DNA Science Workshop for VCE Biology Teachers

Nitric Oxide - Science Magazine's 1992 Molecule of the Year

By Elizabeth Finkel as broadcast on ABC's *Ockham's Razor* on the 28/8/94

When I was a science student, I remember wondering whether there were in fact any great discoveries left to be made. Its a sentiment that crops up now and then, especially after major breakthroughs. In 1920, Paul Dirac discovered the laws that demystified the behaviour of the electron. It was predicted soon after that physics as we know it would be finished in six months. There were similar sentiments aired in 1966 when Nirenberg, Ochoa and Khorana cracked the genetic code. You'd have to admit that decoding the secret of life is a hard act to follow.

But for those of you wanting to make your own mark on science, don't despair. Discoveries that break new ground continue to occur. The story of Nitric Oxide is a case in point..

If you've ever read about the gas Nitric Oxide, it's probably been in relation to pollution. Nitric Oxide is one of those gases released by car exhausts. It ends up creating photochemical smog - the scourge of cities like Los Angeles.

But in the minds of physiologists worldwide, all that is in the past. Today NO is a star performer, no less than Science Magazine's 1992 molecule of the year. This little gas has answered long-standing questions about how blood vessels dilate, nerve transmission, and learning and memory. And its clinical applications will probably give us new treatments for stroke, hypertension, Alzheimer's disease, cancer and even impotence.

It all began about six years ago. Blood vessels had long been known to produce a factor that dilated them, but no- one had been able to identify this mystery substance. It went by the name of EDRF (Endothelial Cell Derived Relaxing Factor). Scientists knew that EDRF was produced by the mushy cells inside the blood vessel and then diffused out to relax the surrounding muscular band.

It was a shock to the scientific community when in 1987, a number of researchers independently came to the conclusion that EDRF was probably the gas, nitric oxide. A two atom gas with a three second lifespan was a most unlikely candidate for such an important biological messenger. (These days such titles go to rather more complex molecules like prostaglandins or steroids or peptides).

But NO as the blood vessel relaxing factor, began to make more and more sense. For decades doctors have been using nitro drugs to treat angina and high blood pressure without knowing why these drugs worked. The effects of these drugs had been accidemtly discovered in munitions factories. Women working with nitroglycerine had very low blood pressure. Now it's realized that angina drugs like nitroglycerine or Sodium nitroprusside break down in the body to release nitric oxide.

Nitric oxide has pretty much revolutionized our understanding of blood vessel control. A whole new field of NO chemistry has opened up and we can probably expect a new range of drugs for treating hypertension and angina in the near future. But let's move on to a second area where NO has made a big splash.

Researchers studying nerve transmission also had a mystery to solve. Nerve cells or neurons, ferry messages around our body, from sensory organs to the brain to the spinal chord and to muscles. They are very much like wires carrying electrical signals around a circuit. Along the length of a single neuron, the signal is transmitted electrically. But where two neurons meet, there is a gap and to cross the gap, the message has to be carried by a chemical called a neurotransmitter.

For many years now, scientists have known that the nervous system uses several different neurotransmitters. In fact nerves are generally named for the type of neurotransmitter they use. For example nerves supplying skeletal muscles commonly use acetylcholine and are called cholinergic nerves, while many brain neurons use a substance called GABA and are called Gabinergic nerves. Knowing which nerves use which neurotransmitter, underpins the modern use of anaesthetics, sedatives and stimulants which all work by affecting the levels of neurotransmitters.

But nerves in the intestine, lung and penis have long presented a mystery. Researchers have not been able to nail down the neurotransmitter being used. In fact these nerves have been named for what they are not, NANC nerves which stands for not adrenergic , not cholinergic.

Well you guessed it, recent findings show that NANC nerves use nitric oxide as their neurotransmitter. That discovery has put a whole new category of nerve transmission into the textbooks. Researchers now speak of nitrergic nerves alongside the other categories.

Some researchers are puzzled as to how a gas could possibly act as a neurotransmitter. As David Hearst of Melbourne University puts it, "nitric oxide breaks every rule of nerve transmission." Neurons generally go to a great deal of trouble to release their neurotransmitters with precision and speed. They package precise quantities of neurotransmitter into little torpedoes that lie ready and waiting at the nerve terminal. When detonated by a nerve signal, the torpedoes spew their contents precisely at targets on the receiving neuron.

But nitric oxide as a neurotransmitter breaks all the rules. Once released by the transmitting neuron, the gas just diffuses out in all directions. Dr.Hearst wonders how enough nitric oxide molecules could reach the receiving neuron to trigger a response. But such technicalities aside, let's proceed to yet another hot bed of nitric oxide research.

There's a third area, perhaps the most exciting of them all, where NO, has revolutionized scientific thinking -- the brain. It may be the molecule that "memories are made of".

Imagine the mesh of billions of entangled neurons that is our brain. That overwhelming complexity ensures that we never run out of the capacity to learn and store memories, but how are specific tasks and memories stored away in that meshwork?.

When we carry out a new task, like learning a new game, neurons scattered throughout the learning centres of the brain become activated. As we repeat the moves of the game and it becomes more familiar, connections between specific neurons strengthen, allowing the nerve signals to move along more easily - a memory circuit has been created.

It is the ability of brain neurons to change the strength of their connections, their so-called plasticity, that makes learning and memory possible. The process by which neurons change the strength of their connections is called long term potentiation (LTP). And understanding how neurons do it is the key to understanding the molecular details of the learning process -- the holy grail for brain researchers.

Researchers now believe that NO has a key role to play in LTP. Consider two neurons that are part of a learning circuit. Researchers have known for some time that it is the neuron at the receiving end of the signal that initiates the strengthening process.. The highly aroused neuron appears to ensure its continued association with the neuron that excited it in the first place by releasing a mystery substance referred to as the retrograde messenger. NO now appears likely to be that substance. Its release from an aroused neuron appears to set in train the events leading to LTP.

NO seems to fit the bill for the role of retrograde messenger very nicely. It diffuses rapidly and slips easily in and out of cell membranes. It also self -destructs within seconds, making for a very precise signal. NO as the retrograde messenger also makes sense of recent scientific reports that have upset a classic dogma. It was thought that LTP was a private affair between consenting neurons. But a growing number of researchers report other neurons getting in on the act. NO being so diffusible would be expected to influence surrounding neuron connections.

NO may yet win the dazzling title of "the brain's memory molecule", but it may also play a deadly role -- in stroke damage. Exactly what causes the massive brain cell death seen after stroke has long puzzled researchers. When brain cells are deprived of oxygen, they pour out huge quantities of the neurotransmitter glutamate. Neurons in the vicinity of this flood, seem to shrivel up and die. But it has never been understood why; there were vague notions that somehow they died of overexcitement. But NO may provide a more precise explanation.

The neurotransmitter glutamate is thought to be the trigger that normally releases NO. But while a little bit of NO is good for brain power, a lot is bad. NO is toxic at high doses. In fact, macrophages, the "Rambos" of our immune system, use it to incinerate cells. Many researchers now believe that NO may be responsible for much of stroke damage. The sequence of events seems to be: oxygen starvation leads to the pouring out of neurotransmitter, that leads to the out of control production of NO and that leads to brain damage.

That theory is supported by animal studies. The studies show that if NO inhibitors are used, more than 70% of stroke damage can be prevented.

Speaking clinically, we should be hearing a lot more about NO. With vascular disease and stroke as the major killers in western societies , it's no secret that NO research is a hot item on the R and D agendas of many a drug company. We can expect improved treatments for angina and hypertension and hopefully a long awaited new treatment for stroke. Already at large are NO-based treatments for septic shock - the dramatic drop in blood pressure that occurs when infections get out of control. The blood pressure drops because of all that NO being sprayed around by macrophages. NO inhibitors are now being used to treat that condition. We may also soon have a NO - based treatment for impotence. NO is the neurotransmitter used by nerves supplying the penis. With arousal, the nerves release nitric oxide which dilates the blood vessels leading to erection. If things go well for researchers at the Johns Hopkins Medical school in Baltimore, we may soon have a NO-releasing penile patch on the market.

NO has come a long way. Despite dubious beginnings, it is now one of physiology's bright stars. It has solved mysteries in blood vessel control and nerve transmission. It may yet explain much about memory formation, stroke and who knows what else. As a recent review put it, even if only half the claims for NO are borne out, it is set to have a remarkable impact on biology and medicine.