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Effects of direct current on renal function

An experimental study in pigs

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Summary. Electric current from an external source was introduced between electrodes operatively placed into the ureters and positioned in the renal pelves of 13 pigs. Urinary excretion via the cathodic kidney showed a marked increase. The renal plasma flow and glomerular filtration rate diminished with increasing voltage, but no significant difference was found between the cathodic and the anodic kidney. The fractional sodium excretion by the cathodic kidney was 80% higher, indicating that the electric current mainly affected tubular function. A possible clinical application for electric fields in the kidneys is discussed.

Key words: Application of electric fields in the kidneys – Renal function – Unilateral electrolyte excretion – Cathodic excretion of fluid

Cell and tissue membranes are electrically more resistant than various body fluids such as interstitial tissue fluid, blood plasma, and urine. The resistance of blood-vessel walls is high in relation to that of blood plasma. Thus, selective pathways exist for the flow of electric current in blood and tissue. In vivo, these phenomena are represented by vascular-interstitial closed electric circuits (VICCs) powered by differences in metabolic or injury potential between blood and tissue [4]. The various conductive components of these VICCs [2, 11] are also the sites of induction of electrochemical reactions, particularly at electrode-equivalent surfaces of redox proteins embedded in cellular membranes.

In the present study, an artificial flow of electric current was superimposed over conductive components of the urinary tract in pigs. In a previous study [11], the same technique was used to render one kidney anodic and the contralateral organ cathodic. Following intravenous injection of an electronegatively charged radiographic contrast medium (Urografin), it was predominantly excreted by the anodic (+) kidney. Injection of the cytochemical compound Adriamycin, which is electropositively charged, led to its excretion by the cathodic kidney (−). Therefore, the use of such effects to direct a charged compound to only one kidney seems possible. The same principle has also been attempted in rats [2], with the application of weak currents between the vena cava and the bile duct resulting in changes in bile-salt secretion.

In the present experiments, one electrode was introduced into each ureter. From an external electric source, current was introduced between the electrodes and was conducted over the renal capillaries by the urine and via the blood plasma of vessels between the kidneys. One kidney was rendered electropositive (anodic) and the contralateral organ was made electronegative (cathodic). The effects on renal anatomy and function were studied.

Materials and methods

The experiments were performed on 13 pigs that were aged 3–4 months and weighed ca. 30 kg. The animals were given intravenous barbiturate anaesthesia and were intubated and artificially ventilated with nitrous oxide and oxygen. Rehydrex ($6\,ml/h^{-1}/kg^{-1}$ was given via an ear vein. Small doses of intravenous Mebumal were given repeatedly when required. The ureters were exposed retroperitoneally via a midline anterior incision. An 8 Ch catheter with multiple side holes along its tip was introduced into each incised ureter and the tip was guided to the renal pelvis. The ureters were then ligated around the catheters. Platinum-iridium metal wires were used as electrodes; they were passed into the catheters and guided up to the tips. An electric current was established between the electrodes and was conducted through the kidneys via the urine and the vascular blood plasma of both kidneys (Fig. 1).

Voltage was applied to the two electrodes using a processor that was especially constructed for treatment with direct current ([4], p 293), which enables a stable level of voltage to flow between the electrodes through the conducting tissue fluids. One electrode (usually the left) was made anodic and the other was rendered cathodic. Voltage was applied stepwise at 1, 3, 6, and 9 V for 30 min. Six of the pigs were exposed to 6 V, another six were exposed to a maximum of 9 V and one was subjected to 12 V.

Renal function was studied using a clearance technique. First 0.5 ml/kg of a solution containing 85 mg inulin (Laevosan)/ml and 30 mg paraaminohippurae (PAH)/ml (Merck, Sharp & Dohm) was given intravenously as a loading dose and was then infused at a

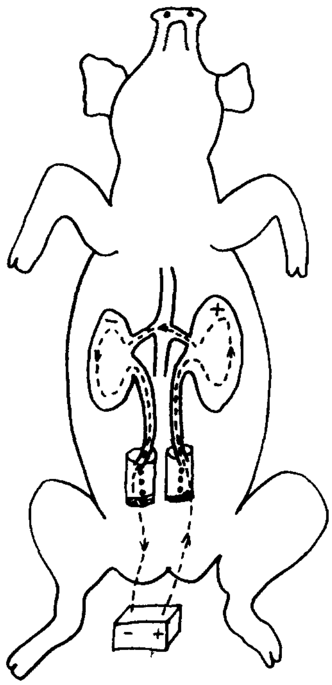

Fig. 1. Experimental setup with the ureters operatively ligated and provided with platinum electrodes. Voltage applied to the electrodes induces a flow of current in the urine, over the glomeruli and vascular blood plasma. One kidney is made electropositive and the contralateral organ is rendered electronegative. The electric fields alter the function of both kidneys. Anions (−) in the blood are excreted via the anodic (+) kidney and cations (+), through the cathodic (−) organ. Fluid excretion through the cathodic kidney is enhanced

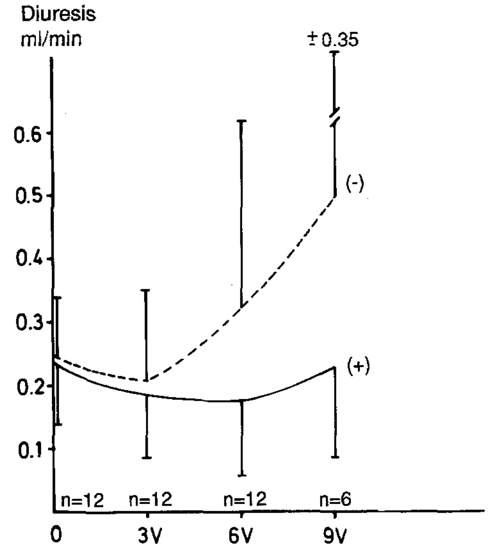

Fig. 2. Kidney function in 12 cathodic (−) and 12 anodic (+) porcine kidneys exposed to increasing voltage in an electric field

constant rate of 0.5 ml/min using a motor-driven syringe. After equilibraton for 60 min, urine and blood (from a catheter in the caval vein) were sampled for analysis of the glomerular filtration rate (GRF) and renal plasma flow rate (RPF) during two basal 30-min periods and two voltage periods. Blood samples were taken midway through each period.

Inulin and PAH levels were determined spectrophotometrically [1, 3], and serum and urinary osmolality was measured by freezing-point depression using a Knauer osmometer. Sodium concentrations in serum and urine were determined with a flame photometer (JL 143) and chloride concentrations were measured using a chloride titrometer (Amino-Cotlove). All analyses were carried out in duplicate. The filtration factor (FF) was calculated as C_{IN}/C_{PAH}. Fractional excretion of sodium (C_{Na}/C_{IN}) and fractional excretion osmol (C_{osmol}/C_{IN}) were calculated from total serum concentrations. For statistical calculations, regression analysis, paired observations, and Student's *t*-test were used. All values were expressed as means (±SD).

Results

Morphological changes

The cathodic kidneys were more oedematous than the anodic organs; moreover, their weight was greater and their color was pale greyish-red. The anodic kidneys were smaller and dark red. The ureters and pelves were cut open and the mucosa were carefully examined. Varying degrees of brownish discoloration of the ureteral mucosa occurred at sites at which the anodic electrode had been in contact with the wall, and one animal exhibited a ureteral perforation. The clearance values for this pig were therefore excluded from analysis due to possible leakage of urine. Histological examination revealed small areas of superficial necrosis in the pelvic mucosa in animals in which 9 V had been used. Apart from some oedema in both the cortex and the medulla of the cathodic kidneys, no pathological changes was seen in the glomeruli or tubules.

Functional changes

During the basal control period, no significant differences in the production of urine, RPF, GFR, or tubular excretion of sodium and chlorides were found between the anodic and the cathodic kidneys. The urinary output of the anodic organ decreased slightly and that of the cathodic kidney increased on the application of 3, 6, or 9 V (Fig. 2), although the differences were not statistically significant. At 1 V, no difference was observed. Gas was continuously produced at the eletrodes, appearing as bubbles in the urine around each catheter.

The impact of the electric field on the glomeruli resulted in an almost parallel reduction in the GFR in both kidneys (Table 1) and the RPF diminished correspondingly. However, no significant differences was found between the anodic and the cathodic organs (Table 1). The fractional excretion of sodium by the cathodic kidney increased to levels that were significantly higher than those observed for the anodic kidney (Fig. 3) following the application of 6 V ($P<0.05$; Student's *t*-test). The fractional excretion of chloride remained largely unaltered throughout the experiment and was equal on both sides. The anodic evolution of chlorine and oxygen gas and the cathodic development of hydrogen gas in the urine were

Table 1. Glomerular and tubular functions during the basal period and after induction of electric fields between the kidneys of 12 pigs

Measured functions	Basal period	Kidneys	3 V	6 V
Glomerular filtration rate (ml/min)	30 ±13.9	Anodic	23.6 ±14.4	21.4 ±15.7
	31.7 ±14.2	Cathodic	20.4 ±13.2	25.3 ±18.2
Renal plasma flow (ml/min)	91.6 ±42.4	Anodic	78.6 ±49.8	53.6 ±33.4
	99.1 ±59.4	Cathodic	75.8 ±55.7	51.2 ±30.3
Filtration factor (%)	0.3 ± 0.06	Anodic	0.31 ± 0.06	0.35 ± 0.11
	0.29 ± 0.08	Cathodic	0.34 ± 0.05	0.37 ± 0.07
Fractional osmole excretion (%)	1.62 ± 0.75	Anodic	1.74 ± 0.64	1.75 ± 0.69
	1.75 ± 0.69	Cathodic	2.12 ± 1.13	1.98 ± 0.62

No statistically significant difference in any variable was found between anodic and cathodic kidneys (Student's *t*-test)

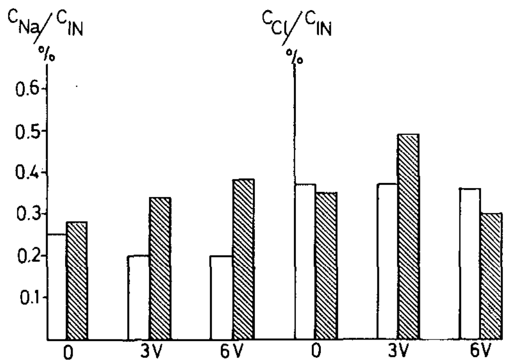

Fig. 3. Fractional excretion of sodium (C_{Na}/C_{IN}) and chlorides (C_{Cl}/C_{IN}) in 12 pairs of porcine kidneys exposed to increasing voltage. *Blank bars,* Anodic (+) kidneys; *striped bars* cathodic (−) kidneys. According to Student's *t*-test, the difference in sodium excretion was statistically significant ($P < 0.05$), whereas that in cloride excretion was not. Cloride escaped uncontrolled as chlorine gas bubbles from the urine in the anodic ureteral catheter

not determined. The fractional excretion of osmoles (C_{osmol}/C_{IN}) by the cathodic kidney was higher than that by the anodic organ (Table 1).

Discussion

A physiological exchange of compounds and cellular elements in blood and tissue fluid takes place as in vivo electrophoresis under the influence of differences in metabolic or injury potential [4]. The components of this VICC system [4, 5, 9] form an electrogenic circulation distinct from the mechanical circulation via vascular-interstitial pathways. It also connects with other electrically conducting components such as nerves [6–8, 10].

In the urinary tract, the electrolytes in urine make contact with blood plasma over renal ("leaking") capillaries; in the normal state, the ureters are also connected via intravesical urine. Therefore, a urinary-vascular closed circuit connection exists that may be activated, e. g., by regional polarization induced by injury to a ureter or a kidney. A distant electrophoretic effect on the contralateral kidney is a possible explanation for the well-known delay of excretion in ureteral colic.

Ligation of each ureter around an inserted catheter with an indwelling electrode interrupts the electric connection between the two ureters over the bladder. Direct current can thus be directed though the kidneys and their vessels from an external source of electric power. It is then possible to test the influence of an artificially applied electrophoretic flow of current on renal functions, thus establishing a situation analogous to that which can be presumed to occur following spontaneous activation of the urinary-vascular closed circuit in response to various pathological polarizations.

In the present preliminary experiments, the excretion of urine by the cathodic kidney was much greater than that observed for the anodic organ (Fig. 2). This is in accordance with transport of a dielectric (e. g., H_2O in electro-osmosis) current from the anod to the cathode, which occurs in the presence of a negatively charged matrix ([4], p 79). The matrix in these experiments consisted of the renal channels lined with cells carrying a surplus of negative, fixed charges on the cellular membranes. The movement of fluid to the cathodic kidney was also reflected by the pale, swollen appearance of that organ as opposed to the dark red, smaller, and denser anodic kidney.

The influence of the electric field on transport of the test substances resulted in a parallel reduction in the GFR and, possibly, the RPF in both kidneys. Previous studies ([4], p 140) have likewise indicated that both an electropositive and an electronegative field produce contractions in the segmental arterial capillaries in vivo, at least in capillaries of the canine mesentery. These contractions are associated with a transfer of electrons via proteins in the walls of endothelial cells [4, 5], which is a prerequisite for spontaneous in vivo electrophoresis between blood and tissue fluid. In the present experiments, an equivalent electrode function in the cells of the tubular apparatus may have been induced by the applied electric field.

Anodic and cathodic excretion of various charged compounds in urine occurs. Some excreted compounds are modified by the anodic acidity or the cathodic basicity on electron exchange at the electrode surfaces. The excess of osmoles excretion by the cathodic kidney as compared with the anodic organ may depend on the formation of chlorine and oxygen gases. Excretion of sodium ions was clearly greater in the cathodic than in the anodic urine. These preliminary findings indicate that functional changes can be selectively induced in the kidneys by the application of the different voltage to the ureters. Such changes can be expected to proceed as follows: cathodic kidney, increased excretion of fluid and of cations; anodic kidney, decreased excretion of fluid and increased excretion of anions.

In addition, we found that injury to the ureteral mucosa predominantly occurs at the anodic electrode; however, cathodic electrode reactions also occur. By placement of the electrodes in an protracted position in the catheters, these drawbacks might be overcome at a voltage of up to 9 V. Effects on the renal function were observed at levels as low as 3 and 6 V; when voltage higher than 9 V was used, local mucosal injuries always occurred at the anode. Studies of modified transport over a urinary-vascular closed circuit using applied current will therefore require careful consideration concering the application of different voltage, particularly in prolonged studies.

Conclusions

These preliminary studies show that water and sodium excretion are increased from the cathodic kidney as compared with the anodic organ when a flow of direct current is applied between electrodes inside each ureter. Furthermore, it has previously been shown that electrically charged compounds such as radiographic contrast media and cytotoxic drugs (Adriamycin) are unilaterally directed to a selected kidney on the application of direct current. Further studies on the electrochemical and transport phenomena induced by such treatment may lead to a deeper understanding of renal function and may even result in the development of new therapeutic options.

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