Renal hypertrophy in metabolic acidosis and its relation to ammonia excretion

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The chronic ingestion of NH₄Cl causes a true growth of the rat kidney. This involves a symmetrical increase in wet weight, dry weight, and nitrogen of the kidney tissue. Total DNA and RNA are also elevated, indicating that both cell numbers and cell size have increased. The renal hypertrophy in chronic metabolic acidosis is the same order of magnitude as that seen in the remaining kidney after unilateral nephrectomy. The renal growth stimulating effects of acidosis and unilateral nephrectomy are additive. In the acidic rat the renal hypertrophy that occurs after unilateral nephrectomy can maintain a high rate of ammonia excretion without any further change in renal glutaminase activity of the remaining kidney. Thus in certain species the stimulation of renal growth may play a part in the increasing capacity to excrete ammonia during sustained metabolic acidosis.

During sustained metabolic acidosis man and certain lower animals show a progressive increase in the capacity to excrete ammonia in the urine. This process may continue until practically the entire load of acid anions is excreted as the ammonium salt (6). As this happens the rate of sodium excretion declines, and there is a progressive improvement in sodium conservation as acidosis continues. The nature of the mechanisms underlying this adaptation in ammonia excretion has been of considerable interest to physiologists, but is not yet well understood. The renal extraction of glutamine, the major source of urinary ammonia (16), is increased in acidosis (5, 13, 16). Whether this can account for the change in ammonia excretion, or coincides temporally with it, has not been determined. Kidney slices (2) and homogenates from chronically acidic rats and guinea pigs (4, 11) have been shown to produce more ammonia in vitro from glutamine than similar tissue preparations from normal or alkalotic animals. These changes have been interpreted in terms of induced adaptations in one or more glutaminase enzymes (11). In the dog, however, which shows par excellence the developing change in ammonia excretion in acidosis, no change can be demonstrated in the rate of ammonia formation from glutamine by surviving kidney tissue in vitro (8). Since renal glutaminase activity in the dog is considerably higher than in the rat (10) it may not “need” to increase to meet the ammonia excretion demands of acidosis. Thus an induced increase in glutaminase enzymes is probably not the whole explanation for the animal’s increasing capacity to excrete an acid load as the ammonium salt.

For this reason we decided to look at other aspects of renal metabolism during experimentally induced metabolic acidosis. It was reasoned that perhaps the glutaminase changes that had been observed, particularly in the rat, might represent one manifestation of a more general increase in rate of protein synthesis in the kidney. If this were so, then the adaptation in ammonia excretion could be explained simply in terms of increased renal tissue mass. By the same token the total glutaminase activity of acidotic kidney tissue should be even greater if the acidosis occurred in an animal whose kidney was undergoing rapid regeneration, as after unilateral nephrectomy.

For these reasons it was decided to begin our study by comparing the effects of acidosis on ammonia-producing capacity of kidney tissue from rats with two kidneys—regenerating at a normal rate—with that from animals with one remaining kidney undergoing rapid regeneration after unilateral nephrectomy. These experiments have shown that chronic metabolic acidosis in the rat causes a true renal hypertrophy of about the same magnitude as that seen after unilateral nephrectomy. Furthermore, when the rat with one remaining kidney is made acidic, the degree of hypertrophy is even greater than with either acidosis or unilateral nephrectomy alone. These results support the idea that renal growth may play a role—along with enzyme changes and increased glutamine extraction—in producing the...
METHODS

All experiments were carried out on female albino rats of the Holtzman strain weighing between 200 and 250 g. They were housed in individual cages kept in a constant-temperature room at 74 °F, and fed Purina laboratory chow ad libitum. Metabolic acidosis was produced by substituting 0.28 m NH₄Cl for the drinking water given the controls. All animals drank nearly equivalent amounts of water or NH₄Cl were selected for use. Both control and NH₄Cl animals were maintained on their respective regimens for 7 days.

For measurement of ammonia excretion, rats were transferred for a 4-hr period each morning, at the same time, into individual metabolism cages that had been previously scrubbed and washed down with distilled water. No food or drinking bottles were present. The bladder was emptied by suprapubic pressure, 5 ml of tap water were given by stomach tube, and the urine collection begun. At the end of the collection period the residual bladder urine was again expressed by suprapubic pressure, and the cage bottom washed with a known volume of distilled water. Urine and washings were collected in calibrated centrifuge tubes. Ammonia was determined on the diluted urine by the Conway microdiffusion method (1).

Unilateral nephrectomy was carried out under ether anesthesia through a midline incision over the lumbar spine. The adrenal gland was left in place.

For in vitro measurement of renal tissue ammonia production and oxygen consumption, rats were killed by decapitation, exsanguinated, and one or both kidneys removed. The organ was rapidly decapitated, divided longitudinally, and the medulla cut out with fine scissors. The cortex was quickly weighed on a torsion balance, and at 30 min the flasks were placed in cracked ice. Three consecutive oxygen consumption readings were taken, and at 30 min the flasks were placed in cracked ice. Flask contents were removed and centrifuged in the cold room for 10 min. Incubation was continued. Three consecutive oxygen consumption readings were taken, and at 30 min the flasks were placed in cracked ice. Flask contents were removed and centrifuged in the cold room for 10 min. Ammonia was determined on an aliquot of the clear supernatant fluid by the Conway microdiffusion method. The amount of ammonia liberated from protein, in the absence of added glutamine, was negligible in these homo- genate supernatants. Nitrogen was determined on a 1-ml sample of the original homogenate, after digestion, by micro-Kjeldahl distillation and titration. Oxygen consumption and ammonia production from glutamine. The addition of 100 μmoles glutamine to each flask was well above a rate-limiting concentration in tissue from both normal and acidic rats.

FIG. 1. Wet weight, dry weight, and total nitrogen values for kidneys from 4 groups of rats as indicated at bottom of figure. "Regenerating" refers to remaining kidney after unilateral nephrectomy. Each bar represents mean of observations on 9 animals. Black dots define standard error of the mean. P values are over the two bars that they compare.

For the incubation period 1 ml of this homogenate was placed in iced Warburg flasks previously charged with MgCl₂, 10 μmoles; ADP, 4.2 μmoles; inorganic phosphate, 200 μmoles as sodium phosphate buffer 0.2 m pH 7.4; and glutamine, 100 μmoles. Final volume of flask contents was 3 ml. The center well contained 0.2 ml 2 N NaOH and a filter-paper wick for CO₂ absorption. Flasks were placed on their manometers, gassed during shaking for 3 min with 100% O₂ in the thermostatic bath at 37 °C. After temperature equilibration for 10 min, incubation was continued. Three consecutive oxygen consumption readings were taken, and at 30 min the flasks were placed in cracked ice. Flask contents were removed and centrifuged in the cold room for 10 min. Ammonia was determined on an aliquot of the clear supernatant fluid by the Conway microdiffusion method. The amount of ammonia liberated from protein, in the absence of added glutamine, was negligible in these homogenate supernatants. Nitrogen was determined on a 1-ml sample of the original homogenate, after digestion, by micro-Kjeldahl distillation and titration. Oxygen consumption and ammonia production from glutamine. The addition of 100 μmoles glutamine to each flask was well above a rate-limiting concentration in tissue from both normal and acidic rats.

Preliminary studies showed that 200 μmoles/flask inorganic phosphate at pH 7.4 was optimal for both oxygen consumption and ammonia production from glutamine. The addition of 100 μmoles glutamine to each flask was well above a rate-limiting concentration in tissue from both normal and acidic rats.
ammonia production rates were then expressed as microliters and microequivalents, respectively, per milligram tissue nitrogen per hour.

Kidney weights, nitrogen, and nucleic acids were always determined on one kidney of intact rats, or on the remaining one of unilaterally nephrectomized animals. For dry-weight determinations kidneys were divided longitudinally, placed in weighed aluminum-foil pans, and dried to constant weight at 85°C in a vacuum oven for 20 hr. Tissue weights were measured on a torsion balance, and total nitrogen determined on the dried tissue, after digestion, by the micro-Kjeldahl method.

DNA and RNA were determined in perchloric acid filtrates of kidney cortex by the Schmidt-Tannhäuser-Schneider technique (3). All steps in the procedure up to the final readings were carried out in the cold room at 4°C. Final readings were made in perchloric acid solutions in the Beckman spectrophotometer. DNA was read at 268 mμ and compared with standards made from dried calf thymus DNA. RNA was read at 260 mμ and compared with standards made from dried yeast RNA. (Pure calf thymus DNA was kindly given by Dr. Ernest Kay of our Department of Biochemistry, and pure yeast RNA was obtained from Sigma Biochemical Co., St. Louis, Mo.)

RESULTS

Effects of acidosis and unilateral nephrectomy on kidney growth. These effects are shown in Fig. 1. Each bar in the histogram represents the mean of the observations on nine animals with the standard error of the mean shown as the black dots. All observations were made on the 7th day after start of NH₄Cl or unilateral nephrectomy, or both. We note from the first two bars of each plot (C and A) that acidosis alone caused a highly significant increase in kidney wet weight, dry weight, and total nitrogen. This change was quantitatively similar to that produced by unilateral nephrectomy (bar R). When unilaterally nephrectomized rats were made acidic in addition, their remaining kidney grew even larger (bar RA). The effects of the two stimuli apparently potentiate one another; with both there is a significantly greater increase in wet weight, dry weight, and total nitrogen than with either acidosis or unilateral nephrectomy alone. These changes represent true growth. In each case the kidney nitrogen was the same when expressed on the basis of dry weight. Thus new tissue protein was synthesized, as a result of these stimuli, in proportion to other cell constituents. The increased weight was not just an increase in water, or fat, but a true new growth.

We had to ask at this point whether this kidney growth was solely the result of NH₄Cl ingestion, with its attendant acidosis, whether it is a specific effect of the ammonium ion, or whether it might also be related to the more nonspecific intake of nitrogen and/or an increased load of solute. To test these possibilities, the experiments shown in Table 1 and Figs. 2 and 3 were performed.

In the experiment shown in Table 1 an attempt was made to test the three variables of acidosis, solute load, and the specificity of the ammonium ion as they affect kidney growth. All solutions were isosmolar (0.28 M) with the NH₄Cl given the rats to produce acidosis. It will be noted that the usual significant increase in wet and dry weight was seen in the NH₄Cl group. Those drinking NaCl also showed a significant, but less marked, increase in kidney wet and dry weight. We have noted this same phenomenon in three additional experiments. It should be noted that the NaCl group drank three or four times as much solution each day as the NH₄Cl group. Thus solute load, in the case of NaCl, does cause some renal hypertrophy, but not as much as NH₄Cl ingested in much smaller amounts. Neither NaHCO₃ nor ammonium citrate caused significant renal growth in this experiment.

Next, experiments like those shown in Figs. 2 and 3 were performed. Three groups of rats were compared: one drinking 0.28 M NaCl served as controls; another drank 0.28 M NH₄Cl, and a third a urea solution containing nitrogen in a concentration equivalent to that in the 0.28 M NH₄Cl. Figure 2 shows that only NH₄Cl drinking produced acidosis. Arterial blood pH was determined on aortic blood drawn anaerobically from these animals under light ether anesthesia. All samples from NH₄Cl-drinking rats were significantly below those from urea and NaCl groups. In Fig. 3, NaCl and NH₄Cl groups both had larger kidneys containing more nitrogen than the urea group that drank volumes of solution equivalent to those on NH₄Cl. Therefore it is clear that nitrogen alone in the NH₄Cl is not the cause of the growth. Here, as in Table 1, an equivalent load of 0.28 M NaCl produced kidneys not quite as large as those of the NH₄Cl group. In addition to these results, it can be reported that rats who have lived in an atmosphere of 8% CO₂ for 7 days and thus have sustained a chronic respiratory acidosis do not show a significant change in renal wet or dry weight or nitrogen. Therefore, the renal hypertrophy seen in chronic NH₄Cl ingestion is apparently predominantly a response to the ingestion of NH₄Cl, with a possible less-specific component of solute load also playing a role. It should be
pointed out that there is a good deal of quantitative variability in these experiments from group to group of rats. The qualitative differences reported have been repeatedly observed, but the quantitative values for the parameters measured may vary considerably from group to group of rats delivered from week to week. For this reason the importance of including a control group of the same shipment of rats in each experiment must be emphasized.

Nucleic acids. In an attempt to define more precisely the nature of the kidney growth seen in acidosis, and after unilateral nephrectomy, measurements were made of DNA and RNA in the kidneys of both types of animals. The results of these studies are shown in Table 2. With acidosis we saw the usual increase in kidney weight. At the same time total RNA and DNA increased significantly. After unilateral nephrectomy, kidney weight was also up, and both DNA and RNA were increased even more. When the unilaterally nephrectomized rat was made acidoic, wet weight and total DNA and RNA were still higher. Thus the total amount of both these nucleic acids in the whole kidney parallels the changes in organ weight and total nitrogen. This supports the conclusion that in both chronic NH4Cl acidosis and after unilateral nephrectomy there is true tissue growth involving formation of new cells.

The data on concentration of these two nucleic acids indicate that there is also increase in size of individual cells. Although DNA content increases in each of the groups of rats, its concentration in the tissue decreases. With acidosis alone, although total RNA content increases, RNA concentration in the kidney is unchanged. This could mean either a proportionate increase in RNA and cytoplasmic mass, or an increase in the number of cells each containing equivalent amounts of RNA. With unilateral nephrectomy, and even more so when this was combined with acidosis, both RNA content and concentration in the kidney rose significantly, indicating that in these conditions cytoplasmic RNA increased even more than its non-RNA constituents.

Thus both acidosis and unilateral nephrectomy stimulate kidney growth. In both situations there is stimulation of cell division and increase in size of individual cells. On the basis of the increment in DNA per gram increase in wet weight, the changes are similar in both types of stimulated growth. The additive effects of both acidosis and unilateral nephrectomy in stimulating kidney growth are well illustrated in these nucleic acid data, as they are in the weight and nitrogen observations shown in Fig. 1.

In vitro studies. Homogenates were made, as described above, from kidneys of these four groups of rats. They were incubated with glutamine and phosphate buffer pH 7.4—optimal conditions for glutaminase I activity—and the oxygen consumption and ammonia formation of the tissue observed. The results of these studies are graphically shown in Fig. 4. The right-hand side of the figure shows in the first two bars the increased capacity of isolated homogenized kidney from acidotic rats to produce ammonia from glutamine. This has been repeatedly observed by other workers (4, 11). The third bar shows the ammonia produced by the homogenate of remaining kidney 7 days after unilateral nephrectomy. There is a slight increase over the control, but it is not statistically significant. Tissue from unilaterally nephrectomized-acidotic rats (last bar) shows about the same percent increase in ammonia formation as that from animals with two kidneys. Therefore we cannot say that the remaining kidney tissue after unilateral
RENAL HYPERFUNCTION AND AMMONIA EXCRETION

TABLE 2. Effects of chronic metabolic acidosis and unilateral nephrectomy on wet weight and nucleic acid content of rat kidney

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Wet Wt</th>
<th>DNA</th>
<th>RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/t</td>
<td>mg/g wet wt</td>
<td>g/t</td>
</tr>
<tr>
<td>Control</td>
<td>0.78 ± 0.01</td>
<td>4.33 ± 0.13</td>
<td>6.30 ± 0.09</td>
</tr>
<tr>
<td>Acidosis</td>
<td>0.93 ± 0.07</td>
<td>4.92 ± 0.10</td>
<td>7.53 ± 0.10</td>
</tr>
<tr>
<td>Uninephrectomy</td>
<td>1.00 ± 0.07</td>
<td>5.18 ± 0.10</td>
<td>8.64 ± 0.10</td>
</tr>
<tr>
<td>+ acidosis</td>
<td>1.09 ± 0.07</td>
<td>5.41 ± 0.10</td>
<td>11.00 ± 0.10</td>
</tr>
</tbody>
</table>

Values are means of each group ± se. In each group N = 6. Statistical differences are all related to control observations.

nephrectomy has greater glutaminase activity, nor is it more stimulated by NH₄Cl than in animals with two kidneys regenerating at a normal rate.

On the left-hand side of the figure are shown oxygen consumption rates in these same kidney homogenates in the presence of glutamine and an optimal concentration of phosphate. Since previous studies of this sort have been done without reported measurements of oxygen consumption rates (4, 9, 11), these observations are of interest. In kidney homogenates from acidotic rats the rate of oxygen consumption, with glutamine, is significantly higher. Neither the rate nor its increase with acidosis is significantly different in remaining kidney tissue from unilaterally nephrectomized rats.

The time course of this increased oxygen consumption parallels the development of the increased ammonia formation by kidney tissue in acidosis. This is shown in Fig. 5. Each dot represents the mean of two observations on kidney homogenates made from acidotic rats on each of 8 days after the start of NH₄Cl ingestion. The correlation between these two functions as seen in this figure has been observed in two additional confirming experiments. The steepened slope of the curve around the 5th day has no apparent significance, since it was not a regularly observed phenomenon.

We next asked about the basis for this increased aerobic oxidation of glutamine in "acidotic" tissue. More ammonia is being formed from the amide of glutamine, but this is an anaerobic process. At the same time, however, more glutamic acid is being formed by this deamination, and the oxidation of this glutamic acid is aerobic, so that perhaps the increased oxygen consumption in the acidotic tissue is simply the result of more glutamic acid having been generated from glutamine. This and other speculations prompted the experiment shown in Fig. 6. Here homogenates from acidotic rats were incubated in 100% oxygen with three different and equivalent levels of glutamine, or its two main products: glutamic and a-ketoglutaric acids. Rate of oxygen consumption was measured. Since we had used 100 μmoles of glutamate (well above a rate-limiting concentration), this was chosen as the highest amount of each substrate added. It is evident that with glutamine and a-ketoglutarate, oxygen consumption was optimal down to the lowest level of substrate tested (25 μmoles/flask). But with glutamate, oxygen consumption fell off as substrate concentration was reduced. Thus at 100 μmoles of glutamine, more glutamic acid would be formed in the acidotic tissue and thus oxygen consumption rate would increase.

There is another interesting aspect of these data, and that is the very high aerobic oxidation rate of glutamine in relation to glutamic acid, and to a lesser extent α-ketoglutaric. In the assimilation of glutamine, both the deamination of its omega amide group and transamination of its alpha amino group are anaerobic. Thus, when glutamine is incubated with viable tissue in the presence of ATP and Mg²⁺ ions, one would perhaps expect its aerobic oxidation rate to equal that of its oxidizable products: glutamic or α-ketoglutaric acids. Yet, as we see here, its rate of oxidation is considerably higher than either of these at all substrate levels studied. This suggests that the aerobic oxidation of glutamine is
FIG. 5. Experiment showing parallel temporal development of change in oxygen consumption with glutamine and ammonia production from glutamine in centrifuged homogenates of kidney cortex from rats drinking 0.28 M NH₄Cl.

qualitatively different from either of its major oxidizable products, and may involve enzymes and/or pathways different from the known ones for glutamic or α-ketoglutaric acids.

Perhaps there is oxidative deamination of glutamine, utilizing the NADP-linked glutamic dehydrogenase system. This raises the possibility that some ammonia produced in the kidney from glutamine might come from the α-amino group under normal aerobic circumstances. Experiments in our laboratory make this an unlikely possibility, however. When glutamine containing 95 atoms percent excess N¹⁵ in the amide group is used in our aerobic homogenate system described here, the free ammonia formed contains 90 atoms percent excess N¹⁵, indicating that most of it has come from the amide group.³ Alternatively glutamine may represent an "active" form of glutamate or α-ketoglutarate, and have a greater affinity or specificity for the assimilative mechanisms used by it and its metabolites. Glutamine could also permeate the mitochondrial membrane more easily than the other two metabolites, and thus have a higher rate of oxidation. These data emphasize the need for more study of the aerobic oxidative metabolism of glutamine in mammalian tissues.

Glutaminase increase and renal hypertrophy in regulation of ammonia excretion in chronic acidosis. Since we have shown that the kidney hypertrophies in chronic metabolic acidosis, it was logical to ask at this point about the role of this process in the expanding capacity of the kidney to excrete ammonia in chronic acidosis. To answer this question, in part, two experiments were performed with similar results. One of these is shown graphically in Fig. 7. After several days acclimatization to diet and surroundings, all animals drank tap water and control measurements of ammonia excretion were made. Then the rats were divided into two groups of six each. One was allowed to drink 0.28 M NaCl, and the other drank 0.28 M NH₄Cl. All rats were kept on these regimens for 5 days during which there were daily urine collection periods of 4 hr at the same time each morning for measurement of ammonia excretion. The figure shows that among the NaCl drinkers there was no significant change in ammonia excretion. However, the NH₄Cl drinkers developed a greatly increased rate that had reached a plateau by the 3rd day. By the 5th day on NH₄Cl, we know that the renal glutaminase activity has increased markedly and that the kidneys have undergone significant growth. Therefore when these changes in the two kidneys of the acidic rats were fully developed, both control and acidic rats were unilaterally nephrectomized. Then all animals were continued on their same regimens, with daily measurements of ammonia excretion made as before. During this period we would expect all remaining kidneys to hypertrophy, those on NH₄Cl to an even greater extent (Fig. 2 and Table 1). We would not, however, expect any significant further increase in renal glutaminase enzymes (Fig. 4). Thus any regained capacity of the remaining kidneys to excrete ammonia after unilateral nephrectomy should result from increased renal tissue mass, or some function associated with it, rather than further induction of glutaminase activity. The data show that the control nonacidotic rats showed no significant change in their rate of ammonia excretion. The acidic rats, after unilateral nephrectomy, showed very little change in ammonia excretion; indeed, by 2 days after operation they had completely regained their prenephrectomy capacity to excrete ammonia. This regained capacity followed the time course of the renal hypertrophy in such unilaterally nephrectomized animals where significant compensatory hypertrophy has already occurred by 36 48 hr.⁴

³ These experiments were performed by Dr. Daniel O'Donovan in our laboratory, and I am grateful for his permission to quote it.

⁴ These experiments were performed by a medical student, Mr. Tunde Solola, during tenure of a summer fellowship in our laboratory.
The mechanism of renal hypertrophy following unilateral nephrectomy is still not well understood. Perhaps removal of one kidney either releases a growth-stimulating factor for the remaining kidney, or reduces below a critical level the circulating concentration of some factor that normally inhibits kidney growth. This hypertrophy involves both new cell formation and enlargement of existing cells (12). The synthesis of new DNA accompanying the increased mitosis in compensatory renal hypertrophy has been observed by Simpson (14) using P32 incorporation into DNA. We have been able to confirm this observation in our laboratory. Threlfall et al. (15) have also observed a significant increase in DNA content of the remaining kidney at 48 hr, and the experiments reported here confirm this finding, although there is considerable quantitative variation in the results from experiment to experiment.

It is not the purpose of this paper to present a comprehensive review of compensatory renal hypertrophy; much work needs to be done before we have any real understanding of this remarkable process. Rather I wish only to record here the observed renal hypertrophy that occurs in chronic NH4Cl acidosis, to point out its relation to compensatory hypertrophy after unilateral nephrectomy, and discuss its possible relation to the regulation of ammonia production and excretion by the kidney. I also want to emphasize that this hypertrophy is a true growth of the kidney, involving synthesis of new DNA, RNA, and tissue protein, and further that the growth-stimulating effects of NH4Cl and unilateral nephrectomy are additive. Although both DNA and RNA increase in both types of renal growth, there are definite differences in their patterns of increase, indicating differences in the relative rates of increase in cell numbers and cell size in the two circumstances. These differences in pattern of nucleic acid change and the additive effects of acidosis and unilateral nephrectomy on total RNA, DNA, and protein synthesis indicate that the two stimuli affect the renal cellular machinery for protein synthesis in an additive way.

The experiments shown in Fig. 7 show that renal hypertrophy, or some function of it, without any change in glutaminase activity, can significantly affect rate of ammonia excretion. It is possible that the continued high rate of ammonia excretion by the remaining kidney after uninephrectomy resulted from a further stimulation of its ammonia-producing capacity by a relative increase in the acid load presented to it as NH4Cl. Perhaps in the dog, where no change in renal glutaminase is observed in acidosis (8), there is already enough basal enzyme activity to meet the demands for increased ammonia production and excretion in acidosis. Pitts implies this in his recent review (7). Dog kidney glutaminase activity is considerably higher than that of the rat under normal circumstances (10), and therefore these enzymes may not be saturated with glutamine in normal animals with their prevailing rates of renal glutamine extraction. In metabolic acidosis, when the kidney extracts more glutamine from its arterial blood, these enzymes could therefore produce more ammonia from it without any induced enzyme change. Conversely there could be an increase in total kidney mass of the type seen here in the rat, without any change in enzyme concentration per unit mass of tissue. Either circumstance would result in an increasing capacity to excrete ammonia without any observable change in tissue glutaminase concentration. Thus degree of enzyme saturation in the normal state, induced enzyme
change, and induced renal growth may all be factors underlying the expanding capacity to excrete ammonia in acidosis. In different species these several variables, and perhaps others as well, may operate to relatively different extents in producing the over-all change in ammonia excretion.

REFERENCES


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