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A NEW LOOK AT PHYSIOLOGIC RESPIRATORY RESPONSE TO H_2S POISONING

HARRIET M. AMMANN

U.S. EPA, Environmental Criteria and Assessment Office, MD52, Research Triangle Park, NC 27711 (U.S.A.)

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Summary

Ever since the role of the carotid bodies in controlling ventilation was elucidated by Heymans in 1932, researchers have puzzled over the seeming paradox presented by the action of hydrogen sulfide gas on the nervous system. The dominant effect is depression of function, but the neural receptors of the carotids appear to be stimulated, resulting in hyperpnea at sublethal exposures. This paper examines the effect in light of the known cellular mechanisms of H_2S poisoning, which inhibits the enzyme cytochrome oxidase, stopping oxidative metabolism. The argument is made that H_2S affects the carotid sensors in the same manner as reduced oxygen tension, thus resulting in increased rate and depth of ventilation.

Introduction

According to the National Institute for Occupational Safety and Health (NIOSH) of the U.S. (1977) [1], hydrogen sulfide is the leading cause of sudden death in the workplace. It is an acutely toxic gas used as a reagent and intermediate in the preparation of other reduced sulfur compounds. It is also a by-product of desulfurization processes in the oil and gas industries and such diverse pursuits as viscose rayon production, sewage treatment, and leather tanning.

The immediate effect of the inhalation of 1000—2000 ppm or more of the gas is respiratory paralysis after a breath or two, due to inhibition of the respiratory center of the brain [2, 3]. At concentrations of 500 to 1000 ppm, respiratory paralysis is preceded by a period of rapid breathing or hyperpnea, and death will result unless the victim is removed from exposure and artificially ventilated [2, 4—6].

At concentrations between 250 and 500 ppm, the gas is extremely irritating to the mucous membranes of the respiratory tract and the eyes. Pulmonary edema, which can be life-threatening, almost always occurs. Extended exposure to the gas at concentrations above 50 ppm can result in pulmonary edema, although dryness and inflammation of the epithelia of the entire respiratory tract are more common. The epithelia of the eye,

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especially of the conjunctiva and the cornea, are similarly affected, resulting in "sore eye" or "gas eye".

Only at relatively low concentrations not associated with significant damage except to the eyes, is the obnoxious, rotten egg-like odor of the gas, a warning of its presence. At levels above ~ 150 ppm the olfactory sense is lost, and pain from the irritant effect on the eyes stops as the poison anesthetizes the nerve endings in those mucous membranes. The effects of the gas on humans is summarized in Table 1.

TABLE 1

Effects of exposure to H_2S in humans at various concentrations in air

CLINICAL EFFECTS	H_2S CONCENTRATION, ppm
ODOR PERCEPTION THRESHOLD	0.1 -0.2
OFFENSIVE ODOR	3.0 -5.0
OCCUPATIONAL EXPOSURE LIMIT (O.E.L.)	10.0
SERIOUS EYE INJURY	50.0 -100.0
OLFACTORY PARALYSIS	150.0 -200.0
PULMONARY EDEMA, THREAT TO LIFE	300.0 -500.0
STRONG NERVOUS STIMULATION OF RESPIRATION	500.0 -1000.0
RESPIRATORY PARALYSIS, IMMEDIATE COLLAPSE, DEATH	1000.0 -2000.0

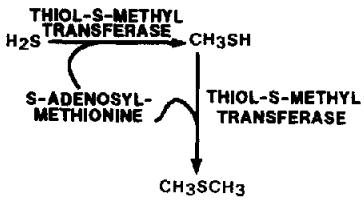
Hydrogen sulfide is not a cumulative poison since it is metabolized and excreted. There is insufficient evidence to conclude that direct permanent damage is caused through chronic exposure, although data are lacking to state unequivocally that such damage does not occur.

Discussion

Ever since Heymans et al. (1932) [5] elucidated the controlling role of the carotid bodies in the reflex governing ventilation, researchers have puzzled over the seeming paradox presented by the action of hydrogen sulfide on the nervous system. While the dominant effect is a depression of function manifested as a paralysis of ventilation and loss of a sense of smell, the neural receptors of the carotid and aortic bodies appear to be stimulated at concentrations between 500—1000 ppm. The resulting stimulation produces hyperpnea.

Resolution of this seeming functional contradiction requires a new look at the metabolism of hydrogen sulfide, together with its physiologic effect.

H_2S is metabolized along three general pathways which can be summarized as methylation, oxidation, and reaction with metallic ion or disulfide-containing proteins [7]. The methylation pathway is traced in Fig. 1, oxidation in Fig. 2. These two routes constitute detoxification processes for the poison [8, 9]. Oxidation results in sulfates which can be readily excreted by the kidney [9], and is the primary detoxification pathway.



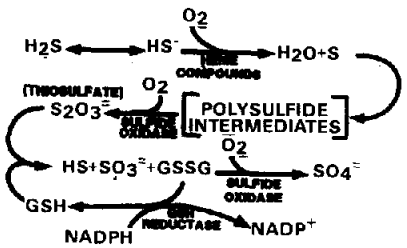


Fig. 1. Methylation pathway for H_2S detoxification.

Fig. 2. Oxidation pathway for H_2S detoxification.

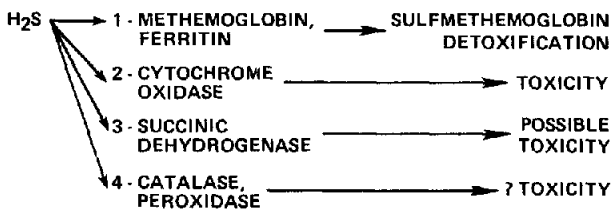


Fig. 3. Interaction of H_2S with metalloproteins.

Reaction with metal ion-containing protein is the primary route for toxicity of the H_2S [10] as seen in Fig. 3.

Many enzymes contain metal ions that react with hydrogen sulfide. Most significant among these is the intracellular mitochondrial enzyme cytochrome oxidase. This is the final enzyme of the mitochondrial respiratory chain, and transfers electrons and hydrogen ions to oxygen to form water. Without oxygen as the final electron acceptor, all electron transport down the chain is stopped, and oxidative metabolism, which is the primary energy source for mammalian cells, ceases. Work by Wever et al. (1975), Nicholls (1975), Nicholls et al. (1976), Petersen (1977), Smith et al. (1977), and Smith and Gosselin (1979) [10—15] showed that H_2S causes chemical reduction of one of the hemes of this enzyme, preventing electron transfer to oxygen. Chance and Schoener (1966) [16] found the action of hydrogen sulfide to be a more potent inhibition of cytochrome oxidase than that produced by hydrogen cyanide.

Tissues most sensitive to the action of this poison are those that have the highest oxygen demand: nervous and cardiac tissues. That the respiratory center of the brain is immediately paralized at concentrations above 1000 ppm is witness to this sensitivity.

More sensitive are the chemosensors which are associated with ventilatory control, which are located in the carotid bodies (at the bifurcation of the common carotid arteries carrying blood to the brain), and the aortic bodies in the aortic arch (see Fig. 4). They respond at concentrations of 500 ppm and greater.

Normally these chemosensors stimulate ventilation of the lungs in the extreme case when the partial pressure of oxygen in the arterial blood going to the head falls from 100 mmHg into the 30—60 mmHg range. When this occurs, the number of impulses from the chemosensors to the respiratory center in the medulla increases sharply (see Fig. 5).

As a result, the rate and depth of lung ventilation increases to the point of hyperpnea, or extemely rapid breathing (see Fig. 6).

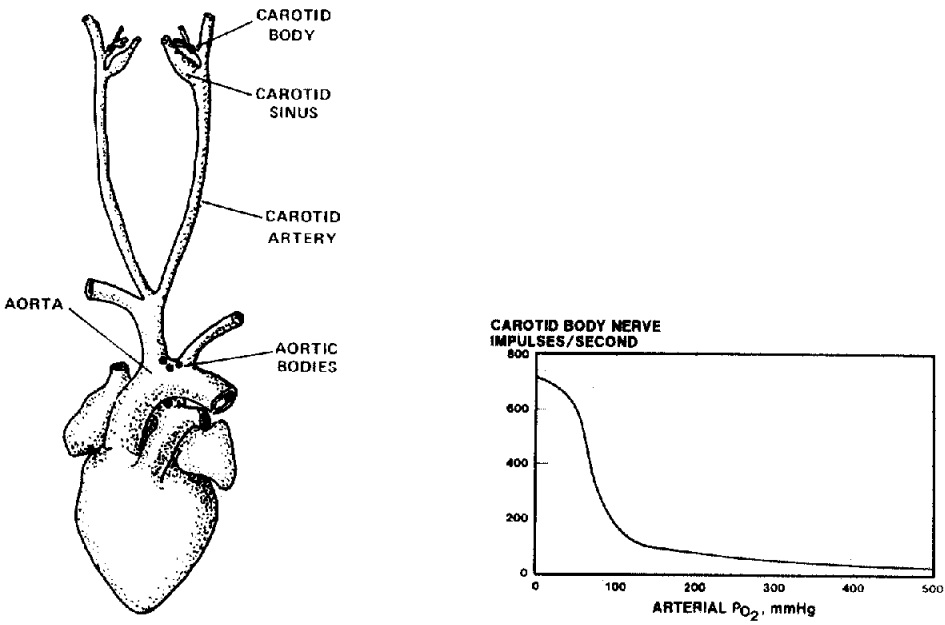


Fig. 4. Location of chemosensors sensitive to $p0_2$ in the carotid and aortic bodies.

Fig. 5. Effect of arterial $p0_2$ on impulse rate from the carotid body of a cat [17].

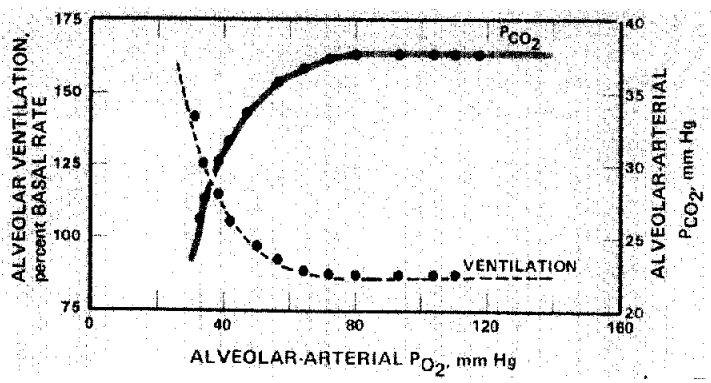


Fig. 6. Effect of arterial $p0_2$ on the alveolar ventilation (and on subsequent decrease in $p0_2$) [17].

One of the puzzling aspects of H_2S poisoning has been that hyperpnea occurs at sublethal doses of the gas. Hyperpnea indicates a stimulation of neural respiratory control tissue, yet the known mechanism of toxicity for H_2S is depression of function due to cessation of oxidative metabolism. Heymans (1932) showed that the chemosensors of the carotid and aortic bodies were involved in H_2S hyperpnea but neither he, nor others who elucidated the toxic mechanism of H_2S, have explained this seeming paradox.

The contention of this paper is that this paradox can be resolved if the effect of the halting of oxidative metabolism on the function of the carotid and aortic bodies is considered. The chemosensors have no mechanism for distinguishing decrease in oxygen concentration (decreased pO_2) from unavailability of oxygen due to inhibition of cytochrome oxidase by hydrogen sulfide. As hydrogen sulfide binds to cytochrome oxidase and inhibits it, electrons and hydrogen ions cannot be transferred to oxygen. To put this conversely, oxygen becomes unavailable as an oxidizing agent for the respiratory cytochrome chain and oxidative metabolism stops. Blockage of oxidative metabolism has the same effect as a decrease in oxygen supply, or decreased pO_2 in the arterial blood.

Both decreased pO_2 and H_2S denial of oxygen to cytochrome oxidase results in activation of carotid and aortic chemoreceptors, with an increase in signals to the respiratory center. The respiratory center in turn responds with increased signals to the ventilatory muscles, and hyperpnea results.

It is important, from a practical standpoint, that workers and potential rescuers of victims of H_2S poisoning are aware that hyperpnea is part of the clinical picture of response to H_2S toxicity. As exposure reaches sublethal concentrations (~500 ppm), the victim increases the rate and depth of ventilation. Rapid breathing can increase dosage to the victim, as well as use oxygen in respirators far more rapidly than normal breathing does.

This paper has been reviewed in accordance with the U.S. EPA peer review policies but does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

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