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COMMENTARY

Oxygen is an essential gasotransmitter directly sensed via protein gasoreceptors

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Abstract

The current restrictive criteria for gasotransmitters exclude oxygen (O_2) as a gasotransmitter in vertebrates. In this manuscript, I propose a revision of gasotransmitter criteria to include O_2 *per se* as a signaling molecule and 'essential gasotransmitter' for vertebrates. This revision would enable us to search for protein-based O_2-binding sensors (gasoreceptors) in all cells in the brain or other tissues rather than specialized tissues such as the carotid body or gills. If microorganisms have protein-based O_2-binding sensors or gasoreceptors such as DosP or FixL or FNR with diverse signaling domains, then eukaryotic cells must also have O_2-binding sensors or gasoreceptors. Just as there are protein-based receptor(s) for nitric oxide (GUCY1A, GUCY1B, CLOCK, NR1D2) in cells of diverse tissues, it is reasonable to consider that there are protein-based receptors for O_2 in cells of diverse tissues as well. In mammals, O_2 must be acting as a gasotransmitter or gaseous signaling molecule via protein-based gasoreceptors such as androglobin that very likely mediate acute sensing of O_2. Accepting O_2 as an essential gasotransmitter will enable us to search for gasoreceptors not only for O_2 but also for other nonessential gasotransmitters such as hydrogen sulfide, ammonia, methane, and ethylene. It will also allow us to investigate the role of environment-derived metal ions in acute gas (or solute) sensing within and between organisms. Finally, accepting O_2 *per se* as a signaling molecule acting via gasoreceptors will open up the field of gasocrinology.

KEYWORDS
essential gasotransmitter, gasocrine, gasoreceptor, gasocrinology

In biochemistry textbooks, amino acids that are derived from the environment and that cannot be synthesized by cells are classified as essential amino acids.[1] However, according to current criteria for gasotransmitters, oxygen (O_2) is excluded as one of the gasotransmitters and is not even mentioned as a potential candidate for gasotransmitters.[2,3] Such a restrictive criterion has not been applied for the classification of essential amino acids. If we were to apply the same restrictive criterion used for gasotransmitters to amino acids, essential amino acids might not even be considered amino acids. They might instead be referred to by alternative names, such as "small amino molecules." I propose that for any organism whose cellular physiology, signaling, metabolism, or behavior requires gasotransmitters that they do not synthesize, such gasotransmitters must be considered as "essential gasotransmitters" or "essential gaseous signaling molecules" for those organisms. This approach would allow us to consider and investigate the role of O_2 and other environment-only-derived gases as essential gasotransmitters or signaling molecules.[2,3]

Another ongoing debate revolves around the general applicability of the term "gasotransmitters."[4,5] In my opinion, the use of different terms such as "gasotransmitters" (gaseous transmitter) or "gaseous

signaling molecules" tends to divide researchers rather than unite them. Ultimately, if there is a receptor involved, whether it is considered a transmitter or signaling molecule becomes less relevant. Therefore, it may be beneficial to agree on a unifying terminology such as "receptor" or "gasoreceptor" for gas- or gasotransmitter-sensing proteins that directly interact with gas (or solute).[6] Proteins whose structures can be altered depending on the interaction state with gasotransmitters or gaseous signaling molecules (directly or via cofactors such as heme or iron–sulfur cluster or metal ions) and trigger a cellular signaling event via its additional domains (e.g., histidine kinase or phosphodiesterase or guanylate cyclase or DNA binding or RNA binding or protease) are very likely gasoreceptors.[6-8] An example of such structural changes is the reported nitric oxide (NO)–cysteine interaction or the repositioning of the β H-NOX (heme nitric oxide/oxygen) protein domain, which can regulate soluble guanylate cyclase activity, an NO receptor or gasoreceptor.[9,10] For instance, oxytocin is a neuropeptide-based neurotransmitter.[11] Nevertheless, we have a unified terminology for oxytocin-sensing protein, which is a G-protein-coupled receptor, commonly referred to as an "oxytocin receptor." Both the neurotransmitter research community and the endocrinology research community consistently refer to the oxytocin-sensing protein as an oxytocin receptor. Even in nonvertebrate organisms, oxytocin orthologue–sensing proteins are referred to as receptors.[12] We don't see the neurotransmitter community referring to them as sensors and the endocrinology community referring to them as receptors. This unity has led to a comprehensive understanding of the identity and the role of oxytocin receptors and their orthologues in both non-mammalian and mammalian model organisms.[13] However, in the gasotransmitter versus gas-sensing research community, it appears that this unity is lacking.[7,14] The gasotransmitter community refers to the NO-sensing protein-soluble guanylate cyclase as a "receptor," whereas soluble guanylate cyclase involved in O_2 sensing in *Caenorhabditis elegans* is referred to as "O_2 sensor."[14,15] We could argue whether the lack of unity is an issue and whether it makes any difference to call a gas-sensing protein a sensor or a receptor. In my opinion, it matters, especially if it can unite researchers across diverse research fields, as the implications are about not only human health but also the loss of valuable resources due to incomplete scientific knowledge propagated by partial and biased scientific manuscripts that largely ignores knowledge from research on microorganisms. For instance, if there is a protein-based receptor for NO in cells, then there must also be a protein-based receptor for O_2 in cells. However, the majority of recent scientific literature on O_2-sensing mechanisms (on plants or mammals), including notable announcements such as the 2019 Nobel Prize award in the field of physiology or medicine, does not mention a protein-based receptor for O_2.[8,16-20] This scenario reminds me of Plato's allegory of the cave, and we are still tied down by the weight and prestige of such awards and scientific journals. If bacteria have O_2-sensing protein receptors such as DosP (direct sensor of O_2, an O_2-binding heme-based phosphodiesterase) or FixL* (truncated sensor protein FixL, an O_2-binding heme-based kinase), or FNR (fumarate and nitrate reductase, an O_2-binding iron–sulfur cluster-based transcriptional activator), then it is very likely that other organisms also possess O_2-binding protein receptors with diverse signaling domains and/or DNA-binding transcriptional factors.[21-23]

It is important to explicitly mention "protein-based receptors or gasoreceptors" for O_2 in literature reviews to enable the addition of O_2-binding protein-based receptors in Wikipedia page on O_2 sensing. This is essential for raising awareness about the role of O_2 receptors, not only among scientists but also among students who switch to nonlibrary-based sources of scientific information.[24] In both developed and developing countries, assignments to students are increasingly being completed using AI-based tools like ChatGPT, which also depend on information from Wikipedia pages.[25] Failing to acknowledge protein-based O_2-sensing receptors in literature reviews delays not only the dissemination of knowledge but also progression of the oxygen-sensing research field in vertebrates and plants.[25]

Another issue is the overlooked role of O_2 *per se* as a signaling molecule in vertebrates.[26,27] The majority of the O_2-based developmental and disease animal model studies focus on aerobic respiration, hypoxia, ROS (reactive oxygen species)–induced oxidative stress, or ROS as a signaling molecule.[17,28–30] However, O_2 *per se* also acts as a signaling molecule, as evidenced by the presence of O_2-sensing protein gasoreceptors with diverse functions in various organisms.[5,6,8,18] Despite evidence suggesting the signaling role of O_2, its lack of explicit classification as a gasotransmitter or even as a candidate gasotransmitter is perplexing.[2,3] This ambiguity hinders the challenge, validation, refutation, or further study of O_2's role in gasocrine signaling.[6] "A gasocrine signaling occurs when a gasotransmitter or gaseous signaling molecule can bind to a protein-based gasoreceptor (or sensor protein or chemoreceptor protein) in its molecular state (or as solute) and trigger a cellular signal or response."[6]

A systematic investigation of O_2 as a signaling molecule will facilitate the search for the identity and role of all O_2 gasoreceptors, similar to the research that identified soluble guanylate cyclase as one of the receptor for the mammalian nonessential gasotransmitter, NO.[9] In eukaryotic organisms, due to the importance of tightly regulated extracellular and intracellular O_2 levels, gasoreceptors for O_2 are likely expressed in nearly every cell that O_2 can diffuse into rather than being restricted to specialized tissues such as the carotid body.[31,32] In my opinion, O_2-binding proteins such as androglobin, known as a spermatogenesis-inducing factor, and whose expression appears not to be affected by hypoxia, are among the candidate gasoreceptors for O_2.[33,34] I also wonder if cytochrome C oxidase could serve as an O_2 gasoreceptor, considering cytochrome C oxidase assembly appears to be regulated by O_2 in yeast and isolated mitochondria.[35] This mechanism is reminiscent of the role of O_2 in FNR activity, a bacterial O_2 gasoreceptor or sensor, which is regulated by dimerization states due to direct O_2 binding.[22]

If we accept gasoreceptors for O_2 or O_2 as an essential gasotransmitter, then we must also reconsider gasoreceptor-focused experiments where O_2 has not been excluded as a ligand (Table 1). This includes experiments conducted primarily under conditions that did not test the effect of O_2.[36,37] For instance, NO/CO gasoreceptor-based circadian regulators such as Drosophila E75 (ecdysone-induced protein 75) and mammalian CLOCK (Clock Circadian Regulator) do

TABLE 1 List of essential and non-essential gasotransmitters and protein gasoreceptors that can sense such signaling molecules and trigger a cellular response.

Gasotransmitter type	Gasotransmitter molecule	Protein gasoreceptors (mammalian unless stated)
Essential	O_2	DosP (*E. coli*), FNR (*E. coli*), FixL* (*R. meliloti*), GCY-35 (*C. elegans*), ADGB?
	?	?
Non-essential	NO	GUCY1A2 , GUCY1A3, GUCY1B2, GUCY1B3, CLOCK, NR1D2, E75 (*D. melanogaster*)
	H_2S	? (VEGFR2?, CD36?)
	CO	CLOCK, NR1D2, E75 (*D. melanogaster*)
	CH_4	?
	C_2H_4	?
	NH_3	?
	?	?

not appear to function as O_2 gasoreceptor.[38-40] However, it remains unclear whether NO/CO gasoreceptor NR1D2 (nuclear receptor subfamily 1, group D, member 2, also known as REV-ERBβ) acts as a gasoreceptor for O_2 or not (personal communication with Stephen W. Ragsdale, University of Michigan, USA and Keith Pardee, University of Toronto, Canada).[36,37] Accepting O_2 as an essential gasotransmitter or essential gaseous signaling molecule and recognizing O_2-binding sensor proteins as protein gasoreceptors would unite diverse researchers across different research fields. This acceptance would enable us to explore the identity and role of gasoreceptors not only for O_2 but also for other gaseous signaling molecules or nonessential gasotransmitters such as H_2S (hydrogen sulfide), ammonia, methane, and ethylene in animals.[36,37,41-46] This approach would also facilitate consideration of the ethical implications of engineering cow's microbiome to produce altered levels of methane without a full understanding of the identity and the role of methane gasoreceptors.[47] Investigating the identity and role of gasoreceptors in gasocrine signaling will open up the field of gasocrinology, which encompasses not only gasocrine interactions within organisms but also between different organisms and/or man-made machine-derived gases.[48,49] It may also allow us to better understand the fundamental mechanisms and general principles underlying disease ontogeny, animal behavior, and to develop better drugs, or to better understand the reasons why drugs fail in clinical trials, or why cells would require environment-derived metal ions to sense gases, or if there are gases that can be sensed without the need for metal ions. Additionally, it could help us appreciate the need for animal model-based curiosity-driven basic science research to understand the role of gasocrine signaling in development, behavior, and disease ontology.[50] Finally, if O_2 is a gasocrine signaling molecule between organisms, then it is essential to identify all the factors that can intefere with O_2-mediated gasocrine signaling.[51] It is also essential to identify and investigate the role of all the other gasocrine signaling molecules within and between organisms acting via protein gasoreceptors.

AUTHOR CONTRIBUTIONS

Savani Anbalagan: conceptualization, writing of the original draft, and review and editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The author is the creator of the terms and concepts of 'gasoreceptor', 'gasocrine signaling' and 'gasocrinology'.

DISCLOSURES

The author employed ChatGPT for correcting the scientific English. The author takes full responsibility for the content of this manuscript.

ETHICS STATEMENT

Not applicable.

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