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Pharmacokinetics of rinse solutions at 4° celsius

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Introduction

With the introduction of University of Wisconsin (UW) solution in liver preservation, rinsing of the graft before reperfusion with either blood or synthetic solutions has become a standard procedure [1, 2]. Synthetic rinse solutions were developed not only to rinse out potassium and metabolites from the liver graft, but also to apply protective substances during the rinse-out phase [2–4]. In this study, we investigated the uptake of radiolabelled adenosine as an example of the uptake of low molecular protective substances during a rinse with a high viscosity solution at 4 °C.

Materials and methods

Experiments were carried out according to the guidelines of the local animal ethics committee. Male Wistar rats (270–320 g) were used in all experiments. After intraperitoneal anaesthesia with pentobarbital, livers and kidneys were flushed out through the aorta (10 ml solution at 2 ml/min) and the portal vein (5 ml at 1 ml/min) with 4 °C cold UW solution. Livers and kidneys (en bloc) were excised and stored at 4 °C with a portal and an aortic catheter ligated in the respective vessel. Microdialysis membranes were placed in livers (10-mm membrane) and kidneys (5-mm membrane) and perfused at 10 µl/min with a Krebs-Henseleit buffer in a similar set-up as described by Van Wylen et al [5]. After 2 h of storage, livers and kidneys were rinsed at 4 °C or 37 °C with UW supplemented with ^{3}H-adenosine. Effluent from the microdialysis membranes was collected and counted in a beta counter. Also, random samples were taken from livers and kidneys and minced in scintillation liquid also to be counted. Results are given as mean counts per minute for the microdialysis effluent and the mean ± SE for the fraction of the recovered radioactivity divided by the total applied radioactivity.

Results

Results are given in Figs. 1 and 2. At 4 °C 12 ± 3 % of the total applied ^{3}H-adenosine was taken up by the liver centre, 6.7 ± 1.6 % by the liver periphery, and 2.0 ± 1.4 % and 1.9 ± 1.1 % by the renal cortex and medulla, respectively. At 37 °C the uptake was considerably higher: 20.7 ± 5.5 % for the liver centre, 12.3 ± 4.1 % for the liver periphery, and 3.0 ± 1.8 % and 2.9 ± 1.7 % for the renal cortex and the medulla, respectively. Diffusion of labelled adenosine from the portal system into the microdialysis membranes was much higher than diffusion of labelled adenosine from the arterial system to the membranes. Diffusion of labelled adenosin from the vascular system in livers to the luminal space of the microdialysis membranes decreased rapidly after appliciation of the rinse.

Discussion

Rinsing livers before reperfusion is implemented to rinse out potassium and/or adenosine in order to avoid cardiac arrythmias [1]. Furthermore, the rinsing of or-

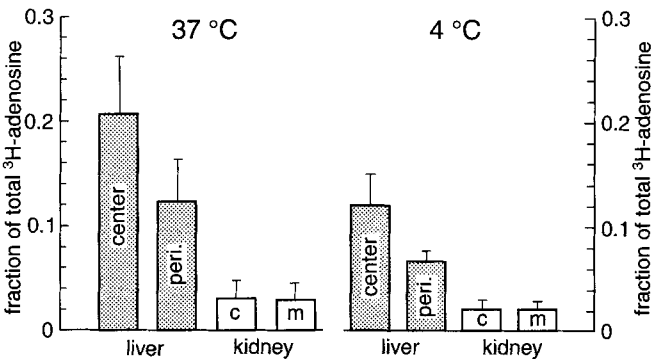

Fig. 1 Uptake of ^{3}H-adenosine by the liver and kidney at 37 °C and at 4 °C (*peri.* Periphery, *c* cortex, *m* medulla)

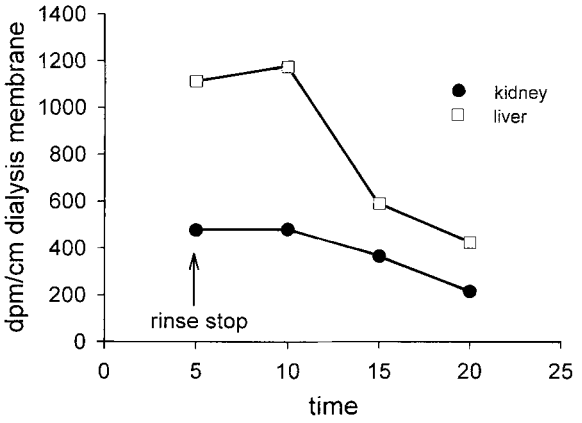

Fig. 2 Diffusion of labelled adenosine from the portal and arterial systems into the microdialysis membranes

gans has improved graft survival by rinsing inflammatory mediators [6] and thus decreasing leucocyte-endothelial and Kupffer cell interaction [7]. Adenosine itself [4] and the rinse temperature have been found to be important factors that improve graft function in experimental liver transplantation [8, 9]. In this study we demonstrated that at 37 °C the amount of adenosine being taken up by the graft from the rinse solution was significantly higher than at 4 °C. At temperatures below the transition temperature of membranes most active transport processes stop and intracellular uptake of protective substances is facilitated by diffusion only or along a pressure gradient. If cytoprotective substances are to be applied during a rinse or a flush-out, temperatures above the transition temperature of cell membranes facilitate that uptake.

References

1. Belzer FO (1990) Correct use of University of Wisconsin preservation solution (letter). Lancet 335 (8685): 362
2. Sanchez-Urdazpal L, Gores GJ, Lemasters JJ, Thurman RG, Steers JL, Wahlstrom HE, Hay EI, Porayko MK, Wiesner RH, Krom RA (1993) Carolina rinse solution decreases liver injury during clinical liver transplantation. Transplant Proc 25 (1 Pt 2): 1574–1575
3. Gao W, Takei Y, Marzi I, Lindert KA, Caldwell-Kenkel JC, Currin RT, Tanaka Y, Lemaster JJ, Thurman RG (1991) Carolina rinse solution – a new strategy to increase survival time after orthotopic liver transplantation in the rat. Transplantation 52: 417–424
4. Gao W, Hijioka T, Lindert KA, Caldwell-Kenkel JC, Lemaster JJ, Thurman RG (1991) Evidence that adenosine is a key component in Carolina rinse reducing graft failure after orthotopic liver transplantation in the rat. Transplantation 52: 992–998
5. Van Wylen DG, Schmit TJ, Lasley RD, Gingell RL, Mentzer RM Jr (1992) Cardiac microdialysis in isolated rat hearts: interstitial purine metabolites during ischemia. Am J Physiol 262 (6 Pt 2): H1934–1938
6. Schilling M, Tilton B, Storck M, Hammer C, Abendroth D (1993) Mediator clearing effects of rinse solution in lung preservation. Transplant Proc 25: 3212
7. Post S, Palma P, Rentsch M, Gonzalez AP, Menger MD (1993) Differential impact of Carolina rinse and University of Wisconsin solutions on microcirculation, leucocyte adhesion, Kupffer cell activity and biliary excretion after liver transplantation. Hepatology 18: 1490–1497
8. Bachmann S, Caldwell-Kenkel JC, Oleksy I, Steffen R, Lemaster JJ, Thurman RG (1992) Warm Carolina rinse solution prevents graft failure from storage injury after orthotopic rat liver transplantation with arterialization. Transplant Int 5: 108–114
9. Takei Y, Gao WS, Hijioka T, Savier E, Lindert KA, Lemasters JJ, Thurman RG (1991) Increase in survival of liver grafts after rinsing with warm Ringer's solution due to improvement of hepatic microcirculation. Transplantation 52: 225–230