Abstract—The role of nitric oxide in lipoygenase metabolism after a process of ischemia-reperfusion in pancreas transplantation has been evaluated in this study. Sprague-Dawley rats were randomized into three groups, as follows: Group I.—Control animals not surgically manipulated; Group II.—Pancreas transplantation, after 12 h of organ preservation; Group III.—Same as II but with administration of N\textsuperscript{\textdagger} nitro-L-arginine methyl ester (a nitric oxide synthase inhibitor) (10 mg/Kg) prior to organ revascularization. The results show post-transplantation increases in leukotriene B\textsubscript{4} and 12-hydroxyeicosatetraenoic acid levels in pancreatic tissue. Nitric oxide synthase inhibition reversed the increases in 12-hydroxyeicosatetraenoic acid, but was unable to modify leukotriene B\textsubscript{4} increases suggesting the existence of a direct effect of nitric oxide on the 12-lipoygenase metabolism in pancreas transplantation.

INTRODUCTION

Ischemia and reperfusion (I-R) associated with organ transplantation leads to an inflammatory response which results in tissue injury (1). It has been suggested that the production of oxygen-derived free radicals (OFR) is the major reason for tissue damage after reperfusion (2, 3). Additional mechanisms of injury, reported from different models of I-R, include microcirculatory disturbances and white blood cell accumulation (4). Microcirculatory alterations associated with the I-R damage may be due to the increases in the production of eicosanoids
Inflammatory cell accumulation could be modulated by different mediators, including superoxide anion ($O_2^-$), Platelet activating factor (PAF), Leukotriene B$_4$ (LTB$_4$), some hydroxyeicosatetraenoic acids (HETEs) and nitric oxide (NO).

In this sense, it has been reported that superoxide anion can promote leukocyte adhesion in postcapillary venules (7). Consequently, it has been implicated as a mediator of I-R inducing leukocyte adhesion (8). PAF which is known to be a potent chemotactic agent for neutrophils, potentiates the production of leukotrienes and superoxide anion from stimulated polymorphonuclear cells and acts directly on vascular endothelium increasing its permeability (9, 10). LTB$_4$ is the most potent chemotactic factor for polymorphonuclear leukocytes that can be produced from arachidonic acid, and it readily induces neutrophil infiltration and activation (11). 12-HETE has been implicated in neutrophil chemotaxis and chemokinesis (12) and in the release of neutrophil lysosomal enzymes (13).

All these mediators act as inductors of the I-R related damage. By contrast, it has been reported that NO, a potent vasodilator agent, prevents leukocyte adhesion in various models of I-R, and it also minimizes the microvascular dysfunctions associated with reperfusion in ischemic tissues (14–16). In addition, NO can react with the superoxide anion (17) and consequently it has been proposed that the antiadhesion properties of NO could be related to its ability to scavenge superoxide anion (18).

NO is formed when L-arginine is converted to L-citrulline by the action of the enzyme NO synthase (NOS) (19). NOS can be present in two forms: a constitutive enzyme calcium- and calmodulin-dependent, and a non-calcium dependent cytokine-inducible enzyme (19). NOS can be inhibited by L-arginine analogues, such as N$^G$-nitro-L-arginine methyl ester (L-NAME).

Although all of the factors described are generally considered to be potent vasoactive mediators, so far there are no convincing results to suggest a central individual role of each one. Complex interactions exist between eicosanoids, OFR, PAF and NO during the development of I-R injury.

In this sense, previous studies of our group have demonstrated alterations of cyclooxygenase and lipoxygenase arachidonate metabolism in the I-R associated to pancreas transplantation. These alterations are correlated with PAF and OFR production (20). Also, NO has been revealed as an important inductor of cyclooxygenase metabolism in pancreas transplantation (21). No studies are known about the effects of NO on the lipoxygenase metabolism during this process. Taking into account the increased lipoxygenaslic metabolism after a process of I-R in pancreas transplantation (20), and the relationship between OFR and NO in various models of I-R (14–18), the purpose of this study is to ascertain if NO production can also modulate the increase in lipoxygenase metabolism observed after a process of I-R associated to pancreas transplanta-