Effect of Nitric Oxide Generators on Ischemia-Reperfusion Injury and Histamine Release in Isolated Perfused Guinea Pig Heart

E.		Masini ^a
F.		Gambassi ^a
S.		Bianchi ^b
L.		Mugnai ^b
M.		Lupini ^a
A.		Pistelli ^a
P.F.		Mannaioni ^a

^aDepartment of Preclinical and Clinical Pharmacology and ^bDepartment of Animal Biology, University of Florence, Italy

Abstract

In an ischemia-reperfusion model obtained in isolated perfused guinea pig heart by means of a double ligature of the left anterior descending coronary artery, the reperfusion of the ischemic myocardium leads to a release of lactate dehydrogenase and histamine, related to a decrease in the microdensitometry of cardiac mast cells and to a tissue calcium overload. The perfusion of the heart with L-arginine and with nitric oxide donors significantly reduces the release of histamine, the loss of mast cell metachromasia and calcium overload. These effects were potentiated by superoxide dismutase.

Correspondence to: Dr. E. Masini, Department of Preclinical and Clinical Pharmacology, University of Florence, I-50134 Florence (Italy)

Endothelium-derived releasing factor is a labile humoral substance which relaxes vascular smooth muscle and inhibits platelet aggregation and adhesion. Its chemical nature has now been identified as nitric oxide (NO) [1]. Isolated rat serosal mast cells release an inhibitor of platelet aggregation which possesses the characteristics of NO and has a negative modulatory action on histamine release [2]. It has been demonstrated that myocardial ischemia-reperfusion inhibits endothelium-dependent relaxation, probably due to reduced NO release, supporting the hypothesis that a lack of NO may play a role in the genesis of vasospasm. In the present study, we have investigated the effect of L-arginine, of its analogue NG-monomethyl-L-arginine and of some nitrovasodilators which spontaneously release NO on ischemia-reperfusion injury, and histamine release in isolated perfused guinea pig heart.

Ischemia-reperfusion was obtained in a Langendorff preparation of guinea pig heart by means of a double ligature and release of the left anterior descending coronary artery. Force of contraction and electrocardiogram were recorded and the perfusates collected for histamine and lactate dehydrogenase release. Calcium content and the densitometric analysis of mast cell metachromasia were determined in left-ventricular samples from control, ischemic-reperfused and drug-treated hearts as described previously [3].

The results obtained show a slight but significant increase in histamine release during ischemia and reperfusion accompanied by a time-dependent leakage of lactate dehydrogenase and

correlated with the tissue calcium overload and a loss of mast cell densi-tometry. The perfusion of the heart with L-arginine, the natural substrate for NO endogenous synthesis, and with some nitrovasodilators, such as sodium nitroprusside and 3-morpholinosydnonimine which spontaneously release NO, decreases histamine and lactate dehydrogenase release, and prevents cardiac calcium overload and mast cell degranulation. These effects were amplified when superoxide dismutase in low concentration (50 IU/ml) was perfused together with the drugs. NG-monomethyl-L-arginine, which inhibits endogenous NO biosynthesis, has an opposite effect. The results here reported suggest that the endogenous formation of NO and molecules able to generate NO are effective in reducing ischemic-reperfusion histamine and lactate dehydrogenase release and might have a beneficial role in the prevention of post-ischemic tissue injury.

258

Masini/Gambassi/Bianchi/Mugnai/Lupini/Pistelli/Mannaioni

References

Ignarro LJ, Buga GM, Wood KS, Byrns RE, Caudhuri G: Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci USA* 1987; 84:9265–9269.

Masini E, Salvemini D, Pistelli A, Ånggård E, Mannaioni PF, Vane JR: Rat mast cells release a nitric oxide like-factor which inhibits platelet aggregation and modulates the release of histamine. *Eur Histamine Res Soc XIX Meet, Kuopio, May 1990*.

3 Masini E, Bianchi S, Gambassi F, Palmerani B, Pistelli A, Carlomagno L, Mannaioni PF: Ischemic-reperfusion injury and histamine release in isolated and perfused guinea-pig heart: Pharmacological interventions. *Agents Actions* 1990;30: 198–201.