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Effect of preservation solutions UW and EC on the expression of matrix metalloproteinase II and tissue inhibitor of metalloproteinase II genes in rat kidney

Wpływ płynów konserwujących UW I EC na ekspresję genów metaloproteinazy II i tkankowego inhibitora metaloproteinazy II

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Matrix metalloproteinases and tissue inhibitor of metalloproteinases play an important role in the regulation of mesangial cell proliferation and may be involved in ischemia-reperfusion injuries. Preservation solutions are thought to diminish the ischemic injury and appropriate choice of the solution should guarantee a better graft function and good prognosis for graft survival. The aim of the study was to examine the effect of preservation solutions UW and EC on the expression of matrix metalloproteinase II and tissue inhibitor of metalloproteinase II genes in rat kidney.

The study was carried out on Wistar rat kidneys divided into 3 groups: kidneys perfused with 0.9% NaCl (control group), with UW, and with EC preservation solution.

The results show an enhancement of *MMP-2* and *TIMP-2* gene expression after 12 min of cold ischemia. This increase was more expressed in kidneys preserved with UW solution in comparison with kidneys perfused with EC solution and 0.9% NaCl. After 24 h of cold ischemia the expression of *MMP-2* and *TIMP-2* genes in kidney perfused with UW solution decreased, while in kidneys perfused with EC it was increased. After warm ischemia the *MMP-2* and *TIMP-2* gene expression increased, whereas it was significantly lower in kidneys perfused with EC solution.

Key words: **UW • EC • matrix metalloproteinase II • tissue inhibitor of metalloproteinase II**

Streszczenie

Metaloproteinazy macierzy oraz tkankowe inhibitory metaloproteinaz odgrywają istotną rolę w regulacji proliferacji komórek mezangium i mogą brać udział w procesie uszkodzenia niedokrwienno-reperfuzyjnego. Płyny konserwujące stosowane są w celu zmniejszenia uszkodzenia niedokrwiennego, ich właściwy wybór może wpływać na dalsze funkcjonowanie przeszczepu.

Celem pracy była ocena wpływu płynów konserwujących UW i EC na ekspresję genów metaloproteinaz macierzy oraz tkankowych inhibitorów metaloproteinaz w nerce szczura.

Badanie przeprowadzone na szczurach rasy Wistar podzielonych na 3 grupy: nerki perfundowane 0,9% NaCl (grupa kontrolna), grupa perfundowana płynem UW, grupa perfundowana płynem EC. Wyniki wykazały nasilenie ekspresji genu *MMP-2* i *TIMP-2* po 12 min zimnego niedokrwienia. Wzrost ten był najbardziej nasilony w nerkach perfundowanych płynem EC w porównaniu z nerkami perfundowanymi płynem UW i 0,9% NaCl. Po 24 h zimnego niedokrwienia ekspresja genów *MMP-2* i *TIMP-2* w nerkach perfundowanych płynem UW zmalała, natomiast EC wzrosła. Po okresie ciepłego niedokrwienia ekspresja genów *MMP-2* i *TIMP-2* wzrosła, jednakże była istotnie mniejsza w nerkach perfundowanych płynem EC.

Słowa kluczowe: **UW • EC • metaloproteinaza II • tkankowy inhibitor metaloproteinazy II**

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Introduction

Matrix metalloproteinases (MMP) are a family of proteins that are capable of digesting extracellular matrix and basement membrane components under physiological conditions. MMP are inhibited by tissue inhibitors of metalloproteinases (TIMP) through formation of non-covalent complexes with MMP [22]. The tissue inhibitor of metalloproteinases comprises a four-member family of homologous MMP inhibitors [11]. The transcription of TIMP is regulated by similar cytokines and growth factors that control MMP expression. MMP and TIMP are involved in many biological processes, such as embryonic development, organ morphogenesis including the kidneys, and angiogenesis. Increased expression or activity of MMP was described in cases of several different glomerular diseases, such as glomerulonephritis IgA nephropathy, and diabetic nephropathy [24,27]. The precise role of MMP and TIMP in organ transplantation has not yet been clarified. However, chronic kidney allograft rejection is characterized by progressive fibrosis in which the regulation of extracellular matrix metabolism appears to be of high significance. Therefore, MMP and TIMP are likely candidates to play an active role in transplantation medicine [1,9].

MMP-2 plays an increasingly recognized role in the regulation of mesangial cell proliferation in cell cultures and in glomerulonephritis. These proteolytic enzymes appear to induce the activation of glomerular mesangial cells [20]. Therefore, a continuous expression of mesangial cell MMP-2 as a result of inflammatory stimuli must finally contribute to the evolution of glomerulosclerosis. The direct effect of MMP-2 on mesangial cell proliferation was confirmed *in vivo*, since infusion of activated MMP-2 into the renal artery demonstrated focal areas of mesangial cell proliferation in rat glomeruli [18]. Moreover, MMP play an important role in ischemia-reperfusion injury [25].

Table 1. Composition of UW and EC storage solutions

Component	Euro-Collins (EC) [mM]	University of Wisconsin (UW) [mM]
Sodium	10	35
Potassium	115	125
Magnesium	30	5
Sulphate	30	5
Phosphate	50	25
Chloride	15	–
Bicarbonate	10	100
Glucose	140	–
Raffinose	–	30
Glutathione	–	3
Adenosine	–	5
Allopurinol	–	1
Hydroxyethyl starch	–	50 g/L
Dexamethasone	–	16 mg/L
Insulin	–	40 U/L
Penicillin	–	2×10^5 U/L

Recent studies show that MMP-2 is involved in several acute biological processes independent of its actions on extracellular matrix proteins [16]. These include platelet activation, regulation of vascular tone and

Table 2. *MMP-2* gene expression in rat kidneys of the control, EC and UW solution groups

Period	Group (X±SD)			p
	Control [cu]	EC [cu]	UW [cu]	
ICI_0	0.22±0.18	0.77±0.47	3.36±1.17*,#	<0.001
CI_{24}	0.30±0.23	1.63±0.71*	0.87±0.43#	<0.001
WI	4.32±1.50	2.14±1.03*	4.08±0.65	<0.01
p	<0.001	<0.001	<0.001	–

ICI_0 – initial period of cold ischemia; CI_{24} – 24 h cold ischemia; WI – warm ischemia; * p<0.05 as compared with control group; # p<0.05 as compared with EC group; cu – conventional unit – multiplication of constant mRNA expression of ribosomal protein L19.

ischemia-reperfusion injury after reperfusion of the transplanted kidney. MMP-2 is activated during oxidative stress injury and is responsible for the degradation of cytoskeletal proteins.

Preservation solutions are thought to diminish the ischemic injury and appropriate choice of the solution should guarantee a better graft function and good prognosis for graft survival. Many studies concerning the influence of preservation solutions on the obtained kidney have been published, but the assessment is still ambiguous [4]. University of Wisconsin (UW) and Euro-Collins (EC) solutions are often compared. The components of both solutions are presented in Table 1.

The aim of the study was to examine the effect of preservation solutions UW and EC on the expression of matrix metalloproteinase II and tissue inhibitor of metalloproteinase II genes in rat kidney.

Material and Methods

Animals

The study was approved by the local ethics committee (No11/02/2002). Male Wistar rats weighing 300–350 g were used in this experiment. They were allowed to acclimatize for a minimum of 10 days prior to the study. The rats were housed in a room maintained at 21±1°C with a 12-h light--dark cycle with the light cycle beginning at 6:00 a.m. All animals were fed standard rat chow and water ad libitum. Food was withheld overnight before surgery.

The rats were divided into 3 groups as follows:
- group NaCl, in which kidneys were perfused with 0.9% NaCl (control group) (n=8);
- group UW, in which kidneys were perfused with UW preservation solution (n=8);
- group EC, in which kidneys were perfused with EC preservation solution (n=8).

Experimental protocol

The rats were anesthetized with ketamine (Ketolar). The abdominal cavity was opened via middle incision. The aorta, vena cava inferior, and finally left and right renal vessels were atraumatically isolated. The catheter (Becton Dickinson Vascular Access Inc., Sandy, Utah USA) was inserted in the aorta. The aorta and vena cava superior were clamped over the right and left renal artery, and then the vena cava inferior was catheterized to enable the outflow of perfusion solution.

The solutions were perfused in the aorta continuously at 100 ml/h for 12 minutes (temperature of the solution +4°C, volume of injected solution 20 ml). The perfusion was performed using a perfusion pump (Duet Nowa Standard 50). Finally, bilateral nephrectomy was performed.

The left kidneys were divided into two equal parts. The upper parts of left kidneys were immediately frozen in liquid nitrogen (cold ischemia 0). The lower parts of left kidneys and right kidneys were placed in cold (0–4°C) UW, EC or 0.9% NaCl solution for 24 hours (cold ischemia 24 h).

The lower parts of left kidneys were frozen using liquid nitrogen. The organs were preserved at the temperature of –70°C until evaluation. Subsequently the right kidneys were incubated in 0.9% NaCl at temp 20°C for 30 min (warm ischemia). Then the kidneys were frozen using liquid nitrogen. The organs were preserved at the temperature of –70°C until evaluation.

The expression of studied genes was assessed using the RT-PCR method as previously described [3].

Statistical analysis

The parameters were statistically evaluated using ANOVA and Tukey test.

Results

The expression of *MMP-2* gene after 12 min of cold ischemia (cold ischemia 0) in kidneys perfused with UW and EC solutions was significantly increased in comparison with kidneys from the control group. Moreover, the *MMP-2* gene expression in kidneys perfused with UW solution was significantly higher in comparison with kidneys perfused with EC solution (Table 2). After 24 h of cold ischemia the *MMP-2* gene expression in control kidneys did not differ from baseline values (cold ischemia 0), in kidneys perfused with EC solution it was increased in comparison with baseline values, whereas in kidneys perfused with UW solution it was decreased.

Table 3. *TIMP-2* gene expression in rat kidneys of the control, EC and UW solution groups

Period	Group (X±SD)			p
	Control [cu]	EC [cu]	UW [cu]	
ICI_0	0.32±0.18	1.78±0.67*	2.83±0.70*,#	<0.001
CI_{24}	0.33±0.14	2.16±0.99*	0.76±0.40#	<0.001
WI	2.19±1.02	2.31±1.23	2.47±1.86	NS
p	<0.001	NS	<0.005	–

ICI_0 – initial period of cold ischemia; CI_{24} – 24 h cold ischemia; WI – warm ischemia; * p<0.05 as compared with control group; # p<0.05 as compared with EC group; NS – non-significant; cu – conventional unit – multiplication of constant mRNA expression of ribosomal protein L19.

The *MMP-2* gene expressions after warm ischemia time were significantly increased in the control group, as well as in kidneys perfused with EC and UW solutions compared with baseline values (cold ischemia 0) and values after 24 h of cold ischemia. Nevertheless, expression of the *MMP-2* gene in kidneys perfused with EC solution was significantly decreased in comparison with kidneys from the control group and perfused with UW solution.

Expressions of the *TIMP-2* gene after 12 min of cold ischemia (cold ischemia 0) in kidneys perfused with EC and UW solutions were significantly increased in comparison with kidneys from the control group. Moreover, the *TIMP*-2 gene expression in kidneys perfused with UW solution was significantly higher in comparison with kidneys perfused with EC solution (Table 3). After 24 h of cold ischemia the *TIMP-2* gene expression in control kidneys and perfused with EC solution did not differ from baseline values (cold ischemia 0), whereas in kidneys perfused with UW solution it was decreased in comparison with baseline values.

The *TIMP-2* gene expression after warm ischemia time was significantly increased in the control group in comparison with baseline values (cold ischemia 0), and values after 24 h of cold ischemia, whereas in kidney perfused with EC and UW solution it did not differ from baseline values (Table 3).

Discussion

The preservation of the harvested organ constitutes a prerequisite for organ transplantation. For kidney preservation, hypothermia storage remains the most common technique in use. However, hypothermic organ preservation is associated with oxygen deprivation, which inevitably leads to some degree of ischemia-reperfusion injury upon transplantation [19]. During the renal storage before transplantation, hypothermic swelling of the medullary thick ascending tubules results in mechanical constriction of the peritubular capillaries and vasa recta [5]. During the reperfusion, a large amount of reactive oxygen agents (superoxide anions, hydroxyl radicals, and hydrogen peroxides) is produced by the re-entry of oxygenated blood in the ischemic tissue. Euro-Collins and University of Wisconsin solutions are the mainstay of therapy for hypothermic storage protection [12,30]. Nevertheless, the delayed graft function related to acute tubular necrosis (ATN) still remains an important complication after transplantation [21]. Recent studies have demonstrated that ischemia and reperfusion contribute to the non-immunological damage that complicates transplantation [17].

In our study we investigated the expressions of *MMP-2* and *TIMP-2* genes in rat kidneys perfused with UW and EC solutions. The cellular and molecular mechanisms underlying the changes during ischemia-reperfusion remain not fully understood. MMP are important regulators of matrix deposition, and uncontrolled matrix remodeling. Our study showed increased expression of the *MMP-2* gene after reperfusion in kidneys perfused with UW solution. After warm ischemia, expression of the *MMP-2* gene was significantly lower in kidneys perfused with EC solution in comparison with control kidneys and perfused with UW solution. The *TIMP-2* gene expression was significantly increased in kidneys perfused with UW solution, whereas after warm ischemia there were no significant differences between studied groups.

MMP-2 and TIMP-2 play important roles in tubular fibrosis and extracellular matrix deposition. Lutz et al. [17] showed that early MMP inhibition resulted in significantly reduced protein excretion that was paralleled by a lower grade of chronic allograft nephropathy. Rodrigo et al. showed that serum MMP-2 was significantly higher in patients with chronic transplant nephropathy than in patients with acute rejection, stable graft function and healthy donors. In an experimental study in chronic renal allograft rejection, mRNAs of MMP-2, MMP-12 and TIMP-1 and TIMP-2 were found to be significantly augmented [26]. Nicholson et al. found that intragraft expression of mRNA for TIMP-1 and TIMP-2 is significantly correlated with human allograft fibrosis and expression of TGF-β [23]. These authors concluded that alterations in the ratio of TIMP and MMP in the transplant kidney may be an important molecular mechanism leading to the development of tubulo-interstitial fibrosis [28].

Renal ischemia-reperfusion injury is the major cause of acute renal failure and may also be involved in the development and progression of some forms of chronic kidney disease.

Previous studies have shown that MMP play an important role in ischemia-reperfusion injury and subsequent progression to chronic allograft nephropathy [15,25]. Upregulation of MMP propagates the inflammatory response that drives ischemia-reperfusion injury. On the other hand,

inhibition of MMP significantly reduces ischemia-reperfusion kidney injury and tubular fibrosis [10,14].

The above reports indicate the important role of MMP in ischemia-reperfusion injury, tubular fibrosis and development of chronic allograft nephropathy.

Previous studies showed the increased expression of MMP-2 and TIMP-2 during I/R.

The enzymatic activity of MMP-2 located on the cell surface is specifically inhibited by TIMP-2 [29]. Hypoxia-induced MMP-2 shows a dual effect, affecting both cell death and cell life. In the I/R model a significant increase was demonstrated both in MMP-2 activity and TIMP-2 protein levels by reoxygenation. The increase in MMP-2 secretion caused by reoxygenation may be stimulated by the oxidative stress which occurs following reoxygenation. Gashe et al. reported that the activation of MMP-2 increased with oxidative stress [7]. TIMP-2 protein level may be interpreted as a compensation mechanism related to increased proMMP-2. In contrast to the findings of previous studies reporting that MMP-2 protein is expressed by endothelial cells, it has been stated that MMP-2 transcription also increases through hypoxia-induced AP-1 (activating protein-1) and hypoxia-inducible factor-1-α [2,13]. However, these responses may be cell-specific and depend on the experimental model and conditions used. Both angiogenesis and cell death involve the degradation of basal membrane and extracellular matrix, as well as the impairment of cell–cell and cell–matrix interactions. It is reported that high levels of MMP cause cells to become detached from the extracellular matrix, directing them toward apoptosis [6]. Reperfusion was also shown to result in structural and biochemical changes in endothelial cells, leading to damaged endothelium [8]. In summary, our results show an enhancement of *MMP-2* and *TIMP-2* gene expression after 12 min of cold ischemia. This increase was more expressed in kidneys preserved with UW solution in comparison with kidneys perfused with EC solution and 0.9% NaCl. After 24 h of cold ischemia the expression of *MMP-2* and *TIMP-2* genes in kidney perfused with UW solution decreased, while in kidneys perfused with EC it was increased. After warm ischemia the *MMP-2* and *TIMP-2* gene expression increased, whereas it was significantly lower in kidneys perfused with EC solution.

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