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Philip W. Hall III, Arnold S. Relman

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Research Article



# ACID EXCRETION IN RUBIDIUM- AND CESIUM-SUBSTITUTED RATS * †

By PHILIP W. HALL, III ‡ AND ARNOLD S. RELMAN WITH THE TECHNICAL ASSISTANCE OF ARLENE M. ROY

*(From the Department of Medicine, Boston University School of Medicine, and the Evans Memorial Department of the Massachusetts Memorial Hospitals, Boston, Mass.)*

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Previous studies have shown that rubidium or cesium can replace a major part of intracellular cation *in vivo,* and can correct the extracellular alkalosis associated with potassium depletion (1). In nephrectomized potassium-deficient animals it was demonstrated that rubidium, like potassium, lowers extracellular bicarbonate concentration by displacement of intracellular protons (2) [the latter perhaps transported out of cells by cationic amino acids (3)]. However, clear quantitative differences can be demonstrated between the effects of rubidium and potassium on extracellular bicarbonate: *a*) chronic administration of RbCl to potassium-deficient alkalotic rats results in extracellular *acidosis,* whereas an equivalent amount of KCl merely restores extracellular bicarbonate concentration to normal (2); and *b*) acute loading of normal rats with RbCl produces a much greater reduction in extracellular bicarbonate than does an equivalent load of KCl (4).

A remarkable feature of the extracellular acidosis produced in normal rats by acute loading with RbCl is the absence of any immediate renal compensation (4). Despite reduction of plasma $CO_2$ content to 13 mMoles per L. there was no reduction in urine pH, and a slight fall, rather than an increase, in ammonium excretion. Since the administration of acid loads to rats ordinarily results in immediate and very large increments in acid excretion (5–7), the present study was undertaken to learn more about this apparently anomalous behavior of the rubidium-loaded kidney. Although loading with cesium does not produce significant extracellular acidosis, it was of interest to study the acid excretion of the cesium-substituted rat as well, and to compare both the cesium and rubidium preparations with the behavior of the normal and the potassium-depleted animal.

## METHODS AND MATERIALS

Male white rats of the Sprague-Dawley strain weighing 200 to 400 Gm. were used in these studies. The animals were divided into four groups. The controls (Group I) consisted of 20 animals fed a low potassium diet for 17 days and then allowed to restore their deficits during a second 17 day period in which they received 20 mEq. per L. of KCl in their drinking water plus the basic diet. There were in addition 20 animals continuously fed on Purina® Chow and never depleted of potassium. Plasma electrolytes were the same in both these subgroups and their subsequent behavior in response to sodium chloride and ammonium chloride loads was indistinguishable. For the purpose of this study, therefore, the depleted-and-then-repleted animals were considered as normal and were grouped together with the Purina®-fed animals, making a total of 40 animals in Group I. Group II consisted of 28 potassium-deficient animals studied immediately after 17 days on the potassium-free diet. Group III was composed of 26 rats which were fed the standard potassium-free diet for 17 days and then given RbCl, 20 mEq. per L., in their drinking water *ad libitum* for the next 17 days. The 30 animals in Group IV were similarly handled, but received 20 mEq. per L. of CsCl in their drinking water.

The plan of the experiment was to observe the 24 hour excretion of acid in each of these groups, under two conditions: *a*) during the administration of NaCl, and *b*) during the administration of an equivalent amount of $NH_4Cl$. Following the preparatory period of feeding described above, each of the four groups was randomly divided approximately in half, one-half receiving an intraperitoneal load of ammonium chloride solution (1 mEq. per 100 Gm. of body weight, in six equal doses about an hour apart), and the other an equivalent amount of sodium chloride. The loading salts were given at a concentration of 250 mEq. per L. Animals were kept in individual metabolic cages during the 24 hour period of study and all urine was collected under mineral

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‡ During tenure as a Research Fellow of the Arthritis and Rheumatism Foundation. Present address: Cleveland Metropolitan General Hospital, Cleveland 9, Ohio.

TABLE I

*Plasma and urine electrolytes*

| | Plasma *mMoles/L.* | | | | Urine *mEq./day/100 Gm. body weight* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $CO_2$ content | | Potassium | | Sodium | | Potassium | | Chloride | |
| | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ |
| Group I (Normal) | 27.2 ± 1.8 (20) | 25.6 + 1.8 (20) | 3.6 ± 0.4 (17) | 3.4 ± 0.4 (18) | 1.18 ± 0.08 (4) | 0.31 ± 0.10 (3) | 0.34 ± 0.19 (6) | 0.38 ± 0.18 (3) | 1.11 ± 0.04 (8) | 1.16 ± 0.12 (10) |
| Group II (K-deficient) | 32.8 ± 3.0 (15) | 29.5 ± 2.9 (13) | 2.6 ± 0.4 (15) | 2.7 ± 0.4 (11) | 0.81 ± 0.05 (3) | 0.25 ± 0.11 (3) | 0.05 ± 0.02 (3) | 0.06 ± 0.10 (3) | 1.04 ± 0.10 (6) | 1.03 ± 0.12 (6) |
| Group III (Rb) | 19.5 ± 2.8 (13) | 16.7 ± 2.3 (13) | | | 1.0 ± 0.10 (3) | 0.31 ± 0.03 (3) | 0.10 ± 0.01 (3) Rb = 0.02 ± 0.01 (3) | 0.19 ± 0.04 (3) Rb = 0.06 ± 0.03 (3) | 1.02 ± 0.10 (6) | 1.07 ± 0.17 (7) |
| Group IV (Cs) | 26.3 ± 2.7 (16) | 19.7 ± 3.8 (14) | 1.9 ± 0.3 (11) Cs = 0.43 ± 0.07 (11) | 1.9 ± 0.1 (11) Cs = 0.40 ± 0.07 (11) | 1.17 ± 0.14 (3) | 0.30 ± 0.10 (3) | 0.06 ± 0.01 (3) Cs = 0.03 ± 0.10 (3) | 0.06 ± 0.01 (3) Cs = 0.03 ± 0.01 (3) | 0.92 ± 0.22 (7) | 0.87 ± 0.18 (6) |

oil using thymol and phenyl mercuric nitrate as preservatives. Animals were deprived of food beginning about 18 hours prior to the day of study and continuing through the remainder of the experiment, but they were allowed unlimited access to drinking water containing 10 per cent glucose.

At the end of the 24 hour study period (about 15 hours after the last dose of salt) the cages were washed down with 10 cc. of distilled water and the washings added to the urine collection. The animals were anesthetized with Amytal Sodium® and exsanguinated from the abdominal aorta. Blood was withdrawn anaerobically into heparinized syringes and the plasma immediately separated for manometric analysis of total $CO_2$ content. In addition, potassium concentration in the plasma was determined by flame photometry in all animals of Groups I, II and IV. Twenty-four hour urine collections were analyzed for: *1*) pH (glass electrode at room temperature), *2*) titratable acidity (titration with standard alkali, undiluted, using a glass electrode), *3*) $CO_2$ content (standard manometric technique), and *4*) ammonia (Conway microdiffusion technique). In addition, approximately half of the urines from each subgroup were randomly selected for chloride analysis (potentiometric titration) and, where appropriate, smaller numbers of urines were analyzed for sodium, potassium or cesium (all by flame photometry) or for rubidium (flame photometry after paper chromatographic separation from potassium).

Homogenates of single whole kidneys removed from a number of animals in each of the four NaCl-loaded subgroups were analyzed for glutaminase I activity by the method described by Richterich and Goldstein (8). In addition, single whole kidneys from three randomly selected rats in each of these groups were also analyzed for sodium and potassium content and, where appropriate, for rubidium or cesium. Tissue was minced, extracted with hot water and then analyzed by techniques similar to those applied to urine.

## RESULTS

### *A. Plasma and urine electrolytes*

Table I lists the results of the analyses of plasma for potassium and $CO_2$ content, and also gives the data relating to electrolyte excretion in the urine. For each of the four major groups two sets of values are given. The columns headed "NaCl" list the results for the subgroups loaded with this salt and the columns headed "$NH_4Cl$" give the data for the subgroups loaded with $NH_4Cl$. Mean values (± S.D.) are given, and the number of animals is indicated in each case by the figure in parentheses below the data. All urinary excretion data are expressed as mEq. per day per 100 Gm. body weight.

*Plasma values.* The mean *potassium concentration* was 3.6 ± 0.4 mEq. per L. in the Group I animals loaded with NaCl and was not significantly different[1] in the $NH_4Cl$ subgroup. In both subgroups studied after potassium depletion (Group II) plasma levels were significantly reduced as compared to the normals. Plasma potassium values were not determined in the Group III (RbCl-loaded) animals, but in the CsCl-loaded rats (Group IV) mean potassium concentrations were significantly lower than in the untreated potassium-deficient group.

Plasma *$CO_2$ content* was normal (27.2 ± 1.8 mMoles per L.) in the NaCl-loaded Group I ani-

[1] Unless otherwise stated, differences between mean values are described as "significant" only when the conventional "t" test yields p values less than 0.01.

TABLE II

*Urine pH and acid excretion*

| | Urine pH | | Acid excretion *mEq./day/100 Gm. body weight* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Ammonium | | Titratable acid | | "Net acid" | |
| | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ | NaCl | $NH_4Cl$ |
| Group I (Normal) | 6.26 ± 0.31 (20) | 5.61 ± 0.26 (20) | 0.37 ± 0.11 (20) | 0.98 ± 0.16 (20) | 0.134 ± 0.058 (20) | 0.23 ± 0.07 (20) | 0.44 ± 0.12 (20) | 1.21 ± 0.18 (20) |
| Group II (K-deficient) | 6.47 ± 0.32 (15) | 6.13 ± 0.34 (13) | 0.55 ± 0.14 (15) | 1.30 ± 0.26 (13) | 0.092 ± 0.043 (13) | 0.18 ± 0.05 (13) | 0.62 ± 0.13 (13) | 1.46 ± 0.26 (13) |
| Group III (Rb) | 6.20 ± 0.28 (13) | 6.04 ± 0.32 (13) | 0.32 ± 0.08 (13) | 0.98 ± 0.15 (13) | 0.107 ± 0.034 (13) | 0.13 ± 0.03 (13) | 0.40 ± 0.09 (13) | 1.08 ± 0.12 (13) |
| Group IV (Cs) | 6.33 ± 0.30 (16) | 6.15 ± 0.21 (14) | 0.39 ± 0.09 (16) | 0.94 ± 0.10 (14) | 0.107 ± 0.042 (16) | 0.11 ± 0.03 (14) | 0.45 ± 0.10 (16) | 1.03 ± 0.10 (14) |

mals and, as expected, slightly but significantly increased in the similarly treated potassium-deficient animals (32.8 ± 3.0 mMoles per L.). Following the administration of $NH_4Cl$ there was only a slight and insignificant fall in $CO_2$ content as compared with the respective NaCl subgroups. As will be shown below, this reflected the fact that in both groups most of the acid load was excreted in the urine during the 24 hour period of study. $CO_2$ content was very low (19.5 ± 2.8 mMoles per L.) in the rubidium-treated animals (Group III) loaded with NaCl but, as in Groups I and II, there was only a small and insignificant further reduction following the $NH_4Cl$. Plasma $CO_2$ content in the Group IV (cesium-treated) animals was normal after loading with NaCl (26.3 ± 2.7 mMoles per L.). but was significantly reduced (19.7 ± 3.8 mMoles per L.) after the administration of $NH_4Cl$.

*Urine electrolytes. Chloride excretion* ranged from 0.87 to 1.16 mEq. per 100 Gm. body weight during the 24 hour period of study, and there were no significant differences between the various groups, except for a small but significant reduction in the acid-loaded Group IV animals, as compared to the normal. Since the total administered load of NaCl or $NH_4Cl$ was 1.0 mEq. per 100 Gm., it is obvious that in each group of animals essentially all of the chloride load was absorbed and excreted.

Mean *excretion of sodium* in the animals loaded with NaCl ranged from 0.81 to 1.18 mEq. per 100 Gm., demonstrating the virtually complete excretion of the sodium load in all groups. During loading with $NH_4Cl$ excretion of sodium was only 0.25 to 0.31 mEq. per 100 Gm.

*Excretion of potassium* was 0.34 mEq. per 100 Gm. in the Group I NaCl-loaded animals and, as expected, much lower in the Group II potassium-depleted rats (0.05 mEq. per 100 Gm.). Loading with $NH_4Cl$ did not significantly change these values. In the Group III rubidium-treated animals, excretion of potassium was also lower than in the normal controls (0.1 mEq. per 100 Gm. in the NaCl subgroup, and 0.19 mEq. per 100 Gm. in the $NH_4Cl$ subgroup), and the excretion of rubidium was only 0.02 to 0.06 mEq. per 100 Gm. In the cesium-treated animals, excretion of potassium and of cesium ranged from 0.03 to 0.06 mEq. per 100 Gm.

*B. Acid excretion*

Table II gives the results of the determinations of urine pH, titratable acidity and ammonium excretion. Also listed is the calculated excretion of "net acid," determined in each animal by the *sum* of titratable acid and ammonium minus any bicarbonate in the urine. Urine bicarbonate, not shown in the table, was very low in the NaCl subgroups and virtually absent in most of the animals loaded with $NH_4Cl$. The symbols and conventions are the same as those used for Table I.

*Urine pH.* There were no significant differences between the mean urine pH values of any of the subgroups during sodium loading (range, 6.20 to 6.47), although the mean pH was highest in the potassium-deficient alkalotic animals. During the excretion of the acid load there was a sharp and significant drop in urine pH in the normal (Group I) animals (mean pH 5.61 ± 0.26). There was a somewhat smaller reduction in the potassium-

TABLE III

*Increments in excretion of "net acid" and ammonium in response to $NH_4Cl$ (1 mEq./100 Gm.)*

| | "Net acid" | Ammonium |
|---|---|---|
| | *mEq./day/100 Gm. body weight* | |
| Group I (Normal) | 0.77 ± 0.18 (20) | 0.61 ± 0.16 (20) |
| Group II (K-deficient) | 0.84 ± 0.26 (13) | 0.75 ± 0.26 (13) |
| Group III (Rb) | 0.68 ± 0.12 (13) | 0.66 ± 0.15 (13) |
| Group IV (Cs) | 0.58 ± 0.10 (14) | 0.55 ± 0.10 (14) |

deficient (Group II) animals (mean pH 6.13 ± 0.34) which was still of significance ($p = 0.01$ to 0.02). However, there were no significant changes with $NH_4Cl$ loading in the rubidium or cesium groups, although in each case the mean urine pH was slightly lower than in the comparable NaCl subgroup.

*Ammonium.* During NaCl loading, excretion of ammonium in the Group II potassium-deficient animals (0.55 ± 0.14 mEq. per 100 Gm.) was significantly higher than that of any of the other groups, the latter ranging from 0.32 to 0.39 mEq. per 100 Gm. Thus, despite severe systemic acidosis, the ammonium excretion (and urine pH) of the rubidium-treated animals was essentially the same as that found in the normal rats.

In every instance excretion of ammonium was significantly increased during the $NH_4Cl$ load, the increase in the mean for each group ranging from 0.55 mEq. per 100 Gm. in the cesium-treated animals up to 0.75 mEq. per 100 Gm. in the potassium-deficient group.

*Titratable acid* was relatively low in all groups during NaCl loading (0.092 to 0.134 mEq. per 100 Gm.) and increased significantly during $NH_4Cl$ loading only in the normal and potassium-deficient animals.

Excretion of *"net acid"* during NaCl loading ranged from 0.40 mEq. per 100 Gm. in the rubidium-treated animals up to 0.62 mEq. per 100 Gm. in the potassium-deficient group. The latter group was significantly higher than the normal controls. "Net acid" increased significantly in every case during acid loading, the mean rate of excretion ranging from 1.03 ± 0.10 mEq. per 100 Gm. in the cesium-treated group to 1.46 mEq. per 100 Gm. in the potassium-deficient group.

Table III lists the *increments* in the excretion of "net acid" and ammonium during $NH_4Cl$ loading, as compared to the excretion during NaCl loading. These values were calculated by subtracting the mean excretion in each group during NaCl loading from the excretion of each individual animal during acid loading. The figures shown are the mean values ± S.D. In parentheses is the number of animals in each group. It is seen that the increment in "net acid" ranged from 0.58 mEq. per 100 Gm. in the cesium group, to 0.84 mEq. per 100 Gm. in the potassium-deficient group. The differences in "net acid" between the cesium-treated animals and both the normal and the potassium-deficient animals were significant, but the rubidium-treated animals were not significantly different from any of the other groups. Almost all of the change in "net acid" was due to a change in ammonium excretion, but group differences in the latter were not as large as in "net acid." Only the Groups II and IV showed any significant difference ($p = 0.02$ to 0.05).

### *C. Kidney tissue analyses*

Table IV summarizes the results of the renal tissue analyses. It should be recalled that only kidneys from NaCl-loaded animals were studied. Because of the small number of electrolyte determinations, individual values as well as means are shown. *Potassium content* was slightly but consistently reduced in the three potassium-depleted animals although sodium content was unchanged. In the rubidium-treated animals, potassium was lower than in the untreated Group II rats, while rubidium content was approximately half that of potassium. The cesium-treated animals had the lowest potassium content of all, with a K : Cs ratio of approximately 2.

The *glutaminase* data are given as means ± S.D. There was a significant rise in enzyme activity in all groups, as compared to the normal, the highest activity being found in the rubidium-treated animals.

## DISCUSSION

Rats are normally capable of immediate and very large ammonium-excreting responses when their extracellular fluid is acidified by acid loads

TABLE IV

*Electrolyte content and glutaminase activity of whole kidneys*

| | Sodium | Potassium | Rubidium or cesium | Glutaminase |
|---|---|---|---|---|
| | *mEq./100 Gm. dry solids* | | | *μMoles $NH_3$/min./100 mg. dry solids* |
| Group I (Normal) | 33.0 | 31.0 | | 18.3 ± 5.1 (11) |
| | 25.5 | 31.0 | | |
| | 27.0 | 32.0 | | |
| | Mean 28.5 | 31.3 | | |
| Group II (K-deficient) | 26.1 | 26.2 | | 28.7 ± 9.4 (10) |
| | 29.1 | 28.6 | | |
| | 27.6 | 28.1 | | |
| | Mean 27.6 | 27.6 | | |
| Group III (Rb) | 25.2 | 20.5 | 10.2 | 57.5 ± 20.7 (9) |
| | 18.4 | 22.2 | 12.4 | |
| | 22.6 | 20.5 | 9.0 | |
| | Mean 22.1 | 20.9 | 10.5 | |
| Group IV (Cs) | 18.9 | 14.5 | 8.3 | 27.6 ± 9.1 (7) |
| | 21.7 | 18.3 | 8.9 | |
| | 26.1 | 16.7 | 8.9 | |
| | Mean 22.2 | 16.5 | 8.7 | |

(5–7). Nevertheless, despite an extracellular $CO_2$ content of only 19.5 mMoles per L., the rubidium-treated rats excreted no more acid during loading with NaCl than did the normal animals, thus failing to show any renal response to this disturbance of acid-base balance. The present results would appear to permit certain limited inferences concerning the nature and significance of this phenomenon.

In the first place, it is clear that "competition" between tubular secretion of hydrogen and potassium or rubidium (9) cannot be the explanation for these results. In previous experiments (4), renal acid excretion was measured during the period of acute loading with rubidium, when renal excretion of rubidium and potassium was very high. Such conditions, which might favor inhibition of acid secretion, were avoided in the present experiments by removing rubidium and potassium from the diet prior to and during the 24 hour period of study. Since rubidium is secreted into the urine more slowly than potassium (10), the net result of this maneuver was that the combined secretion of rubidium and potassium was even lower than the excretion of potassium alone in the normal controls (Table I). In none of the groups was the excretion of potassium, rubidium or cesium particularly high.

Secondly, the enzyme assays shown in Table IV demonstrate that the absence of increased ammonium excretion in the rubidium-loaded rats cannot be due to reduced glutaminase activity. As described by other workers (7), the increased ammonium excretion of the potassium-deficient animals was associated with increased glutaminase activity. However, no further correlations could be made between enzyme activity and ammonium excretion because glutaminase was as high, or higher, in the rubidium and cesium groups, *without* increased excretion of ammonium.

Although the rubidium-induced extracellular acidosis does not stimulate acid excretion, the results of the $NH_4Cl$ experiments indicate that rubidium-loaded kidneys are *capable* of normal and prompt acid-excreting responses when given the proper stimulus. As shown in Table III, the increment in "net acid" excretion in response to the $NH_4Cl$ load was virtually the same in the rubidium-treated animals as in the normal or the potassium-depleted groups. A clear implication of these facts is that the administration of $NH_4Cl$ provided a stimulus for the excretion of acid which was otherwise lacking in the rubidium-treated rats, despite their moderately severe extracellular acidosis. On the other hand, as has been observed before (11), there was a high rate of acid excretion in the potassium-deficient animals despite the presence of extracellular alkalosis. Changes in the kidney itself, which may be independent of the acid-base equilibrium of extracellular fluid, are apparently of prime importance in determining acid excretion. The present experiments do not reveal the nature of this intrarenal regulation, but the data in Table IV show that it is not apt to be related simply to the quantities of alkali metal in renal tissue. Thus, acid excretion was essentially equal in Groups I and IV, despite large group differences in renal content of sodium, potassium and potassium plus cesium.

One reasonable possibility is that renal intracellular acidity is the critical factor determining acid excretion. Intracellular acidosis has been suggested as an explanation of the increased acid secretion of the potassium-depleted kidney (12–14). Conversely, it might also be suggested that in the rubidium-loaded animal intracellular pH is normal or increased, since accumulation of rubidium appears to be associated with the movement of acid *out* of cells (2, 4). Renal tissue pH may

fall only when the addition of a large exogenous acid load results in a net movement of acid back into cells. However, little or nothing is known at present about renal cell pH under any *in vivo* conditions. It is obvious that no conclusions can be drawn until there is more information about renal tissue composition and the internal distribution of acid in potassium-depleted and rubidium- and cesium-substituted animals.

A final topic of interest is the defect in acidification of the urine which was demonstrated in both the rubidium- and cesium-treated animals. In the normal rats, administration of $NH_4Cl$ sharply reduced urine pH coincidentally with the increased excretion of ammonium (Table II). In the rubidium- and cesium-treated groups, although the ammonium response was normal, there was only a very slight and insignificant lowering of urine pH (Table II). Leonard and Orloff have demonstrated that ammonium is not as closely related to urine pH in the normal rat as in dog or man (5). The present observations show that it is possible to produce virtually independent changes in these functions, thus suggesting that establishment of final hydrogen-ion gradients may be an operation which is biochemically or anatomically separate from the ammonium-excreting mechanism. Loss of potassium from cells and substitution of rubidium or cesium in some manner impairs the hydrogen ion gradient process without inhibiting the capacity to excrete ammonium. In untreated potassium depletion, the relative alkalinity of the glomerular filtrate may be, at least in part, responsible for the alkalinity of the urine (11), but this factor clearly cannot be implicated in the rubidium-substituted rats in which the plasma bicarbonate is markedly reduced.

## SUMMARY AND CONCLUSIONS

To learn more about the renal responses of rats loaded with rubidium or cesium, experiments were designed to compare acid and electrolyte excretion during a 24 hour period in: *a*) normal animals, *b*) potassium-depleted alkalotic animals, *c*) rubidium-substituted animals, and *d*) cesium-substituted animals. These groups were compared during administration of NaCl and also during loading with $NH_4Cl$.

During NaCl loading, ammonium excretion was higher than normal in the potassium-deficient animals, but not increased in those treated with cesium or rubidium, despite a significant degree of extracellular acidosis in the latter group. Glutaminase activity was increased in the potassium-deficient animals as well as in those treated with rubidium and cesium. Excretion of potassium (or rubidium or cesium) was minimal and renal potassium content was low in all the experimental groups.

All the animals responded to the $NH_4Cl$ load with a large and approximately equivalent increment in ammonium excretion. However, in contrast to the sharp drop in urine pH in the normal animals, there was no significant change in the acidity of the urine in the rubidium- or cesium-treated groups.

It is thus demonstrated that rubidium-substituted kidneys do not respond to the extracellular acidosis produced by the rubidium, but are nevertheless capable of a normal ammonium response to the administration of an acidifying salt. The data are consistent with the hypothesis that the normal stimulus to ammonium excretion is related to intracellular rather than extracellular acid-base equilibrium. It is tentatively suggested that renal intracellular pH may be normal or increased in the rubidium-substituted animal.

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