Coming two years after his discovery of oxygen, nitric oxide – or NO – was discovered by British chemist, theologian and natural philosopher Joseph Priestley in 1772, one of the first gases to be identified. However, for more than two centuries, this colourless and odourless gas was thought to be extremely toxic. It was only in the second half of the 20th century that researchers begin to recognise its fundamental role in human health and disease. Almost every type of cell in the body is capable of producing NO, where it plays a key role in host defence. Abnormal NO concentration in the body contributes to a wide variety of diseases; the production of too much is implicated in sepsis – a severe whole-body inflammation – meningitis, low blood pressure and rheumatoid arthritis, whereas too little can lead to high blood pressure, strokes, heart attacks and cancer.

The MRC has played an important part in identifying the role of nitric oxide as a signalling molecule and its disease associations, including in sepsis, blood pressure, stroke and cancer.
1970s/1980s: Robert F. Furchgott, Louis J. Ignarro and Ferid Murad undertake the research behind the discovery that endothelial cells produce nitric oxide, shown to relax vascular smooth muscle cells and subsequently dilate blood vessels.  

1987: Sir Salvador Moncada puts forward the hypothesis that the endothelium-derived relaxing factor (EDRF) identified by Robert Furchgott and nitric oxide are the same molecule.  

1992: Researchers at St George’s Hospital Medical School demonstrate that amino acid ADMA inhibits the production of nitric oxide.  

1998: Robert F. Furchgott, Louis J. Ignarro and Ferid Murad are jointly awarded the Nobel Prize in Physiology or Medicine "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system".  

2002: Science names nitric oxide as its molecule of the year.  

2006: The MRC-funded Efficacy of Nitric Oxide in Stroke (ENOS) clinical trial begins its full study. See case study 'The Efficacy of Nitric Oxide in Stroke (ENOS)'.  

2007: MRC-funded research demonstrates the role of the human gene dimethylarginine dimethylaminohydrolase (DDAH) in the regulation of blood pressure. The loss of DDAH activity disrupts the production of nitric oxide. See case study 'The role of DDAH in the regulation of blood pressure'.  

2008: Research undertaken by the MRC Toxicology Unit demonstrates that nitric oxide can change the computational ability of the brain, which has implications for the treatment of neurodegenerative diseases such as Alzheimer’s and Huntington’s disease. See case study 'Nitric oxide in the brain'.  

2010: Research at the MRC Cancer Cell Unit demonstrates that nitric oxide up-regulates the production of MMP, a family of enzymes that may be involved in promoting the progression of the abnormal epithelial cells in Barrett’s Oesophagus to cancer cells.  

2011: Researchers in the MRC Human Nutrition Research group develop a method for measuring nitric oxide in the body and show that nitric oxide production is lower in individuals with metabolic syndrome – those with obesity, high blood pressure and diabetes.  

2012: Professor Charles Hinds at Queen Mary, University of London patents the use of nitric oxide in the treatment of ventilator-associated pneumonia. See case study ‘Use of nitric oxide in ventilator-associated pneumonia’.  

2012: The MRC Clinical Sciences Centre produces molecule L-257, an inhibitor of DDAH, and a candidate drug for the treatment of sepsis. See case study ‘Nitric oxide and sepsis’.
The role of DDAH in the regulation of blood pressure

Dimethylarginine dimethylaminohydrolase (DDAH) is an enzyme found in all cells in the human body. It enables the production of nitric oxide which in turn causes the phosphorylation of proteins that relax the smooth muscle, regulating blood pressure. DDAH does this by breaking down amino acids ADMA and L-NMMA. These amino acids migrate into the blood plasma where they have been shown to inhibit the production of nitric oxide.

Professor Patrick Vallance and Dr James Leiper at University College London demonstrated that deleting the DDAH gene in mice resulted in these mice developing high blood pressure. They also designed specific inhibitors which bind to the active site of human DDAH. These small molecule inhibitors also induced high blood pressure in mice, confirming the importance of DDAH in the regulation of blood pressure.

A better understanding of DDAH could lead to important new treatments. It could help to establish if genetic variation predisposes certain people to cardiovascular diseases, or whether environmental factors exert some of their effects through modulation of DDAH activity.

The Efficacy of Nitric Oxide in Stroke (ENOS)

Professor Philip Bath at the University of Nottingham is investigating whether the application of glycerol trinitrate (GTN), long since used in the treatment of the heart condition angina, could be used to improve the recovery of stroke patients by lowering their blood pressure.

Strokes are caused either by the blood supply to the brain being blocked by a clot (ischaemic) or by a blood vessel in the brain bursting (haemorrhagic). The damage to the brain kills a third of people within a year and leaves another third disabled. Around 70 per cent of patients who have suffered a stroke have elevated blood pressure, and people with high blood pressure recover less quickly and are more likely to die or have another stroke. GTN is converted into nitric oxide in the body, which lowers blood pressure by widening blood vessels. The Efficacy of Nitric Oxide in Stroke (ENOS) assessed the safety and efficacy of GTN given to patients within 48 hours of a severe stroke. The largest of its kind, this international trial involved more than 4,000 patients who were randomly assigned to receive either seven days of GTN (5mg per day), or to no GTN. The researchers found that GTN lowered patients' blood pressure and was safe, but overall it did not improve their recovery, measured by assessment of their cognition, health-related quality of life and their daily life activities at 90 days after the stroke. However, recovery was improved in the patients given GTN within six hours and in women compared to men. That treatment might be effective if started early supports a previous small pilot trial in which GTN improved recovery when given by paramedics outside of hospital, with an average time to treatment of 55 minutes.

Nitric oxide in the brain

Nitric oxide is a chemical messenger which cannot be stored and can rapidly diffuse across cell membranes to act at remote sites. It is broadly localised in the central nervous system, where it influences synaptic transmission and contributes to learning and memory mechanisms.

Professor Ian Forsythe at the MRC Toxicology Unit studied the auditory pathway to explore nitric oxide signalling in the brain. He demonstrated in 2008 that NO is made in response to incoming synaptic activity (activity generated by sound received by the ear) and that it acts to suppress a key potassium ion-channel. These ion-channels keep electrical potential short-lived, but nitric oxide affects their activity, slowing the electrical potentials and reducing information passage along the pathway, acting as a form of control.
Neuronal cell injury and death are prominent features of neurodegenerative disorders such as Alzheimer’s, Huntington’s, and Parkinson’s diseases. NO is known to contribute to neuronal cell damage and death when present at excessive levels, but can promote neuronal survival under physiological conditions. Understanding this important signalling mechanism may hold the key to a better appreciation of the causes of neurodegeneration which contribute to the pathologies of diseases such as Alzheimer’s and Huntington’s.

Nitric oxide and sepsis

The MRC Clinical Sciences Centre has discovered a means of selectively reducing nitric oxide during sepsis. Sepsis is a severe whole-body inflammatory response to an infection. During the response, the body makes vast quantities of NO causing the blood vessels to completely dilate. This leads to a rapid decline in blood pressure, in turn triggering the failure of vital organs. Sepsis causes more than 37,000 deaths in the UK every year, more than breast cancer and bowel cancer combined.

Reducing NO in a non-selective way is unlikely to be useful, as it has both pathological and protective roles throughout the body. However, Dr James Leiper’s group has identified genes encoding the DDAH enzymes which have offered new opportunities to control NO production. DDAH that breaks down the molecule ADMA; ADMA regulates the NO production pathway, and so by inhibiting the gene or the enzyme, the level of ADMA rises, subsequently blocking NO production and leading to an increase in blood pressure.

Dr Leiper has produced a DDAH inhibitor, molecule L-257, which is a candidate drug for the treatment of septic shock and plans for its first clinical trials are underway.

Nearly half the people who develop sepsis will die. The survival rate has not significantly progressed in decades and so the identification of a candidate drug for its treatment may be the first steps in improving these odds.

Use of nitric oxide in prevention of ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most common healthcare-linked infection contracted by patients in intensive care; it is the basis for about half of all antibiotics given in this department. The biggest risk factor for the development of the condition is the presence of a tracheal tube, a tube inserted into the windpipe to maintain a patient’s airway. The tubes interfere with the normal protective upper airway reflexes, prevent effective coughing and encourage the entry of infected secretions from the respiratory and upper digestive tracts. It is estimated that more than 60,000 patients are mechanically ventilated in UK intensive care units annually and the reported incidence of VAP varies from around 10 per cent to more than 30 per cent.

It has been shown that oxides of nitrogen play a key role in the maintenance of host defence against various microbial pathogens. Ordinarily, oxides of nitrogen (NOx) are present in high concentrations in the stomach where they play an important role in maintaining sterility and preventing gastrointestinal infections. Because mechanically ventilated patients are usually sedated, they produce little or no saliva and their swallowing reflex is inhibited or abolished.

Professor Charles Hinds at Queen Mary, University of London, has shown that during critical illness, the production of NOx is reduced. This predisposes colonisation of the stomach and oral cavity by pathogenic bacteria and therefore the subsequent development of VAP. Professor Hinds has patented a system for the external production and local delivery of nitric oxide (NO) and NOx. The solution is designed to restore normal physiological activity of NOx by nasogastric and oral administration.
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