Fact or Fiction?

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Toxic, but Important Body Gases

"*Gases commonly known for their noxious effects at relatively high concentrations are produced by the body continuously and in minute quantities and are capable of exerting crucial physiological activities.*"[1]

Carbon monoxide, nitric oxide and hydrogen sulfide can be toxic, yet it has been recently demonstrated that they are important endogenous (originating within the body) molecules that have profound physiological and pathophysiological effects on the human body.

High levels of carbon monoxide interfere with cellular respiration and pollute the environment. Hydrogen sulfide, another chemical asphyxiant, paralyzes the sense of smell and at lower levels produces the rotten-egg stink prized by children using their first chemistry sets. Nitric oxide, the unstable free-radical, is an industrial gas and environmental pollutant found in cigarette smoke and smog.[1]

Over the past 20 years or so, research into the growing array of so-called gasotransmitters has fundamentally altered classic views of intercellular signaling. Gasotransmitters are a family of endogenous molecules of gases or gaseous signaling molecules, including CO, H_2S, NO and others. These particular gases share many common features in their production and function but carry on their tasks in unique ways, which differ from classical signaling molecules, in the human body.[2]

Mark Greener reports, "They act in systems as varied as gastrointestinal, circulatory and nervous. Gasotransmitters are not stored in vesicles. Rather, exquisitely regulated biosynthetic enzymes are activated when signaling is initiated. Moreover, while the proteins that sense the gases are diverse, the architecture seems highly conserved. The research offers a fresh perspective on processes as diverse as neural control, blood vessel diameter and embryonic development. It also raises numerous new therapeutic and diagnostic opportunities. In fact, physicians already prescribe drugs modulating gasotransmitters to manage erectile dysfunction and angina." Greener predicts that the number of gases produced within the body showing pharmacological actions at low doses is likely to grow. Recent evidence suggests that ammonia is a vasoconstrictor, possibly by acting through intercellular alkalinization. Sulfur dioxide, produced by bacterial metabolism may also have some value.[1]

Carbon monoxide

Although carbon monoxide inhalation can be lethal, our bodies make the molecule naturally in small amounts when an enzyme called heme-oxygenase-1 (HO-1) breaks down a portion of the blood protein hemoglobin.[3] Ventilator-induced lung injury (VILI) is a major cause of morbidity and mortality in intensive care units. The stress-inducible gene product, HO-1 and carbon monoxide, a major byproduct of the oxygenase catalysis of heme, have been shown to confer potent anti-inflammatory effects in models of tissue and cellular injury. Tomas Dolinay notes, "The data from this work leads to a tempting speculation that inhaled CO might be useful in minimizing VILI."[4]

Small amounts of carbon monoxide might alleviate symptoms of multiple sclerosis, a study in mice suggests. The finding may offer a treatment for MS, which strikes when a person's immune system damages the fatty sheaths that protect nerve fibers in the brain and spinal cord.[3] Other studies of laboratory animals suggest that carbon monoxide in small doses can prevent injury to blood vessels caused by surgery. In this study, rats that inhaled carbon monoxide-laced air for one hour before angioplasty had much less subsequent artery blockage than did rats not receiving the gas. Rats that underwent a vessel transplant also fared significantly better if given carbon monoxide before and after the surgery.[5]

Hydrogen sulfide

Hydrogen sulfide, the compound that gives rotten eggs their odor, can be lethal at high concentrations. It is not something you would think to pump into sick or injured people, but that's exactly what some scientists plan to do. Mitch Leslie reports, "The molecule has proven to be an influential physiological signal, with effects on everything from blood flow to hormone secretion. Eager to capitalize on these newfound capabilities, scientists are trying to exploit hydrogen sulfide to tame the side effects of common painkillers."[6]

Researchers in Seattle reported that exposure to hydrogen sulfide gas can lower the heart rate, metabolism and body temperature in lab mice.[7] Mice in the study revived and appeared healthy when exposure to the gas ended. This is one step in helping researchers understand about hibernation and torpor in animals.[8]

Why is this of interest? Some animals regularly slow down their metabolic rates, or the speed at which their bodies function. Every day, certain types of hummingbirds go into a state called torpor where their heart rates drop, breathing slows and body temperature plunges. Bears go into a similar type of hibernation for entire seasons. This type of suspended animation could offer protection for humans after a heart attack or stroke, and it could help people survive while waiting for an organ transplant.[9]

Hydrogen sulfide could also help in cases of erectile dysfunction. A study with primates showed that injection of sodium hydrogen sulfide increased penile length and was capable of dilating with blood to bring about the erection of a body part.[10] Studies with nitric oxide, discussed next, led Pfizer to develop Viagra.[11]

Nitrogen oxides

Nitrogen oxides are major components of air pollution from auto exhaust and industrial combustion. Ground level ozone is formed by a photochemical reaction of nitrogen dioxide to yield nitric oxide and an oxygen atom. The nitrogen oxides also contribute to the formation of acid rain. Obviously, nitric oxide is part of a family of bad gases. Or is it?

An industrial gas and environmental pollutant, nitric oxide was named "Molecule of the Year" by *Science* magazine in 1992. Editor Daniel E. Koshland, Jr., wrote, "In the atmosphere it is a noxious chemical, but in the body in small controlled doses it is extraordinarily beneficial."[12] In 1998, the Nobel Prize for Medicine was awarded for discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system. Tiny puffs of nitric oxide mediate an extraordinary range of biological properties in our bodies, ranging from destruction of tumor cells to the control of blood pressure. It relaxes blood vessels, quells inflammation, nudges the hypothalamus to release hormones, and even transmits signals between the brain's neurons.[13] There are other observed effects of NO on the human body. For more information see this column, in the April 2002 issue of *Plating & Surface Finishing*.

Perf1uorocarbons

Although not toxic like the previously discussed items, nor produced naturally by the human body, perfluorocarbons (PFCs) are worth some discussion. PFCs are compounds derived from hydrocarbons by replacement of hydrogen atoms by fluorine atoms. They are chemically inert, thermally stable, non-toxic and extremely potent greenhouse gases with a lifetime up to 50,000 years. Industrial applications include use in refrigerating units as CFC replacements, plasma cleaning of silicon wafers, use with high voltage components, either as dielectric fluids or as coolants, and in cosmetic formulations where the oxygen dissolved in the perfluorocarbon is claimed to have an anti-aging effect on the skin.[14]

A huge amount of interest has been shown in perfluorocarbons for medical applications, due to their remarkably low toxicity, lack of biological activity, short retention time in the body and their ability to dissolve gases, especially oxygen and carbon dioxide. How would you like your lungs purged with perfluorocarbons? Well this isn't as far-fetched as it might first sound.[15] W. Wayt Gibbs reports, "Normally, fluid in the lungs is a bad thing. In fact, many of the insults that frequently cause lungs to give out - shock, pneumonia, burns, gunshots - harm the organs by drowning them one tiny air sac at a time. Gases such as oxygen cannot displace the plasma, but a liquid could if it were dense enough. Enter perfluorocarbons: colorless, odorless fluids that are biologically inert, that evaporate in air but do not mix with water, absorb oxygen and carbon dioxide but readily give it up and that are denser than water and most bodily fluids."[16]

Other applications include the field of eye surgery where the properties of PFCs - immiscible in water, optically clear and injectable - has led to the commercialization of a number of PFCs. Also, because PFCs have high oxygen solubility, a number of researchers are investigating the possibility of using them to treat ulcers and burns. Perfluorocarbon emulsions are effective at bringing oxygen to skin tissues, which significantly enhances healing rates and prevents reoccurrence of the treated condition.[17]

Summary

Edward Calabrese of the University of Massachusetts - Amherst is a strong proponent of hormesis, a scientific term that means low doses help and high doses hurt. He's concerned that if researchers don't begin regularly probing the effects of agents at very low doses, scientists will continue to miss important health impacts - both good and bad of pollutants, drugs and other agents. Janet Raloff points out, "Regulatory agencies don't require scientists to evaluate a poison at exposures below that at which no harm is apparent. This dose is referred to as the NOAEL, for 'no observable adverse-effects level.'"[18]

Two obvious benefits can accrue from testing effects at low doses: (1) medical help might be found from items otherwise known to be toxic and (2) if traces of certain pollutants are not as dangerous as previous estimates had suggested, perhaps some overly stringent regulations could be changed. Dream on . . . **P&SF**

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