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T. Hauet
H. Baumert
D. Mothes
T. Germonville
J. C. Caritez
M. Carretier
F. Journe
M. Eugene
J. P. Tillement

Lipid peroxidation after cold storage and normothermic reperfusion: the effect of trimetazidine

T. Hauet · H. Baumert D. Mothes · T. Germonville · J. C. Caritez · M. Carretier · F. Journe
Groupe de Recherche en Transplantation Multiviscérale and Institut National de Recherche Agronomique, Le Magneraud, Poitiers, Surgères, France

M. Eugene
Laboratoire de RMN, Paris, France

J. P. Tillement
Laboratoire de Pharmacologie, Creteil, France

T. Hauet (✉)
Service de Néphrologie, Centre Hospitalier, 17019 La Rochelle, France

Abstract Ischemia reperfusion injury is still a leading cause of early graft dysfunction after transplantation. Trimetazidine (TMZ) has been postulated to be protective against renal damage from oxygen free radicals. The aim of this study was to assess the effect TMZ during cold storage (CS) and normothermic reperfusion in an isolated perfused pig kidney model. Three groups were studied: control group, immediately perfused (G0), 48 h CS in Euro-Collins solution (G 1), and 48 h CS in Euro-Collins solution plus TMZ (G 2). Glomerular filtration rate (GFR) and fractional sodium reabsorption ($FRNa^+$) were calculated during reperfusion from urine and perfusate samples. Lipid peroxidation was determined by the renal tissue level of Schiff bases (SB) and malondialdehyde (MDA) after reperfusion. A histological evaluation was performed after reperfusion. Renal function was significantly improved and lipid peroxidation reduced after preservation in Euro-Collins solution plus TMZ. Functional data were closely related to histological damage. In conclusion, TMZ is a useful protective agent against renal damage induced by CS.

Key words Ischemia reperfusion · Trimetazidine · Isolated perfused kidney · Renal transplantation

Introduction

The reperfusion of previously ischemic tissue has been shown to be associated with exacerbation of cellular injury. Cadaveric donor kidneys are subjected to varying degrees of warm and cold ischemia before transplantation. Renal damage may occur from both prolonged lack of oxygen and reactive oxygen species generated after reperfusion. Lipid peroxidation is a critical pathway of tissue injury by reactive oxygen species in postischemic acute renal failure. Trimetazidine (TMZ) has been reported to exert beneficial effects in ischemic injury and to protect against hypoxic stress [1]. The aim of this study was to investigate TMZ for its abilities to limit oxidative membrane damage to kidneys during cold storage (CS) and reperfusion and to improve outcome in an isolated perfused pig kidney model [2, 3].

Materials and methods

Three groups of kidneys from Large White pigs were studied: (1) control group, immediately perfused (G0, $n = 6$); (2) kidneys preserved for 48 h at 4 °C in Euro-Collins (EC) solution (G 1, $n = 8$); and (3) kidneys preserved for 48 h at 4 °C in EC solution plus 10^{-6} *M* TMZ (G 2, $n = 8$). After cold storage, reperfusion was performed at 37 °5 C via the renal artery using a modified Krebs solution containing creatinine (85 µmol/l), a mixture of 22 amino acids, bovine serum albumin (5.0 g/100 ml) and *D*-glucose (10 mmol/l). The perfusion medium was gased with a mixture of 0_2 and CO_2 and the perfusion flow rate (PFR) was adjusted during perfusion to maintain a mean arterial perfusion pressure of 100 mmHg. Urine and perfusate samples were collected for determination of glomerular filtration rate (GFR) and sodium reabsorption after 15, 30, 60, 90 and 120 min of reperfusion. Lipid peroxidation was determined by renal tissue levels of Schiff bases and malondialdehyde immediately after cold ischemia and at 120 min as previous described [3].

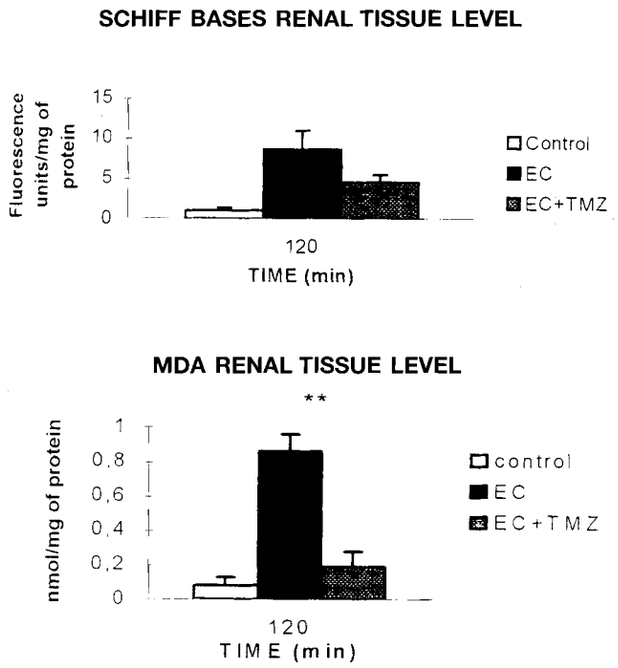

Fig. 1 Lipid peroxidation markers after reperfusion. * $P < 0.05$, ** $P < 0.01$

Results

After 48 h of cold ischemia, kidneys from G1 showed a significantly lower PFR (ml/min per g) than kidneys from G2: 2.4 ± 0.2 versus 1.19 ± 0.1 at 15 min 2.8 ± 0.2 versus 1.4 ± 0.1 at 60 min and 3.4 ± 0.3 versus 1.5 ± 0.17 at 120 min ($P < 0.01$). In G2 GFR (µl/min per g) was significantly higher than in G1: 82.5 ± 5.8 versus 22.1 ± 3.1 at 15 min, 135 ± 9.6 versus 41.2 ± 5.6 at 60 min and 3.4 ± 0.3 versus 1.5 ± 0.17 at 120 min ($P < 0.01$). Sodium reabsorption (%) was significantly higher in G2 than in G1: 68.4 ± 8.1 versus 26.2 ± 8.6 at 15 min, 64.3 ± 6.2 versus 21 ± 7.9 at 60 min and 54.6 ± 6.3 versus 18.6 ± 6.3 at 120 min ($P < 0.01$). Lipid peroxidation was also limited in G2 kidneys after reperfusion (Fig. 1).

Discussion

Experimental results have suggested that TMZ has direct effects on mitochondrial function, intracellular acidosis and intracellular calcium accumulation during reperfusion [4]. The addition of TMZ to the EC preservation solution improved PFR and renal function during reperfusion as a result of limiting medullary and interstitial edema which consequently reduced intrarenal vascular resistance. TMZ in the flush and storage solution led to a significant reduction in lipid peroxidation, particularly after normothermic reperfusion. This antioxidant effect is probably related to a better preservation of mitochondria and cellular homeostasis during cold ischemia and reperfusion. In conclusion, renal functional recovery after prolonged cold storage is improved by the addition of TMZ to the preservation solution. It is suggested that the mechanism of action is related to a protective effect against oxidative damage during cold ischemia and normothermic reperfusion.

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