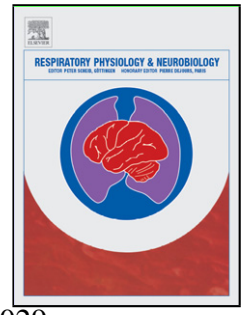


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# Fate of intracellular $H_2S/HS^-$ and metallo-proteins.

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Kenneth Olson has recently developed a theoretical model to predict how endogenously-generated intracellular molecules of $H_2S$ would diffuse within and outside the cells (Olson, 2013). Clarifying this question is of major interest since intracellular $H_2S$, which is mostly present under the form of its sulfhydric anion $HS^-$, has been hypothesized to be an important actor involved in the transduction of the response to hypoxia (Olson, 2011a).

One of the major implications of Olson's model, which suggests little, if any, diffusion outside the cytoplasm of endogenously-generated $H_2S$, is that studies supporting a physiological role for this gas, based on its determination in the extracellular milieu -blood for in-vivo experiments or "bath" for tissular or cellular preparations- should be considered with a high degree of skepticism. This notion corroborates results from previous studies (Furne et al., 2008; Whitfield et al., 2008) wherein major methodological pitfalls preventing accurate determination of $H_2S/HS^-$ in the extracellular milieu were identified, accounting for the unrealistic high (microM) baseline levels of sulfide in the blood and in tissues reported in the literature. Although attempts are being made to measure/visualize intracellular $H_2S/HS^-$ (Lin et al., 2013), theoretical models, such as the one proposed by Olson (Olson, 2013), represent an essential step in the development of a rational frame of reference aimed at predicting the fate of endogenous – or exogenous- $H_2S$.

Prediction of the changes in sulfide concentrations remains difficult: the amount, the rate, the site as well as the mechanisms of regulation of the "production" of $H_2S$ are far from being established or understood, while the "oxidative" properties of the mitochondria for this gas varies from tissue to tissue and possibly from cell to cell. $H_2S$ is also a very reactive molecule.

In the reducing milieu of the cytoplasm, sulfhydration of cysteine residues (Mustafa et al., 2009) may be limited, but the interactions of $H_2S$ with metallo-proteins are certainly quantitatively significant and pertinent to include into any prediction model. It is $H_2S$ reactivity with metal compounds, i.e. ferric iron (methemoglobin) (Haouzi et al., 2011a; Smith and Gosselin, 1966; Van de Louw and Haouzi, 2012) or oxidized cobalt (hydroxocobalamin) (Smith, 1969; Truong et al., 2007; Van de Louw and Haouzi, 2012), which has been offered as a rationale for developing antidotes against $H_2S$ poisoning. Similarly, Zn compounds have been used to decrease $H_2S$ in the colon (Suarez et al., 1998).

Intra-cytoplasmic and intra-mitochondrial metallo-proteins are as abundant (Dupont et al., 2006) as they are diverse (Karlin, 1993); actually, a large proportion of the pool of proteins present in a cell does contain metal compounds including Fe, Zn, Cu or Co at various levels of oxidation (Waldron et al., 2009). These molecules constitute a large sink in the mitochondria and the cytoplasm for the nM or pM concentrations of $H_2S$ produced in a cell. As a result, prediction of the kinetics or the changes in the amplitude of intracellular soluble $H_2S$ may prove to be quite challenging.

In addition to this "trapping effect", enhanced, reduced or even novel functions of metallo-proteins may emerge from the presence of metallo-sulfide. The long list of intracellular metallo-proteins potentially involved in the systemic response to hypoxia includes molecules ranging from myoglobin to some of the most fundamental components of the electron chain, from superoxide dismutase (Searcy et al., 1995) to carbonic anhydrase, and from angiotensin-converting enzyme (Laggner et al., 2007) to various heme proteins. It is, after all, through the combination of $H_2S/HS^-$ with the cytochrome C oxidase that the dreadful toxicity of $H_2S$ seems to operate (Dorman et al., 2002).

Incorporating all relevant factors potentially interacting with $H_2S$ in a cell is a real challenge, but the development of theoretical models providing realistic anticipation of the fate of $H_2S$ must be pursued to clarify the physiological effects of endogenous sulfide -if any- and, as cautioned by Olson, to separate hype from hope (Olson, 2011b).

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