The Root of Impotence

Does nitric oxide hold the key?

By MICHAEL STROH

A decade ago, nitric oxide hardly seemed destined for biological greatness. In fact, its only known role in living things was as an energy source for lowly bacteria. But all that has changed.

In the last few years, scientists have found nitric oxide (NO) all over the human body. Within the immune system, it acts as a deadly Molotov cocktail that macrophages toss at invading microorganisms and renegade tumor cells. In the vascular system, nitric oxide relaxes blood vessels and helps regulate blood pressure. In the brain, the molecule seems to play a role in learning and memory.

Now researchers at the University of California, Los Angeles (UCLA) have uncovered another of nitric oxide's roles: It brings about the male erection. This discovery fills a huge gap in scientists' knowledge about how men get erections. More important, it may help answer the nagging question: Why *can't* some men get erections?

An estimated 10 million men in the United States are impotent — that is, they are unable to have sexual intercourse. Although several things can trigger impotence — including diabetes, nerve damage and certain medications — urologists believe that in most cases the underlying cause is a problem with blood flow through the penis.

And that is exactly what the UCLA team found nitric oxide governs. Many urologists now wager that if something goes wrong with nitric oxide in the penis, impotence results.

Basically, an erection is an act of hydraulics. "For an erection you need two essential things," says urologist Iñigo Saenz de Tejada of Boston University Medical Center. "One is you need blood to come in. The other is you need to trap that blood."

To accomplish this, the penis contains two long, expandable sacs called the corpora cavernosa, each of which has a tough, fibrous outer wall and a spongy inner wall of smooth muscle tissue. Arteries hooked up to the sides of the sacs pipe in blood, while veins drain it out through vessels located between the sacs' inner and outer walls.

In a limp penis, the smooth muscle inside the sac is contracted; blood flows in and drains right out. In aroused males, however, nerves spark the smooth muscle in the penis to relax. The arteries feeding the sacs open up and shoot blood into the corpora cavernosa. As blood floods the chamber, the spongy inner walls balloon and squeeze the venal drainpipes, choking them off. Thus, blood flowing in cannot leave, and the penis grows erect.

Although the nuts and bolts of an erection seem simple, until recently many fundamental mysteries remained, notes UCLA pharmacologist Louis J. Ignarro in the May 1992 JOURNAL OF NIH RESEARCH. For instance, how do nerves signal the smooth muscle in the penis to relax?

The break came in 1987. Jacob Rajfer, a urologist at the UCLA School of Medicine, made a wrong turn on the way back to his office and ended up standing at the door to an unfamiliar laboratory. On the door hung a sign: "Pharmacology — Smooth Muscle Lab."

Serendipity had struck. Rajfer had been studying impotence for years and had a hunch that the condition often arises when smooth muscle in the corpora cavernosa fails to relax. However, at the time no one knew much about smooth muscle in the penis, except that under the microscope it appeared identical to smooth muscle elsewhere in the body — in the arteries or in the intestines, for example. But nobody understood what caused smooth muscle anywhere in the body to relax. When Rajfer walked into the lab, he learned that Ignarro, its director, had found the answer — for arterial smooth muscle, at least — only weeks earlier.

Ignarro's team found that when certain neurotransmitters in the blood bind to receptors on the endothelium — a layer of cells lining the insides of arteries — these cells begin to manufacture nitric oxide. Moreover, the molecule then diffuses into the adjacent layer of smooth muscle cells that surrounds the endothelium and sets off a chemical reaction that causes them to relax.

Rajfer was intrigued. Smooth muscle in the corpora cavernosa also had an endothelial lining. Could the same process be at work in the penis?

"It was natural to think that maybe a variety of tissues could make NO," says Ignarro. "With those thoughts in mind, I figured: Let's see whether nitric oxide can produce an erection."

Ignarro, Rajfer and several co-workers performed two simple experiments to test their hypothesis. After removing strips of tissue from a rabbit's corpus cavernosum, the group electrically stimulated the nerves that attach to the smooth muscle in the tissue. Almost immediately, the muscle relaxed; at the same time, the researchers measured a jump in the amount of nitric oxide in the tissue.

Although suggestive, the experiment didn't prove that nitric oxide could trigger an erection. So in a second experiment, the group worked backwards through the problem.

Ignarro knew from previous experiments that the body produces nitric oxide when an enzyme called NO synthase reacts with L-arginine, an amino acid. Furthermore, he knew of chemicals that thwart NO synthase and prevent it from making nitric oxide.

With these ideas in mind, the UCLA group repeated the experiment on the rabbit tissue, but this time they added chemicals to stop nitric oxide production. When they juiced up the nerves with electricity, the smooth muscle remained taut. The researchers concluded that nitric oxide was indeed responsible for an erection, at least in rabbits. They reported their findings in the Sept. 13, 1990 NATURE.

To see if this finding held true in humans, the researchers obtained tissue from the corpora cavernosa of both impotent and potent men and repeated the experiments. They got the same results, which they reported in the Jan. 9, 1992 NEW ENGLAND JOURNAL OF MEDICINE.

But the riddle wasn't solved yet. During their experiments on rabbit tissue, the group made a discovery that started them scratching their heads anew. Some smooth muscle in the tissue had a damaged endothelium that could no longer make nitric oxide. However, when the researchers electrically stimulated the nerves in the tissue, the smooth muscle relaxed, suggesting that nitric oxide in the corpora cavernosa is being manufactured somewhere else besides the endothelial cells.

The UCLA group and researchers from several other universities are now racing to discover where else in the penis nitric oxide is made, and that means looking for the enzyme NO synthase.

"Where is this chemical made? That's our $64 million question," says Rajfer.

To ferret out NO synthase in the corpora cavernosa, the team plans to use immunohistochemistry, a technique that takes advantage of an antibody's ability to seek out foreign invaders in the body. In their case, however, the researchers will use antibodies much as trackers would use dogs.

First they will make antibodies that respond only to NO synthase and attach a special marker to them. Then they will turn these antibodies loose in tissue taken from a human corpus cavernosum. When the antibodies find the NO synthase, they'll latch on to their quarry, causing the marker to be released. The researchers should then know all the sites where NO synthase is secreted in the penis.

"Once we know exactly where NO synthase is made," says Ignarro, "I think we will be a lot closer to understanding what the possible defects [involved] in impotence may be.

"We have evidence that in the severely impotent patient, stimulation of the nerves results in the formation of much less NO, but we don't know what that means. Is there less NO synthase? Is there a defect in the enzyme? We have to do molecular biological studies to determine more precisely what the problem is."

Researchers differ on where they expect to find NO synthase in the penis, but Ignarro thinks common sense points to the neurons, or nerve cells. "When the nerves are stimulated," says Ignarro, "relaxation of the corpus cavernosum occurs quickly. And that suggests that perhaps the nerves are releasing NO."

In fact, at least one group may already have found this.

In a report soon to appear in SCIENCE, neuroscientist Solomon H. Snyder of Johns Hopkins University School of Medicine in Baltimore says his group has immunohistochemical evidence that nerves throughout the corpora cavernosa do indeed harbor NO synthase. Interestingly, if independent studies bear this out, the Johns Hopkins team may have found more than just the manufacturing plant for nitric oxide in the penis. "The major implication is that maybe NO is a member of a new class of neurotransmitters," Snyder says.

Neurotransmitters are usually stored in compartments at the ends of neurons. When called upon, these chemicals are spewed out of their container and over to an adjacent neuron, where they bind to a unique protein receptor, much as a key fits a lock. Nitric oxide, however, appears to be made on demand in the neurons and diffuses from cell to cell rather than binding to any receptor. "It's very atypical," Snyder says.

"The bottom line," says Saenz de Tejada, "is that NO is becoming a very interesting substance, not only in the penis, but everywhere."

And at least in the case of impotence, scientists aren't the only ones excited about nitric oxide. "Since we reported this thing," says Rajfer, "it seems like everyone with impotence wants to come see us." And if they can't come in, they write. So far, Rajfer says he has received hundreds of letters from people with questions about nitric oxide. "I tell them it's only a laboratory finding at this point," he says. "And it's probably just the first of a series of things that need to be discovered before we can come up with a better treatment than we have now."

As the two most common treatments for impotence are a penile implant or an injection directly into the penis, the excitement over nitric oxide is understandable. "Everyone who walks into my office asks for a pill," says Saenz de Tejada. And more research on nitric oxide's role in the penis, he says, may provide something as simple as that. □