), the terminal enzyme of the electron transport chain, and that expression of these atypical subunits is itself regulated by the chronic hypoxia-sensing transcription factor HIF2 α (Moreno-Dominguez et al., 2020). This finding is conceptually important because it suggests that the acute, second-to-second oxygen-sensing system discussed throughout this review and the slower, transcription-dependent HIF system introduced in Section 1.2 are not entirely independent after all; HIF2 α appears to help configure the very mitochondrial machinery that the acute system then relies on, effectively tuning the sensitivity of the fast pathway using the slow pathway's own transcriptional output. If this proves to be a general phenomenon rather than a carotid-body-specific curiosity, it would offer a satisfying, if still incomplete, bridge between the two oxygen-sensing systems this review deliberately separated in its opening section.

5.2. AMPK, falling ATP, and rising AMP

One well-studied downstream consequence of slowed mitochondrial ATP synthesis is activation of AMP-activated protein kinase (AMPK), the cell's central energy-sensing enzyme, which is switched on

as the AMP-to-ATP ratio rises. Direct evidence links AMPK activation to hypoxic signalling in oxygen-sensing cells: pharmacological and genetic manipulation of AMPK activity was shown to modulate the calcium responses these cells generate in response to mitochondrial inhibition, supporting a role for AMPK as an intermediary linking slowed oxidative phosphorylation to downstream channel or effector modulation (Evans et al., 2005). AMPK is an attractive candidate precisely because it sits downstream of virtually any manipulation that impairs oxidative phosphorylation, which makes it mechanistically economical, though this same property makes it harder to establish AMPK as specifically an oxygen sensor rather than simply a general energy-stress responder that happens to be activated during hypoxia along with several other pathways.

5.3. Gasotransmitters: carbon monoxide and hydrogen sulphide

A rather different, and in some ways more elegant, proposed mechanism involves two gaseous signalling molecules acting in opposition to one another. Under normoxic conditions, the enzyme heme oxygenase-2 (HO-2) continuously generates carbon monoxide (CO), which activates protein kinase G and, through that pathway, restrains the activity of cystathionine- γ -lyase (CSE), the principal enzyme producing hydrogen sulphide (H₂S) in these cells. Hypoxia is proposed to inhibit HO-2 activity, lowering local CO production; with less CO available to restrain it, CSE activity rises, local H₂S concentration increases, and H₂S itself is thought to inhibit the same potassium channels already implicated in the membrane model (Rocher & Aaronson, 2024). This HO-2/CSE axis is appealing because it offers a genuinely graded, concentration-dependent signal, rather than an all-or-nothing switch, and because both CO and H₂S are well-established biological signalling gases with independently documented effects on ion channel gating in other physiological contexts.

5.4. Metabolite sensing: lactate, acidosis, and Olfr78

A slowed electron transport chain also means glycolysis has to pick up more of the cell's energy demand, and the resulting rise in lactate production, along with the accompanying fall in local pH, provides yet another potential hypoxia signal. Lactate and acidosis are proposed to act at least partly through Olfr78, an olfactory-family receptor unexpectedly expressed in carotid body glomus cells, and this metabolite-driven signal appears to specifically potentiate the inhibition of TASK-family background channels, adding an acid-sensing dimension to the oxygen-sensing story that is mechanistically distinct from, but likely synergistic with, the more direct oxygen-dependent pathways discussed above (Rocher & Aaronson, 2024).

6. The Redox Controversy: Does Hypoxia Increase or Decrease ROS?

6.1. The Redox Theory

Perhaps the single most contentious question in this entire field, and the one this review devotes the most space to because it exemplifies just how unsettled supposedly basic mechanistic details can remain even after decades of dedicated study, concerns the direction of change in mitochondrial reactive oxygen species during hypoxia. One influential school of thought, associated principally with Stephen Archer, E. Kenneth Weir, and Evangelos Michelakis, proposes what has become known as the Redox Theory: that hypoxia actually reduces mitochondrial ROS production and shifts the cytosol toward a more chemically reduced state, and that this reduction specifically alters redox-sensitive thiol (cysteine) groups on the regulatory subunits of KV channels, particularly Kv2.1, causing them to close (Weir & Archer, 1995). Supporting evidence for this view has come from chemiluminescence measurements in whole perfused lungs and in isolated pulmonary artery rings showing decreased ROS output during hypoxia, and from work demonstrating that mitochondrial function itself differs systematically between vascular beds in ways that track their oxygen-sensing behaviour (Michelakis et al., 2002). The logic underpinning this model is worth spelling out a little further, because it is genuinely elegant on its own terms. Under normal, well-oxygenated conditions, a small but steady trickle of electrons leaks from the electron transport chain to generate a baseline level of ROS, which the Redox Theory proposes keeps relevant cysteine residues on the channel in a mildly oxidised, and therefore channel-open, state. As oxygen becomes scarce, electron flow through the chain slows overall, and with it, the theory proposes, so does this baseline ROS leak; the cysteine residues drift toward a more reduced chemical state as a direct consequence, and it is specifically this shift toward reduction, not oxidation, that the model holds responsible for closing the channel. Michelakis and colleagues extended this logic further by comparing mitochondria isolated from different vascular beds, and reported that pulmonary artery mitochondria, which come from oxygen-sensitive tissue, behaved electrochemically differently from mitochondria isolated from systemic (non-oxygen-sensing) arteries in ways broadly consistent with the Redox Theory's predictions, offering a tissue-comparative line of evidence alongside the more direct pharmacological and chemiluminescence data (Michelakis et al., 2002).

6.2. The Mitochondrial ROS Theory

A directly opposing school, associated principally with Paul Schumacher and Gregory Waypa, proposes essentially the reverse: that hypoxia paradoxically increases mitochondrial ROS generation, specifically superoxide released from Complex III at the outer, cytosol-facing (Qo) site of the electron transport chain, and that this superoxide, rapidly converted to hydrogen peroxide, diffuses into the cytosol where it oxidatively modifies the same, or functionally related, thiol-sensitive targets proposed by the Redox Theory, but produces the opposite (oxidising, rather

than reducing) chemical signal (Waypa et al., 2001; Waypa et al., 2002). Using genetically encoded, compartment-targeted redox sensors capable of distinguishing signals in the cytosol from those confined to the mitochondrial matrix or intermembrane space, this group has reported that hypoxia reproducibly increases oxidant signal specifically in the cytosolic and intermembrane-space compartments of pulmonary artery smooth muscle cells, a pattern they argue is inconsistent with the global reduction in ROS proposed by the opposing model (Waypa et al., 2010).

6.3. Why the disagreement has persisted, and why it matters

It would be tidy to report that one side has since been vindicated, but that is not really an honest description of where the field currently stands; both camps have continued to publish supporting data for their respective positions using different measurement techniques, different antioxidant and mitochondrial-inhibitor tools, and, in some cases, different cell preparations, and each side has raised legitimate methodological objections to the other's measurement approach (Waypa & Schumacker, 2005). One especially candid assessment published under the pointed title “Mechanisms of hypoxic pulmonary vasoconstriction: can anyone be right?” surveyed the by-then already substantial list of competing proposals and concluded that the honest answer might be that several partially correct mechanisms coexist, rather than any single model being wholly right while all its rivals are wholly wrong (Ward & Aaronson, 1999) — a conclusion this

review's own reading of the subsequent quarter-century of evidence tends to support. Part of the difficulty is technical: chemiluminescence-based ROS assays, used heavily in the earlier redox-theory literature, are now recognised to have real limitations in specificity and sensitivity, while the more recent genetically encoded redox sensors, though more specific, report a signal from wherever the sensor happens to be targeted, and results can differ depending on that subcellular targeting. This is not a trivial academic squabble: because the redox theory and the mitochondrial ROS theory predict opposite pharmacological interventions, antioxidant therapy should, in principle, worsen the ROS-driven contraction in one model while having no effect, or even the opposite effect, in the other, resolving this question has direct implications for whether antioxidant or pro-oxidant strategies would be rational therapeutic approaches to pulmonary hypertension, discussed further in Section 9.

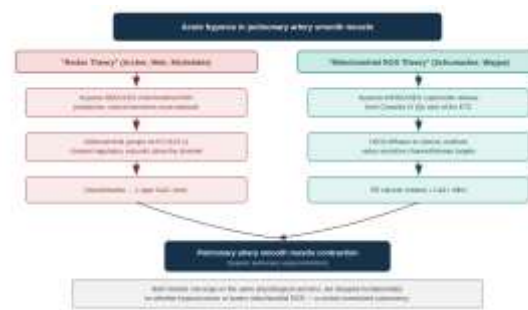


Figure 2: Two competing, still-unreconciled models of mitochondrial redox oxygen sensing

Table 2: The Redox Theory versus the Mitochondrial ROS Theory

Feature	Redox Theory	Mitochondrial ROS Theory
Proposed direction of ROS change with hypoxia	Decrease	Increase
Proposed cytosolic redox state	More reduced	More oxidised
Principal proponents	Archer, Weir, Michelakis	Schumacker, Waypa
Key measurement method	Chemiluminescence (lucigenin/luminol)	Genetically encoded, compartment-targeted redox sensors (RoGFP)
Proposed channel target	KV (Kv2.1) thiol groups	Same/related thiol-sensitive targets, opposite chemical direction
Representative citation	Weir & Archer, 1995	Waypa et al., 2010

7. Hypoxic Pulmonary Vasoconstriction: The Same Principles, a Different Organ

7.1. Physiological role of HPV

Hypoxic pulmonary vasoconstriction (HPV) is, in a sense, physiological logic running in reverse compared with most of the rest of the vascular system: whereas systemic arterioles typically dilate in response to local hypoxia to bring more blood to a starved tissue, pulmonary arterioles do the opposite, constricting in regions of the lung that are poorly ventilated. The physiological rationale is sound: there is no benefit in perfusing an alveolus that has little oxygen to offer, and diverting blood flow toward better-ventilated regions of the lung improves overall ventilation-perfusion matching and arterial

oxygenation. This reflex is intrinsic to the pulmonary vasculature itself, persisting even in isolated, denervated lung preparations, which points to a mechanism residing locally within the pulmonary artery smooth muscle cell (PASMC) rather than depending on any central nervous system input.

The response also unfolds over a genuinely biphasic time course that is worth understanding in its own right, since it hints at more than one underlying mechanism operating on different timescales. An acute phase of vasoconstriction develops within seconds to a few minutes of the onset of alveolar hypoxia and is generally attributed to the direct potassium-channel-mediated mechanism this review has focused on throughout. If the hypoxic stimulus

persists, however, a second, more sustained phase of vasoconstriction develops over the following one to two hours, is more resistant to washout, and is thought to involve additional contributions from the vascular endothelium and from calcium-sensitisation pathways within the smooth muscle itself, rather than being explained solely by the initial channel-closure event (Sommer et al., 2016). Left running for weeks to months rather than hours, the same stimulus drives a third, structural phase, vascular remodelling with smooth muscle hypertrophy and eventual fixed pulmonary hypertension, which is the clinically important, and largely irreversible, end point discussed further in Section 9.1.

7.2. The same debate, restaged in a different cell type

Remarkably, essentially the entire mechanistic argument described in Sections 3 through 6 for the carotid body reappears, largely unchanged, in the pulmonary vasculature literature. PSMCs express oxygen-sensitive KV channels whose inhibition during hypoxia depolarises the cell and opens voltage-gated calcium channels, closely paralleling the membrane model described for glomus cells (Rocher & Aaronson, 2024). And the same redox controversy described in Section 6 was, in fact, largely fought out using pulmonary artery preparations in the first place; the Redox Theory and the Mitochondrial ROS Theory are both, at their core, theories about PASM oxygen sensing, with their implications subsequently extended to the carotid body and other oxygen-sensitive tissues rather than the reverse.

7.3. An integrated, multi-pathway view

Rather than treating the AMPK pathway, the two competing redox theories, the gasotransmitter axis, and metabolite sensing as mutually exclusive competitors for the title of “the” oxygen-sensing mechanism, current thinking increasingly favours a more pluralistic view: several of these pathways probably operate in parallel within the same PASM, converging on the shared endpoint of potassium channel closure, with their relative contributions likely varying by vascular segment, by species, and by whether the hypoxic exposure is acute or sustained (Rocher & Aaronson, 2024). This is a less satisfying answer than a single, clean mechanism would be, but it is probably the more honest one, and it mirrors the same channel-diversity argument already made for the carotid body in Section 3.4.



Figure 3: Multiple, non-mutually-exclusive signalling pathways proposed to link hypoxia to K⁺ channel closure in pulmonary artery smooth muscle cells

8. A Brief Comparative and Evolutionary Detour

It is easy, having spent this much of a review discussing mammalian carotid bodies and pulmonary arteries, to assume that oxygen-sensitive potassium channels are a peculiarly mammalian, or even peculiarly medical, curiosity. They are not. Hypoxic pulmonary vasoconstriction itself, first documented by von Euler and Liljestrand in the cat, has since been shown to occur, at least partially, in reptiles and quite possibly in fish as well, suggesting the underlying reflex predates the mammalian lineage by a considerable margin. More strikingly, aquatic vertebrates possess their own, independently studied version of the entire acute oxygen-sensing story described in Sections 2 through 4, located not in a carotid body but in specialised neuroepithelial cells (NECs) scattered through the gill epithelium.

Zebrafish gill NECs are morphologically similar to mammalian carotid body glomus cells, and elegant patch-clamp work has shown that they too respond to hypoxia through inhibition of a background potassium conductance, membrane depolarisation, a rise in intracellular calcium, and subsequent neurotransmitter release driving the fish's ventilatory response (Jonz et al., 2004). Given that fish and mammals diverged from a common ancestor several hundred million years ago, the fact that both lineages independently arrived at, or more likely both inherited and separately refined, such a similar cellular strategy, a background or voltage-gated potassium channel whose direct inhibition by hypoxia drives depolarisation-triggered neurosecretion, is a striking illustration of just how fundamental and evolutionarily conserved this sensing mechanism appears to be. It also offers working physiologists a genuinely useful comparative model system: zebrafish gill preparations are considerably more experimentally tractable for certain genetic manipulations than mammalian carotid body tissue, and findings from this simpler system have repeatedly informed, and been informed by, the mammalian literature this review has focused on throughout.

9. Clinical and Translational Relevance

It would be easy for a review this focused on unresolved cellular mechanism to leave the

impression that this is a purely academic argument with little bearing on patient care. That impression would be a mistake. The same oxygen-sensing machinery this review has spent eight sections dissecting sits directly upstream of several genuinely common and genuinely serious clinical problems, spanning the full range of a human lifespan from the first breaths after birth to the chronic respiratory disease of old age, and the sections that follow are intended to make that clinical relevance concrete rather than merely gestured at.

9.1. Chronic hypoxia and pulmonary hypertension

While acute HPV is protective, redirecting blood flow sensibly within a single breathing cycle, sustained hypoxia, as occurs in chronic obstructive pulmonary disease, chronic exposure to high altitude, or obstructive sleep apnoea, drives the same underlying pathways toward a maladaptive outcome: chronic vasoconstriction contributes to vascular remodelling, and over months to years this can progress to pulmonary hypertension and eventually right heart strain. Because the acute signalling pathways described in Sections 5 and 6 are thought to also initiate the chronic remodelling response, resolving the redox controversy in particular carries direct therapeutic weight: if the mitochondrial ROS theory is correct, targeted antioxidant strategies would be a rational avenue for limiting pathological pulmonary vascular remodelling, whereas the redox theory would predict a very different, and in some respects opposite, therapeutic strategy.

9.2. High-altitude adaptation and maladaptation

Populations with many generations of high-altitude ancestry, most extensively studied in Tibetan and Andean populations, show blunted hypoxic ventilatory and vasoconstrictive responses compared with recent lowland migrants to altitude, an adaptation that appears to trade a smaller acute response for lower long-term pulmonary vascular strain. Because the carotid body and PASMC signalling pathways discussed throughout this review are the proximate machinery underlying both the ventilatory and vasoconstrictive responses to altitude, they represent a plausible, though not yet fully characterised, site of evolutionary adaptation, and lowland visitors who fail to acclimatise adequately remain at risk of high-altitude pulmonary oedema, a condition in which exaggerated, patchy HPV is thought to play a central pathophysiological role.

9.3. Carotid body tumours and dysregulated chemoreception

Carotid body paragangliomas, though rare, are tumours arising directly from the glomus cells discussed throughout Section 2, and some are associated with germline mutations in succinate dehydrogenase (SDH) subunit genes, part of the same mitochondrial electron transport chain machinery implicated in the mitochondrial hypothesis of oxygen sensing. This connection is more than incidental: SDH mutations impair Complex II function, and the resulting disruption of normal mitochondrial

signalling is thought to contribute to both the pseudohypoxic cellular phenotype and the abnormal proliferative signalling seen in these tumours, linking a rare oncological condition directly back to the basic oxygen-sensing physiology this review has described.

9.4. Sleep-disordered breathing and chemoreceptor sensitivity

Carotid body chemosensitivity is not a fixed property but can itself be altered by disease, and there is longstanding interest in whether abnormally heightened chemoreceptor sensitivity contributes to the unstable breathing pattern seen in some forms of sleep apnoea and in heart failure-associated periodic breathing, potentially through some of the same pathways, particularly gasotransmitter and mitochondrial signalling, discussed in Section 5. This remains an active area of investigation rather than settled fact, but it illustrates how directly the basic cell physiology covered in this review connects to genuinely common clinical problems, well beyond the specialised research settings in which the underlying mechanisms were first described.

9.5. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) provides perhaps the most common real-world setting in which the mechanisms discussed throughout this review actually matter to a working clinician. Regional hypoxia downstream of destroyed or poorly ventilated lung units triggers the same hypoxic pulmonary vasoconstriction described in Section 7, but because so much lung tissue is typically affected in advanced disease, the reflex that is locally protective in a single hypoxic alveolus becomes globally maladaptive when it operates across large portions of both lungs simultaneously, contributing to the pulmonary hypertension that complicates a meaningful proportion of severe COPD cases and worsens their prognosis. Supplemental oxygen therapy, one of the few interventions consistently shown to extend survival in COPD patients with resting hypoxemia, almost certainly exerts at least part of its benefit by relieving exactly this chronic, pathological vasoconstrictive drive, which is a satisfying, if retrospective, piece of clinical validation for the basic cellular mechanisms this review has described.

9.6. Persistent pulmonary hypertension of the newborn

At the opposite end of the age spectrum from COPD, persistent pulmonary hypertension of the newborn (PPHN) offers another clinically important, if mechanistically distinct, illustration of this review's subject matter. Successful transition from the fetal to the neonatal circulation depends on pulmonary vascular resistance falling sharply within the first few breaths of life, a process that depends heavily on the same oxygen-sensitive vascular smooth muscle machinery discussed in Section 7, now running in reverse: rising, rather than falling, oxygen tension needs to open, rather than close, the relevant potassium channels to permit pulmonary

vasodilation. When this normal transition fails, pulmonary vascular resistance remains pathologically elevated after birth, blood is shunted away from the lungs, and the resulting hypoxemia can be severe and life-threatening, underscoring that the same molecular machinery this review has focused on for its role in acute hypoxic vasoconstriction is equally essential, in its normal, unimpaired state, for the single most important vascular transition of early postnatal life.

10. What We Still Do Not Know

10.1. Channel identity remains genuinely ambiguous

After thirty-five years, it is a fair and somewhat humbling summary to say that no single potassium channel has been unambiguously and universally established as “the” oxygen sensor in either the carotid body or the pulmonary vasculature. KV, BKCa, and TASK channels each have credible supporting evidence in at least some preparations, and the most defensible current position, as this review has tried to make clear, is that multiple channel types likely contribute in a tissue- and species-dependent combination, rather than a single channel accounting for the entire phenomenon (Rocher & Aaronson, 2024). A useful analogy might be drawn to early cardiac electrophysiology, where it eventually became clear that the cardiac action potential could not be explained by any single ion channel acting alone but instead required the coordinated, overlapping contributions of several distinct conductances; oxygen sensing in the carotid body and pulmonary vasculature may simply be a comparably multi-channel phenomenon that the field has been slower to fully accept, perhaps because the original, elegantly simple 1988 finding created an expectation of comparable simplicity in the eventual mechanistic explanation, an expectation that thirty-five years of subsequent work has not entirely borne out.

10.2. The redox controversy remains the field's most conspicuous unresolved question

Section 6 described this in detail, and it bears repeating here as a genuinely open problem rather than a settled one: two well-resourced, technically sophisticated research programmes have reached opposite conclusions about whether hypoxia raises or lowers mitochondrial ROS, using increasingly sophisticated tools on both sides, and the disagreement has persisted for over two decades. This is not a sign of poor science; if anything, it reflects how genuinely difficult it is to measure subcellular redox chemistry with the spatial and temporal precision this question demands, and a definitive resolution will likely require further advances in probe technology rather than simply more data collected with existing tools.

10.3. Reconciling in vitro elegance with in vivo complexity

Much of the mechanistic detail described in this review comes from reduced preparations, isolated cells, excised membrane patches, cultured PSMCs,

chosen precisely because they allow the kind of clean, controlled manipulation that reveals mechanism. But the intact carotid body and the intact pulmonary vasculature are considerably more complex than any of these reduced systems, involving paracrine signalling between cell types, blood flow-dependent effects, and systemic neurohumoral input that reduced preparations necessarily strip away. Translating mechanistic clarity gained in isolated cells back into a confident account of what actually happens in an intact, breathing organism remains an unfinished task.

10.4. From mechanism to therapeutics: a gap still to be closed

Finally, and perhaps most practically, none of the mechanistic richness catalogued in this review has yet translated into a widely used, mechanism-specific therapeutic for pulmonary hypertension or related conditions. Existing pulmonary hypertension therapies largely target downstream vascular tone (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin pathway agents) rather than the upstream oxygen-sensing machinery discussed throughout this review, and turning thirty-five years of careful cellular physiology into an upstream, mechanism-targeted therapy remains, honestly, a task for the future rather than an accomplishment of the past.

11. Future Directions

Several concrete next steps follow naturally from the open questions catalogued in Section 10. Further development and refinement of genetically encoded, subcellularly targeted redox and metabolite sensors, building on the RoGFP-based work already discussed, offers the most direct path toward finally resolving the redox controversy, since the disagreement increasingly appears to be a measurement problem as much as a biological one. Conditional, cell-type-specific genetic knockout approaches, removing individual candidate channels selectively from glomus cells or PSMCs in vivo, would help move the field beyond the pharmacological-blocker studies that have historically been vulnerable to off-target criticism. Comparative studies across the high-altitude-adapted human populations mentioned in Section 9.2 could offer a genuinely novel, evolutionarily informed window into which of the candidate pathways matter most under real physiological selection pressure, rather than under the artificial conditions of a laboratory hypoxic chamber. And, finally, closer collaboration between the basic cellular physiologists who have driven this field for thirty-five years and the clinical pulmonary hypertension and sleep medicine communities could help ensure that the next thirty-five years of this research programme produce not just deeper mechanistic understanding, but therapies that actually reach patients.

CONCLUSION

Thirty-five years after a single patch-clamp recording first showed that a potassium channel could be closed directly by low oxygen tension, the field it launched has grown into a rich, technically sophisticated, and genuinely still-contested area of cellular physiology. What is well established bears repeating: hypoxia inhibits one or more potassium channel subtypes in both carotid body glomus cells and pulmonary artery smooth muscle cells, this inhibition depolarises the cell membrane, and depolarisation triggers the calcium-dependent downstream events, neurotransmitter release in one tissue, contraction in the other, that produce the whole-organism physiological response. What remains unresolved is, if anything, more interesting: which channel, sensing what signal, generated by which upstream process, and reconciled through what final common mechanism. The persistence of the redox controversy in particular, argued out over two decades by two serious and well-equipped research programmes reaching opposite conclusions, is a useful reminder that physiology at the molecular level does not always yield tidy, textbook-ready answers on any convenient schedule. For a field this mature to still be having this argument is not a failure; it is a sign that the question was harder, and more worth asking properly, than it first appeared in 1988.

It is worth closing on a broader note about what this particular scientific story illustrates beyond its own subject matter. The oxygen-sensing potassium channel field has, at various points over thirty-five years, been driven by a beautifully simple founding observation, complicated by genuine biological redundancy across channel types, split by a legitimate and still-unresolved mechanistic disagreement between two serious research groups, enriched by comparative evidence from organisms as distantly related as zebrafish, and connected, sometimes unexpectedly, to clinical problems ranging from neonatal pulmonary hypertension to carotid body tumours. Few areas of physiology offer as clear a working illustration of how basic cellular research actually progresses: not through a single decisive experiment that settles every question at once, but through successive waves of technically improving evidence that narrow, without yet closing, the space of plausible mechanisms. Readers encountering this literature for the first time should take that as an invitation rather than a discouragement — there remains, thirty-five years on, genuine and tractable scientific work left to do here, and the next resolution of the redox controversy, or the next candidate channel, may well come from a laboratory reading exactly this kind of synthesis today.

REFERENCES

1. Buckler, K. J. (1997). A novel oxygen-sensitive potassium current in rat carotid body type I cells. *Journal of Physiology*, 498(Pt 3), 649–662.
2. Evans, A. M., Mustard, K. J., Wyatt, C. N., Peers, C., Dipp, M., Kumar, P., Kinnear, N. P., & Hardie, D. G. (2005). Does AMP-activated protein kinase couple inhibition of mitochondrial oxidative phosphorylation by hypoxia to calcium signaling in O₂-sensing cells? *Journal of Biological Chemistry*, 280(50), 41504–41511.
3. López-Barneo, J., López-López, J. R., Ureña, J., & González, C. (1988). Chemotransduction in the carotid body: K⁺ current modulated by PO₂ in type I chemoreceptor cells. *Science*, 241(4865), 580–582.
4. Jonz, M. G., Fearon, I. M., & Nurse, C. A. (2004). Neuroepithelial oxygen chemoreceptors of the zebrafish gill. *Journal of Physiology*, 560(Pt 3), 737–752.
5. López-Barneo, J., Ortega-Sáenz, P., Pardal, R., Pascual, A., & Piruat, J. I. (2008). Mechanisms of acute oxygen sensing by the carotid body: Lessons from genetically modified animals. *European Respiratory Journal*, 32(5), 1386–1398.
6. López-Barneo, J., Pardal, R., & Ortega-Sáenz, P. (2001). Cellular mechanisms of oxygen sensing. *Annual Review of Physiology*, 63, 259–287.
7. Michelakis, E. D., Hampl, V., Nsair, A., Wu, X., Harry, G., Haromy, A., Gurtu, R., & Archer, S. L. (2002). Diversity in mitochondrial function explains differences in vascular oxygen sensing. *Circulation Research*, 90(12), 1307–1315.
8. Moreno-Domínguez, A., Ortega-Sáenz, P., Gao, L., Colinas, O., García-Flores, P., Bonilla-Henao, V., Aragonés, J., Hüttemann, M., Grossman, L. I., Weissmann, N., Sommer, N., & López-Barneo, J. (2020). Acute O₂ sensing through HIF2 α -dependent expression of atypical cytochrome oxidase subunits in arterial chemoreceptors. *Science Signaling*, 13(625), eaay9452.
9. Peers, C. (1990). Hypoxic suppression of K⁺ currents in type I carotid body cells: Selective effect on the Ca²⁺-activated K⁺ current. *Neuroscience Letters*, 119(2), 253–256.
10. Rocher, A., & Aaronson, P. I. (2024). The thirty-fifth anniversary of K⁺ channels in O₂ sensing: What we know and what we don't know. *Oxygen*, 4(1), 53–89.
11. Semenza, G. L. (2012). Hypoxia-inducible factors in physiology and medicine. *Cell*, 148(3), 399–408.
12. Sommer, N., Strielkov, I., Pak, O., & Weissmann, N. (2016). Oxygen sensing and signal transduction in hypoxic pulmonary vasoconstriction. *European Respiratory Journal*, 47(1), 288–303.
13. von Euler, U. S., & Liljestrand, G. (1946). Observations on the pulmonary arterial blood pressure in the cat. *Acta Physiologica Scandinavica*, 12(4), 301–320.
14. Waypa, G. B., Chandel, N. S., & Schumacker, P. T. (2001). Model for hypoxic pulmonary vasoconstriction involving mitochondrial oxygen sensing. *Circulation Research*, 88(12), 1259–1266.
15. Waypa, G. B., Marks, J. D., Guzy, R., Mungai, P. T., Schriewer, J., Dokic, D., & Schumacker, P. T. (2010). Hypoxia triggers subcellular compartmental redox signaling in vascular smooth muscle cells. *Circulation Research*, 106(3), 526–535.
16. Waypa, G. B., Marks, J. D., Mack, M. M., Boriboun, C., Mungai, P. T., & Schumacker, P. T. (2002). Mitochondrial reactive oxygen species trigger calcium increases during hypoxia in pulmonary arterial myocytes. *Circulation Research*, 91(8), 719–726.
17. Waypa, G. B., & Schumacker, P. T. (2005). Hypoxic pulmonary vasoconstriction: Redox events in oxygen sensing. *Journal of Applied Physiology*, 98(1), 404–414.
18. Ward, J. P., & Aaronson, P. I. (1999). Mechanisms of hypoxic pulmonary vasoconstriction: Can anyone be right? *Respiration Physiology*, 115(3), 261–271.
19. Weir, E. K., & Archer, S. L. (1995). The mechanism of acute hypoxic pulmonary vasoconstriction: The tale of two channels. *FASEB Journal*, 9(2), 183–189.