Nongenomic Actions of Aldosterone on the Renal Tubule

David W. Good

Aldosterone plays a major role in the maintenance of sodium, potassium, and acid-base balance through its effects on renal electrolyte excretion. This regulation is achieved through aldosterone-induced stimulation of Na$^+$ absorption, K$^+$ secretion, and H$^+$ secretion by the distal nephron, particularly segments of the collecting duct.1–3 These classical actions are mediated through binding of aldosterone to the intracellular mineralocorticoid receptor (MR). The hormone–receptor complex translocates to the nucleus, where it promotes gene transcription and the production of proteins that modulate the expression and activity of the epithelial Na$^+$ channel (ENaC) and other ion transport proteins.1,4–6 Regulatory actions of aldosterone via the MR play an important role in the normal maintenance of blood pressure but also have been implicated in the pathogenesis of hypertension and the progression of renal disease.6–9

In addition to their classical actions, aldosterone and other steroid hormones influence cell processes through nongenomic mechanisms.10,11 Nongenomic effects of aldosterone have been demonstrated in many different epithelial and non epithelial tissues and are defined by (1) an insensitivity to inhibitors of transcription (actinomycin D) and translation (cycloheximide) and (2) a rapid time course (seconds to a few minutes) that is incompatible with gene regulation and de novo protein synthesis. A rapid onset of action is a sufficient but not necessary criterion for a nongenomic effect. Some nongenomic effects can occur with a slower time course. An additional feature often associated with nongenomic effects is that they are not blocked by spironolactone and/or other MR antagonists, consistent with mediation via a nonclassical aldosterone receptor.10,11 Although compelling evidence exists for rapid effects of aldosterone unrelated to the MR, a novel aldosterone receptor for nongenomic regulation has not been identified, and there is evidence that nongenomic actions of aldosterone can be mediated via the classical MR.12 Thus, the role of classical versus nonclassical receptors in mediating nongenomic effects of aldosterone remains controversial. An additional area of uncertainty has been whether nongenomic mechanisms are relevant to aldosterone-induced regulation of renal tubule function, skepticism fueled in part by the fact that most experiments on renal cells have been carried out using cell culture systems. Recently, however, studies using isolated, perfused tubules have established with certainty that aldosterone can regulate the transepithelial transport function of native renal tubules through nongenomic pathways.

This review presents a concise update of nongenomic effects of aldosterone on the mammalian renal tubule. Emphasis is placed on ion transport proteins regulated by aldosterone through nongenomic mechanisms, the signal transduction pathways that mediate this regulation, and the possible physiological relevance of nongenomic pathways to the function of nephron segments. Current information is presented with the goal of identifying gaps in knowledge and stimulating future work in this area. The reader is referred to recent reviews for discussion of nongenomic effects of aldosterone on other tissues, including the cardiovascular system.10–14

Ion Transport Proteins and Signal Transduction Pathways

A number of ion transport proteins important for the absorptive and secretory functions of renal tubules have been reported to be targets for nongenomic regulation by aldosterone. This section summarizes these transport effects, along with the signal transduction pathways involved (Table).

Na$^+$/H$^+$ Exchange

At least 8 mammalian Na$^+$/H$^+$ exchanger isoforms (NHE1 through NHE8) have been identified.15 There is evidence for nongenomic regulation of NHE1 and NHE3 by aldosterone in renal cells. NHE1 is expressed ubiquitously in the plasma membrane of nonpolarized cells and in the basolateral membrane of epithelial cells, where it plays a role in essential functions, such as the regulation of intracellular pH and cell volume, cell growth, and adhesion and migration.15–17 NHE3 is expressed selectively in the apical membrane of certain renal and intestinal epithelial cells, where it mediates transepithelial absorption of Na$^+$ and secretion of H$^+$ necessary for renal HCO$_3^-$ absorption.1,15,18–20

NHE1

Stimulation of plasma membrane Na$^+$/H$^+$ exchange was identified as an early response of various renal cells to aldosterone,21–23 but whether this regulation occurred independent of changes in gene expression was not established. Nongenomic stimulation of Na$^+$/H$^+$ exchange by aldosterone was confirmed subsequently in a subtype of Madin–Darby canine kidney cells (MDCK-C11), a cell line that exhibits...
Nongenomic Regulation of Ion Transport Proteins by Aldosterone in Renal Cells

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The nongenomic stimulation of NHE1 by aldosterone in MDCK-C11 cells required the parallel activation of a membrane H+ conductance, possibly to permit H+ recycling that prevents the local formation of H+ gradients that could impair Na+/H+ exchange regulation.24,31 Blocking activation of the H+ conductance with Zn2+ or inhibitors of protein kinase C (PKC) prevented the rapid effect of aldosterone to increase Na+/H+ exchange activity. There are no reports in other cell systems that nongenomic stimulation of Na+/H+ exchange by aldosterone depends on the parallel activation of an acid loading mechanism; thus, it is unclear whether this represents a cell-specific property of aldosterone regulation in MDCK-C11 cells.

Rapid stimulation of Na+/H+ exchange by aldosterone in MDCK-C11 cells depended on an increase in intracellular Ca2+ concentration due to increased Ca2+ uptake from the extracellular fluid.24 Aldosterone also induced rapid phosphorylation of extracellular signal-regulated kinase (ERK)1/2, and inhibiting ERK1/2 activation prevented the aldosterone-induced increase in Na+/H+ exchange activity.26 Study of the interaction between the 2 signaling pathways showed that preventing the increase in intracellular Ca2+ eliminates the aldosterone-induced stimulation of Na+/H+ exchange but does not prevent increased ERK phosphorylation,24,26,32 whereas blocking ERK activation inhibits the increase in intracellular Ca2+.32 These results suggest that activation of ERK is necessary but not sufficient to stimulate Na+/H+ exchange and that the aldosterone-induced increase in NHE1 activity is mediated through an ERK-dependent increase in intracellular Ca2+. In other cell systems, nongenomic activation of Na+/H+ exchange by aldosterone involves activation of PKC.10 In MDCK-C11 cells, PKC inhibitors prevented the aldosterone-induced increase in Na+/H+ exchange activity, but this was attributed to an indirect effect due to inhibition of the H+ conductance linked to Na+/H+ exchange activity.31

NHE1 is expressed in virtually all segments of the renal tubule (see Reference 33 for relevant references). Despite the extensive literature supporting nongenomic regulation of this transporter by aldosterone, there have been no studies testing for an effect of aldosterone on basolateral Na+/H+ exchange in a mammalian nephron segment. Hence, it is unknown whether this prevalent regulatory effect is of significance for renal tubule function. Aldosterone-induced changes in cell pH or Na+ concentration via NHE1 could affect the activity of other renal transport proteins important for ion absorption and secretion or generate a permissive intracellular pH for subsequent nuclear events and protein processing. In addition, NHE1 functions as a signaling molecule to regulate a variety of vital cell functions, including epithelial transport, by controlling the organization of the actin cytoskeleton.16,17,34 Of relevance, basolateral NHE1 has been shown to regulate apical NHE3 and transepithelial HCO3−/H+ absorption in the renal medullary thick ascending limb (MTAL) through cytoskeletal remodeling.34 Other transport proteins important for renal function are regulated through cytoskeletal interactions, including ENaC, the renal outer medullary K+ channel (ROMK) potassium channel, and the Na+/K+2Cl− cotransporter NKCC2 (see References 17 and 34 for relevant references). This suggests that aldosterone could regulate multiple transporters nongenomically through NHE1-induced cytoskeletal reorganization.

NHE3
Apical NHE3 mediates the majority of NaCl, NaHCO3, and fluid absorption by the renal proximal tubule and virtually all of NaHCO3 absorption by the MTAL.3,15,18–20,34 Regulation of NHE3 is critical for the normal maintenance of extracellular fluid volume, blood pressure, and acid–base balance.18 Recent studies using rat MTALs perfused in vitro have identified NHE3 as a target for nongenomic regulation by aldosterone. Physiological concentrations (IC50=0.6 nM) of aldosterone added to the basolateral solution induced a rapid (<5-minute) inhibition of HCO3− absorption that was the result of a decrease in apical NHE3 activity.20,35 This inhibition was not blocked by inhibitors of transcription or translation or by spironolactone and was not reproduced by glucocorticoids, indicating a high degree of specificity for aldosterone.35 Aldosterone inhibited NHE3 through a reduction in the exchanger’s maximal velocity.20 In OKP cells, a cell culture model of renal proximal tubule, glucocorticoids induced an acute increase in maximal velocity of NHE3 that was not blocked by cycloheximide, consistent with nongenomic regulation.26 This effect was the result of glucocorticoid-induced exocytic insertion of...
NHE3 from intracellular vesicles to the plasma membrane. Whether the nongenomic regulation of NHE3 by aldosterone in the MTAL may involve membrane trafficking requires further study.

Aldosterone inhibits NHE3 in the MTAL through rapid activation of the ERK1/2 signaling pathway. Aldosterone increases ERK activity 2-fold in microdissected MTALs, and blocking ERK activation prevents the effects of aldosterone to inhibit NHE3 and HCO₃⁻ absorption. The increase in ERK activity is not blocked by actinomycin D or spironolactone. The ERK pathway thus has emerged as an important nongenomic signaling mechanism for aldosterone in the MTAL and collecting duct cells and is a key mediator of aldosterone-induced regulation of both the NHE3 and NHE1 Na⁺/H⁺ exchangers.

The preceding results suggest that, in addition to its regulation of classical targets such as ENaC and the Na⁺-K⁺ ATPase, aldosterone may influence sodium, volume, and acid–base balance through nongenomic regulation of NHE3. Whether aldosterone influences NHE3 activity through nongenomic actions in other epithelial tissues remains to be determined.

**Vacuolar H⁺-ATPase**

Proton secretion via vacuolar H⁺-ATPases in the collecting duct is the final step in urine acidification and is finely regulated to maintain acid–base homeostasis. Aldosterone influences net acid excretion and acid–base balance through genomic stimulation of the apical H⁺-ATPase in collecting ducts. A rapid effect of aldosterone on H⁺-ATPase activity has been described recently. In outer medullary collecting ducts microdissected from normal mice, exposure to 10 nM aldosterone for 15 minutes increased H⁺ extrusion from acid-loaded, type A intercalated cells. This effect was independent of Na⁺ and blocked by concanamycin, consistent with stimulation of an H⁺-ATPase. The aldosterone-induced stimulation was partially reduced by actinomycin D but was unaffected by cycloheximide or spironolactone, suggesting a predominantly nongenomic mechanism. The stimulation was blocked by the PKC inhibitor chelerythrine Cl and by colchicine, suggesting a dependence on microtubules. In mice injected intraperitoneally with aldosterone for 30 minutes, immunocytochemical analysis showed increased apical staining of the a4 H⁺-ATPase subunit in type A intercalated cells. These results suggest that the rapid action of aldosterone involves increased trafficking of H⁺-ATPase to the apical membrane.

Some aspects of the preceding study limit conclusions regarding the physiological significance of the results. First, the stimulation of pump activity was not observed with 1 nM aldosterone, a physiological concentration that typically induces nongenomic effects. Second, the partial block of H⁺-ATPase stimulation by actinomycin D raises uncertainty as to whether the length of treatment with this inhibitor (15 minutes) was sufficient to fully inhibit gene transcription. Third, the transport studies were carried out on unperfused tubules. Thus, it remains to be determined whether the rapid increase in cellular H⁺ extrusion is associated with a physiologically relevant change in transcellular H⁺ secretion.

Despite these issues, the results provide important evidence for rapid regulation of ion transport by aldosterone in native renal tubules and identify the vacuolar H⁺-ATPase in intercalated cells as a focal point for future studies of nongenomic regulation.

**ENaC**

ENaC is located in the apical membrane of principal cells in the connecting tubule and collecting duct, where it mediates transepithelial Na⁺ absorption. The regulation of ENaC is critical for the maintenance of Na⁺ and volume balance and normal blood pressure. Aldosterone stimulates Na⁺ absorption in collecting ducts by increasing ENaC activity. This occurs through changes in gene transcription via the classical MR, resulting in the induction of regulatory proteins, such as SGK1, that lead to an increase in the activity and number of functional channels in the apical membrane. In addition to this classical regulation, there is evidence for rapid activation of ENaC by aldosterone through nongenomic mechanisms. Na⁺ channel activity was assessed using whole cell patch clamp techniques in principal cells freshly isolated from rabbit cortical collecting ducts (CCDs). Exposure to 100 nM aldosterone increased the activity of a highly selective, amiloride-sensitive Na⁺ conductance within 1 to 2 minutes. This effect was not prevented by spironolactone but was blocked by S-adenosyl-L-homocysteine, suggesting that transmethylation reactions may play a role in nongenomic, as well as early genomic, regulation of ENaC by aldosterone.

Caution is warranted with respect to the physiological significance of the above findings for collecting duct function. The rapid stimulation of ENaC was reported only for a pharmacological concentration of aldosterone, and specificity of the Na⁺ channel stimulation for aldosterone was not established (glucocorticoids were not tested). Also, aldosterone did not stimulate Na⁺ channel activity in principal cells isolated from CCDs of rats. In previous studies examining the acute in vitro effects of aldosterone in the isolated, perfused CCD, a rapid stimulation of Na⁺ absorption has not been reported. It should be noted, however, that these studies were not designed to analyze Na⁺ transport immediately after aldosterone addition, and measurements of absorptive Na⁺ flux were not reported until 30 to 120 minutes after bath aldosterone addition. Based on the patch clamp data for ENaC in principal cells, further work is needed to assess whether nongenomic pathways are relevant to aldosterone-induced stimulation of collecting duct Na⁺ absorption.

**Na⁺-K⁺ ATPase**

In addition to stimulating ENaC, aldosterone increases Na⁺-K⁺ ATPase activity through transcriptional regulation in collecting duct principal cells, resulting in a coordinated regulation of apical and basolateral membrane transport proteins that promotes an efficient increase in transcellular Na⁺ absorption. Two studies have implicated a possible role for nongenomic pathways in aldosterone-induced Na⁺ pump regulation in renal cells. In CCDs microdissected from adrenal-intact rats, aldosterone increased ouabain-sensitive ⁸⁶Rb uptake within 30 minutes at a half-maximal concentra-
tion of 1 nM. This effect was partially reduced by actinomycin D and cycloheximide; however, ≈30% of the stimulation of pump activity persisted in the presence of the 2 inhibitors. In MDCK cells, aldosterone at 10⁻⁴ to 10⁻⁶ M increased Na⁺ pump activity at 15 minutes with a plateau at 60 minutes, as assessed under maximal velocity conditions by a cytochemical assay and specific [H]ouabain binding. The increase in activity was blocked by colchicine but was unaffected by cycloheximide over 30 minutes. In both MDCK cells and CCDs, the stimulation of Na⁺ pump activity was unchanged in the presence of ionophores to increase membrane Na⁺ permeability. Hence, the increase in Na⁺-K⁺ ATPase activity is unlikely to be the indirect result of increased apical Na⁺ uptake via aldosterone-induced ENaC activation. On the other hand, in MDCK cells, pump activation by aldosterone was prevented by pretreatment with dimethylamiloride, an inhibitor of Na⁺/H⁺ exchange. This raises the possibility that nongenomic stimulation of Na⁺-K⁺ ATPase in collecting duct cells depends on Na⁺/H⁺ exchange, whereby aldosterone induces a rapid increase in NHE1 activity, resulting in a rise in intracellular pH that secondarily increases Na⁺-K⁺ ATPase activity. Thus, although nongenomic regulation of Na⁺-K⁺ ATPase activity by aldosterone appears likely in renal cells, further work is needed to determine whether this involves direct or indirect coupling of nongenomic pathways to pump activation.

Other
Aldosterone influences renal Na⁺ absorption through regulation of the thiazide-sensitive NaCl cotransporter in the distal convoluted tubule, but the possible role of nongenomic mechanisms is unknown. Aldosterone stimulates the Na⁺-K⁺-2Cl⁻ cotransporter NKCC1 in cardiac myocytes through nongenomic mechanisms. NKCC1 is expressed in the connecting tubule, collecting duct, and juxtaglomerular apparatus, where it participates in processes such as Cl⁻ secretion, renin secretion, and tubuloglomerular feedback (see References 53 and 54 and references therein). Whether aldosterone influences NKCC1 in the kidney has not been explored. Finally, aldosterone affects a number of signaling pathways in renal cells in addition to those listed in the Table, including cAMP/protein kinase A (PKA), calcineurin, Src, and heat shock proteins. Their possible significance for nephron function is considered below.

Function of Defined Nephron Segments and Whole Kidney
Studies using isolated nephron segments and segment-derived cell lines have identified the MTAL, segments of the collecting duct, and possibly the proximal tubule as sites of nongenomic regulation by aldosterone. Findings relevant to specific nephron segments and their potential significance for tubule function are presented briefly below. Rapid effects of aldosterone on whole kidney function in vivo also are summarized.

MTAL
The MTAL has been identified conclusively as a target for nongenomic regulation, with aldosterone inducing rapid inhibition of apical NHE3 and HCO₃⁻ absorption. Although inhibition of NHE3 appears counterintuitive for the physiological function of aldosterone to promote renal Na⁺ retention, this effect in the MTAL may serve an important function for acid–base homeostasis. In the proximal tubule, NHE3 is the primary mediator of Na⁺ absorption, both as NaCl and NaHCO₃. In the MTAL, NHE3 mediates absorption of NaHCO₃, which accounts for the majority of Na⁺ absorption, is mediated by NKCC2. Thus, in the MTAL, changes in NHE3 activity are important for HCO₃⁻ absorption and acid–base balance but have little impact on net Na⁺ absorption. Within this context, the inhibition of NHE3 by aldosterone in the MTAL may play a key role in enabling the kidney to regulate Na⁺ balance and extracellular fluid volume while maintaining acid–base balance. Activation of the renin–angiotensin–aldosterone system by sodium and volume depletion promotes renal Na⁺ retention but also induces multiple transport effects that tend to increase renal net acid excretion and promote metabolic alkalosis. The latter includes stimulation of HCO₃⁻ absorption by angiotensin II in segments of the proximal and distal tubule, stimulation of ammonium secretion by angiotensin II in the proximal tubule, and stimulation of H⁺ secretion by aldosterone in segments of the collecting duct (see Reference 35 for relevant references). The direct action of aldosterone to inhibit H⁺ secretion and HCO₃⁻ absorption in the MTAL would oppose these changes in the proximal and distal tubules. In this way, nongenomic regulation of NHE3 by aldosterone in the MTAL would tend to minimize changes in H⁺ excretion and maintain acid–base balance while permitting regulated changes in Na⁺ excretion that are necessary for regulation of extracellular fluid volume and blood pressure. This counterregulatory function of the MTAL is magnified further by the concurrent inhibition of HCO₃⁻ absorption by angiotensin II, which is additive to inhibition by aldosterone. Consistent with this view, rapid infusion of aldosterone into intact rats induced a significant change in renal Na⁺ excretion with no effect on urinary pH or acid excretion. On the other hand, the nongenomic inhibition of HCO₃⁻ absorption in the MTAL may contribute to acid–base disorders associated with changes in systemic potassium balance. For example, an increase in NHE3 activity and HCO₃⁻ absorption in the MTAL in response to a reduced plasma aldosterone level could contribute to the increased renal HCO₃⁻ absorptive capacity that promotes metabolic alkalosis in K⁺ depletion.

Absorption of NaCl by the MTAL is important for the maintenance of Na⁺ balance and blood pressure and for the excretion of a concentrated or dilute urine. NaCl absorption depends on apical NaCl uptake via NKCC2, apical K⁺ recycling via ROMK, and basolateral Cl⁻ efflux via CIC-Kb Cl⁻ channels. It is unknown whether these transport proteins undergo rapid regulation by aldosterone or if they are regulated by the ERK signaling pathway, which is rapidly activated by aldosterone in the MTAL. Lastly, aldosterone has been shown to induce a rapid increase in cAMP in a human distal cell line isolated by immunomagnetic separation using anti-Tamm–Horsfall monoclonal antibody, a marker of thick ascending limb cells. If this effect is confirmed for
native MTALs, then aldosterone could stimulate NaCl absorption nongenomically via cAMP.\textsuperscript{62}

### Collecting Ducts

The CCD, outer medullary collecting duct, and inner medullary collecting duct have been identified as sites of nongenomic regulation by aldosterone. Although a direct, nongenomic action of aldosterone to regulate transepithelial transport in these segments has not been demonstrated, some key areas for future investigation can be identified. As noted earlier, aldosterone rapidly increases H\textsuperscript{+}-ATPase activity in the mouse outer medullary collecting duct\textsuperscript{58} and ENaC activity in principal cells isolated from rabbit CCD.\textsuperscript{42} suggesting that nongenomic pathways may contribute to the physiological actions of aldosterone to stimulate H\textsuperscript{+} secretion and Na\textsuperscript{+} absorption by collecting duct segments. The latter possibility is supported by the finding in the CCD cell line RCCD\textsubscript{2} that aldosterone induces an early (2-hour) increase in short circuit current that is not blocked by actinomycin D or cycloheximide.\textsuperscript{60} Given that ENaC, ROMK, and the Na\textsuperscript{+}-K\textsuperscript{+} ATPase can be activated by cell alkalinization,\textsuperscript{50,64} aldosterone could influence Na\textsuperscript{+} absorption or K\textsuperscript{+} secretion in the collecting duct indirectly by increasing cell pH through nongenomic stimulation of NHE1.\textsuperscript{26} This hypothesis has been advanced previously\textsuperscript{21,24,64} but has yet to be tested directly in mammalian collecting duct segments.

With respect to signaling pathways, aldosterone induces a rapid increase in ERK activity in both MDCK\textsuperscript{26,32} and M-1\textsuperscript{65} collecting duct cell lines. Although ERK appears to play a role in the regulation of Na\textsuperscript{+} transport by aldosterone, this role is incompletely defined. In a cell line derived from mouse principal cells (mpkCCD\textsubscript{14}), inhibition of ERK rapidly decreased short circuit current under both basal and aldosterone-stimulated conditions, effects attributed to a decrease in Na\textsuperscript{+}-K\textsuperscript{+} ATPase activity.\textsuperscript{66} This suggests that the early activation of ERK by aldosterone may facilitate the stimulation of Na\textsuperscript{+} absorption through a permissive role that maintains the function of the basolateral Na\textsuperscript{+} pump. On the other hand, activation of ERK by aldosterone or other stimuli over a longer period leads to downregulation of ENaC by facilitating its interaction with Nedd4-2, which results in channel internalization and degradation.\textsuperscript{67–69} Thus, ERK may be a component of a negative feedback mechanism for posttranslational control of ENaC turnover after aldosterone stimulation. Hence, rapid, nongenomic, and longer-term genomic activation of ERK may subserve different regulatory roles for aldosterone-dependent Na\textsuperscript{+} absorption. In microdissected rat CCDs, aldosterone induced a transcription-independent increase in the activity of calcineurin,\textsuperscript{57} which has been implicated in the regulation of Na\textsuperscript{+}-K\textsuperscript{+} ATPase activity.\textsuperscript{70,71}

Last, but of significant interest, aldosterone at physiological concentrations caused a rapid (<4-minute), 2- to 3-fold increase in intracellular cAMP in microdissected rat inner medullary collecting ducts.\textsuperscript{53} This increase occurred independent of the V\textsubscript{1} and V\textsubscript{2} vasopressin receptors and was additive to increases in cAMP induced by arginine vasopressin. These findings raise the possibility that aldosterone may act via nongenomic mechanisms to regulate a number of cAMP-dependent collecting duct functions, such as H\textsubscript{2}O absorption via aquaporin-2 H\textsubscript{2}O channels and urea absorption via UT-A urea transporters.\textsuperscript{62}

### Proximal Tubule

Very limited information is available on whether aldosterone may influence proximal tubule function through nongenomic mechanisms. In cultures of proximal tubule cells derived from human renal cortex, aldosterone induced a rapid (1-minute) increase in intracellular cAMP and a transient increase in intracellular Ca\textsuperscript{2+} concentration.\textsuperscript{56} The Ca\textsuperscript{2+} response was not blocked by spironolactone and could not be reproduced with hydrocortisone. Whether this regulation occurs in native proximal tubules is unknown; however, cAMP and Ca\textsuperscript{2+} are important regulators of ion transport and the absorptive functions of proximal tubule segments. Aldosterone has been shown recently to increase the apical abundance and activity of NHE3 in proximal tubules of adrenalectomized rats in vivo and in a human proximal tubule cell line\textsuperscript{72,73}; however, these effects are long term (3 to 5 days), and the possible role of nongenomic mechanisms was not reported. Nevertheless, when combined with the additional observations that NHE3 is regulated via a nongenomic pathway by glucocorticoids in a proximal tubule-derived cell line (OKP)\textsuperscript{36} and that NHE3 is a target for nongenomic regulation by aldosterone in the MTAL,\textsuperscript{20} there exists a strong basis for the hypothesis that aldosterone may influence proximal Na\textsuperscript{+} and fluid absorption through nongenomic regulation of NHE3.

### Whole Kidney

A rapid effect of aldosterone on the kidney was described as early as 1958 by Ganong and Mulrow.\textsuperscript{74} Direct injection of aldosterone into the aorta or renal artery of adrenalectomized, anesthetized dogs decreased Na\textsuperscript{+} excretion and increased K\textsuperscript{+} excretion within 15 minutes or less, consistent with a nongenomic mechanism. Thus, in this study, the rapid actions of aldosterone coincide with its classical genomic actions to promote Na\textsuperscript{+} retention and K\textsuperscript{+} excretion. In contrast, in recent studies of adrenal-intact, anesthetized rats, intravenous infusion of aldosterone induced an increase in Na\textsuperscript{+} excretion within 15 minutes, with no detectable change in Cl\textsuperscript{−}, K\textsuperscript{+}, or HCO\textsubscript{3}\textsuperscript{−} excretion or urine pH.\textsuperscript{61} The significance of this effect remains to be determined, because it is opposite to aldosterone’s antinatriuretic function. It is unclear whether the differing effects on Na\textsuperscript{+} and K\textsuperscript{+} excretion in the 2 studies are the result of the difference in species, the hormonal or electrolyte status of the animals before aldosterone administration, or other factors.

### Receptor Mechanisms for Nongenomic Regulation

Although nongenomic effects of aldosterone are clearly established, the receptor mechanisms responsible remain unclear. Nongenomic actions of aldosterone can be mediated through 2 general mechanisms: (1) activation of nonclassical receptors, possibly membrane-associated, and (2) rapid signals generated through the classical MR (Figure). This section summarizes evidence for these 2 mechanisms, focusing on renal cells, and attempts to delineate briefly some of
Nongenomic Aldosterone Effects on Renal Transport

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The rapid actions of aldosterone to increase Na\(^+\)/H\(^+\) exchange in MDCK cells and to increase PKC activity and short circuit current in RCCD\(_2\) cells. These findings suggest that the rapid actions of aldosterone in 2 collecting duct cell lines involve interaction with a receptor at the cell surface. In RCCD\(_2\) cells, both aldosterone and aldo-BSA induced rapid phosphorylation of the MR that depended on PKC. If cellular entry of aldo-BSA is excluded in these experiments, then the results are consistent with aldosterone acting via a cell surface receptor to activate PKC, which, in turn, leads to phosphorylation of the MR. If confirmed, this could provide a mechanism for integration of nongenomic and genomic pathways, whereby rapid aldosterone signals could modify the transcriptional activity of the MR through phosphorylation.

**Glucocorticoids Plus Carbenoxolone**

11β-Hydroxysteroid dehydrogenase type 2 (11βHSD2) prevents cortisol and other glucocorticoids from activating the MR, in part by converting them to receptor-inactive metabolites. Inhibiting 11βHSD2 with carbenoxolone removes this protection and allows glucocorticoids to activate MRs. In the MTAL, which expresses 11βHSD2 and 11βHSD activity, the nongenomic effect of aldosterone to inhibit HCO\(_3^-\) absorption is not reproduced with high concentrations of cortisol or corticosterone either in the absence or presence of carbenoxolone. This result, coupled with the additional finding that the aldosterone-induced transport inhibition is not blocked by spironolactone, argues against mediation by the classical MR. It should be noted, however, that this interpretation of the glucocorticoid-carbenoxolone experiment, for any system, depends on the assumptions (1) that the cells do not contain mechanisms (2) nongenomic and genomic pathways, whereby rapid aldosterone signals could modify the transcriptional activity of the MR through phosphorylation.

**Membrane Binding Studies**

Radioligand binding studies of membrane preparations from several tissues, including pig kidney, reported specific binding sites for aldosterone that exhibit binding affinity, steroid selectivity, and sensitivity to MR antagonists that are not consistent with the kinetic and pharmacological properties of the classical MR. As presented in a separate, critical analysis, variability in the affinity and specificity of steroid binding among the different tissue preparations makes it unclear whether these studies point to a clearly defined membrane receptor.

**MR Antagonists**

With few exceptions noted below, the rapid, nongenomic effects of aldosterone on ion transport and signaling pathways in nephron segments and renal cell lines (Table) are not blocked by spironolactone, providing evidence that they are mediated through a receptor distinct from the classical MR. This interpretation has been complicated, however, by the recent observation in nonp epithelial tissues that nongenomic effects of aldosterone that are not blocked by spironolactone (a closed E-ring antagonist) are blocked by the water-soluble, open E-ring MR antagonists RU28318 and canrenoate. The latter result is inconclusive with respect to mechanism, because it is subject to at least 2 alternative explanations: (1) a nonclassical aldosterone receptor that is blocked by opening antagonists but not by spironolactone or (2) nongenomic actions of aldosterone that are mediated through the classical MR

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**Regulation via Nonclassical Receptors**

Several lines of evidence support the view that nongenomic actions of aldosterone are mediated through receptors other than the MR and that these nonclassical receptors may be membrane-associated proteins, as described below.

**Aldosterone–BSA Conjugates**

The rapid actions of aldosterone to increase Na\(^+\)/H\(^+\) exchange in MDCK cells and to increase PKC activity and short circuit current in RCCD\(_2\) cells are reproduced using aldosterone in MDCK cells and to increase PKC activity and short circuit current in RCCD\(_2\) cells.63 These findings suggest that the rapid actions of aldosterone in 2 collecting duct cell lines involve interaction with a receptor at the cell surface. In RCCD\(_2\) cells, both aldosterone and aldo-BSA induced rapid phosphorylation of the MR that depended on PKC. If cellular entry of aldo-BSA is excluded in these experiments, then the results are consistent with aldosterone acting via a cell surface receptor to activate PKC, which, in turn, leads to phosphorylation of the MR. If confirmed, this could provide a mechanism for integration of nongenomic and genomic pathways, whereby rapid aldosterone signals could modify the transcriptional activity of the MR through phosphorylation.

**Glucocorticoids Plus Carbenoxolone**

11β-Hydroxysteroid dehydrogenase type 2 (11βHSD2) prevents cortisol and other glucocorticoids from activating the MR, in part by converting them to receptor-inactive metabolites. Inhibiting 11βHSD2 with carbenoxolone removes this protection and allows glucocorticoids to activate MRs. In the MTAL, which expresses 11βHSD2 and 11βHSD activity, the nongenomic effect of aldosterone to inhibit HCO\(_3^-\) absorption is not reproduced with high concentrations of cortisol or corticosterone either in the absence or presence of carbenoxolone. This result, coupled with the additional finding that the aldosterone-induced transport inhibition is not blocked by spironolactone, argues against mediation by the classical MR. It should be noted, however, that this interpretation of the glucocorticoid-carbenoxolone experiment, for any system, depends on the assumptions (1) that the cells do not contain mechanisms (2) nongenomic and genomic pathways, whereby rapid aldosterone signals could modify the transcriptional activity of the MR through phosphorylation.

**Membrane Binding Studies**

Radioligand binding studies of membrane preparations from several tissues, including pig kidney, reported specific binding sites for aldosterone that exhibit binding affinity, steroid selectivity, and sensitivity to MR antagonists that are not consistent with the kinetic and pharmacological properties of the classical MR. As presented in a separate, critical analysis, variability in the affinity and specificity of steroid binding among the different tissue preparations makes it unclear whether these studies point to a clearly defined membrane receptor.

**MR Antagonists**

With few exceptions noted below, the rapid, nongenomic effects of aldosterone on ion transport and signaling pathways in nephron segments and renal cell lines (Table) are not blocked by spironolactone, providing evidence that they are mediated through a receptor distinct from the classical MR. This interpretation has been complicated, however, by the recent observation in nonp epithelial tissues that nongenomic effects of aldosterone that are not blocked by spironolactone (a closed E-ring antagonist) are blocked by the water-soluble, open E-ring MR antagonists RU28318 and canrenoate. The latter result is inconclusive with respect to mechanism, because it is subject to at least 2 alternative explanations: (1) a nonclassical aldosterone receptor that is blocked by opening antagonists but not by spironolactone or (2) nongenomic actions of aldosterone that are mediated through the classical MR

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**Regulation via Nonclassical Receptors**

Several lines of evidence support the view that nongenomic actions of aldosterone are mediated through receptors other than the MR and that these nonclassical receptors may be membrane-associated proteins, as described below.

**Aldosterone–BSA Conjugates**

The rapid actions of aldosterone to increase Na\(^+\)/H\(^+\) exchange in MDCK cells and to increase PKC activity and short circuit current in RCCD\(_2\) cells are reproduced using aldosterone conjugated to BSA (aldo-BSA) to prevent its entry into the cells. Efforts to verify that the ald-o-BSA conjugates or dissociated aldosterone did not enter the cells to interact with the cytosolic MR included dialysis to remove uncoupled aldosterone, confirmation of a low BSA endocytic activity, and fluorescence microscopy to confirm that aldosterone but not ald-o-BSA induced rapid phosphorylation of the MR that depended on PKC. If cellular entry of aldo-BSA is excluded in these experiments, then the results are consistent with aldosterone acting via a cell surface receptor to activate PKC, which, in turn, leads to phosphorylation of the MR. If confirmed, this could provide a mechanism for integration of nongenomic and genomic pathways, whereby rapid aldosterone signals could modify the transcriptional activity of the MR through phosphorylation.

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MR but for some reason are not blocked by spironolactone. The finding that open-ring antagonists but not spironolactone block rapid aldosterone action is contrary to the ligand binding affinity of the classical MR for these compounds (spironolactone is a high-affinity antagonist, whereas RU28318 and canrenoate are low-affinity antagonists); hence, it has been argued that the first interpretation (a nonclassical receptor with antagonist sensitivity different from the classical MR) is more likely. An ability of open-ring MR antagonists to block nongenomic regulation by aldosterone has not been reported for epithelial cells; however, most studies in renal cells have tested only the effects of spironolactone. In one exception, the rapid activation of ERK by aldosterone in CCD M-1 cells was not blocked by either closed-ring (spironolactone or canrenoate) or open-ring (RU28318 or canrenoate) MR antagonists, supporting a nonclassical receptor. Eplerenone, a newer, high-specificity, low-affinity MR antagonist that blocks some, but not all, nongenomic effects of aldosterone in cardiovascular tissues has not been tested directly in renal cells. Studies of renal epithelia using a broader spectrum of MR antagonists may provide added insights, particularly if used to analyze nongenomic aldosterone responses in cells lacking the MR (see below). The fact that spironolactone does not block regulation of a wide array of ion transport and signaling effects by aldosterone in numerous renal cell types provides a compelling argument for responses mediated through receptor proteins other than the MR.

**MR Knockout Mouse**

The most convincing evidence that aldosterone induces nongenomic responses independent of the MR has been obtained from the MR knockout mouse. In skin fibroblasts cultured from wild-type and MR knockout mice, the addition of 10 nM aldosterone induced increases in cell Ca²⁺ and cAMP within 1 minute. These effects were not blocked by spironolactone and could not be reproduced with cortisol. Of significant interest, the magnitude of the increase in cell cAMP was 5 times greater in cells from the MR knockout versus wild-type mice at similar basal cAMP levels. This suggests that nongenomic aldosterone pathways may be upregulated in cells in which the classical genomic pathway is absent. If confirmed in other systems, this would have important implications for compensatory adaptations of cells to aldosterone that may occur in clinical protocols in which genomic regulation is chronically inhibited using MR antagonists (see below). Studies of renal tubules isolated from MR knockout mice will be important to provide definitive evidence for rapid actions of aldosterone through nongenocical receptors and to advance our understanding of the cellular locations, functions, and molecular mechanisms of these nongenomic events.

Although none of the individual studies summarized above provides definitive proof of a nonclassical aldosterone receptor in renal cells, they represent an accumulation of evidence that reasonably supports the existence of aldosterone receptors distinct from the MR. Possible mechanisms for nonclassical receptor-mediated aldosterone actions are discussed below.

**Regulation via the Classical Mineralocorticoid Receptor**

Rapid, nongenomic effects of aldosterone may be mediated through the classical intracellular MR. Evidence for this mechanism includes the following: (1) nongenomic regulation that is inhibited by spironolactone and other MR antagonists, (2) nongenomic effects of aldosterone that are reproduced by cortisol in the presence but not in the absence of carbenoxolone to inhibit 11βHSD2, and (3) transfection of cells with the MR that reconstitutes spironolactone-sensitive, nongenomic aldosterone actions. With respect to the kidney, spironolactone has been shown to block some rapid, nongenomic effects of aldosterone, including Src activation in M-1 cells, stimulation of calcineurin in dissected CCDs, and early stimulation of Na⁺/K⁺ ATPase activity in MDCK cells. Also, in M-1 cells, cortisol reproduced the nongenomic effect of aldosterone to increase ERK activity in the presence but not in the absence of carbenoxolone. The latter finding is consistent with mediation via the MR; however, caution again is warranted in the interpretation of this result, because it can alternatively be explained by a nonclassical aldosterone receptor that is intracellular and binds cortisol when 11βHSD2 is inhibited. A mechanism for nongenomic signaling via the MR in renal cells involves spironolactone-sensitive release of heat shock proteins into the cytoplasm from MR complexes in response to aldosterone binding, leading to the activation of downstream effectors, such as calcineurin and Src. Of note, the transcription-independent activation of calcineurin by aldosterone in the CCD requires 30 minutes to develop, presumably because of time required for disassociation of the heat shock protein–MR complex. The longer time course for activation of calcineurin compared with that for other nongenomic signals, such as cAMP and ERK (<5 minutes), may reflect aldosterone actions mediated through different receptors and/or differing complexities of aldosterone-induced signaling pathways. The significance of nongenomic signaling via the MR for aldosterone-induced regulation of epithelial transport remains to be established. As noted above, nearly all of the nongenomic effects of aldosterone on ion transport in renal cells, as well as in the colon, are unaffected by spironolactone, suggesting a prevalence of signaling via nonclassical receptor mechanisms in epithelial aldosterone target tissues.

**Possible Receptor Mechanisms: Insights From Estrogen Signaling**

To date, a novel aldosterone receptor for nongenomic signaling has not been identified. Aldosterone has been reported to selectively increase the activity of PKCα in a cell-free assay system using a purified commercial enzyme, suggesting that a direct aldosterone–PKCα interaction may contribute to nongenomic signaling. In MDCK cells, rapid aldosterone signaling involved interaction with the epidermal growth factor receptor (EGFR), in which aldosterone increased EGFR phosphorylation on tyrosine, and inhibitors of EGFR tyrosine kinase activity decreased aldosterone-induced activation of ERK. These effects appear to depend on the presence of epidermal growth factor and may involve aldosterone acting indirectly via Src to potentiate epidermal...
growth factor–EGFR signaling.91 Whether these mechanisms are relevant to aldosterone-induced regulation of renal tubule function remains to be determined. However, transactivation of the EGFR is involved in rapid signaling by other steroid hormones and appears to play a role in resistance to endocrine hormone therapy.92–94

Of considerable interest is the possibility that nongenomic effects of aldosterone may be mediated through membrane-associated receptors. Such receptors could take several forms: they could be integral membrane proteins accessible at the cell surface or located in signaling complexes in close proximity to the plasma membrane; they could be novel aldosterone receptors unrelated to the MR or modified classical MRs that are associated with the plasma membrane and mediate rapid aldosterone signaling but are transcriptionally inactive. Information on specific receptor mechanisms mediating rapid aldosterone actions is lacking; however, it is conceptually instructive to consider briefly relevant receptor mechanisms involved in nongenomic signaling by estrogen.

First, nongenomic signaling can occur through novel membrane receptors that are unrelated to the classical estrogen receptors (ERs) ERα and ERβ. GPR30 is a G protein-coupled, 7-transmembrane receptor that specifically binds estrogen and mediates nongenomic estrogen signaling through ERK, adenyl cyclase, and intracellular Ca2+ pathways.101–104 A different, as yet unidentified, plasma membrane receptor mediates nongenomic, cGMP-dependent Ca2+ signaling by estrogen in pancreatic β cells.97,98 This receptor, which has a functional equivalent in Drosophila,99 is activated not only by estrogen but also by the catecholamines epinephrine, norepinephrine, and dopamine, properties similar to the mammalian α-adrenergic receptor.97,99

Second, nongenomic signaling can occur through adapter proteins that couple the classical ERs to signaling proteins in the cytoplasm. For example, the protein MNAR/PELP1 mediates interaction of ERs with Src, resulting in the formation of an ERα-MNAR-Src complex that leads to increased Src activity and the activation of downstream signaling components, such as ERK.94,100,101 The classical ERs also interact with linker proteins, such as Shc, that mediate their translocation to the plasma membrane102 and with specialized scaffolding proteins, such as striatin,103 that target the ER to caveoli, invaginated lipid-raft domains of the plasma membrane that compartmentalize multiple signaling proteins.101,104 The latter mechanisms incorporate the ER into signaling complexes in the vicinity of the plasma membrane that mediate rapid, nongenomic signaling on estrogen–ER binding, resulting in the activation of downstream pathways including ERK, phosphatidylinositol 3-kinase/Akt, and endothelial NO synthase.101–104 Activation of these pathways does not require that the membrane-bound receptors be accessible at the cell surface, because they can be accessed by steroids traversing the cell membrane. A posttranslationally modified ER that functions as an integral membrane protein has been hypothesized based on receptor antibody binding and surface biotinylation studies, but its existence has not been proven.94,104

The estrogen studies outlined above establish several important mechanisms for nongenomic steroid signaling, including novel membrane receptors. It should also be noted that brassinosteroids, the steroid hormones of plants, regulate cellular processes through direct binding to the extracellular domain of plasma membrane–localized receptors.105 Whether similar mechanisms contribute to nongenomic aldosterone signaling in target epithelial cells, and the identity of the proteins involved, are crucial areas for future research.

Integration of Nongenomic and Genomic Actions

Nongenomic pathways may interact with genomic mechanisms to provide an integrated system of control of cellular responses.11 This section summarizes, and offers speculation on, possible interactions that may contribute to aldosterone-induced regulation of renal epithelial function.

Aldosterone may act through rapid, nongenomic pathways to modulate its own genomic response. In RCCD2 cells, aldosterone induced both early, nongenomic and late, genomic stimulation of the amiloride-sensitive Na+ current.63 Pretreatment of the cells for 1 hour with inhibitors of PKCα prevented both the early and late responses. However, inhibiting PKC 2.5 hours after aldosterone addition (ie, after completion of the early response) did not prevent the late increase in Na+ transport.63 These results suggest that early signaling events triggered by aldosterone may be necessary for the development of the later, genomic response, and implicate PKC as a mediator of cross-talk between the nongenomic and genomic regulatory pathways.

Additional signaling pathways may contribute to the interplay of nongenomic and genomic aldosterone pathways. ERK and cAMP, which are activated rapidly by aldosterone in a variety of renal cells,26,37,55,56,65,106 can increase the activity and expression of the early aldosterone-induced protein SGK1,107–109 which regulates multiple ion transport proteins in renal cells, including ENaC, ROMK, and the Na–Cl cotransporter.5,6,40 The cAMP/PKA pathway also may regulate ENaC independently of SGK through phosphorylation and inhibition of Nedd4-2, which results in increased expression of ENaC in the cell membrane.41 Rapid stimulation of ERK and cAMP by aldosterone in renal cells is not blocked by spironolactone. Hence, nongenomic mechanisms, such as those described above, could explain the inability of spironolactone to block the intracellular redistribution of ENaC to the apical domain of connecting tubule and CCD cells in response to aldosterone infusion or a low Na+ diet in rats in vivo.110 The ERK and cAMP/PKA pathways may thus be candidate mediators, and SGK1 and Nedd4-2 potential effectors, for the integration of nongenomic and genomic pathways involved in aldosterone-induced control of renal ion transport (Figure).

Aldosterone also may act via nongenomic mechanisms to induce changes in gene expression that are distinct from, or convergent with, genomic changes mediated through the MR. In A6 cells, aldosterone at a supraphysiological concentration (1 μmol/L) caused an early downregulation of mRNA for the transcription factors c-myc, c-jun, and c-fos that was not prevented by actinomycin D or cycloheximide, suggesting that aldosterone may act via nongenomic pathways to modulate mRNA stability.111 These gene changes would tend to
promote/preserve cell differentiation that is necessary for vectorial ion transport and raise the possibility that nongenomic regulation of gene expression could contribute to aldosterone-induced control of ion transport proteins. Rapid activation of ERK and cAMP/PKA by aldosterone in renal cells may activate transcription factors such as cAMP response element binding protein, leading to changes in gene expression of transporters such as the Na+–K+ ATPase and aquaporin 2.

In addition to influencing its own genomic response, aldosterone can act through nongenomic pathways to modify the response of renal cells to other steroid hormones. In the rat MTAL, 1,25-dihydroxyvitamin D3 inhibits HCO3 absorption via a genomic pathway, and this inhibition is markedly enhanced by aldosterone through nongenomic activation of ERK. The mechanism by which aldosterone upregulates the genomic vitamin D$_2$ response is unknown but may involve ERK-mediated phosphorylation of coactivator proteins, such as the retinoid X receptor, that are necessary for the transcriptional activity of the vitamin D$_2$ receptor. Whether aldosterone can modulate the regulatory effects of other hormones through nongenomic mechanisms in the kidney or whether aldosterone may modulate vitamin D$_2$ action in other cells remains to be determined.

**Implications for Renal Disease**

There is evidence of a role for aldosterone in the pathogenesis of progressive renal disease and the development of hypertension. This evidence is centered around the beneficial effects of MR blockade. Aldosterone antagonism with spironolactone or eplerenone has been shown to reduce proteinuria, renal vascular lesions, renal fibrosis, and nephrosclerosis in several conditions, including diabetic nephropathy, glomerulonephritis, and systolic hypertension. These beneficial effects in some cases occur independent of changes in hemodynamics and blood pressure. It is unknown whether nongenomic pathways play a role in aldosterone-mediated renal injury; however, nongenomic mechanisms may contribute to aldosterone-induced mesangial cell injury or to increased renal vascular resistance and arterial hypertension when endothelial integrity is compromised. It is conceivable that the identification of novel mechanisms for nongenomic aldosterone signaling could lead to new therapeutic strategies for slowing the progression of renal disease. For example, one could envision the development of mechanisms or cell-specific ligands or drugs that target nongenomic pathways to decrease detrimental effects of aldosterone, such as glomerular damage or fibrotic responses, while retaining favorable actions, such as collecting duct K$^+$ secretion to prevent the complication of hyperkalemia. This type of therapeutic approach has been formulated for estrogen, including the selective targeting of nongenomic ER signaling as a means to prevent endocrine resistance in breast tumors and the use of specific receptor ligands that reproduce the beneficial nongenomic effects of estrogen on bone mass without inducing the unfavorable genomic effects on reproductive tissue. The possible role of nongenomic mechanisms in other pathophysiological processes, such as aldosterone escape or pseudohypoaldosteronism, remains to be determined.

**Conclusions**

It is now firmly established that aldosterone acts through nongenomic pathways to regulate many different ion transport proteins and signaling pathways in a variety of renal epithelial cells. In addition, studies using isolated, perfused tubules demonstrate directly that aldosterone regulates the transepithelial transport function of nephron segments via nongenomic mechanisms. Nongenomic sites of regulation include not only classical aldosterone targets, such as ENaC, but also transport proteins (NHE3) and nephron sites (proximal tubule) not considered previously to be direct targets for aldosterone-induced regulation. Although studies of cell models will continue to be essential to define the biochemical and molecular mechanisms of rapid aldosterone action, a challenge for the future is to translate the information from segment-derived cell lines to intact, native tubules to identify nongenomic responses that are relevant to aldosterone-induced regulation of renal tubule function. Only then can we begin to understand how nongenomic pathways contribute to the physiological and pathophysiological control of electrolyte and fluid balance and how they may contribute to the role of aldosterone in clinical renal disease. As discussed above, some nongenomic effects of aldosterone that appear in isolation to be counterintuitive, such as inhibition of NHE3 in the MTAL, may in fact play important homeostatic or counterregulatory roles when viewed in the overall context of nephron function. A major unanswered question concerns the receptor mechanisms responsible for rapid aldosterone signaling, in particular the molecular identity of a putative aldosterone membrane receptor, and the extent to which nongenomic responses are mediated through nonclassical receptors or the classical MR. Insights from estrogen studies indicate that rapid steroid signaling is complex and includes both novel steroid membrane receptors and novel mechanisms for rapid signaling through classical cytoplasmic receptors. Renal tubules from mice with targeted knockout of the MR should prove useful for uncovering nonclassical receptor signaling mechanisms and in identifying nephron segments in which MR-independent regulation takes place. Other important questions include whether transactivation of growth factor receptors plays a physiological role in nongenomic aldosterone signaling in renal tubules, whether nongenomic pathways undergo compensatory regulation when genomic pathways are genetically or biochemically disrupted, and how nongenomic pathways modify or converge with genomic pathways to regulate long-term aldosterone responses. Of interest is whether rapid aldosterone signaling via ERK and cAMP/PKA may modulate genomic regulation via SGK1 and Nedd4-2, providing a mechanism for the fine control of multiple transport proteins, including ENaC. Future studies to unravel the complexity and significance of nongenomic signaling undoubtedly will lead to important discoveries that expand our current understanding of the cellular mechanisms through which aldosterone regulates renal tubule function.
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Disclosures
None.

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