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Effects of Glucose in Protected Ischemic Kidneys*

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Summary. Energy reserves (TAN) and anaerobic substrates (glucose, glycogen) are lower in renal than in myocardial tissue. Euro-Collins-solution contains nearly 200 mmol/l glucose, while the HTK-solution of Bretschneider contains none. Therefore the influence of glucose on kidney lactate production, on energy reserves (TAN), intrarenal pH and on morphology during the protection of ischemic kidneys was analysed using either Euro-Collins-solution, or modified "Euro-Collins-solution", containing mannitol instead of glucose, or HTK-solution with and without the addition of 5, 10 and 20 mmol/l glucose. Glucose content changed during kidney perfusion with Euro-Collins-solution from about 60 to 800 $\mu mol/g_{dw}$. While intrarenal pH decreased from 7.1 to 5.1 in Euro-Collins-kidneys during 420 min of ischemia at 25 °C, pH decreased to 6.7 with the modified, mannitol containing "Euro-Collins-solution". In HTK-protected kidneys intrarenal pH decreased with increasing glucose addition to the solution. Although *T*otal *A*denine *N*ucleotides are highest at the end of ischemia with Euro-Collins-solution, structural protection after the same ischemic stress was best in HTK-protected kidneys without glucose addition. We conclude that glucose stimulated lactate production, reduced interstitial pH in the kidney even in combination with a highly buffered solution and that it might cause greater membrane permeability leading to a structural detoriation. Mannitol seemed more appropriate than glucose in this respect, although other substances, which provide energy substrate and prevent structural damage, may exist.

Key words: Euro-Collins-solution, Glucose, HTK-solution, Intrarenal pH, Lactate, Renal ischemia.

Introduction

During ischemia glycolysis is not adequate to meet organ energy demand. The content of energy reserves (ATP, ADP, AMP) [5, 14–16, 19, 28, 31, 32, 38, 55–57], as well as of anaerobically available substrates (glucose, glycogen) [23, 33, 42, 46] is lower in ischemic kidneys, than (for example) in the myocardium [8–13, 29, 30, 40].

The *H*istidine-*T*ryptophan-*K*etoglutarat-solution of Bretschneider, provides good protection against renal ischemia for 2 h at close to body temperature, [36, 40] and contains no glucose apart from 1 mM K-α-Ketoglutarat, which, beside its membrane protective properties, could also serve as a substrate for the proximal tubules [18, 34, 47]. Nevertheless, glucose might serve as an energy source, at least for the distal tubules [1, 2, 17, 22, 23, 33, 42, 53, 54]. The Euro-Collins-solution contains nearly 200 mM glucose [20, 21, 26] (Table 1), but this stimulates renal glycolysis, especially at higher temperatures i.e. 15, 25 and 35 °C [37, 38].

We investigated the effect of the addition of glucose (5, 10 and 20 mmol/l) to the HTK-solution with a histidine/histidine-HCl buffer of 200 mM, to discern any improvement in the protection of energy reserves (*T*otal *A*denine *N*ucleotides, TAN) in comparison with HTK-protection without glucose admixture, whilst excessive intrarenal acidosis was avoided. The exchange of glucose for mannitol in the Euro-Collins-solution might also prevent the excessive acidosis, otherwise seen with this perfusate [37].

Materials and Methods

Experiments were performed on 72 kidneys of mongrel dogs with a median body weight ($\bar{x}$) of 32 kg. After premedication with 90 mg piritramide[1] and 0.5 mg atropine[2], anesthesia was induced about 30 min later with 5–10 mg/kg sodium thiopental[3], and 0.1 mg fentanyl dihydrogencitrate[4], and continued with a combination of fentanyl dihydrogencitrate, isoflurane[5] (0.5–0.7 Vol%) and N_2O/O_2

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1 Dipidolor; Janssen GmbH, Düsseldorf, FRG
2 Atropinsulfat Drobena; Drobena Arzneimittel GmbH, Berlin, FRG
3 Trapanal; Byk Gulden, Konstanz, FRG
4 Fentanyl-Janssen; Janssen GmbH, Neuss. FRG
5 AErrane-Isofluran (Isofluran), Ohio Medical Pharma-Vertrieb GmbH, Puchheim, FRG

Table 1. Composition of different kidney protective solutions

	HTK-solution by Bretschneider	Euro-Collins-solution	Sacks II-solution
Na^+	15	10	14
K^+	10	115	126
Ca^{++}	–	–	–
Mg^{++}	4	–	8
Cl^-	50	15	16
HCO_3^-	–	10	20
HPO_4^{--}	–	43	51
$H_2PO_4^-$	–	15	18
Glucose	–	198	–
Tryptophan	2	–	–
Ketoglutarat	1	–	–
Mannitol	30	–	208
Buffer	Histidine Histidine-HCl	Bicarbonate Phosphate	Bicarbonate Phosphate
Osmolarity: calculated	310 mosmol/l	406 mosmol/l	461 mosmol/l
measured	~ 300 mosmol/l	~ 360 mosmol/l	~ 400 mosmol/l
pH	7,3 (8 °C)	7,2 (20 °C)	7,2 (20 °C)
pO_2	~ 200 mmHg (37 °C)	~ 100 mmHG (37 °C)	

(all concentrations are expressed as mmol/l)

(79:21). Respiration was maintained via an endotracheal tube with a Dräger respirator AV1[6], with an end-expiratory CO_2 value of about 5.5% measured continuously with a Datex CO_2 analyser[7]. Fluid balance was maintained by 500–1,000 ml Tutofusin[8] and 500 ml glucose 5%[9] until kidney perfusion with the protective solutions, either with HTK-solution of Bretschneider[10] (without and with addition of 5, 10 or 20 mmol/l glucose) or with Euro-Collins-solution[11] or with modified "Euro-Collins-solution" (198 mmol/l mannitol instead of 198 mmol/l glucose). The dogs received 1.250 I.U. heparine[12] 20 min before perfusion.

The arterial blood pressure was continuously measured with a Statham element (P 23 ID)[13] via a catheter lying in the a. brachialis and was maintained around RR 120/80 mmHg with a heart rate of about 80/min.

After laparotomy the kidneys were freed from the peritoneum and the v. cava inferior and the aorta abdominalis were dissected proximal and distal to the origin of the left and right vv. renales and aa. renales.

If more than one renal artery to each kidney existed, then all vessels originating from the aorta were ligated 5 cm proximal and distal to the renal arteries. A catheter, either for single kidney perfusion [43], or for simultaneous perfusion of both kidneys, was inserted into the aorta abdominalis distal to the origins of the aa. iliacae communes and pushed up towards the origin of the renal arteries.

An appropriate perfusion catheter was threaded into the renal artery, or if both kidneys were to be perfused, into that part of the aorta whence each renal artery originated. During this procedure a flow of about 100 ml/min was maintained by a peristaltic pump[14], to avoid any ischemia prior to the protective perfusion with the 8 °C HTK-solution (Table 1); the catheter was then fixed with a ligature around the renal artery or with two ligatures around the aorta proximal and distal to the origin of the renal arteries. By raising perfusion flow to 400–500 ml/min x 100 gww, a pressure of about 100 mmHg within the first minute of perfusion was achieved. The renal vein was incised and clamped close to the v. cava inferior within 30–40 s to allow the perfusate to escape.

If kidneys were perfused with the Euro-Collins-solution, because of its high potassium content (115 mmol/l) (Table 1) and the consequent danger of cardiac arrest, the perfusion flow was only raised after the venous incision. Otherwise, extrasystoles occurred, leading to cardiac arrest.

After the 6–10 min of perfusion of the kidneys with the HTK- or Euro-Collins-solutions, the kidneys were excised within a minute and were incubated in the respective solution at 25 °C. A total of 26 kidneys was used for continuous intrarenal pH-measurement at the corticomedullary border, as previously described [37] and 46 kidneys were used for biochemical analysis of ATP[15], ADP[16], AMP[16], glucose [4] and lactate [35], with 10 tissue samples over 7 h obtained from each kidney. Each tissue sample consisted of about 2/3 cortex and about 1/3 medulla. In addition to biochemical analysis, tissue was fixed in 1.5% glutaraldehyde for light microscopy both at the beginning of ischemia and after 6 h of ischemia in the same kidney.

Results

The renal glucose content was between 60–70 μmol/gdw before protective perfusion. After perfusion with the HTK-solution the glucose content fell to about 10 μmol/gdw.

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6 Dräger Respirator AVl, Dräger Werke, Lübeck, FRG
7 Datex Instrumentation OY; Espoo, Finnland
8 Tutofusin; Pfrimmer & Co. GmbH, Erlangen, FRG
9 Glucose 5% Braun; B. Braun Melsungen AG, Melsungen, FRG
10 Kardioplegische Lösung HTK nach Bretschneider; Dr. Franz Köhler Chemie GmbH, Alsbach, FRG
11 Euro-Collins-Lösung; Dr. E. Fresenius, Bad Homburg v. d. H., FRG
12 Heparin-Natrium Braun 2.500 I.E./5 ml; B. Braun Melsungen AG, Melsungen, FRG
13 P 23 ID; Gould Statham Instr., Oxnard, USA
14 Doppelpumpe 102000; Stöckert Inst., München, FRG
15 Testkombination ATP, Boehringer Mannheim GmbH, Mannheim, FRG
16 Testkombination ADP/AMP, Boehringer Mannheim GmbH, Mannheim, FRG

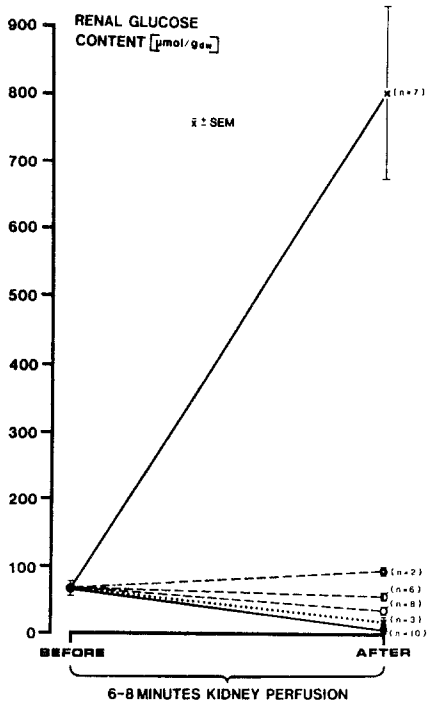

Fig. 1. Renal glucose content before and after kidney perfusion with HTK-solution for 6–10 min without o——o and with different admixture of glucose (5, 10, and 20 mmol/l – – –) and with Euro-Collins-solution containing 198 mmol/l glucose x——x and with modified "Euro-Collins-solution" containing 198 mmol/l mannitol instead of glucose. Figs. 1–4: —•— HTK solution (without glucose); – –o– – HTK solution (5 mmol/l glucose); – –•– – HTK solution (10 mmol/l glucose); – –o– – HTK solution (20 mmol/l glucose); ——x—— Euro-Collins-solution (198 mmol/l glucose); ···x··· "Euro-Collins-solution" (198 mmol/l mannitol)

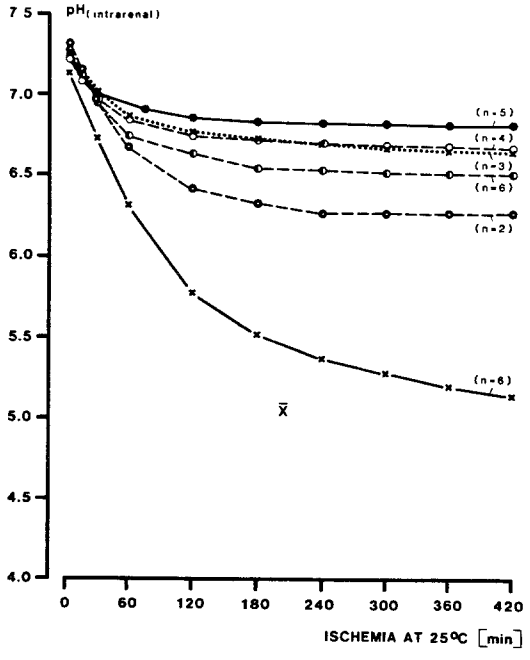

Fig. 2. Tissue acidification during renal ischemia at 25 °C after perfusion with HTK-solution without —— and with different admixture of glucose – – – and with Euro-Collins-solution with and without glucose

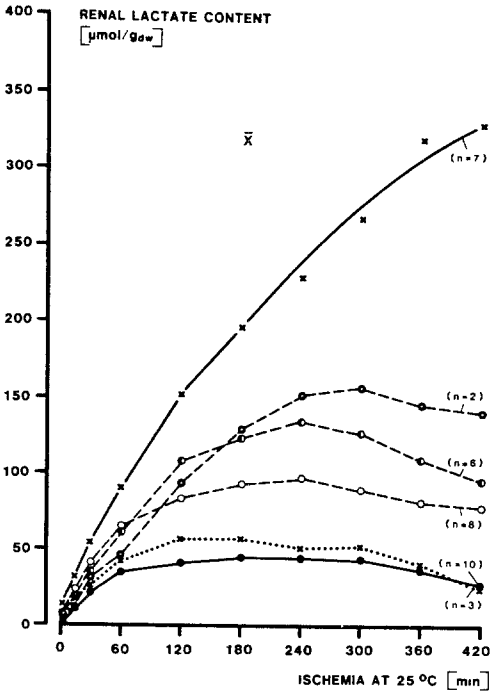

Fig. 3. Renal lactate content (same conditions as in Fig. 2)

After perfusion with HTK-solution with 5 mmol/l glucose, the glucose content of the kidney was about 35 µmol/gdw.

After perfusion with HTK with 10 mmol/l glucose, the glucose content rose to 60 µmol/gdw and after perfusion with HTK-solution with 20 mmol/l glucose a further increase to 90 µmol/gdw (Fig. 1), was evident.

After perfusion with Euro-Collins-solution, containing 198 mmol/l glucose, renal glucose content rose to about 800 µmol/gdw. When glucose was exchanged for mannitol in the Euro-Collins-solution, the glucose content was about 20 µmol/gdw (Fig. 1), after perfusion.

The intrarenal pH decreased from 7.25 to 6.8 after 7 h of complete ischemia at 25 °C under HTK-protection. With admixture of 5 mmol/l glucose the pH decreased to 6.7, with admixture of 10 mmol/l glucose to pH 6.5, and with admixture of 20 mmol/l glucose to pH 6.25 (Fig. 2).

The intrarenal pH in Euro-Collins-kidneys fell from pH 7.15 to 5.2 after 7 h of ischemia at 25 °C. After replacing the glucose in the solution by mannitol, the intrarenal pH fell from pH 7.25 to below pH 6.8 after 7 h protection with the solution (Fig. 2).

The renal lactate content rose in HTK-protected kidneys from about 4 µmol/gdw to about 45 µmol/gdw during ischemia of 3 to 4 h at 25 °C. The addition of 5 mmol/l glucose increased the lactate level to about 95 µmol/gdw, the addition of 10 mmol/l glucose increased to this 130 µmol/gdw and the addition of 20 mmol/l glucose caused an elevation to 150 µmol/gdw (Fig. 3).

The renal lactate content in Euro-Collins kidneys rose from 14 µmol/gdw to 330 µmol/gdw during 7 h of ischemia

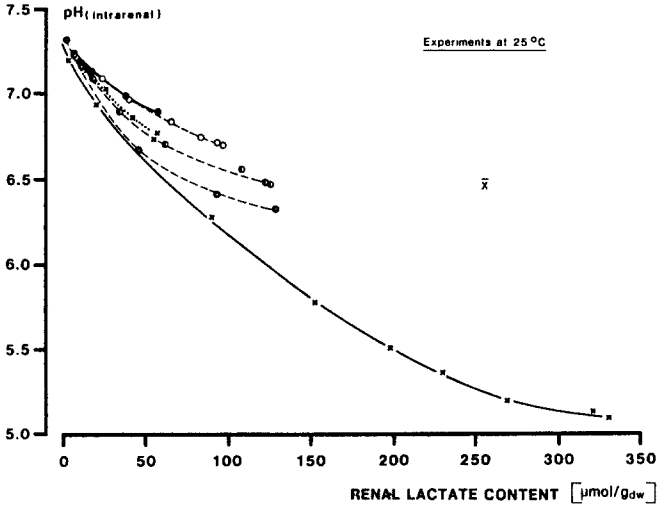

Fig. 4. Degree of tissue acidification compared with the renal lactate content taking identical points in time during renal ischemia at 25 °C after perfusion with the HTK-solution without —— and with different admixture of glucose – – – and with Euro-Collins-solution with and without glucose

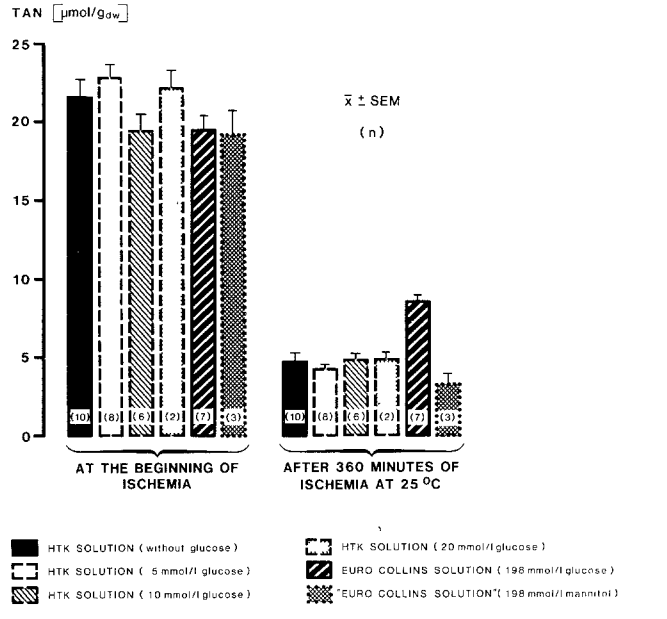

Fig. 5. *T*otal *A*denine *N*ucleotide during renal ischemia at 25 °C after kidney perfusion with HTK-solution without —— and with different admixture of glucose – – – and with Euro-Collins-solution with and without glucose

at 25 °C. In "Euro-Collins-kidneys" with mannitol instead of glucose the lactate level rose to about 60 µmol/gdw (Fig. 3).

When intrarenal pH-values were plotted against lactate levels, it was evident that at the same lactate content, for example 25, 50 or 75 µmol/gdw, the highest pH-values were found with both HTK-solution and with HTK-solution with the admixture of 5 mmol/l glucose. The lowest pH values were found using Euro-Collins-solution with 198 mmol/l glucose. The results with 10 and 20 mmol/l glucose in the HTK solution lie in between. Modified "Euro-Collins-solution" is in this respect very similar to HTK-solution with addition of 10 mmol/l glucose (Fig. 4).

*T*otal *A*denine *N*ucleotides with HTK-solution, was initially about 22 µmol/gdw. After 360 min of ischemia at 25 °C TAN declined to about 5 µmol/gdw. In kidneys perfused with HTK with 5 mmol/l glucose the initial TAN was 23 µmol/gdw, with the addition of 10 mmol/l about 20 µmol/gdw and with addition of 20 mmol/l about 22 µmol/gdw. In Euro-Collins-protected kidneys the initial TAN was about 19 µmol/gdw. After 360 min of ischemia the TAN was 8 µmol/gdw and thus about 1.5 times higher than in HTK-protected kidneys. In "Euro-Collins-kidneys" (mannitol instead of glucose) the initial TAN was 19 µmol/gdw and after 360 min of ischemia at 25 °C decreased to 3.5 µmol/gdw (Fig. 5).

Five minutes after protective perfusion with the HTK the glomerulus had an tuft of capillaries, a free glomerular capsule and unfolded slightly a vacuolated epithelium in the proximal tubule (Fig. 6a).

After 360 min of ischemia at 25 °C with this perfusate a glomerulus with an unfolded tuft of capillaries and little cell detritus within the glomerular capsule was apparent; the cytoplasma of proximal tubuli was moderately vacuolated and partially condensed (Fig. 6b).

After 360 min of ischemia at 25 °C with HTK-protection (with addition of 20 mmol/l glucose) the glomerulus had a retracted tuft of capillaries and an enlarged glomerular capsule; proximal tubuli showed vacuolated cytoplasma, condensed (pycnotic) nuclei and a partial loss of brush border with cell detritus within the tubular lumen (Fig. 7).

Five minutes after protective perfusion with Euro-Collins-solution the glomerulus also had an unfolded capillary tuft and a free glomerular capsule; proximal tubuli have a segmentally vacuolated cytoplasma (Fig. 8a). After 360 min of ischemia at 25 °C with Euro-Collins-protection

Fig. 6a, b. Exp. 387 left kidney, renal ischemia of (a) 5 and (b) 360 min under HTK-protection at 25 °C; kidney cortex: a glomerulum with unfolded tuft of capillaries and free glomerular capsule, slightly vacuolated proximal tubulus epithelia. b glomerulum with unfolded tuft of capillaries and little cell detritus within glomerular capsule; proximal tubuli with moderately vacuolated and partially condensed cytoplasma; Goldner-Masson, x240 ▶

Fig. 7. Exp. 446 left kidney, renal ischemia of 360 min under HTK-protection (with addition of 20 mmol/l glucose) at 25 °C; kidney cortex: glomerulum with retracted tuft of capillaries and enlarged glomerular capsule, proximal tubuli with vacuolated cytoplasma, condensed (pycnotic) nuclei, partial loss of brush border and cell detritus within the tubular lumen; Goldner-Masson, x240

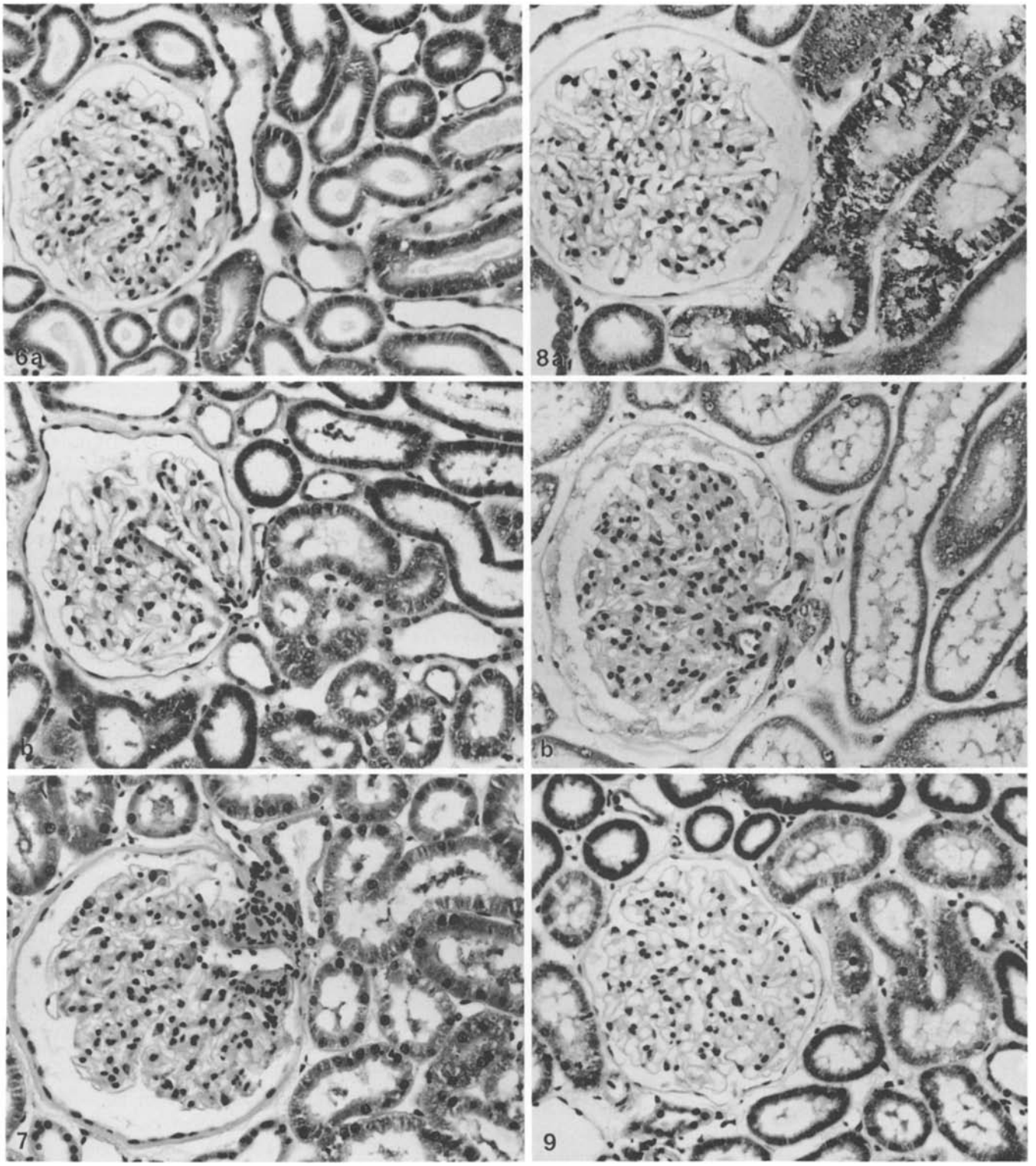

Fig. 8a, b. Exp. 445 left kidney, renal ischemia of (a) 5 and (b) 360 min of ischemia under Euro-Collins-protection; kidney cortex: a glomerulum with unfolded tuft of capillaries and free glomerular capsule, proximal tubuli with segmentally vacuolated cytoplasma. b glomerulum with collapsed tuft of capillaries and cell detritus within the enlarged glomerular capsule. Proximal tubuli with largely flattened epithelia, loss of brush border and cell detritus within the lumina, Goldner-Masson, x240

Fig. 9. Exp. 357 right kidney, 360 min of ischemia under "Euro-Collins-protection" (mannitol instead of glucose); kidney cortex: glomerulum with unfolded tuft of capillaries and free glomerular capsule, proximal tubuli epithelia partially vacuolated, partially condensed; interstitial edema, Goldner-Masson, x240

the glomerulus developed a collapse of the capillary tuft and cell detritus appeared within the enlarged glomerular capsule. Proximal tubuli showed flattened epithelia, and a loss of brush border with cell detritus within the lumina (Fig. 8b).

After 360 min of ischemia at 25 °C with "Euro-Collins-protection" (mannitol instead of glucose) the glomerulus had an unfolded tuft of capillaries and a free glomerular capsule; the epithelia of the proximal tubuli were partially vacuolated and partially condensed; the interstitual space was enlarged by edema (Fig. 9).

Discussion

The beneficial protective effect of the *cardioplegic* solution HTK of Bretschneider is effective during *renal* ischemia as well, as we have shown in an analysis of postischemic function. During HTK-protection, renal ischemia up to 120–135 min at 32–34 °C is reversible during 2–3 h after reperfusion with blood [36, 40].

After ischemia, glycolysis begins [30, 31, 44, 47, 49–55], which leads to an increase of lactate and to a rising tissue acidosis in unprotected kidneys [6, 7, 23–25, 27, 37, 38, 48, 51–53]. By preischemic perfusion of the kidneys with the histidine-buffered HTK-solution an irreversible, damaging acidosis can effectively be prevented [37]. Through the ionic composition of the solution, there is not only enough buffer capacity in the extracellular space, but also the energy demand for maintenance of structure and ionic milieu of the organ is reduced by withdrawal of sodium and calcium, and by a slightly increased potassium [8–13, 29, 30]. Thus the interval before energy content becomes critical is prolonged by a factor of 2–3 [38]. Therefore, long before damaging acidosis occurs, the shortage of energy reserves is a limiting factor for kidneys under HTK-protection. Any further improvement in protection must influence that factor, which primarily limits its effectiveness.

A lack in energy could, in principle, be eliminated by further reduction of energy demand during ischemia or by offering more substrate prior to and during ischemia, so as to meet energy demand during ischemia. As a further reduction of energy demand is hard to achieve with the HTK-solution [39], we attempted to improve the level of energy reserves by offering more substrate. A higher preischemic substrate supply can in principle be reached in two ways,

- firstly, by systemic glucose administration prior to the protective perfusion [41, 42] and
- secondly, by glucose addition to the HTK-solution.

The first method has two effects: The preperfusion-diuresis will be increased by the osmotic effect of glucose, and the existing concentration-gradients between kidney cortex and medulla will be washed out prior to protective perfusion so that the organ can more easily be perfused with an aqueous solution, such as HTK with an osmolarity of about 300 mosmol/l [41]. The other effect is that in a normal metabolic situation, the glucose supplied can, in principle, be taken up intracellularly through the usual transport and metabolic routes. The disadvantage of this method is the variable uptake of glucose into the cells [1, 2, 17, 22, 23, 33, 34, 45–47]. There is the practical disadvantage that in man unusually high glucose quantities (~ 75 g glucose) must be given to obtain a positive effect [45].

Addition of glucose to the HTK-solution is in principle possible, as the HTK-solution contains 30 mmol/l mannitol (Table 1), and this mannitol could be exchanged in part or totally for glucose. The advantage of this method is that glucose needs not be given systemically and that the glucose quantities in the solution were precisely controlled. The question therefore arises, whether the positive metabolic effect, which we have seen on systemic glucose administration prior to protective perfusion [42] could also be reached by admixture of glucose to the HTK-solution.

The concentration of glucose found in unprotected renal tissue is reached after perfusion with the HTK-solution with admixture of 10 mmol/l glucose to the HTK-solution (Fig. 1). Nevertheless, a concentration of 5 mmol/l glucose already leads to a lower pH than in kidneys protected with the HTK-solution without admixture of glucose (Fig. 2), though a much higher lactate production only occurs at glucose concentrations of 10 or 20 mmol/l in the HTK-solution (Fig. 3). Plotting intrarenal pH against lactate, taking identical points in time for the two measurements, it becomes evident that at the same lactate content – for example 25, 50 or 75 μmol/gdw – with increasing glucose admixture to the solution, the intrarenal pH is lower (Fig. 4). This effect may be due less to the slightly higher osmolarity of the HTK-solution with glucose additions (5 mmol/l = 2%, 10 mmol/l = 3% and 20 mmol/l = 7%) – perhaps with the exception of the 20 mmol/l glucose admixture – than to a "specific glucose effect". Thus, this "specific glucose effect" might bring about a greater permeability of the cell membrane, for at the same total lactate content (i.e. intra- and extracellular) a lower interstitial pH (i.e. extracellular) can occur [37], if more H^+-ions have left the cell. This assumption is supported by morphologic, data, which showed a deterioration of kidney structure with higher glucose-content in the protective solution. This effect may be explained by the influence of nonenzymatic glycosylation of proteins with consequent changes in structure and stability of membranes. This N-glycosylation has been described as a change in membrane properties with a marked reduction in stability [3] and may explain the supposed increase in permeability of the membrane.

In kidneys perfused by Euro-Collins-solution with a glucose concentration of about 200 mM, the glucose content was nearly 800 μmol/gdw, thus 16 times higher than in kidneys prior to perfusion or in untreated kidneys [39]

(Fig. 1). As the Euro-Collins-solution contains an oxygen pressure of about 100 mmHg (Table 1), oxygen demand during perfusion of the kidney cannot be completely met, resulting in an increase in lactate and a decrease in ATP during perfusion [39]. The high intrarenal glucose content of 800 μmol/gdw caused an increasing acidosis during ischemia, especially at temperatures above 5 °C [37]. Replacing the glucose in the Euro-Collins-solution by the same osmotic concentration of mannitol, the glucose concentration in the kidney decreased during perfusion from about 50 μmol/gdw to about 20 μmol/gdw (Fig. 1) and the intrarenal pH decreased during ischemia, even at an incubation temperature of 25 °C, only to 6.7, not to 5.2 °C as with the "normal" Euro-Collins-solution (Fig. 2); the lactate content increased only to 50 μmol/gdw rather than to 330 μmol/gdw (Fig. 3). The intrarenal pH at a given lactate content within the kidney was between the HTK-solution without glucose addition and the original Euro-Collins-solution (Fig. 4). In kidneys, protected with Euro-Collins-solution, an explanation for the shift of the relation between total lactate-content and extracellular pH in direction of acidosis, is given by increased permeability of the cell membrane for H^+-ions.

If the glucose in the Euro-Collins-solution is exchanged for mannitol, the modified "Euro-Collins-solution" becomes very similar to the Sacks-solution. Considering the disadvantageous effects of glucose in the Euro-Collins-solution, the superior results obtained with the Sacks-solution [50] are explicable.

Therefore we found a discrepancy between metabolic and structural protection with Euro-Collins-solution. The highest level of TAN after 360 min of ischemia was attained with this solution (Fig. 5), but it was accompanied by a structural detoriation (Fig. 8). Total adenine nucleotides was lower with HTK-solution after 360 min of ischemia than under Euro-Collins-protection (Fig. 5), but structural alteration was reversible [40], considering a Q_{10}-value between 35 and 25 °C of about 2–3 [38].

To summarize, glucose had the following effects in protected kidneys:

1. it stimulated lactate production and caused structural disintegration
2. it reduced interstitial pH in the kidney even in combination with a highly buffered protective solution
3. it might have been the cause of greater membrane permeability.

Therefore we conclude that glucose was not the correct substrate during anaerobic kidney preservation and – was not an appropriate osmotic agent. Mannitol is more appropriate, but there might be even better substances which could provide the required metabolic and osmotic effects.

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