Hydrogen sulfide as a regulator of respiratory epithelial sodium transport: the role of sodium-potassium ATPase. Focus on “Hydrogen sulfide contributes to hypoxic inhibition of airway transepithelial sodium absorption”

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Central to the integrity of all organisms is the recognition of what is in (me) and what is out (not me). Many membrane-based activities are required to keep what is “me” differentiated and protected from what is “not me”. Recognition of this difference between inside and outside and the importance of the regulatory processes needed to maintain the internal environment of the cell and extracellular space at stable and nonequilibrium values was essential to Walter Cannon’s concept of homeostasis. Sodium-potassium ATPase (Na+/K+-ATPase) generates a nonequilibrium distribution of potassium and sodium across the cell membrane. This electrochemical gradient is used to power the transport or exchange of a large number of molecular homeostatic processes. In this issue of American Journal of Physiology—Regulatory, Integrative and Comparative Physiology, Krause et al. (7) eloquently show that endogenous production of the gasotransmitter, H2S, by airway epithelial cells significantly contributes to hypoxia-induced inhibition of epithelial sodium transport, specifically by inhibiting Na+/K+-ATPase activity.

Transepithelial sodium absorption in the respiratory tract is a crucial process for the maintenance of the volume and composition of epithelial lining fluid, and its disruption is associated with lung diseases, such as pulmonary edema (hypoaosorption) or cystic fibrosis (hyperabsorption). The mechanisms by which the epithelium can sense changes in oxygen and how they, in turn, lead to aberrant fluid movement continues to interest researchers in this field. H2S is produced by amino acid metabolism, but it is rapidly degraded to sulfate by mitochondria in the presence of oxygen. Under hypoxic conditions, H2S concentrations have the potential to act as physiologically significant endogenous concentrations of H2S that are capable of inhibiting basolateral sodium movement by Na+/K+-ATPase through an unknown mechanism, restricting the electrochemical driving force for apical sodium entry via ENaC, which may lead to impaired transepithelial sodium absorption.

Questions arising from this study are whether this is a direct interaction with the pump or an indirect inhibition, for example, via alteration of basolateral K+ channels (2, 3), and what the chemical basis for the observed effects of H2S is. Is H2S present in its gas form or (more likely) in its anionic form, H2S/HS−? H2S/HS− may target cysteine residues by persulfidation due to the addition of HS− to thiolate or a sulfenic group to differentially affect protein function (4). H2S also mediates its effects through interactions with another major gasotransmitter, nitric oxide (6), which the authors have previously shown can impair airway epithelial sodium reabsorption by interfering with the activity of the Na+/K+-ATPase (1).

What are the physiological concentrations of H2S? The concentration of H2S that can be generated in vivo remains a controversial subject compounded by inaccuracies in the methods applied to measuring H2S (10), but physiologically significant concentrations in the respiratory tract are only likely to occur under hypoxic conditions. In other tissues, the capacity to degrade H2S is quite large (8) (which seems appropriate, since H2S is toxic at higher concentrations), and so the suggestion by the authors that H2S may inhibit transepithelial sodium transport and increase the alveolar lining fluid to enhance mucociliary transport in the presence of infectious agents that produce H2S seems unlikely, unless hypoxia is also present to inhibit the degradation of H2S.

As noted above, the regulation of H2S is a little odd. Many signaling molecules are regulated at the level of production. The signaling molecule, the product, provides negative feedback and inhibits its own production. H2S, on the other hand, is produced in abundance (as shown so effectively by the authors when they inhibited the synthetic enzymes to block the effects of H2S), and regulated instead by oxygen-dependent degradation of H2S by mitochondria. It is interesting that hypoxia-inducible factor-1α (HIF-1α) is similarly regulated by degradation, and this degradation also originates from an oxygen-dependent process; hydroxylation of proline or asparagine within HIF-1α, which targets the protein for proteolytic degradation (12). This strategy is logical for hypoxic activation in any second messenger system in which oxygen is not required for second messenger production, but is required for degradation and is rate limiting by virtue of a relatively high Km for oxygen in one or more of the degradative enzymes. Circumstances that exist for both H2S and HIF-1α.

These findings raise the question: could H2S be considered as an oxygen sensor in the respiratory epithelium rather than simply an effector or mediator under hypoxic conditions? H2S...
may be considered an oxygen sensor through its inhibition of oxidative phosphorylation or due to the inverse metabolic relationship between oxygen availability and oxygen-dependent degradation of endogenous H$_2$S (9). This new role of H$_2$S as an oxygen sensor has already been discussed for a variety of tissues, including the carotid body (5, 11), but is likely to remain a somewhat controversial hypothesis for the respiratory epithelium due to the relatively limited data on H$_2$S in the lung. Moreover, there is no requirement for oxygen in the interaction of H$_2$S with its targets. It seems more appropriate to see the mitochondria and the initial oxygen-requiring step in the degradation of H$_2$S by the membrane-bound sulfide:quinone oxidoreductase as the sensor in alveolar epithelial cells and likely in the carotid body. Thus, the function of H$_2$S as a downstream effector of homeostatic regulation, which Krause et al. (7) have amply demonstrated for transepithelial sodium transport, may generate more interest for future research.

REFERENCES


