NO escape

US researchers think they have found a new way to control the release of nitric oxide in the body so that it can be used in medicine to improve the recovery and prognosis of patients with vascular disorders.

The NO molecule – more commonly known as an environmental pollutant – has become something of a medical superstar recently because it was found to play a leading role in a variety of physiological processes. NO is involved in blood vessel dilation and blood pressure control, neurotransmission and even sexual arousal.

However, NO is very reactive, and so has a very short lifespan in the body. This makes it difficult to study and even harder to control for medical use. Now, Larry Keefer of the National Cancer Institute (Frederick, MD, USA) and his coworkers have devised an NO-releasing compound, which they can use to target particular sites with NO. The compound is a diazeniumdiolate, and was prepared by reacting nitric oxide with L-proline in methanolic sodium methoxide. According to Keefer this compound can be infused directly as an alkaline solution to generate NO with a two-second half-life, meaning its effects are localized to areas immediately downstream of the site of infusion. [*J. Med. Chem.* (1996) 39, 4361].

The compound could be useful in preventing relapse following vascular surgery. Grafting and by-pass operations often result in tissue scarring and blood clot formation. NO released near the grafted tissue should bring the body's repair systems under control and allow healing to take place more steadily and so be safer.

Infusing this short-acting NO delivery agent at higher rates extends the area that can be treated successfully, Keefer explains. For example, administering it intravenously to sheep with drug-induced pulmonary hypertension selectively reduced the pressure in the pulmonary artery without affecting the blood pressure outside the lung.

Keefer and his coworkers have also blended their diazeniumdiolates into an insoluble polymer. The polymer stops the NO being released from the reactive diazeniumdiolate spontaneously. In contact with blood plasma, however, NO is rapidly and continuously released. Alternatively, explains Keefer, the non-polymeric NO–diazeniumdiolate complex can be infused slowly into the affected site using a syringe. Either way, the rapid release of NO once at the site means the action is limited to only that area, precluding peripheral side-effects.

The researchers have tested the effects of the NO-polymers on Teflon grafts used to repair damaged blood vessels in laboratory baboons. They found that clotting takes place at a much lower rate than in control animals. Anticoagulant drugs are normally given to human patients with vascular grafts, but these drugs are not without side-effects. Keefer's NO-releasing materials might allow their use to be avoided. "It is early days yet, however," he says, "we must conduct more toxicity studies and further proof-of-concept work before planning clinical applications."

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Unique post-doc system at SUNBOR

SUNBOR (Suntory Institute for Bioorganic Research, Osaka, Japan) was initially set up as the Institute of Food Chemistry in 1946 under the sponsorship of Kotobukia Ltd (Osaka, Japan) as a nonprofit-making organization. In 1963 Kotobukia changed its name to Suntory, and the company is now established as Japan's leading producer and distributor of western-style liquor products and the biggest producer of whisky, with a share of over 60% of the Japanese market. The initial remit was 'to contribute to advancement in health and nutrition of the Japanese people', but this has since expanded to cover many areas of the natural sciences. At its fiftieth anniversary celebration symposium last year, experts were invited to speak on key areas of interest to the institute, including glutamate receptors in brain function, chirality, retinal proteins, metalloproteins and new approaches to pest control. The institute has expertise in the latest mass spectrometric (MS/MS and LC/MS), NMR (FT-NMR) and other analytical techniques (CD/ORD), and is also experienced in DNA sequencing and synthesis to investigate cellular communication via neurotransmitters and hormones in humans and animals.

One major research programme involves the investigation of toxins, novel peptides and other compounds derived from insects, earthworms, squid and seacucumber. Most research is directed toward the investigation of novel leads through detailed structure–activity analysis and the subsequent identification of promising candidates for development.

A unique characteristic of SUNBOR, introduced by Professor Koji Nakanishi, is the 'pair system' of research in which a senior and junior member of staff work closely on a particular research project. The post-doctoral system, although long established in the West, came late to Japan and is still not fully developed. Professor Nakanishi appreciated the need for external input into the traditional Japanese approach to research. It was his idea to bring foreign staff to SUNBOR to profit from its excellent research facilities while bringing in creativity and a fresh scientific perspective. SUNBOR has been able to recruit post-doctoral researchers from all over the world, and only the very largest corporations, such as Sony and Mitsubishi, have similar systems. As evidence of its success, there is always a waiting list for post-doctoral positions at SUNBOR, and new foreign members of staff integrate quickly with the help of experienced staff members, who help find accommodation

