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Research Article

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AN ANALYSIS OF THE MECHANISM OF THE INHIBITORY INFLUENCE OF K^+ ON RENAL H^+ SECRETION *

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On the basis of previous studies from this laboratory (1), the hypothesis was advanced that the reabsorption of HCO_3^- by the kidney is mediated by two distinct H^+ secretory systems. One system, termed the pCO_2-dependent H^+ secretory system, has a maximal HCO_3^- reabsorptive capacity (HCO_3^- Tm) which is dependent upon plasma CO_2 tension and independent of carbonic anhydrase. The second system, termed the carbonic anhydrase-dependent H^+ secretory system, has a fixed HCO_3^- Tm which is dependent upon carbonic anhydrase but independent of plasma pCO_2.

In addition to CO_2 tension and carbonic anhydrase activity, H^+ secretion is influenced by K^+ (2–9). According to present concepts, there is competition between H^+ and K^+ for exchange with Na^+ in the distal tubule (7).

The present study, therefore, was undertaken to determine the extent to which K^+ influences each of the two distinct H^+ secretory systems and also to gain further insight into the relationship between H^+ and K^+ secretion.

METHODS

Studies were performed on 9 female mongrel dogs anesthetized with sodium pentobarbital. An endotracheal tube fitted with an inflatable cuff was inserted into the trachea and connected to a Bird assisted-respiratory anesthesia unit. The concentration of CO_2 in inspired air could then be varied over a wide range by changing the relative flow rates of 100 per cent CO_2 and 100 per cent O_2 into the respirator. Methods for collecting and analyzing blood and urine have been described previously (1).

The effect of K^+ loading on the relationship between the maximal HCO_3^- reabsorptive capacity and plasma pCO_2 before and after inhibition of carbonic anhydrase was studied in 6 dogs. These dogs had been pre-fed 4.5 g KCl twice daily for 7 to 10 days. For comparison, previous experiments on dogs not given KCl served as controls (1).

To insure that filtered HCO_3^- always exceeded the HCO_3^- Tm, the plasma HCO_3^- concentration was elevated by an initial injection of 12 g $NaHCO_3$ and maintained at this high level by a constant infusion of isotonic $NaHCO_3$ at the rate of 10 ml per minute. Potassium chloride was infused throughout the experiment at the rate of 40 μEq per kg body weight per minute. After starting the infusion of KCl, there was always an equilibration period of at least 90 minutes, which preliminary experiments had established as adequate to permit K^+ excretion to attain a constant rate. In each experiment plasma pCO_2 was increased in step-wise fashion by raising the concentration of CO_2 in the inspired air. After each change in plasma pCO_2 an equilibration period of 15 minutes elapsed before starting the collection period. The procedure was then repeated in each dog after the administration of acetozolamide, 50 mg per kg body weight.

Because the infusion of KCl and the increase of plasma pCO_2 inevitably resulted in a greater cumulative K^+ load at the end than at the beginning of the experiments, the procedure was reversed in three studies: plasma pCO_2 was immediately raised to the maximal value and then progressively lowered by diminishing the CO_2 tension of inspired air, while K^+ was infused at a constant rate throughout the experiment. This procedure produced high plasma CO_2 tensions with small K^+ loads and low CO_2 tensions with high K^+ loads.

The effect of cellular buffers on the relationship between cellular H^+ concentration and plasma CO_2 tension was studied by measuring the pH of kidney homogenate at different CO_2 tensions. The homogenate was prepared by grinding a dog kidney without dilution in a Waring blender. Sodium cyanide and iodoacetate were added to minimize formation of metabolic acids. The homogenate was then equilibrated at 38° C with various mixtures of CO_2 and O_2 to give CO_2 tensions ranging from 30 to 300 mm Hg. At each CO_2 tension the pH of the homogenate was measured with a Beckman glass electrode and a Vibron pH meter. The titration was then repeated in the reverse direction, with CO_2 tensions lowered from 300 to 30 mm Hg; identical results were obtained.

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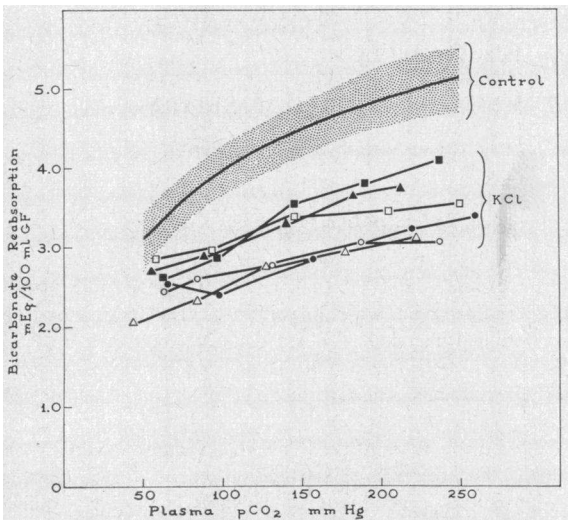

FIG. 1. THE EFFECT OF K^+ ADMINISTRATION ON THE RELATIONSHIP BETWEEN HCO_3^- REABSORPTION AND PLASMA pCO_2 IN THE PRESENCE OF INTACT CARBONIC ANHYDRASE. The shaded area represents the range of HCO_3^- reabsorption at different plasma CO_2 tensions in control dogs not fed KCl and was obtained from previously published experiments (1).

RESULTS

Figure 1 summarizes the effects of K^+ administration on HCO_3^- reabsorption in the presence of an intact renal carbonic anhydrase enzyme system as the plasma pCO_2 is progressively elevated from 50 to 250 mm Hg. A sample protocol of this type of experiment is given in Table I (Dog 122, 0 to 230 minutes). Potassium markedly depressed HCO_3^- reabsorption in each experiment in comparison with control values.[1] These results are comparable with those obtained by Roberts, Randall, Sanders and Hood (8) in similar experiments.

These studies were repeated in the same dogs after the administration of acetazolamide, as shown in Figure 2. A sample protocol is pre-

[1] The inhibitory effects of KCl administration on HCO_3^- reabsorption cannot be attributed to any influence of Cl^-, since serum [Cl^-] did not change appreciably during the experiments. Moreover, in other studies the infusion of Cl^- (as NaCl) at twice the rate used in the present investigation did not alter the HCO_3^- Tm (10).

TABLE I

The effect of KCl on the maximal bicarbonate reabsorptive capacity at different plasma CO_2 tensions *

Time	Treatment	Plasma				C_{In}	Urine			Bicarbonate		
		K^+	HCO_3^-	pCO_2	pH		Flow	pH	K^+	Filt.	Excr.	Reab.
min		*mEq/L*	*mEq/L*	*mm Hg*		*ml/min*	*ml/min*		*μEq/min*	*μEq/min*	*μEq/min*	*mEq/100 ml GF*
	Dog 122; wt 11 kg; pre-fed with 4.5 g KCl twice daily for 10 days											
0	Anesthesia, sodium pentobarbital; infuse 0.15 M $NaHCO_3$ at 10 ml/min and KCl at 440 μEq/min											
100	Prime 12 g $NaHCO_3$											
	Breathing:											
120–130	room air	4.7	59.1	59	7.6	54.4	12.5	7.88	313	3,218	1,693	2.80
145–155	9% CO_2	4.2	58.9	88	7.41	53.1	10.4	7.82	296	3,125	1,557	2.95
170–180	17% CO_2	4.7	59.0	145	7.21	61.0	8.6	7.66	297	3,601	1,514	3.42
195–205	23% CO_2	4.7	59.0	205	7.06	56.0	8.4	7.49	299	3,307	1,372	3.45
220–230	29% CO_2	6.0	59.4	247	6.98	60.1	8.6	7.38	330	3,565	1,319	3.57
235	Acetazolamide 550 mg i.v.; continue infusion											
255–265	room air	6.2	54.6	75	7.46	47.0	10.4	7.74	336	2,565	1,700	1.84
280–290	9% CO_2	7.0	53.8	103	7.32	48.2	9.8	7.67	383	2,597	1,624	2.02
305–315	17% CO_2	7.8	54.7	162	7.13	48.7	10.4	7.52	387	2,662	1,592	2.20
340–350	23% CO_2	7.7	52.2	208	7.00	50.0	8.8	7.44	425	2,609	1,474	2.27
365–375	29% CO_2	7.7	54.4	255	6.93	48.8	10.2	7.33	422	2,660	1,539	2.30
	Dog 135; wt 14.0 kg; pre-fed with 4.5 gm KCl twice daily for 8 days											
0	Anesthesia, sodium pentobarbital; infuse 0.15 M $NaHCO_3$ at 10 ml/min and KCl at 560 μEq/min											
150	Prime 12 g, $NaHCO_3$; acetazolamide 700 mg i.v.											
180–190	23% CO_2	6.27	50.3	217	6.96	36.4	5.6	7.40	310	1,810	900	2.49
205–215	17% CO_2	6.51	50.7	184	7.04	35.7	6.8	7.43	340	1,809	977	2.33
230–240	9% CO_2	6.50	49.5	140	7.15	33.4	7.5	7.50	325	1,650	932	2.15
255–265	room air	6.81	46.1	101	7.26	35.0	7.8	7.62	352	1,613	930	1.95
280–290	Hypervent.	7.32	45.1	47	7.58	38.1	8.2	7.83	410	1,717	1,189	1.39
290–300	Hypervent.		44.8	42	7.63	37.0	8.6	7.86	401	1,657	1,201	1.23
300–310	Hypervent.		41.2	43	7.58	37.4	7.4	7.89	425	1,539	1,094	1.19

* Plasma bicarbonate concentrations have been corrected for a Donnan factor of 1.05.

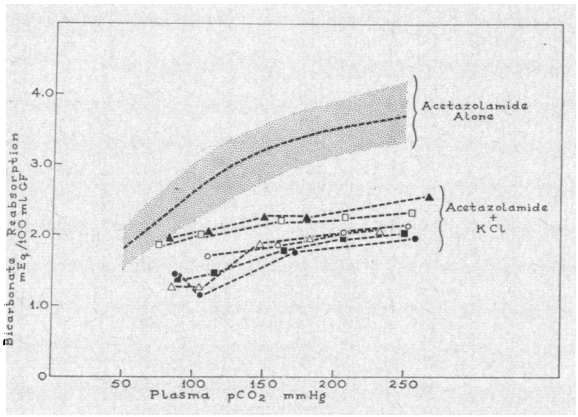

FIG. 2. THE EFFECT OF K^+ ADMINISTRATION ON THE RELATIONSHIP BETWEEN HCO_3^- REABSORPTION AND PLASMA pCO_2 AFTER INHIBITION OF CARBONIC ANHYDRASE. The shaded area represents the range of HCO_3^- reabsorption at different CO_2 tensions in dogs given acetazolamide but not fed KCl (1).

sented in Table I (Dog 122, 235 to 375 minutes). Here again, K^+ administration produced marked depression of HCO_3^- reabsorption. It is particularly noteworthy in both Figures 1 and 2 that K^+ impaired the response to increases in plasma CO_2 tension, as indicated by a flattening of the slopes. In some experiments there was almost no rise in HCO_3^- reabsorption as the plasma CO_2 tension was elevated.

One possible explanation for the flattening of the slopes observed in dogs given K^+ is that the degree of inhibition progressively rose during experiments as a consequence of increasing serum K^+. To exclude this possibility the experiment was reversed (Figure 3; Table I, Dog 135) by starting with high and ending with low plasma CO_2 tensions. Unlike previous experiments, maximal K^+ loads were present when plasma CO_2 tensions were lowest. In spite of this, the depressant effects of K^+ on bicarbonate reabsorption were most marked at higher CO_2 tensions, exactly as in the previous experiments. The flattening of the slopes in Figures 1 and 2 in animals given K^+ cannot, therefore, be attributed to progressive increases in the K^+ load as CO_2 tension is increased.

DISCUSSION

The present studies clearly establish that K^+ administration markedly depresses the capacity of the kidney to reabsorb HCO_3^-. Moreover, the fact that K^+ depresses the HCO_3^- Tm after carbonic anhydrase activity has been completely inhibited by acetazolamide indicates the profound influence of K^+ on the pCO_2-dependent, carbonic anhydrase-independent H^+ secretory system.

To determine whether, in addition, K^+ may inhibit the carbonic anhydrase-dependent system,[2] the effect of K^+ was assessed by examining the HCO_3^- Tm before and after acetazolamide administration in individual experiments. In dogs given KCl, the capacity of the carbonic anhydrase dependent H^+ secretory system was estimated by subtracting the HCO_3^- Tm after acetazolamide from the HCO_3^- Tm before acetazolamide. The differences were determined at various CO_2 tensions and were then plotted against plasma pCO_2 in Figure 4. For comparison, the contribution of carbonic anhydrase to HCO_3^- reabsorption in control dogs (i.e., animals not given supplemental KCl) was also plotted in Figure 4 and amounted to a mean value of 1.3 mEq per 100 ml glomerular filtrate (GF) with a range, as indicated by the shaded area, from 1.0 to 1.5 mEq per 100 ml GF. As previously noted in normal dogs (1), the contribution of carbonic anhydrase to the HCO_3^- Tm was reasonably constant at all CO_2 tensions.

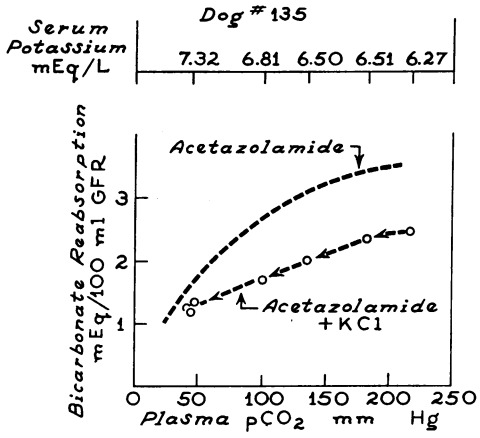

FIG. 3. THE EFFECT OF K^+ ADMINISTRATION ON HCO_3^- REABSORPTION AFTER INHIBITION OF CARBONIC ANHYDRASE.

[2] The contribution of carbonic anhydrase to HCO_3^- reabsorption is defined as the difference between the HCO_3^- Tm before and after the administration of sufficient acetazolamide to inhibit carbonic anhydrase completely. In a previous paper (1) evidence was advanced to support the view that carbonic anhydrase inhibition was virtually complete with the doses of acetazolamide given.

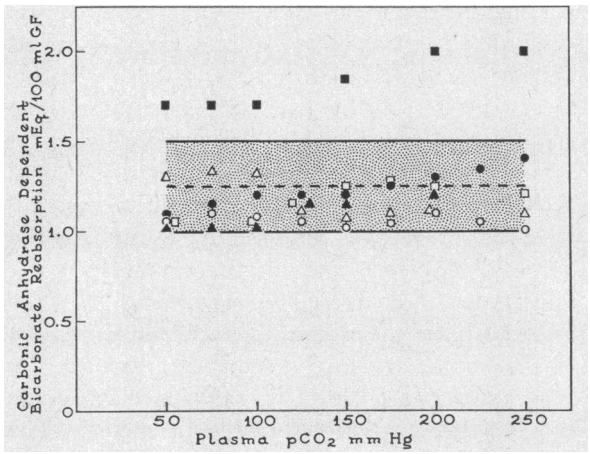

FIG. 4. THE EFFECT OF K^+ ON THE HCO_3^- TM OF THE CARBONIC ANHYDRASE DEPENDENT H^+ SECRETORY SYSTEM. The shaded area represents the range obtained in control dogs not fed KCl (1).

With one exception this was also the case in the dogs given K^+. The differences obtained in the dogs given K^+ fell either above (1 dog) or within (5 dogs) the shaded area. Thus it is obvious that K^+ administration did not diminish the contribution of carbonic anhydrase to H^+ secretion. Since K^+ has no effect on the carbonic anhydrase-dependent system, it seems reasonable to conclude that the profound depression in HCO_3^- reabsorption that results from the administration of K^+ is mediated solely through the pCO_2-dependent H^+ secretory system.

In previous studies it was demonstrated that the contribution of the carbonic anhydrase-dependent system to HCO_3^- reabsorption was constant at all plasma CO_2 tensions. This was interpreted to mean that this H^+ secretory system is insensitive to changes in intracellular H^+ concentration. The fact that K^+ administration did not depress the contribution of carbonic anhydrase to HCO_3^- reabsorption indicates that this system is insensitive to changes in intracellular K^+ concentration as well.

Since K^+ exerts its effect entirely through the pCO_2-dependent H^+ secretory system, and since this system is markedly sensitive to changes in intracellular H^+ concentration, it is tempting to postulate that K^+ influences H^+ secretion by some competitive process. According to this theory, as originated by Berliner, Kennedy and Orloff (7), Na^+ is reabsorbed in exchange for either H^+ or K^+, depending on the relative intracellular concentrations of these ions. By raising intracellular K^+, therefore, H^+ secretion would be blocked, as a result of which HCO_3^- reabsorption would fall.

It should be emphasized that this theory of competitive inhibition is grounded to a large extent on the demonstration of a reciprocal relationship between K^+ and H^+ secretion. The acute administration of K^+ has been shown to raise urine pH, to lower ammonia and titratable acid excretion (2, 3, 6, 9), and to block HCO_3^- reabsorption (8), while K^+ deficiency augments the reabsorption of HCO_3^- (4, 5, 8) and promotes the excretion of ammonia and titratable acid (11–13). Conversely, respiratory acidosis depresses (14, 15) and respiratory alkalosis accelerates K^+ excretion (16–18). This reciprocity between H^+ and K^+ secretion, while suggestive, does not constitute conclusive evidence of competition for a common secretory pathway. Such experimental procedures, by inducing reciprocal changes in the relative intracellular concentration of the two ions, could mimic competitive inhibition even though completely separate secretory processes were involved. In addition, much of the evidence showing an inhibitory effect of K^+ on H^+ secretion is obtained in experiments designed to test the ability of the kidney to produce maximal pH gradients between urine and blood. In such experiments, the total capacity of the system to secrete H^+ is not tested; the actual changes in H^+ secretion under such circumstances represent only a very small proportion of the H^+ secretory capacity. Furthermore, the maximal pH gradients that can be established are dependent not only on the characteristics of the transport system itself, but on other factors as well, such as intracellular pH, urine flow rate, and permeability of the anions across distal tubular cells. Therefore, experiments that test the *capacity* to secrete H^+ rather than the ability to generate pH *gradients* may afford a more reliable means of investigating the mechanism by which K^+ inhibits H^+ secretion.

In the present studies the nature of the inhibitory effect of K^+ on the capacity of the pCO_2-dependent, carbonic anhydrase-independent H^+ secretory system to reabsorb HCO_3^- was examined by means of Michaelis-Menten kinetics. The legitimacy of applying rate-limiting kinetics as a means of examining competitive and non-

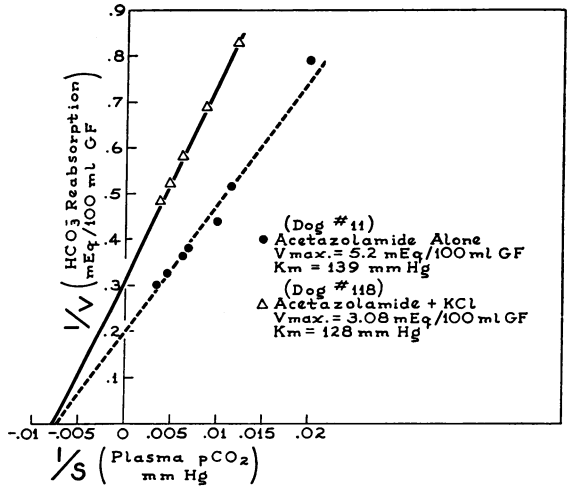

FIG. 5. DOUBLE RECIPROCAL PLOT OF HCO_3^- REABSORPTION AGAINST PLASMA pCO_2. In the usual Lineweaver-Burk plot the reciprocal of the substrate concentration is plotted along the abscissa and the reciprocal of the rate of reaction is plotted along the ordinate. Although intracellular H^+ concentration, not plasma pCO_2, is the immediate substrate for the reaction, it is assumed that intracellular $[H^+]$ is a linear function of plasma pCO_2, as indicated in Figure 6. Consequently, the reciprocal of plasma pCO_2 is plotted as if it were the actual substrate. The expression, HCO_3^- reabsorption per 100 ml GF, which is plotted along the ordinate, has the dimensions of concentration rather than rate. However, since the volume of solution (100 ml GF) is continually renewed with time, the expression also reflects the rate of HCO_3^- reabsorption. The intercept at the vertical axis is equal to $1/V_{max}$ and the intercept at the horizontal axis is $-1/Km$.

competitive inhibition depends on whether the process under consideration is limited by a single rate-limiting step. The fact that the relation between HCO_3^- reabsorption and plasma pCO_2 is curvilinear suggests that one or more rate-limiting processes are involved. To determine whether a single or several rate-limiting processes are responsible for this curvilinear relationship, the reciprocal of HCO_3^- reabsorption was plotted against the reciprocal of plasma pCO_2 (Lineweaver-Burk plot). The fact that a straight line was obtained from such a plot (Figure 5) suggests that a single rate-limiting process is involved. That this is not the passive consequence of a failure of increasing pCO_2 to elicit commensurate rises in intracellular H^+ concentration is indicated by the linear relation of H^+ concentration to pCO_2 in the titration of kidney homogenate (Figure 6). It seems probable, therefore, that the single rate-limiting step, as disclosed by the linear double reciprocal plot, reflects the rate-limiting characteristics of the H^+ transport system and permits the application of Michaelis-Menten kinetics.

It is a general characteristic of competitive inhibition, as disclosed by Michaelis-Menten kinetics, that increasing amounts of substrate should gradually overcome an inhibitory influence. If, then, K^+ depresses the HCO_3^- Tm by competitive inhibition of H^+ secretion, the inhibitory effects of K^+ should be progressively overcome by raising pCO_2. It is clear from Figures 1 and 2 that increasing plasma pCO_2 did not overcome the inhibitory influence of K^+ on HCO_3^- reabsorption.

The nature of the inhibitory effect was examined in greater detail by means of double reciprocal plots of HCO_3^- reabsorption and pCO_2 for normal and K^+-loaded dogs (Figure 5). Such plots permit an analysis of the effect of K^+ on the Michaelis-Menten constants, V_{max} and Km, of the pCO_2-dependent, carbonic anhydrase-independent H^+ secretory system. The V_{max} represents the maximal rate of H^+ secretion (equivalent to the HCO_3^- Tm) at an infinitely high concentration of intracellular H^+, where intracellular H^+ concentration is considered a linear or near linear function of plasma pCO_2. The Km represents the level of plasma pCO_2 at which the H^+ secretory system is half saturated with H^+ and conse-

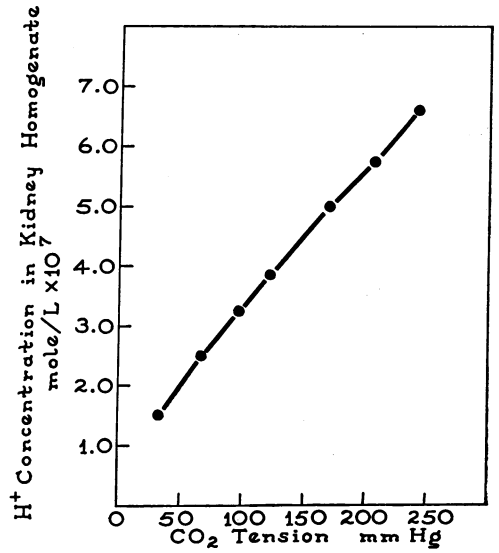

FIG. 6. THE RELATIONSHIP BETWEEN pCO_2 AND H^+ CONCENTRATION OF KIDNEY HOMOGENATE. See Methods for explanation.

TABLE II

Michaelis-Menten constants for the pCO_2-dependent, carbonic anhydrase-independent bicarbonate reabsorptive system in dogs with and without potassium administration

Dog	Acetazolamide alone		Dog	Acetazolamide + KCl	
no.	V_{max}	*Km*	*no.*	V_{max}	*Km*
3	5.88	161	113	3.64	167
7	5.25	91	116	2.78	40
8	5.45	95	118	3.20	143
11	5.20	138	119	2.66	61
13	4.70	137	121	2.38	61
14	5.26	90	122	2.40	35
17	5.40	87	135	3.22	70
18	5.32	103	137	3.02	85
			138	2.95	115
Mean	5.31	113		2.92	86
SE	±0.12	± 10		±0.13	± 15
p				<0.001	0.50

quently is functioning at half the maximal rate. In general, competitive inhibitors increase the Km without altering the V_{max}, while whole noncompetitive inhibitors depress the V_{max} without changing the Km. Figure 5 shows that double reciprocal plots of HCO_3^- reabsorption against plasma pCO_2 for both control and K^+-loaded dogs gave straight lines. It is further noted that K^+ decreased the V_{max} from 5.3 to 3.2 mEq per 100 ml GF without significantly altering the Km. Table II indicates that similar effects were obtained in the other K^+-loaded dogs. These results, although by no means conclusive, suggest that K^+ inhibits the pCO_2-dependent H^+ secretory system by a noncompetitive, rather than a competitive process.[3]

Despite these suggestive results, it should be emphasized that a kinetic analysis of the type undertaken here can by no means conclusively exclude competitive inhibition. The kinetics of a competitive process might be obscured by complex physiologic alterations in the renal tubular cell as a result of K^+ loads. Such alterations include progressively mounting intracellular concentrations of K^+ or intracellular alkalinization. The first possibility is unlikely in view of the studies in which pCO_2 was elevated to high levels at the start of the experiment and gradually reduced, as K^+ was continually infused, so that the cumulative K^+ load was much higher at the lower CO_2 tensions. Despite this, the absolute depression of the HCO_3^- Tm by K^+ was greater during respiratory acidosis than at lower CO_2 tensions (Figure 3).

The second possibility—i.e., that competitive inhibition in the presence of progressively mounting intracellular alkalinization secondary to K^+ administration might generate the kinetics of a noncompetitive process—cannot be excluded. Since under normal circumstances changes in plasma CO_2 tension are linearly related to changes in the H^+ concentration of renal tubular cells (Figure 6), plasma pCO_2, rather than intracellular $[H^+]$, can be used as the substrate for HCO_3^- reabsorption in the manner illustrated in Figure 5. However, if K^+ administration markedly increases intracellular $[HCO_3^-]$ (19),[4] then the relation between plasma pCO_2 and intracellular $[H^+]$, and consequently between plasma pCO_2 and HCO_3^- reabsorption, would be altered in such a manner that any given increment in plasma pCO_2 would result in a smaller increase in both intracellular $[H^+]$ and HCO_3^- reabsorption. The kinetic consequences of this change would be a flattening of the curves relating pCO_2 to HCO_3^- reabsorption, and a simulation of the characteristics of noncompetitive inhibition even though the underlying mechanism were competitive.

On the basis of present evidence, therefore, the nature of the reciprocal relationship between K^+ and H^+ secretion cannot be established. This reciprocity could result from noncompetitive inhibition or from a process of competitive inhibition in which intracellular alkalinization plays a significant role.

SUMMARY

The effect of K^+ on the relationship of the HCO_3^- Tm to plasma pCO_2 was studied in dogs

[3] No attempt is made in this study to distinguish noncompetitive from uncompetitive inhibition.

[4] The *in vitro* studies of Anderson and Mudge (19) on kidney slices disclose that when extracellular $[HCO_3^-]$ was below 25 mEq per L and extracellular $[K^+]$ was increased from 0 to 10 mEq per L, a maximal rise of 10 per cent of intracellular $[HCO_3^-]$ occurred. Very little increase in intracellular $[HCO_3^-]$ occurred when extracellular $[K^+]$ was increased in the presence of normal $[HCO_3^-]$ in the medium. If these *in vitro* data can be extrapolated to the present studies, where extracellular $[HCO_3^-]$ averaged approximately 50 mEq per L, the rise in intracellular $[HCO_3^-]$ which would result from K^+ loads would be minor, and not nearly sufficient to cause the curves relating pCO_2 to HCO_3^- reabsorption to diverge.

before and after inhibition of carbonic anhydrase. It was found that K^+ depressed HCO_3^- reabsorption to an equal extent before and after administration of acetazolamide, indicating that the depressant effect of K^+ on HCO_3^- reabsorption was mediated entirely through a pCO_2-dependent, carbonic anhydrase-independent system.

The mechanism of the inhibitory effect of K^+ was examined by means of Michaelis-Menten kinetics. From the fact that the inhibitory effects of K^+ were greatest at high pCO_2 tensions and that the V_{max}, but not the Km, was lowered, it was suggested that the action of K^+ may be mediated by a process of noncompetitive inhibition or by a competitive process in which intracellular alkalinization plays a significant role.

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