Fact or Fiction?

Jack W. Dini
1537 Desoto Way
Livermore, CA 94550
E-mail: jdini@attbi.com

NO—From Pollutant To Molecule of the Year

An unlikely wonder drug is the unstable, free-radical NO (nitric oxide) gas, which is found in cigarette smoke and smog.[1] Ten years ago, no one would have dreamt how important nitric oxide is within our bodies. Now, it is being implicated in everything from memory to blood pressure.[2]

NO, an industrial gas and environmental pollutant, 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."[3] In 1998, the Nobel Prize for Medicine was awarded for discoveries concerning NO as a signaling molecule in the cardiovascular system. Tiny puffs of NO mediate an extraordinary range of biological properties in our bodies, ranging from destruction of tumor cells to the control of blood pressure.[4]

So what is NO? It is the simplest of the oxides of nitrogen. Other oxides of nitrogen include nitrous oxide (N_2O) and nitrogen dioxide (NO_2). Nitrous oxide is also known as laughing gas and is used in medicine as an anesthetic, while nitrogen dioxide exists mainly as a dimer (N_2O_4). It forms brown fumes, and is highly toxic.[2]

The higher nitrogen oxides (NO and NO_2) are major contributors to air pollution from auto exhaust and industrial combustion. Ground-level ozone is formed by a photochemical reaction of NO_2 to give NO and an oxygen atom. The atom then reacts with an oxygen molecule to form ozone (O_3). The nitrogen oxides also contribute to the formation of acid rain. It is surprising, therefore, that this somewhat-toxic gas could be an important new drug.[1]

In the body, NO is extremely short-lived. It exists for about six to ten seconds before it is converted by oxygen and water into nitrates and nitrites.[5]

Here are some observed effects of NO in the human body on physiological systems and diseases:[1]

- Lungs. NO reduces blood pressure in the lungs without affecting the pressure in the rest of the body.
- Heart. It has been known for a long time that nitroglycerin, which chemically releases NO, can relax blood vessels near the heart and increase blood flow. New drugs that also release the signal molecule NO are being developed.
- Shock. White blood cells release large amounts of NO to kill bacteria; however, this release also can cause blood vessels to dilate, leading to dangerously low blood pressure. So, NO has helpful and harmful roles in septic shock.
- Cancer. White blood cells may use the NO that they release to fight tumor formation.
- Brain. NO mediates intercellular communication in the brain.
- Diagnostic analyses. Some inflammatory diseases can be diagnosed by analyzing NO production by the lungs and intestines.
- Impotence. Studies of the role of NO in penile erection led to the development of Viagra™.*
- Alzheimer's disease. The role of NO produced by the body in neurodegenerative diseases also is being studied. Although some studies indicated a toxic effect, the evidence was not conclusive.
- Schizophrenia. This disease involves a disturbance within the arginine-NO pathway in the brain.[2]
- Others. Some of the most dramatic potential applications of NO are in parasitology and tropical diseases.[4] NO may help treat sickle cell anemia.[6]

NO is the first gas to be approved as a drug product. Although oxygen and N_2O (laughing gas) have been used medically for many years, they never were subjected to the current rigorous approval process. Most of the anesthetic gases are actually volatile liquids; therefore, NO is unique in the pharmaceutical industry.[1]

NO & Earthquake Prediction

Recent research indicates that NO concentration in the atmosphere changes noticeably before an earthquake. Matsuda and Ikeya[7] reported that the concentration of NO eight days before the Kobe, Japan earthquake was 199 ppb—about 10 times higher than the average peak of 19 ppb. The concentration of NO was also found to have increased before other major earthquakes (magnitude >5.0) in Japan. Atmospheric discharges by electric charges or electromagnetic waves before earthquakes are postulated as having generated the NO. Also, emanation of NO from the ground might be expected before an earthquake if active oxygen (called peroxy radicals) were formed underground by the fracture of rock and reacted with nitrates in nature.[7]

Two issues with this that have to be addressed, however, are weather conditions and traffic. A single natural lightning strike produces 1,000 mol molecules of NO. Also, NO is generated by combustion of fuel, so the effects of human activities complicate the interpretation of the data. The authors[7] suggest that measurement of NO should be made at a remote area to study the background variation of the NO produced in

** Pfizer Inc., New York.*

nature, so one can distinguish its concentration from that generated by human activities. Perhaps someday we will truly have a method for predicting earthquakes.

NO & Fireflies

Light is the firefly's language of love, and until recently, neurobiologists have not been able to identify the missing link that triggers the firefly's burst of light. It appears that this phenomenon also depends on NO.[8] As noted earlier, the role of NO in humans led to the development of Viagra™. (Perhaps human males are more closely related to fireflies than one might ever have thought.)

Summary

The next time you hear about a "pollutant of the month," remember that perhaps in 10 to 20 years, some scientists will discover how important this "pollutant" is for human existence. Culotta and Koshland[9] sum it up best: "Some scientists speculate that nitric oxide is merely the first of a soon-to-be-discovered new class of signaling molecules—gases that swiftly pass through a cluster of cells and then vanish. Preliminary evidence hints that one candidate for such an airy messenger may be carbon monoxide, another molecule that today has a shady reputation."

Perhaps some future column... ***P&SF***

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