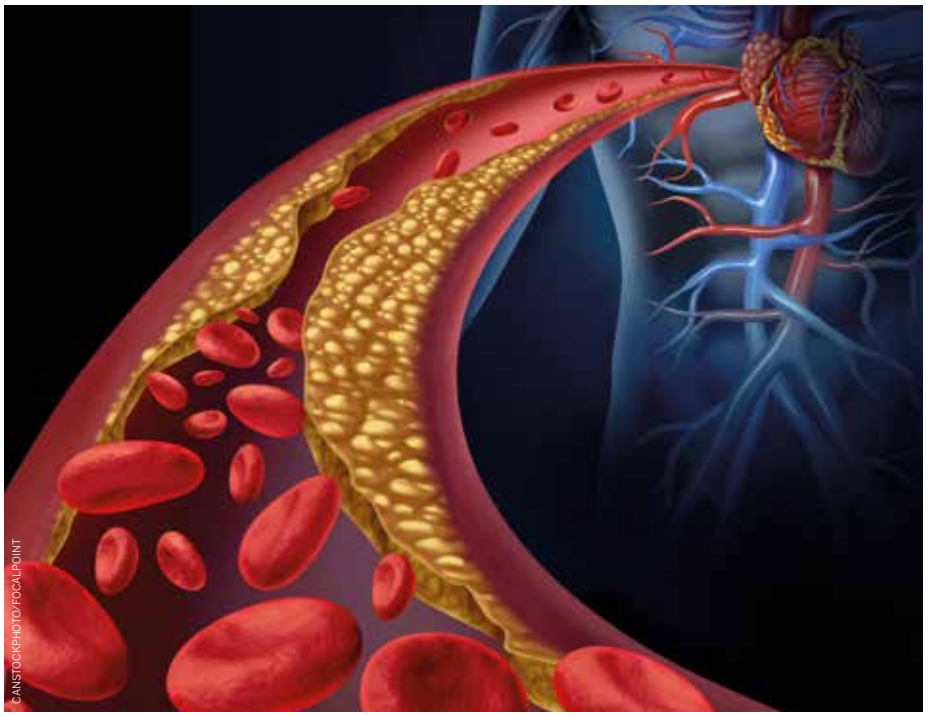

‘Target nitric oxide synthase directly’

Ulrich Förstermann receives this year’s Ariëns Award for his work on endothelial nitric oxide synthase and its role in atherosclerosis.

Since 1985 the Dutch Society for Pharmacology (NVF) has shown its appreciation for the work carried out by outstanding international pharmacologists by presenting the annual Ariëns Award, named in honour of the Dutch professor Everhardus Jacobus Ariëns, one of the founders of the field of pharmacology. This year’s winner is Professor Ulrich Förstermann, now working as CSO and Dean of Medicine at the Johannes Gutenberg University Medical Center in Germany. ‘I saw the list of previous recipients of the award and it is certainly an honour to be among them.’ Förstermann published over 430 research papers – which earned over 21,000 citations – and several book chapters. He is best known for his identification in 1991 of endothelial nitric oxide synthase (eNOS) and its product nitric oxide. Förstermann: ‘A decade earlier, researchers knew that endothelial cells did something that made smooth muscle cells in the vascular system relax. The problem was that we just didn’t know why. It could have been an electrical or chemical signal. In 1984 we demonstrated that it was a short-lived chemical. But it took seven more years to identify the enzyme that produced it. Our subsequent publications on eNOS were quite a breakthrough.’

‘It took 7 years to identify the enzyme’

Protective functions

The findings by the Förstermann team sparked off the efforts of other research groups to decipher the exact role of the eNOS in oxidative stress, a major cause of atherosclerotic cardiovascular diseases. ‘The enzyme converts the amino acid arginine to nitric oxide’, says Förstermann. ‘This compound has major protective functions in the vascular system. It not only dilates blood vessels – important in preventing atherosclerosis – but also reduces the chance of platelet adhesion and aggregation – important in preventing thrombosis.’

In disease situations, eNOS turns from being a good guy into a bad guy. ‘In oxidative stress in the vascular system the main source of the superoxide radical is NADPH oxidase’, explains Förstermann. ‘This enzyme is upregulated and overactive in such circumstances. This in turn leads, by means of a complex mechanism, to the uncoupling of eNOS, meaning that the enzyme is no longer producing the protective nitric oxide but the damaging agent superoxide and leads to several developments, for instance the expression of adhesion molecules and the adhesion of white cells. This cascade eventually results in the development of atherosclerotic plagues in the arterial wall.’

Direct protection

Several classical drugs used to treat high blood pressure, such as some beta blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) are able to downregulate NADPH oxidase as well as target their primary goal. In turn, this action also normalises the function of eNOS. This could contribute to the cardiovascular protective effects of these compounds.

Förstermann: ‘However, giving pressure-reducing agents to anyone who is in danger of developing atherosclerosis is not an option given that not all patients also have high blood pressure. If they are given anyway it could make the patient fall unconscious. It would be best if we could make a compound that directly protects eNOS from uncoupling. This disease is a major health problem in industrialised countries and therefore such an approach is worth investigating.’ ●