The epithelial sodium channel (ENaC) is a heteromultimer composed of three subunits, each having two membrane-spanning domains with intracellular amino and carboxyl termini. Several hormones and proteins regulate channel activity, but the molecular nature of this regulation is unknown. We conducted experiments to determine a possible new site within the carboxyl terminus of the α-subunit involved in enhanced channel activity through endogenous kinases. When an α-subunit that was truncated to remove a PY motif was expressed in Xenopus oocytes with wild type human β- and γ-ENaC subunits, channel activity was greatly enhanced. The removal of the entire intracellular carboxyl terminus of the α-subunit eliminated this enhanced basal activity. Using several point mutations, we localized this site to two amino acid residues (Pro596-Gly598) near the second membrane-spanning domain. The nonspecific kinase inhibitor staurosporine inhibits basal channel activity of wild type ENaC but was ineffective in inhibiting channels mutated at this site. The major effect of these mutations was not on channel kinetics but was largely, if not entirely, on the number of active channels on the cell surface. This region is potentially important in effecting kinase-mediated increases in ENaC activity.

The epithelial sodium channel (ENaC) is a heteromultimer composed of three subunits (α, β, and γ), which permit the entry of sodium across the apical membrane of the renal collecting duct, distal colon, lung, and other epithelial cells (1–3). ENaC plays a central role in sodium homeostasis and blood pressure control. Activating mutations, such as truncations of the intracellular carboxyl-terminal regions of β-hENaC and γ-hENaC, produce Liddle’s syndrome, an autosomal dominant form of hypertension (4–6). Inactivating mutations produce pseudohypoaldosteronism, a disorder characterized by hypotension (7, 8).

Regulation of ENaC activity is of critical importance not only in sodium balance and blood pressure regulation but also in regulating the composition of airway fluid, sweat, and saliva (1, 3, 9). Considerable effort has been directed at determining the humoral factors that can influence ENaC activity, but relatively little is known about the molecular events involved. It is well established that agents that increase adenylate cyclase activity and cAMP can alter ENaC activity acutely (10, 11). Activation of protein kinase C can also influence ENaC activity (12, 13). However, the effects of activating these second messenger systems are cell-specific (14, 15), and not all epithelial cells expressing ENaC respond to these agents (16–18).

The topology of each of the ENaC subunits includes two membrane-spanning domains, a large extracellular loop, and intracellular amino and carboxyl termini (19–21). Evidence is accumulating that ENaC activity may be mediated in part through these intracellular regions. Mutations in the NH2 terminus of αENaC can severely reduce function (22, 23). More attention has been directed at the carboxyl termini, since patients with Liddle’s syndrome have mutations in this region of the β- and γ-subunits (4, 24–29). The mutations that produce this syndrome disrupt the PY motif (PPPPXXX), a region responsible for binding proteins with a WW domain (30). The protein Nedd4 has been strongly implicated in binding to this region (31–34), and defects in the PY motif cause more ENaC to reside in the membrane (6, 32, 33, 35, 36). To date, there is little information about other proteins that might interact with intracellular domains of ENaC subunits; nor is there much information about other intracellular regions that might play a role in regulating ENaC function.

There is suggestive evidence that regions of the carboxyl termini other than the PY motif are involved in regulating ENaC activity. Snyder et al. (6) showed that mutating the tyrosine residue in the PY motif of the α-subunit (to alanine) increases the ENaC current to the same extent as comparable mutations in the β- and γ-subunits. Truncation of the entire carboxyl termini of the β- or γ-subunits also produces a large increase in current. In contrast, truncation of the carboxyl terminus of the α-subunit does not increase ENaC current (6, 37). Schild et al. (5) have also reported a smaller response to truncating the α-subunit compared with the β- and γ-subunits. These results suggest that the carboxyl terminus of the α-subunit may possess a domain(s) capable of regulating ENaC function in a direction opposite to that of the PY motif. Perhaps this regional functional diversity could explain why no patients with Liddle’s syndrome have been described with truncations or mutations in the carboxyl terminus of the α-subunit (2).
As we began to examine the role of the carboxyl-terminal regions in greater detail, we found that the kinase inhibitor staurosporine strongly inhibited wild-type hENaC currents heterologously expressed in *Xenopus* oocytes. Truncation of the carboxyl terminus of β- or γ-hENaC, when expressed with the wild type partner subunits, did not alter the response to staurosporine. However, when the carboxyl terminus of α-hENaC was truncated, the inhibitory effect of staurosporine was eliminated (37).

These results, taken together, prompted us to hypothesize that there is a region within the carboxyl terminus of the α-subunit that enhances sodium current. Furthermore, we postulated that endogenous kinases exist in *Xenopus* oocytes (and in mammalian epithelial cells) that enhance the activity of ENaC. These kinases could act, directly or indirectly, via a region in the intracellular carboxyl terminus of the α-subunit that is physically separate from the PY motif. The following report provides evidence that this hypothesis is correct.

**MATERIALS AND METHODS**

The hENaC expression and current recordings have been described previously (32, 37). The coding regions of the α-, β-, and γ-hENaC subunits were cloned into the PGEMHE plasmid and expressed using cRNA injections after *in vitro* transcription with the mMessage mMach message kit (Ambion). *Xenopus laevis* (Nasco) oocytes were isolated as described previously (6, 32, 37). Briefly, oocytes were defolliculated with collagenase and stored in frog Ringer solution consisting of 115 mM NaCl, 2.5 mM KCl, 1.8 mM CaCl2, 10 mM HEPES, 5 mM sodium pyruvate, and 100 μM gentamicin. Each oocyte was injected with 0.1–1 ng of cRNA for each hENaC subunit carried in 50 nl of nuclease-free water. Currents were recorded in frog Ringer solution 48 h after injection. Whole cell currents were recorded using an OC-725C oocyte voltage clamp (Warner Instruments). Single channel currents were recorded in the cell-attached mode at room temperature with 110 mM LiCl in the pipette and frog Ringer solution in the bath. Single channel currents were recorded using an Axopatch 2B (Axon Instruments). The pClamp software suite (Axon Instruments) was used for coordinating voltage clamp amplifier command potentials, current acquisition, and data analysis. Statistical procedures were applied using SigmaStat software (SPSS Science) using analysis of variance and subsequent paired analysis as appropriate. Values are mean ± S.E.

In an effort to improve oocyte viability, some preparations were incubated in frog Ringer solution supplemented with 10 μM amiloride after injection of RNA; amiloride was removed just before each current recording. The presence of amiloride in the incubation medium did not have any apparent effects on the qualitative relationships between wild type and experimental groups. Since not all groups could be evaluated on the same batch of oocytes and the control amiloride-sensitive currents were substantially between batches, we normalized all whole cell current magnitudes to the wild type controls of each day. We evaluated the mutations that produced significant changes in current in multiple batches with control oocytes having different magnitudes of current. This approach permitted us to test a range of basal currents for effects of stimulatory and inhibitory mutations. All reported currents are those that demonstrated inhibition by 25 μM amiloride.

Truncation mutations were constructed using the Exsite PCR-based site-directed mutagenesis kit (Stratagene), and the point mutations were constructed using the QuikChange site-directed mutagenesis kit (Stratagene). For both strategies, since the entire hENaC coding region was amplified by PCR (not just the mutated sequence), we sequenced the mutated region to ensure the correct sequence had been changed. We controlled for possible PCR errors in other regions by producing another clone of the intended mutant with a separate PCR and verifying the functional difference where there was one.

A cDNA clone of human SGK1 was generated using a nested PCR strategy on total RNA from human renal papilla. The initial PCR primer pair was AGCTTCTTGTGTCCTCCCG (positions 16–34 based on the numbering in GenBank accession number Y1000299) and GGCTCCACCAAAAGGCTAAC (positions 1389–1411). The second round of amplification was performed with a primer pair internal to the first pair, ATGAGCGTGAACACTGAGGC (positions 43–62) and AAAC-CAAGCCCTAAGACGGTG (positions 1339–1358). The resulting ampli-con, which included the full coding region, was cloned using the PCR-Script Amp cloning kit (Stratagene) and sequenced completely. Human SGK was subsequently subcloned into the PGEMHE plasmid for in vitro transcription of cRNA. The amount of cRNA injected for human SGK was 2 ng/oocyte, which was double the amount of each hENaC subunit injected in these experiments.

Staurosporine was purchased from Biomol, and all other chemicals were purchased from Sigma.

**RESULTS**

We hypothesized that there was a region in the intracellular carboxyl terminus of α-hENaC that permitted a high level of channel activity when all three wild type subunits were expressed. We therefore sought to determine a specific region that, when mutated, would display a reduction in endogenous channel activity. Fig. 1 shows the numbered positions of some key amino acid residues and their positions relative to the predicted second transmembrane domain (M2) and the PY motif.

**Mutations Influencing Endogenous ENaC Function**—We first evaluated the S627X (*n* = 43) and S594X (*n* = 18) truncations. The S627X truncation removes the PY motif and all amino acids downstream but leaves most of the region between M2 and the PY motif intact. This mutation should cause the current to increase, because removing the PY motif would eliminate the inhibitory region. Such a mutation would disrupt binding to Nedd4 and increase surface expression of ENaC (6, 31, 32). Fig. 2 shows that this truncation indeed increased current 4.5-fold. Next, we tested the S594X truncation, which removes nearly the entire carboxyl terminus downstream of M2. This mutant produced currents that were not significantly different from wild type control currents. This result is consistent with the previous report (6) and suggests that there is a region between amino acids Ser594 and Ser627 that enhances ENaC current.

Next, we examined a series of point mutations in the Ser594–Ala502 region. Substituting all three residues, Ser594, Pro505, and Gly506, with alanine (AAA594; *n* = 11) resulted in markedly decreased currents (11.5% of wild type control currents; Fig. 2). Two other consecutive triple alanine substitutions, AAA597 (*n* = 9) and AAA600 (*n* = 7), did not cause a reduction in current; in fact, AAA597 caused an increase in current (Fig. 2). These results suggest that the Ser594, Pro505, and Gly506 residues participate in molecular events that increase ENaC function. The lack of a reduction in current with the other AAA mutations demonstrates that the AAA594 effect is not a general property of AAA mutations in that region. We hypothesized that the currents from the SS54X mutant were not different from control, because this truncation eliminated at least two functional regions: one that caused a decrease in current (the PY motif) and one that caused an increase in current (Ser594). To test this hypothesis, we constructed a mutant (AAA594/S627X) that eliminated both the stimulatory region and the inhibitory region. As predicted, AAA594/S627X (*n* = 8) resulted in currents that were not different from either wild type controls or S594X mutants (Fig. 2).

We asked which of the mutations in the AAA594 construct were critical to the change in function. P595A (*n* = 24) or G596A (*n* = 17) caused a significant reduction in current,
that the region between Ser594 and Ser615 was important in regulating ENaC currents that were similarly inhibited by staurosporine. In contrast, truncation S594X (n = 12) produced currents that were only 50% reduced in comparison with wild type (Fig. 3). Truncations were recorded from oocytes expressing wild-type and mutant hENaC along with wild type β- and γ-subunits. Currents were normalized to the α-hENaC wild type controls for each oocyte batch. The diagrams on the left indicate the nature of the α-hENaC C-terminal mutation with reference to M2, position Ser594, and the PY motif. The asterisks represent a statistical difference (p < 0.05) from wild type control. The number of oocytes in each group ranged from 7 to 43.

whereas S594A (n = 8) had no effect (Fig. 2), indicating that the proline and glycine residues are critical for normal function. The lack of effect of mutating the Ser594 residue suggests that even if this residue is directly phosphorylated by endogenous kinases, there is minimal effect on ENaC function.

Mutations Affecting Actions of Endogenous Kinases—To determine whether the positive regulatory region described in Fig. 2 was also the region involved in enhanced ENaC activity by endogenous kinases (37), we tested the acute response of these mutants to 100 nM staurosporine (Fig. 3). Truncations T646X (n = 4), S627X (n = 11), and S615X (n = 4) produced currents that were similar to those we tested for endogenous ENaC activity. In contrast, truncation S594X (n = 12) produced currents that were not inhibited by staurosporine. These results suggested that the region between Ser594 and Ser615 was important in producing a stimulatory effect that could be reduced by inhibiting an endogenous kinase.

We assessed the effect of staurosporine on point mutations identical to those we tested for endogenous ENaC activity. ENaC currents in oocytes expressing AAA594 (n = 8) were apparently insensitive to staurosporine (Fig. 3). However, since these currents were relatively small (<1 μA at −60 mV), we considered the possibility that we could have missed the inhibition. We therefore tested the staurosporine sensitivity of the currents produced by the AAA594/S627X mutation (n = 7), since these currents were similar to those from wild type hENaC (Fig. 2). As shown in Fig. 3, these currents were not inhibited by staurosporine and thus indicate that the residues in positions 594–596 are important for the response to staurosporine. Currents produced by either AAA597 (n = 12) or AAA600 (n = 3) were staurosporine-sensitive (Fig. 3). When we tested the single amino acid substitution mutants S594A (n = 12), P595A (n = 18), and G596A (n = 10), we found that only P595A currents showed substantial insensitivity to staurosporine.

Staurosporine is a nonspecific kinase inhibitor. Recently, SGK has been shown to increase ENaC currents in oocytes (38, 39). We therefore tested the hypothesis that this Ser594 region might be important in mediating this SGK effect. An additional rationale is that Ser594 is a consensus serine for phosphorylation by SGK (40, 41). However, as shown in Fig. 4A, co-expressing SGK increased current by ~2-fold in both wild type ENaC and the S594X mutation. These results make it unlikely that the inhibition of current by staurosporine is the result of inhibiting an endogenous SGK-like kinase.

The disruption of the Pro595-Gly596 locus might perturb a binding site important for a kinase involved in phosphorylating a nearby residue. Inspection of the neighboring sequence reveals that Ser590 is a potential target for several kinases. We therefore mutated this residue to alanine and tested the effects of staurosporine in oocytes. There was no effect of the mutation on basal current, and staurosporine had the same effect in wild type and mutated hENaC currents (Fig. 4B).

We also tested the effects of another kinase inhibitor, chelerythrine (10 μM), on wild-type and AAA594 mutants. This inhibitor is less potent than staurosporine in this assay (37), but is more specific for protein kinase C. The effects on wild-type currents were the same as before, ∼50% reduction. However, as in the case of staurosporine, chelerythrine had no effect on currents produced by the AAA594 mutation (data not shown).

Single Channel Analysis of α-hENaC Mutants—These mutations identify a specific region of α-hENaC (Pro595-Gly596) that appears to be required for the normal expression of ENaC currents and staurosporine sensitivity. We examined the mechanism by which this region affects ENaC function using single channel current recordings. This analysis allows us to assess whether the decrease in whole cell current produced by a mutation is caused by a decrease in the single channel conductance (g) or the probability of a channel being open (P).

We reasoned that the mutant AAA594 (which caused a ∼90% decrease in current) presented the best opportunity to evaluate whether changes in these single channel properties could explain the reduction in whole cell current.
Fig. 4. SGK and staurosporine effects on currents with other mutations in α-ENaC. A, human SGK was subcloned into the pGEMHE vector and coexpressed with wild type ENaC α the S94X truncation of α-ENaC. The lack of the majority of the COOH terminus including the Ser⁹⁴⁰ residue, a possible phosphorylation site for SGK, did not alter SGK’s ability to enhance current (n = 15 in each group; *, p < 0.02 compared with control). B, the Ser⁹⁴⁰ site of α-ENaC was mutated to alanine (S590A) and coexpressed with wild type β- and γ-ENaC. Wild type hENaC and the mutant were incubated with 100 nM staurosporine for 30–120 min. This mutation produced no change in basal current or the effect of staurosporine (n = 34–39 in each group from six batches of oocytes; *, p < 0.05 compared with controls by analysis of variance and subsequent Dunn’s test for multiple comparisons).

Fig. 5A shows single channel recordings from an oocyte expressing AAA594 channels. The current amplitude for channel openings at −60 mV was −1 pA. Since wild type single channel currents have a similar magnitude (6, 32), this result eliminates the possibility that the reduced whole cell current in this mutant could be caused by a 90% decrease in g. The individual Pₒ values for 14 patches are shown in Fig. 5B and demonstrate the high variability that we (6, 32) and others (5) have previously reported. The mean value of 0.27 is not appreciably different from our previously reported values under the same conditions. These results make it extremely unlikely that changes in g or Pₒ can explain all of the reduction in whole cell current produced by AAA594.

The Number of hENaC Channels in the Membrane—We directed our efforts at determining whether the reduced hENaC current in the AAA594 mutants might have been due to a reduced number of channels in the membrane. A mutation in the β-hENaC subunit (S520K) when expressed with wild type α- and γ-subunits increases the Pₒ of all ENaC channels to >0.9 (42). We expressed β(S520K) in combination with wild type and mutant α-ENaC, reasoning that if all channels in the membrane had a Pₒ approaching 1.0, then any decrease in whole cell current caused by a mutation in α-hENaC must be caused by a smaller number of functional channels in the membrane. First, we determined the effect of α(AAA594) on Pₒ by injecting equimolar α(AAA594) and β(S520K) with γ(wt) and measured single channel currents. These channels (an example of which is shown in Fig. 6A) were characterized by a slightly lower value for g (slope conductance = 6.5 picosiemens), long openings, and uncharacteristically brief closures. The Pₒ values for a population of these channels are >0.9 (Fig. 6B) with the exception of one patch (of seven). In the one patch with a Pₒ of

Fig. 5. Single channels from AAA594 mutants demonstrate typical wild type hENaC characteristics. A, representative single channel activity recorded from a cell-attached patch in an oocyte expressing αAAA594βγENaC channels. The holding voltage was −60 mV, and downward deflections are channel openings. There were at least two channels in this patch. B, Pₒ values for each of 14 cell-attached patches studied are displayed on the left half (Ind), and the average Pₒ value for these patches of 0.27 ± 0.06 is on the right.

Fig. 6. Single αAAA594βRESβγENaC channels demonstrate high Pₒ kinetic characteristics. A, representative single channel activity recorded from a cell-attached patch in an oocyte expressing αAAA594βRESβγENaC channels. The holding voltage was −60 mV, and downward deflections are channel openings. There was apparently only one hENaC channel in this patch. The brief, large amplitude spikes are probably the stretch-activated nonselective cation channel, which is present in all oocyte membranes. B, Pₒ values for each of 14 cell-attached patches studied are displayed on the left half, and the average Pₒ value for these patches of 0.27 ± 0.06 is on the right.
The carboxyl-terminal region of α-hENaC contains at least two domains that can regulate the function of the heteromultimeric molecular complex. The PY motif acts as an inhibitory domain (31–33). We now show that the Pro595 region is responsible for the effect of endogenous kinases remains unclear. There is no convincing evidence for in vivo phosphorylation of any region of the α-hENaC carboxyl terminus (45), although in vitro phosphorylation has been reported (46). The lack of effect of mutating Ser594 indicates that even if this residue is phosphorylated, the functional effects on ENaC current are minimal. Mutating Pro595 had the most dramatic effect both on basal current and on the ability of staurosporine to reduce current (Figs. 2 and 3). From this perspective, we speculate that Pro595 impacts an important secondary conformation. When we model the secondary structure of this region using the plot (Fig. 8) of the Chou-Fasman secondary structure prediction module of the GCG computer program (Pharmacopeia, Inc.), we see that replacing the proline with an alanine is predicted to result in the loss of a major turn. Not only is this immediate region distorted by the Pro595 mutation, this inhibitor produces a less complete inhibition of current than does staurosporine (37). Inhibitors of cAMP have no effect on ENaC activity in oocytes (37). The precise nature of the Pro595 region that is responsible for the effect of endogenous kinases remains unclear. There is no convincing evidence for in vivo phosphorylation of any region of the α-hENaC carboxyl terminus (45), although in vitro phosphorylation has been reported (46). The lack of effect of mutating Ser594 indicates that even if this residue is phosphorylated, the functional effects on ENaC current are minimal. Mutating Pro595 had the most dramatic effect both on basal current and on the ability of staurosporine to reduce current (Figs. 2 and 3). From this perspective, we speculate that Pro595 impacts an important secondary conformation. When we model the secondary structure of this region using the plot (Fig. 8) of the Chou-Fasman secondary structure prediction module of the GCG computer program (Pharmacopeia, Inc.), we see that replacing the proline with an alanine is predicted to result in the loss of a major turn. Not only is this immediate region distorted by the Pro595 mutation, but the orientation of the remainder of the carboxyl terminus is probably also altered. This effect raises the possibility that the interactions disrupted by mutating Pro595 may not be confined to the immediate region. Although the truncation experiments (Figs. 2 and 3) reinforce the likelihood that this region is quite important, there could be effects on other sites resulting from a major alteration in secondary structure. Evidently, the potential phosphorylation site Ser590 is not involved (Fig. 4B).

The P595A mutation reduced both basal current and the inhibition by staurosporine. However, the G596A mutation had a pronounced reduction of basal current but little or no difference in the staurosporine effect. The reason for this apparent difference is not clear. It is possible that measuring the fractional inhibition of current when the starting value is low may not be quantitatively consistent. Alternatively, the relationship between basal ENaC activity and endogenous kinase activity may not be tightly linked via this region. We have no data addressing this matter.

We can infer general molecular explanations for the importance of the Pro595 region from the present data. It is possible
that a kinase interacts with this region and phosphorylates a nearby residue (although apparently not Ser\(^{594}\) or Ser\(^{596}\)). It is also possible that a kinase interacts with this region but phosphorylates a distant residue, perhaps on a distal portion of α-ENaC, a different ENaC subunit, or another associated protein. Alternatively, this site might interact with a protein that is phosphorylated by an endogenous kinase or a protein that interacts with a phosphorylated protein. The idea that another region within the carboxyl terminus of α-ENaC is involved with regulating channel activity has recently been proposed by Copeland et al. (47). These investigators observed that a region between the Pro\(^{595}\) locus and the PY motif is necessary to permit actin to alter the gating characteristics of the homomeric channel studied in bilayers. Whether there is a functional connection between any of these regions remains to be determined.

We surmise that the major mechanism by which mutations in the PG region produce a change in current is by changing the number of functional channels on the cell surface. This conclusion rests with the negative evidence of a change in single channel properties (Fig. 4) and the positive effect of a mutation that maintains the channel in a largely open configuration (Fig. 5). While the data are adequate to make this general conclusion, they are not sufficiently sensitive to eliminate the possibility that this region does participate in some way in modulating channel gating. This argument has been raised with the idea that a kinase interacts with this region and phosphorylates a nearby residue (although apparently not Ser\(^{594}\) or Ser\(^{590}\)). It is insensitive.

In our view, the use of the β(SS20K) mutation to produce a channel complex with a high \(P_o\) (Fig. 6; Ref. 42) increases the certainty with which we can conclude that there is a change in surface expression. We emphasize that this technique identifies functionally active channels and would not detect silent channels residing in the membrane. In this regard, some investigators have proposed that there are a large number of ENaC complexes on the cell surface that have a very low \(P_o\) (76). The resolution of these questions will require more sensitive and specific techniques than those currently available.

The conclusion that a major effect of endogenous kinases acting via a growing body of evidence suggesting that surface expression is a major mechanism of ENaC regulation. There is solid evidence that increasing SGK activity increases ENaC current by increasing surface expression in oocytes (43). There is also good evidence that CAMP increases ENaC current by increasing surface expression in mammalian epithelial cells (11). In addition to the actions of kinases, structural factors can produce changes in surface expression. Examples of such “structural changes” include mutations causing Liddle’s syndrome (6, 33, 35), changes in syntaxin expression (48, 49), and alteration in Nedd4 (32, 33). Perhaps regulation of ENaC surface expression and function by kinase activity might be linked to the integrated actions of some or all of these proteins.

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Regulation of Epithelial Sodium Channel Activity through a Region of the α-Subunit: EVIDENCE FOR INTRACELLULAR KINASE-MEDIATED REACTIONS
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