TRENDS IN HEALTH CARE

From unknown to superstar: nitric oxide now central to research

By Kay Nolan
World Editor

Twelve years ago, when one of the first scientific papers on the biomedical effects of nitric oxide gas (NO) on the human body was submitted for publication, reviewers rejected it. One reviewer commented to the effect that, "Nitric oxide is a factor in air pollution, but it's well known that it has no biological function."

The fact that within the past decade, NO has been discovered to affect nearly every imaginable bodily function shows how unpredictable basic science research can be. It also demonstrates how exciting research can be because recognition of the role of NO has spurred new research into dozens of medical disorders.

And the Medical College is truly at the forefront of work in this area, with more than 25 scientists doing major research projects involving nitric oxide and nearly 20 more doing smaller research projects. This article can only mention a few, which by no means diminishes the significance of other projects.

Nitric oxide (NO) is ubiquitous in the human body. It is continually biosynthesized in the central and peripheral nervous systems, the brain, blood vessels, musculoskeletal tissue, and the body's immune system (white blood) cells. Because it's unstable and changes into nitrate, its effects were long underestimated.

The bodily functions that NO is now thought to regulate are many:

* **peripheral nervous system:** gastrointestinal motility and regional blood flow
* **brain:** behavior, memory, and response to pain
* **skeletal muscle:** metabolism and muscle contractility
* **immune system;** the ability to kill viruses, microbial parasites and certain cancer cells
* **blood vessels:** blood pressure

Researchers at the Medical College, including Owen W. Griffith, PhD, Professor and Chairman of Biochemistry, were among the first to discover that NO is produced in the endothelial cells that line blood vessels and that it can lower blood pressure by causing the vessels' smooth muscles to relax.

The news about NO and blood pressure was phenomenal: Did this mean that people with apparently hereditary high blood pressure produce less than ideal amounts of NO? What about dangerously low blood pressure? People suffering from a bacteria infection that they can't fight, perhaps because they have cancer, AIDS, or another disease that compromises their immune systems, may go into septic shock, which is accompanied by low blood pressure.

If NO could be altered, perhaps blood pressure could be regulated. Dr. Griffith and his colleagues have developed and patented NO inhibitors. Studies proved that inhibiting NO synthesis in animals causes animals' blood pressure to significantly increase. Whether these inhibiting agents will help treat septic shock is still under investigation.

Other uses for NO inhibitors are possible: NO is thought to mediate brain tissue injury caused by cerebral ischemic stroke. Similar NO-mediated damage may be responsible for nerve degeneration in diseases such as Parkinson's and amyotrophic lateral sclerosis (Lou Gehrig's Disease).

NO is also thought to increase sensation of pain. For example, in some studies, NO inhibitors stopped migraine headache pain in its tracks. Nitric oxide is believed to act as a messenger between the brain and nerve cells.

And while studying how NO helps healthy cells perform, it was discovered that NO can send messages to cancer cells that helps the immune system attack them. Macrophages (one type of white blood cell) produce large amounts of NO, which diffuses into tumor cells, interfering with the tumor's cell division and growth.

So in some circumstances, it may be desirable to stimulate, rather than inhibit NO production in patients.

In a fascinating twist, NO appears to be simultaneously beneficial and harmful regarding buildup of fatty deposits in arteries. NO alone apparently helps prevent such buildup, particularly in healthy arteries. However, in lab studies by Neil Hogg, PhD, Assistant Professor of Biophysics, and Balaraman Kalyanaraman, PhD, Professor of Biophysics, NO has been found to combine with superoxide, a by-product of the body's use of oxygen, to form peroxynitrite, an oxidant that exacerbates diseased arteries.

Because NO is a "free radical," an atom or group of atoms with an unpaired electron, the College's **Electron Paramagnetic Spectroscopy (EPR) Center** is ideal for conducting NO research. The center, world-renowned for inventing instruments to analyze free radicals and for leading research in the area, has many investigators doing current research involving NO. Dr. Kalyanaraman and his colleagues are pursuing the role of NO and superoxide in mediating the cardiotoxicity of anti-cancer anthracycline drugs.

John Baker, PhD, Associate Professor of Surgery (Cardiothoracic) and his colleagues have discovered that NO levels seem to be higher in the hearts of children who have cyanotic congenital heart disease and that these higher levels of NO seem to enable the children to better tolerate heart surgery. Animal studies are now under way to determine whether it's possible to increase tolerance to heart surgery among patients with other forms of heart disease by artificially increasing NO levels.

Many other studies involving nitric oxide are taking place here and elsewhere. An estimated 3,000 to 4,000 papers on nitric oxide research are now published yearly.

The College is clearly a major player in a major scientific trend.