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The Reabsorption of Creatinine from the Rabbit Bladder

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Summary. Using a radioisotope technique the reabsorption of creatinine from normal, inflamed and chronically obstructed bladders of rabbits was investigated. The reabsorption of creatinine from normal bladders was minimal. Chronic obstruction lead to a rise of the reabsorption rate. The most marked reabsorption however was found with the inflamed bladders. This difference of creatinine reabsorption is statistically significant and it was detectable in the ^{14}C-creatinine content of the blood, ^{14}C-creatinine content of the renal pelvis urine and in the activity loss in the bladder urine. The vesical reabsorption of creatinine corresponds in principle with the urea reabsorption which was investigated earlier by the same method. The extent of reabsorption is however different and urea is reabsorbed to a substantially greater extent.

Key words: Reabsorption from the bladder, Reabsorption of creatinine, Functional condition of the bladder epithelium.

One of the functions of the mucosa of the bladder is the prevention of reabsorption of renally excreted substances. Reabsorption would diminish the effective performance of the kidneys and unpredictably influence the quantitative analysis of substances in the serum which are excreted by the kidney. The determination of the degree of exchange between the bladder and the blood under normal and pathological conditions would allow corrections to be applied in the appropriate circumstances when disease alters the functional condition of the bladder epithelium (6).

With the introduction of radioisotope tracer techniques it has become possible to measure bladder-blood substance exchange under physiological conditions. The relationships for urea and various ions have already been determined (5). As far as we know there have been no measurements of the reabsorption of creatinine from normal, inflamed and congested bladders. The following animal experiments were performed in order to examine creatinine reabsorption from the healthy and diseased bladder.

Material and Methods

The experiments were performed on male rabbits, all fathered by the same male and weighing between 3.600 and 5.000 grams. The solution used for the reabsorption studies was approximately equivalent to physiological urine and contained the following substances: urea 2.5 g%, creatinine 0.1 g%, disodium sulphate 0.2 g%, sodium dihydrogenphosphate 0.2 g%, sodium chloride 1.5 g%, potassium chloride 0.17 g%, hippuric acid 0.07 g% and uric acid 0.05 g% dissolved in water. pH was approximately 5.34, the depression of freezing point amounted to 1.19 °C and the specific gravity 1.021 g/cm^3. For the reabsorption experiment 10 ml of this solution was instilled into the bladder after 0.1 ml of a physiological sodium chloride solution containing 20 µc ^{14}C-creatinine had been added. We used creatinine (carbonyl-^{14}C) hydrochloride obtained from the Radiochemical Centre Amersham U.K. All experiments were performed on animals anaesthetised with 300 to 400 mg Thiogenal [R]1, a thiobarbiturate. The experiments were carried out on animals with normal bladders, on animals with inflamed bladders and on animals with chronic bladder outflow obstruction. To produce inflammation of the bladder epithelium 20 ml of a mustard oil were instilled into the bladder 24 hours before the reabsorption tests were carried out. Following emptying of the bladder with an urethral catheter the mustard oil solution was injected

[1] Bayer AG, D-5090 Leverkusen

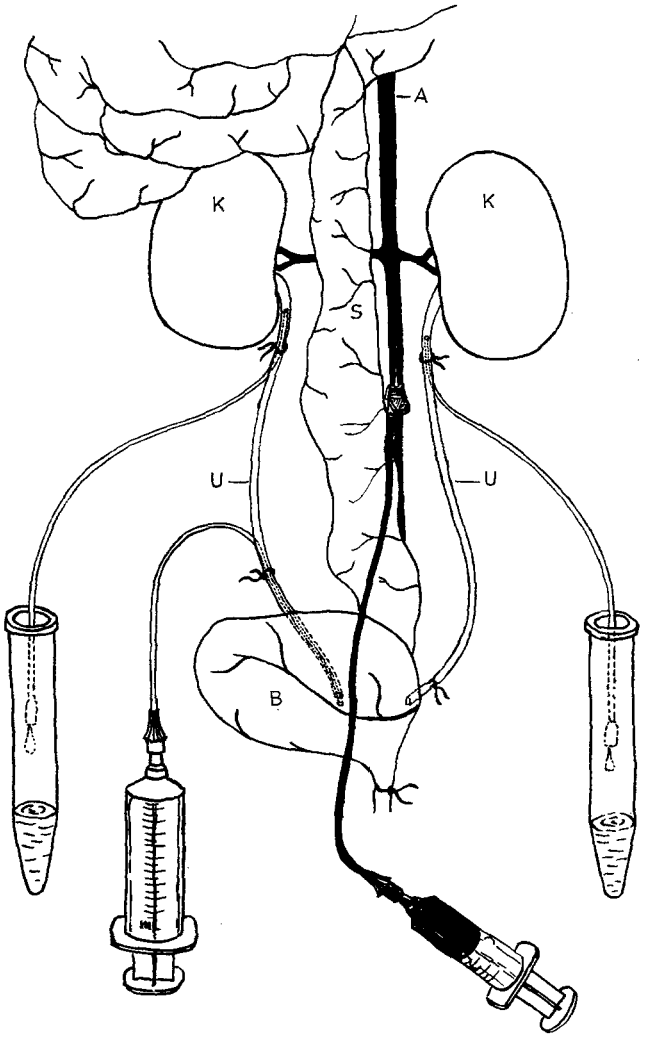

Fig. 1. Sketch of the operation site for the investigation of creatinine absorption from the bladder. Both ureters are intubated proximally for drainage of renal pelvis urine. The bladder is catheterised via the right ureter. The bladder neck is ligated. A cannula is placed in the aorta for blood sampling. (A = Aorta, B = Bladder, K = Kidney, S = Sigmoid Colon, U = Ureter)

and allowed to remain in the bladder for 10 minutes. Animals for the outflow obstruction experiments were prepared 4 to 5 weeks before the reabsorption tests in the following way: the bladder neck was opened with a small lower abdominal section and a Nelaton-catheter size 12 Charriére was inserted into the bladder neck. A 00-Mersilene thread was passed around the bladder neck and tied sufficiently tightly to allow the catheter to be withdrawn easily. After removing the catheter the non-reabsorbable thread encircled the bladder neck loosely.

The technique for the reabsorption tests has been described in previous papers (4, 5) and only the basic steps of this technique will be repeated here (Fig. 1). After opening the abdomen with a Midline incision from the xiphoid to the os pubis both ureters were identified. The ureters were intubated with thin plastic vein catheters passed into each renal pelvis in order to collect urine continuously. Through one of the two ureters a third catheter was passed distally into the bladder. The distal end of the opposite ureter was ligated. After emptying the bladder the urethra was ligated at the bladder neck and the radioactive "urine" solution instilled into the bladder via the ureter catheter. For withdrawal of blood the abdominal aorta was punctured. Blood was removed at five-minute intervals for one hour after instillation of the radioactive solution into the bladder. The centrifuge glasses used for collection of the urine from the renal pelvis were changed twice so that three urine fractions were obtained at 20-minute intervals from each kidney during the one hour experiment. At the end of the experiment the bladder was emptied and the urine tested for residual tracer. In this way 13 blood samples, 3 fractions of urine from the renal pelvis, and the bladder "urine" from each animal were examined. The radioactivity was measured in a liquid scintillation counter (Packard model 3380)[2] counting for one minute per glass. We used universal scintillator Insta-Gel (Packard) and Soluene TM 100 (Packard) as solvent. The accuracy of measurement was 90.5 % with a deviation of ± 3 %. The reabsorption tests were performed on 6 animals with healthy bladders, on 5 animals with inflamed bladders and on 7 animals with chronic bladder outflow obstruction.

Results

The radioactivity in the blood and urine samples of the various animals is presented in figures 2 and 3. The activity loss calculated as the difference between instilled radioactivity and that measured after washing out the bladder at the end of the experiment is shown in Table 1.

In the blood samples from the rabbits with healthy bladders radioactivity hardly rose above the minimum detectable level of 2 pc/0.5 ml serum (Fig. 2). In the animals with inflamed or obstructed bladders there was an almost linear rise in the mean serum radioactivity. The mean ^{14}C-creatinine reabsorption in animals with inflamed bladders was significantly higher than for those with chronic outflow obstruction. The highest mean values amounted to 713 pc/0.5 ml serum for animals with inflamed bladders, 213 pc/0.5 ml serum for animals with obstructed bladders.

Similar results were obtained for the ^{14}C-concentration in the renal pelvis urine. The urine

2 Packard Instrument GmbH, D-6000 Frankfurt, Hanauer Landstr. 220

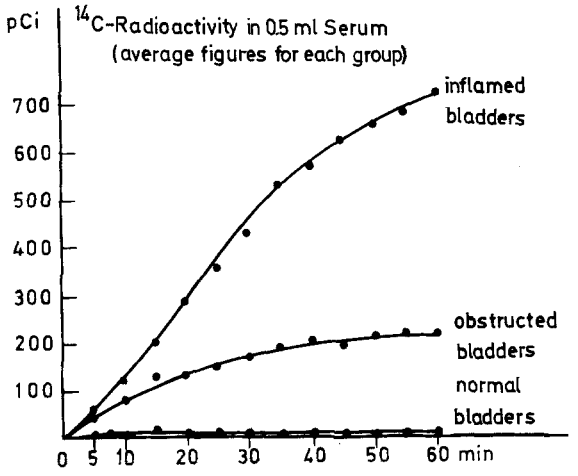

Fig. 2. Serum ^{14}C-creatinine concentrations in rabbits with normal, inflamed and obstructed bladders during the hour following instillation of the tracer in the bladder.

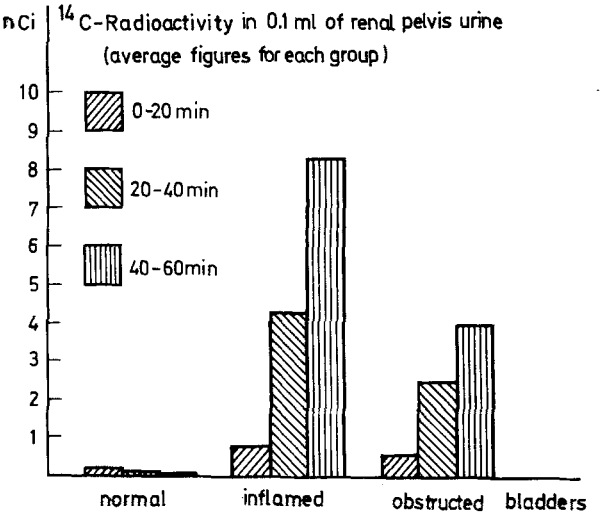

Fig. 3. Mean ^{14}C-creatinine concentrations of 3 renal pelvis urine fractions obtained consecutively from each of the three different groups of rabbits.

Table 1. ^{14}C-creatinine reabsorption of three different groups of laboratory animals (averages were calculated by measurement of the impulse frequency with correction for the efficiency)

	normal bladders	inflamed bladders	obstructed bladders
reduction of the activity in the urine of the bladder after 1 h	1.1 µc 5 %	4.3 µc 22 %	3.7 µc 19 %
creatinine reabsorption from the bladder in 1 h	0.53 mg	2.18 mg	1.86 mg

samples from animals with healthy bladders showed no rise in activity in the successive fractions. The tracer concentration in urine samples from animals with inflamed bladders rose steadily during the experiment. Rabbits with inflamed bladders showed activity of 8.26 nc/0.1 ml renal pelvis urine in the most concentrated third fraction, while in animals with chronically obstructed bladders this value amounted to 3.97 nc/0.1 ml (Fig. 3).

The rise in radioactivity found in blood and renal pelvis urine corresponds to the ^{14}C loss from the bladder (Table 1). Bladders with mucosal changes due to inflammation showed the largest tracer loss (22 % = 4.3 µc) while with normal bladders the ^{14}C content remained practically unchanged (5 % = 1.1 µc). With chronically obstructed bladders the reduction of the instilled ^{14}C-creatinine was about 19 % (= 3.7 µc).

The portion of the total creatinine blood level attributable to reabsorption from the bladder for 1 hour amounted to 0.002 mg% for normal bladders, 0.027 mg% for congested bladders, and 0.075 mg% for inflamed bladders.

Application of the statistical significance tests (Central value tests, t-tests), verified by testing with pairs, showed that inflammation of the bladder as well as a chronic disturbance of the outflow led to a significant rise in reabsorption of ^{14}C-creatinine from the bladder (probability of error 5 %). A larger reabsorption was found with inflammation of the bladder than with a four to five week subvesical outflow obstruction. This difference was also significant with the same probability of error.

Discussion

No exact values are at present known to the authors for the reabsorption of creatinine from healthy and pathologically altered bladders. The relationships for urea and various ions have already been determined (5). A simple analogy for creatinine cannot be assumed because of evidence that creatinine behaves differently on biological membranes than other substances in the urine. For example, Aviram (1) pointed out that creatinine, but not urea, is absorbed in large amounts from intestinal segments used for urinary diversion. Therefore it was necessary to determine the creatinine reabsorption from the bladder under physiological conditions with the help of the radioisotope technique.

For normal bladders we found that only a

small amount creatinine was reabsorbed. Only 5 % of the creatinine was reabsorbed from the rabbit bladder in one hour. The normal bladder wall thus poses a very effective barrier against passage of creatinine, which appears in the bladder in concentrations 100 times greater than in blood. This reabsorption barrier is thought to be due to a high molecular urinary mucoid, produced by the epithelial cells and spread over the inner surface of the bladder (2).

Obstructed bladders reabsorb creatinine to a greater extent than bladders of control animals. For obstructed bladders a mean of 0.027 mg/100 ml plasma of reabsorbed creatinine was found after one hour. The reason for the increased reabsorption in these bladders may not only be a mild cystitis, which was always present, but also a disturbance of epithelial function caused by the chronic obstruction. The pathophysiological mechanism of this reabsorption is however unclear.

An inflammation of the bladder may influence reabsorption in two ways: 1. It can damage the epithelial cells which then no longer adequately fulfill their protective function. 2. Every cystitis is accompanied by increased circulation in the bladder wall. The extent of creatinine reabsorption clearly increased with the degree of severity of the cystitis. The maximum reabsorption in these cases amounted to 0.14 mg creatinine/100 ml plasma.

Creatinine reabsorption is presumably a passive process which follows the laws of diffusion (3). The determining factors of direction and extent of substance exchange are, on the one hand, the ratio of the creatinine concentration in the bladder and in the blood, and on the other hand, the urinary mucoid diffusion barrier of the bladder wall. Since the creatinine concentration in the bladder is usually about 100 times greater than in blood, disturbance of the diffusion barrier must lead to an increased "leakage" from the concentrated creatinine reservoir in the bladder.

The reabsorption of creatinine from normal bladder urine at around 5 % per hour is practically negligible and has no appreciable influence on the actual plasma creatinine level (less than 0.002 mg% per hour). With obstructed bladders 19 % of the creatinine in bladder urine was reabsorbed in one hour. The rise of the plasma creatinine level by 0.027 mg% after one hour cannot at present be detected by conventional chemical laboratory methods.

With an acute cystitis we found a maximum of 0.14 mg% reabsorbed creatinine in the plasma after one hour. Here the chemical laboratory detection limit is just exceeded. Only with diminished renal function will this reabsorption from inflamed or obstructed bladders lead to a substantial rise in plasma creatinine. The reabsorption from the bladder can be considered to be due to an incomplete diffusion barrier. The results of the vesical reabsorption of creatinine therefore correspond in principle with urea reabsorption determined by the same method (5). Because urea is characterised as being an especially easily diffusable substance, it is not surprising that from diseased bladders larger reabsorption figures were found for urea. The activity loss for urea after one hour in the bladder were: normal bladder 6 %, obstructed bladder 43 % and inflamed bladder 76 %.

Our laboratory animal results show that a fraction of the creatinine contained in the bladder is subject to a vesico - renal circulation before final elimination. The active force for this circulation is the concentration gradient between bladder urine and blood. The amount of circulating substance is dependent upon mucosal permeability and therefore on the extent of the disease of the bladder wall. This permeability is very small in the healthy bladder so that this pathway is almost completely blocked. Inflammation or obstruction of the bladder opens this physiological blockade by varying amounts depending on the degree of injury to the mucous membrane. However the resulting additional renal load is easily overcome by normal kidneys. A substantial increase in blood levels is only to be expected in cases of renal insufficiency.

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