NITRIC OXIDE AND EXPERIMENTAL ISCHEMIA-REPERFUSION INJURY

Giuseppe Rossoni
Department of Pharmacological Sciences, University of Milan, Milan, Italy

Nitric oxide (NO) is an important molecule which is involved in different physiological and phatophysiological processes in many organs and the enzymatic L-arginine-NO synthase pathway is now day accepted as the principal source of NO. Endothelial dysfunction leads to NO deficiency a condition found in several cardiovascular disorders including atherosclerosis, hypertension, heart failure, arterial thrombotic disorders, stroke and myocardial ischemia.
The precise role of NO, particularly in myocardial ischemia-reperfusion injury, is controversial whether NO is harmful or protective to the reperfused heart is still a matter of investigation. Over the past decade, an enormous number of studies (>100) have examined the role of NO in modulating the severity of myocardial ischemia-reperfusion injury in experimental animals: the vast majority (73%) have concluded that NO (either endogenous or exogenous) has a protective effect, and this cytoprotective role of NO is similar *in vivo* and *in vitro* studies [1].
On this basis, the major goal in the management of myocardial infarction (the most common cause of congestive cardiac failure) is to reduce post-myocardial infarction complications and mortality by reversing myocardial ischemia and limiting the infarct size. The attempts to achieve these objectives are centred primarily on haemodynamic interventions and nitric oxide (NO)-donors that have shown therapeutical potential. Organic nitrate and nitrate esters represent a time-honoured class of NO-donating agents used in cardiovascular therapeutics since the 19th century. These agents have direct vasoactive effects that have been used to treat ischemic heart disease, heart failure, and hypertension for many years. To overcome the therapeutic limitations of these drugs (half-life, systemic absorption with potentially adverse haemodynamic effects, and drug tolerance) novel NO donors (such as NO-aspirins) that offer selective effects have been developed and investigated. NO-aspirins are a new class of NO donors attached to an aspirin mojety originally designed for gastric mucosal protection. Example are NCX 4016 (2-acetoxy-benzoate 2-[1-nitroxy-methyl]-phenyl ester) that has been shown to display antiaggregatory and antithrombotic activity by a dual mechanism of action involving inhibition of cyclooxygenase and release of NO. Furthermore, NCX 4016, by NO donation, exerts a significant cardioprotection in the rabbit [2] and reduces the infarct size caused by ischemia-reperfusion in the anaesthetized rat [3] and pig [4].

References

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