Interrelationships among Quinidine, Amiloride, and Lithium as Inhibitors of the Renal Na⁺-H⁺ Exchanger*

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We examined the effects of quinidine, amiloride and Li⁺ on the kinetics of Na⁺-H⁺ exchange in microvillus membrane vesicles isolated from the rabbit renal cortex. Quinidine reversibly inhibited the initial rate of Na⁺-H⁺ exchange (Iₑₒ 200 μM). The plot of 1/V versus [quinidine] was curvilinear, with Hill coefficient > 1.0, indicating that the drug interacts at two or more inhibitory sites or at a single site on at least two different conformations of the transporter. Quinidine decreased the V_max for Na⁺-H⁺ exchange and increased the K_m for Na⁺, indicating a mixed-type mechanism of inhibition. In contrast, plots of 1/V versus [amiloride] and 1/V versus [Li⁺] were linear, indicating single inhibitory sites; amiloride and Li⁺ each increased the K_m for Na⁺ with no effect on V_max, indicating a competitive mechanism of inhibition. Addition of Li⁺ increased the intercept with no change in slope of the 1/V versus [amiloride] plot, indicating that Li⁺ and amiloride are mutually exclusive inhibitors of Na⁺-H⁺ exchange. Addition of quinidine increased the slopes of the plots of 1/V versus [amiloride] and 1/V versus [Li⁺], indicating that the binding of quinidine is not mutually exclusive with the binding of amiloride and Li⁺. Results from this and previous studies are consistent with the concept that the inhibitor amiloride and the transportable substrates Na⁺, H⁺, Li⁺, and NH₃ all mutually compete for binding to a single site, the external transport site of the renal Na⁺-H⁺ exchanger. However, our findings indicate that quinidine interacts with the Na⁺-H⁺ exchanger on at least one additional site that is not shared by Na⁺, Li⁺, or amiloride.

In a wide variety of animal cells, a plasma membrane Na⁺-H⁺ exchange system mediates the uphill efflux of H⁺ coupled to the downhill influx of Na⁺ (1–3). This transport system plays a major role in such processes as the regulation of intracellular pH (3), the control of cell volume (4, 5), and the initiation of cell growth and proliferation in response to mitogenic factors (6, 7). In the renal proximal tubule, luminal membrane Na⁺-H⁺ exchange is the predominant mechanism for active secretion of H⁺ and reabsorption of HCO₃⁻ (8). Microvillus (brush border) membrane vesicles isolated from the luminal surface of proximal tubule cells contain a Na⁺-H⁺ exchanger that shares many of the transport properties of Na⁺-H⁺ exchangers found in other tissues (2). Thus, microvillus membrane vesicles have served as a useful model system for characterizing the kinetic properties of the plasma membrane Na⁺-H⁺ exchanger.

One important feature of the Na⁺-H⁺ exchanger is an internal modifier site at which intracellular H⁺, independent of its role as a transportable substrate, can activate the transport system (9–12). Recently, the existence of one or more external modifier sites has been proposed based on the finding that the alternative substrate Li⁺ and the diuretic amiloride act as mixed-type inhibitors of Na⁺-H⁺ exchange (10). However, such mixed-type effects of Li⁺ and amiloride have not been observed in other studies (14–20). Quinidine is an inhibitor of Na⁺-H⁺ exchange in dog erythrocytes (21, 22), but its kinetic mechanism of action is uncertain. In order to define more clearly the number of external substrate and modifier sites, we have evaluated the kinetic interrelationships among quinidine, amiloride, and Li⁺ as inhibitors of the Na⁺-H⁺ exchanger in rabbit renal microvillus membrane vesicles. Our results suggest that amiloride and Li⁺ interact at a single external site where they compete with each other and with Na⁺; quinidine interacts at an additional site that is not shared by Na⁺, Li⁺, or amiloride. An abstract of this study has been published previously (23).

EXPERIMENTAL PROCEDURES

Membrane Preparation—Microvillus membrane vesicles were isolated from rabbit renal cortex by the Mg aggregation method described previously (24). The homogenizing buffer consisted of 200 mM mannitol, 41 mM K⁺, and 80 mM HEPES, pH 7.30. The final membrane pellet was washed by resuspending and resedimenting the vesicles three times in fresh Mg²⁺-free buffer. This medium consisted of 140 mM mannitol, 74 mM K⁺, 52 mM Cl⁻, 42 mM HEPES, 17 mM MES, pH 6.8. The vesicles were then finally suspended in this same medium at a concentration of 12–25 μg of membrane protein/ml, as estimated by the Coomassie Blue dye-binding assay (25). The suspension was made with bovine serum albumin as standard. In the experiments reported with intravesicular pH 7.50, the medium used to wash and suspend the vesicles consisted of 157 mM mannitol, 74 mM K⁺, 52 mM Cl⁻, 42 mM HEPES, pH 7.5.

Na⁺ Influx Studies—Each experiment was performed at least three times using different, freshly made membrane preparations stored at 4°C for less than 18 hr. The specific conditions for each experiment are given in the figure legends. In general, Na⁺ uptake measurements were performed in triplicate or quadruplicate in a randomly ordered sequence at 20°C in an incubation volume of 50 μl which contained 0.1 μCi of ³²Na and 120–250 μg of membrane protein. Uptake periods were always ≤ 5 min and were timed with a metronome as described by Wright et al. (25). The uptake period was terminated by the rapid addition of 3.5 ml of an ice-cold (0–2°C) stop solution consisting of 160 mM LiCl, 2.5 mM TRIS, and 4 mM HEPES, pH 7.5 (26). This mixture was then immediately poured on a wetted 0.65 mm Millipore filter (DWP) and washed with an additional 10.5 ml of stop solution. Filters were placed into vials containing 3.5 ml of Ready-Scan HP (Beckman) and counted by scintillation spectroscopy. The triplicate

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The abbreviations used are: HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; MES, 4-morpholineethanesulfonic acid.

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or quadruplicate uptake values for each specific experimental condition were averaged and values for the nonspecific retention of $^{22}$Na by the filters were subtracted from the values for the incubated samples. During each individual experiment, $^{22}$Na uptake in the presence of 2 mM amiloride was also measured. This value was taken to represent $^{22}$Na uptake via passive diffusion and was subtracted from the experimental values prior to construction of the Dixon and Hanes-Woolf plots that are illustrated. As will be seen in Figs. 2 and 4, this amiloride-insensitive $^{22}$Na uptake was about 10% of the total $^{22}$Na influx measured with pH 6.8 and pH 7.4, the conditions generally employed in this study.

Material—$^{22}$Na was purchased from Amersham Corp. Amiloride hydrochloride was a gift of Merck, Sharp & Dohme Research Laboratories. Quinidine hydrochloride and quinine hydrochloride were purchased from Sigma. All media were prepared with distilled and deionized water and were filtered before use with 0.22 μm Millipore filters.

**RESULTS**

**Time Course of Na\(^+\) Influx**—To determine a time point at which the initial rate of Na\(^+\) influx could be estimated, we measured the early time course of Na\(^+\) uptake, as illustrated in Fig. 1. In this experiment, the membrane vesicles were pre-equilibrated in pH 6.8 buffer, and then Na\(^+\) uptake was measured at external pH 7.4. Uptake was linear with time for 4 s both at low (1 mM) and high (30 mM) Na\(^+\) concentrations, and both in the absence and presence of 200 μM quinidine. Accordingly, in subsequent studies on the kinetics of inhibition of Na\(^+\)-H\(^+\) exchange, the 3-s time point was used to estimate the initial velocity of Na\(^+\) influx.

**Quinidine Inhibition of Na\(^+\)-H\(^+\) Exchange**—The effect of varying concentrations of quinidine on the initial rate of uptake of 1 mM Na\(^+\) in the presence of an outward H\(^+\) gradient (pH 6.8, pH 7.4) is shown in Fig. 2. Approximately 90% of Na\(^+\) influx under these conditions was sensitive to inhibition by amiloride. Previous studies in our laboratory have demonstrated that amiloride-sensitive Na\(^+\) influx in rabbit renal microvillus membrane vesicles occurs via electroneutral Na\(^+\)-H\(^+\) exchange (14, 27). Thus, the dose-dependent inhibition by quinidine of Na\(^+\) influx (left panel of Fig. 2) indicates that this drug inhibits Na\(^+\)-H\(^+\) exchange. The concentration of quinidine causing 50% inhibition of amiloride-sensitive Na\(^+\) influx (I$_{50}$) was 200 μM. At 2 mM quinidine, inhibition equivalent to that caused by 2 mM amiloride was observed, indicating that quinidine can completely inhibit Na\(^+\)-H\(^+\) exchange. This in turn implies that binding of quinidine to the Na\(^+\)-H\(^+\) exchanger fully blocks its activity.

Shown in the right panel of Fig. 2, the Dixon plot (1/V versus [I]) for quinidine inhibition was nonlinear, suggesting that the drug interacts at two or more inhibitory sites, or at a single site on at least two different conformations of the transporter (see “Discussion”). Consistent with this concept, the Hill plot of the data (not shown) yielded a value for $n_{app}$ of 1.40.

Given the fact that quinidine is a weak base, one must consider the possibility that the quinidine inhibition of Na\(^+\)-H\(^+\) exchange observed in Fig. 2 was artifactual and resulted from quinidine entering the intravesicular space by nonionic diffusion, thereby collapsing the outward H\(^+\) gradient that had been imposed. Three sets of findings argue against this possibility, however. First, as shown in Fig. 1, uptake of Na\(^+\) was linear with time in the presence of an outward H\(^+\) gradient and 200 μM quinidine. If quinidine were collapsing the H\(^+\) gradient significantly during the period of initial rate measurement, the plot of Na\(^+\) uptake versus time would have progressively deviated from linearity in the presence of quinidine.

Second, as illustrated in Fig. 3, quinidine caused dose-dependent inhibition of amiloride-sensitive Na\(^+\) influx even in the absence of an outward H\(^+\) gradient (pH 7.5, pH 7.5). The I$_{50}$ for quinidine inhibition was approximately 200 μM and the Dixon plot was nonlinear, just as observed in the presence of an outward H\(^+\) gradient. The Hill plot (not shown) of the data in Fig. 3 yielded a value for $n_{app}$ of 1.59, again consistent with interaction of quinidine at two or more inhibitory sites or at a single site on at least two different conformations of the transporter. Thus, the inhibitory effect of quinidine on Na\(^+\)-H\(^+\) exchange was not diminished when conditions were used to minimize the possible intravesicular accumulation of quinidine by nonionic diffusion.

A third finding arguing against the possibility that quinidine inhibits Na\(^+\)-H\(^+\) exchange by virtue of a weak base effect is the stereospecificity of its inhibitory action. As indicated in Fig. 4, quinidine was more than twice as potent as quinine in inhibiting Na\(^+\)-H\(^+\) exchange. Inasmuch as quinidine and quinine are stereoisomers with similar physical properties, this observation further implies that inhibition of Na\(^+\)-H\(^+\) exchange arises from a direct interaction of quinidine with the Na\(^+\)-H\(^+\) exchanger rather than from a nonspecific weak base effect.

The reversibility of quinidine inhibition was evaluated in the experiment shown in Fig. 5. The uptake of Na\(^+\) was measured into vesicles that had been preincubated for 90 min in the presence of 0, 100, or 500 μM quinidine. At the initiation of the uptake measurement, the concentration of the drug was brought to either 100 or 500 μM, as indicated. The inhibition caused by 500 μM quinidine was more than twice that caused by 100 μM drug, consistent with the dose-response curve shown earlier in Fig. 2 and demonstrating that the binding of quinidine to its inhibitory sites is greater at a drug concentration of 500 μM than at 100 μM. Nevertheless, the inhibition of Na\(^+\) uptake by 100 μM quinidine was the same whether the membranes had been preincubated with 100 or 500 μM drug. Similarly, preincubating the vesicles with 100 μM quinidine had no effect on the subsequent inhibition of Na\(^+\) uptake.
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FIG. 2. Effects of quinidine on Na\(^+\) influx measured in the presence of an outward H\(^+\) gradient. The 3-s uptake of 1 mM \(^{22}\)Na into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Each datum represents the mean ± S.E. for three separate experiments and is expressed as a percentage of the control uptake measured in the absence of quinidine. The right-hand graph is a Dixon plot of the same data after subtraction of the amiloride-insensitive component of Na\(^+\) influx from the Na\(^+\) influx values.

FIG. 3. Effect of quinidine on Na\(^+\) influx measured in the absence of a H\(^+\) gradient. Membrane vesicles were pre-equilibrated for 120 min at 20 °C in 157 mM mannitol, 74 mM K\(^+\), 52 mM Cl\(^-\), 42 mM HEPES, pH 7.5. The 3-s uptake of 1 mM \(^{22}\)Na was then assayed in the same pH 7.5 medium. Other details of the experiment are as described in the legend to Fig. 2.

caued by 500 \(\mu M\) drug. These results suggest that quinidine inhibition is rapidly reversible. Moreover, the lack of effect of preincubating and presumably preloading the vesicles with quinidine suggests that the drug probably inhibits Na\(^+\)-H\(^+\) exchange by binding to the external face of the transporter.

To evaluate the kinetic mechanism underlying quinidine inhibition of Na\(^+\)-H\(^+\) exchange, we measured the initial rate of Na\(^+\) influx as a function of Na\(^+\) concentration in the presence and absence of 200 \(\mu M\) quinidine. The pooled data from six separate experiments are illustrated as Hanes-Woolf...
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![Graph showing comparison of quinine and quinidine as inhibitors of Na⁺-H⁺ exchange.](image1)

**FIG. 4.** Comparison of quinine and quinidine as inhibitors of Na⁺-H⁺ exchange. The 3-s uptake of 1 mM ²²Na into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Each datum represents the mean ± S.E. for three separate experiments.

![Graph showing effect of quinidine on kinetics of Na⁺ influx.](image2)

**FIG. 6.** Effect of quinidine on kinetics of Na⁺ influx. The 3-s uptake of ²²Na into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Na⁺ concentration was varied by replacing KCl with NaCl in the uptake media. Each datum represents the mean for six separate experiments. The regression lines were calculated by the method of least squares.

![Graph showing effect of Li⁺ on kinetics of Na⁺ influx.](image3)

**FIG. 7.** Effect of Li⁺ on kinetics of Na⁺ influx. The 3-s uptake of ²²Na into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Na⁺ concentration was varied by replacing KCl with NaCl in the uptake media. Li⁺ was added by replacing KCl with LiCl. Each datum represents the mean for three separate experiments. The regression lines were calculated by the method of least squares.
in the presence of Li⁺ to that in its absence was 2.13 ± 0.07, and the corresponding ratio of $V_{\text{max}}$ values was 1.02 ± 0.03. Thus, Li⁺ is a strictly competitive inhibitor of Na⁺ influx, which, in turn, implies that the binding of Na⁺ and the binding of Li⁺ are completely mutually exclusive.

To test whether Li⁺ and quinidine are mutually exclusive inhibitors, we measured the influx of 1 mM Na⁺ as a function of Li⁺ concentration in the presence and absence of 200 μM quinidine. The pooled data from three separate experiments are represented as Dixon plots in Fig. 8. The linearity of the plots is consistent with the binding of Li⁺ to a single, saturable site. The effect of quinidine was to increase both the negative x intercept (i.e. $K_i$ for Li⁺) and the slope of the Dixon plot. For the three individual experiments, the mean ratio of the x intercept in the presence of quinidine to that in its absence was 1.41 ± 0.16, and the corresponding ratio of the slopes was 1.59 ± 0.15. The finding that quinidine altered the slope of the Li⁺ Dixon plot indicates that the binding of quinidine and the binding of Li⁺ are not completely mutually exclusive (28).

**Amiloride Inhibition of Na⁺-H⁺ Exchange**—To evaluate the kinetic mechanism underlying amiloride inhibition of Na⁺-H⁺ exchange, we measured the initial rate of Na⁺ influx as a function of Na⁺ concentration in the presence and absence of 20 μM amiloride. The pooled data from three separate experiments are represented as Hanes-Woolf plots in Fig. 9 and demonstrate that amiloride increased $K_{Na}$ with no effect on $V_{\text{max}}$. For the three individual experiments, the mean ratio of the $K_{Na}$ value in the presence of amiloride to that in its absence was 2.99 ± 0.26, and the corresponding ratio of $V_{\text{max}}$ values was 1.01 ± 0.06. Thus, amiloride is a strictly competitive inhibitor of Na⁺ influx, which, in turn, implies that the binding of Na⁺ and the binding of amiloride are completely mutually exclusive.

To test whether amiloride and quinidine are mutually exclusive inhibitors, we measured the influx of 1 mM Na⁺ as a function of amiloride concentration in the presence and absence of 200 μM quinidine. The pooled data from three separate experiments are represented as Dixon plots in Fig. 10. The linearity of the plots is consistent with the binding of amiloride to a single, saturable site. The effect of quinidine was to increase both the negative x intercept (i.e. $K_i$ for amiloride) and the slope of the Dixon plot. For the three individual experiments, the mean ratio of the x intercept in the presence of quinidine to that in its absence was 1.81 ± 0.07, and the corresponding ratio of the slopes was 1.38 ± 0.03. The finding that quinidine altered the slope of the amiloride Dixon plot indicates that the binding of quinidine and the binding of amiloride are not completely mutually exclusive (28).

![Fig. 8. Effect of quinidine on kinetics of inhibition by Li⁺. The 3-s uptake of 1 mM $^{22}Na$ into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Li⁺ concentration was varied by replacing KCl with LiCl in the uptake media. Each datum represents the mean for three separate experiments. The regression lines were calculated by the method of least squares.](image)

![Fig. 9. Effect of amiloride on kinetics of Na⁺ influx. The 3-s uptake of $^{22}Na$ into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Na⁺ concentration was varied by replacing KCl with NaCl in the uptake media. Each datum represents the mean for three separate experiments. The regression lines were calculated by the method of least squares.](image)

![Fig. 10. Effect of quinidine on kinetics of inhibition by amiloride. The 3-s uptake of 1 mM $^{22}Na$ into vesicles pre-equilibrated in pH 6.8 medium was assayed at external pH 7.4, as in the legend to Fig. 1. Each datum represents the mean for three separate experiments. The regression lines were calculated by the method of least squares.](image)
The renal Na\(^+\)-H\(^+\) exchanger can mediate exchanges of Na\(^+\) for H\(^+\) (27), Li\(^+\) for H\(^+\) (15), Na\(^+\) for Na\(^+\) (15), and Na\(^+\) for NH\(_4\)\(^+\) (15). Thus, Na\(^+\), H\(^+\), Li\(^+\), and NH\(_4\)\(^+\) are all substrates for transport by this system. In the present work we find that Li\(^+\) and amiloride each inhibit Na\(^+\) influx by interacting at a single saturable site, we demonstrate that binding of Na\(^+\) is mutually exclusive with the binding of Li\(^+\) and amiloride, and we show that the binding of Li\(^+\) is mutually exclusive with the binding of amiloride. We previously found that the binding of external H\(^+\) is mutually exclusive with the binding of Na\(^+\), Li\(^+\), NH\(_4\)\(^+\), and amiloride (26). Taken together, these observations from present and past studies are entirely consistent with the concept that the inhibitor amiloride and the transportable substrates Na\(^+\), H\(^+\), Li\(^+\), and NH\(_4\)\(^+\) all mutually compete for binding to a single site, the external transport site of the renal Na\(^+\)-H\(^+\) exchanger.

It must be noted, however, that our data indicating simple competitive effects of Li\(^+\) and amiloride conflict with the results of Ives et al. (13) who found that Li\(^+\) and amiloride significantly reduce the \(V_{\text{max}}\) for Na\(^+\)-H\(^+\) exchange in renal microvillus membrane vesicles. One explanation for this disparity is a difference between the methods employed to monitor the initial rate of Na\(^+\)-H\(^+\) exchange. In the present study, we assayed \(^{22}\)Na uptake as a direct measure of Na\(^+\) influx. Ives et al. measured quenching of acridine orange fluorescence as an indirect estimate of the rate of H\(^+\) transport. Thus, it is possible that the mixed-type kinetic effects of amiloride and Li\(^+\) in the study of Ives et al. were due to the indirect method employed. Indeed, amiloride has been reported to decrease the response of acridine orange fluorescence to changes in the transmembrane pH gradient in renal microvillus vesicles (29).

Moreover, amiloride has been found to be a simple competitive inhibitor of the Na\(^+\) site of Na\(^+\)-H\(^+\) exchangers in all other preparations examined to date, including fibroblasts (16), erythrocytes (18), lymphocytes (20), and skeletal muscle cells (19). The kinetic effects of Li\(^+\) have not been similarly evaluated in other preparations, except for one study in which it was found to competitively inhibit Na\(^+\) influx in cultured kidney cells (17).

The present work confirms previous studies on dog erythrocytes indicating that quinidine is an inhibitor of plasma membrane Na\(^+\)-H\(^+\) exchange (21, 22). The kinetic mechanism for inhibition of the renal Na\(^+\)-H\(^+\) exchanger by quinidine differs from that for inhibition by Li\(^+\) and amiloride. Quinidine is a mixed-type inhibitor of Na\(^+\) influx, indicating that binding of quinidine is not mutually exclusive with the binding of Na\(^+\). Similarly, quinidine alters the slopes of the Dixon plots for inhibition of Na\(^+\) influx by Li\(^+\) and amiloride, indicating that the binding of quinidine is also not mutually exclusive with the binding of Li\(^+\) and amiloride. Hence, quinidine must interact with the renal Na\(^+\)-H\(^+\) exchanger on at least one site that is distinct from the external transport site where Na\(^+\), H\(^+\), NH\(_4\)\(^+\), Li\(^+\) and amiloride mutually compete with one another.

In contrast to the linear Dixon plot for inhibition of Na\(^+\)-H\(^+\) exchange by Li\(^+\) and amiloride, the Dixon plot for inhibition by quinidine was curvilinear with a Hill coefficient \(>1.0\). One interpretation of this finding is that quinidine interacts at a second binding site on the Na\(^+\)-H\(^+\) exchanger. If this second quinidine site was the external transport site, it would explain the effect of quinidine to increase the \(K_a\) for Na\(^+\) and the \(K_i\) values for inhibition by amiloride and Li\(^+\). However, a curvilinear Dixon plot with Hill coefficient \(>1.0\) does not necessarily require the presence of more than one binding site for an inhibitor. The velocity equation for an enzyme will in general contain \(I^2\) terms whenever an inhibitor can bind to a single site on two different enzyme forms (28). Accordingly, the interaction of quinidine with a single binding site on both the unloaded and the substrate-loaded forms of the transporter could alternatively account for its nonlinear, mixed-type pattern of inhibition. If binding of quinidine to the transporter altered allosterically the affinity of the external transport site, it would explain the effect of quinidine to increase the \(K_a\) for Na\(^+\) and the \(K_i\) values for inhibition by amiloride and Li\(^+\). Thus, although our data require the presence of at least one quinidine binding site that is distinct from the external transport site of the Na\(^+\)-H\(^+\) exchanger, the possible interaction of quinidine at a second binding site, such as the external transport site, is uncertain.

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