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H_2S, a gasotransmitter for oxygen sensing in carotid body. Focus on "Endogenous H_2S is required for hypoxic sensing by carotid body glomus cells"

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MANY, IF NOT ALL, TISSUES possess the ability to sense hypoxia, and most tissues respond to hypoxia by reducing energy expenditure as a form of self-preservation. The carotid body, however, rapidly responds to hypoxic conditions by initiating cardiorespiratory reflexes in order to increase ventilation and systemic delivery of oxygen rather than initiating mechanisms for local conservation. The carotid body is made up of two types of cells, neuron-like glomus (type 1 cells) and glia-like sustentacular (type II) cells. The glomus cells were identified as the chemoreceptive component of the carotid body nearly 40 years ago in a seminal study by Verna and colleagues (8). Since then, much of the research on the carotid body has been devoted to understanding how glomus cells sense hypoxia and identifying the molecular components of this process.

Following the identification of oxygen-sensitive K^+ channels in glomus cells (3), a model of carotid body responsiveness termed the "membrane hypothesis" was developed. Briefly, hypoxia leads to inhibition of K^+ channels, causing membrane depolarization, opening of voltage-dependent Ca^{2+} channels (VDCC), increasing cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$), and triggering the release of neurotransmitters (7, 8) (Fig. 1). While findings from most research groups agree with the basic process, there is some debate in the field as to the cascade of events leading to the inhibition of K^+ channels, specifically the identity of the "oxygen sensor."

In the current issue of *American Journal of Physiology-Cell Physiology*, Makarenko and colleagues (4) demonstrate that endogenous H_2S is required for hypoxic sensing by glomus cells. H_2S was first labeled a gasotransmitter in 2002 and has been demonstrated to be an important signaling molecule involved in a wide variety of biological effects (9). The majority of H_2S in mammalian tissues is produced by two enzymes, cystathionine γ-lyase (CSE) and cystathionine β-synthase (CBS) (9). Previous studies have demonstrated a role for H_2S in response to hypoxia, and the authors of the current study recently showed that genetic deletion of CSE is sufficient to disrupt the hypoxic response in the carotid body (2, 5, 6). In the current study, Makarenko et al. demonstrate that the glomus cells are the site for H_2S-dependent oxygen sensing in the carotid body (4). The authors demonstrate that the CSE is present in glomus cells and that inhibition of CSE in glomus cells blocks the hypoxia-induced increase in H_2S levels. Inhibition of CSE, either pharmacologically or genetically, also blocks hypoxia-induced secretion of catecholamine, but not high K^+-induced catecholamine secretion in glomus cells. Hypoxia induces an increase in $[Ca^{2+}]_{cyt}$ which the

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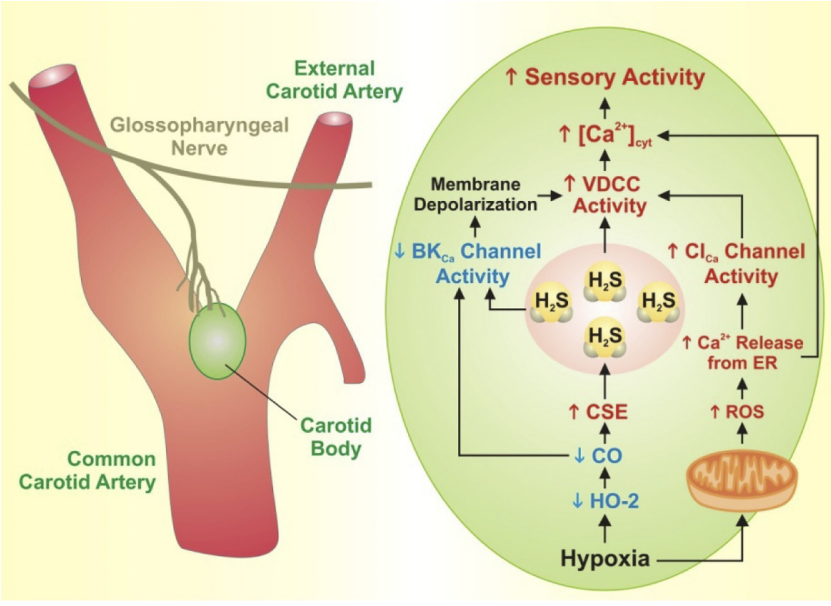

Fig. 1. Proposed mechanisms for hypoxia-mediated increase in sensory activity via H_2S. Under normoxic conditions, cystathionine-γ-lyase (CSE) is inhibited by carbon monoxide (CO) produced via heme oxygenase-2 (HO-2). Hypoxia increases H_2S in glomus cells due to increased activity of CSE as a result of decreased CO. Increased H_2S may directly activate voltage-dependent Ca^{2+} channels (VDCC) or indirectly activate VDCC by causing membrane depolarization via the decrease in the large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel activity. Since CO activates BK_{Ca} channels, decreased CO would lead to decreased BK_{Ca} channel activity and membrane depolarization. Activation of VDCC raises cytosolic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) in the glomus cells and increases the sensory activity. In addition, hypoxia-mediated mitochondrial production of reactive oxygen species (ROS) has been shown to mobilize Ca^{2+} from the endoplasmic reticulum (ER), which not only increases $[Ca^{2+}]_{cyt}$ but also activates the Ca^{2+}-activated Cl^- (Cl_{Ca}) channels and causes further membrane depolarization. The hypoxia-mediated increases in H_2S and ROS may work synergistically to induce membrane depolarization, increase $[Ca^{2+}]_{cyt}$, and eventually enhance the sensory activity.

authors show can be mimicked by addition of an H_2S donor and which is attenuated in $CSE^{-/-}$ glomus cells, demonstrating a role for H_2S in hypoxia-induced rise in $[Ca^{2+}]_{cyt}$ through L-type VDCC. Indeed, the broad spectrum VDCC blocker, Cd^{2+}, and the L-type VDCC specific blocker, nifedipine, both blocked the hypoxia- and H_2S-induced increase in $[Ca^{2+}]_{cyt}$.

The authors propose that H_2S generated by CSE mediates the hypoxic response of glomus cells in the following manner: Under normoxic conditions, hemeoxygenase-2 (HO-2) converts heme to carbon monoxide (CO), biliverdin, and Fe^{2+}. Previous studies demonstrated that CO generated by HO-2 tonically activates the large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels (10) and other types of K^+ channels. CO also suppresses H_2S production by inhibition of CSE. Hypoxia diminishes HO-2 production of CO, resulting in increased H_2S which can inhibit BK_{Ca} channels (2). This leads to membrane depolarization, opening of L-type Ca^{2+} channels, and increased sensory activity (Fig. 1).

Multiple mechanisms have been proposed to mediate oxygen sensing in the carotid body [such as HO-2/CO, AMP-activated protein kinase (AMPK), and mitochondrial reactive oxygen species (ROS)], with evidence presented to support each theory (1, 10). Given that the cardiorespiratory response to hypoxia is essential for survival, it seems possible that a combination of these theories may be involved in oxygen sensing by the carotid body (Fig. 1). The current study by Makarenko et al. provides compelling evidence that H_2S in glomus cells is another critical gasotransmitter required in oxygen sensing in carotid body.

Further studies are needed to define *1*) whether H_2S directly opens VDCC and, if so, which type of VDCC (e.g., L-, T-, N-, R-, and/or P/Q-type) is directly activated and which transmembrane domain and extracellular or intracellular loop of the channel are affected by H_2S; *2*) whether H_2S, in addition to directly activating BK_{Ca} channels, inhibits other types of K^+ channels (e.g., the intermediate- and small-conductance Ca^{2+}-activated K^+ channels, voltage-gated K^+ channels, two-pore domain K^+ channels, and/or inward-rectifier K^+ channels) and regulates other cation (e.g., Na^+- or Ca^{2+}-permeable) and anion (e.g., Cl^--permeable) channels in glomus cells; *3*) whether H_2S synergistically regulates the channel activity with other oxygen-sensing molecules or gasotransmitters, such as CO and nitric oxide; and *4*) whether H_2S-mediated effect on $[Ca^{2+}]_{cyt}$ in glomus cells is sensitive to the cellular redox status. The oxygen sensing in the carotid type I glomus cells must be a complicated process which may require precise coordination of many different sensors, receptors, and effectors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.A.S. and J.X.-J.Y. prepared the figure; drafted the manuscript; edited and revised the manuscript; approved the final version of the manuscript.

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