Brief Review

Aldosterone Regulation of Gene Transcription Leading to Control of Ion Transport

Jean-Daniel Horisberger and Bernard C. Rossier

Aldosterone, like other steroid hormones, initiates its effects by binding to intracellular receptors; these receptors are then able to control the transcription of several genes. The products of these genes eventually modulate the activity of ionic transport systems located in the apical and the basolateral membrane of specialized epithelial cells, thereby modulating the excretion of Na⁺ and K⁺ ions. Considerable progress has been made recently in understanding these mechanisms and the structure of the proteins involved in these processes. A novel principle has been discovered to explain the selective effect of aldosterone on its target epithelia. These tissues exclude competing glucocorticoid hormones by the activity of the 11β-hydroxysteroid dehydrogenase to allow aldosterone, an enzyme-resistant steroid, to bind to its receptors. Aldosterone induces numerous changes in the activity of membrane ionic transport systems and enzymes and cell morphology. Although the enhancement of Na⁺,K⁺-ATPase synthesis and the increase of the number of active Na⁺ channels in the apical membrane appear as both direct and primary effects, the mechanisms of the other effects remain to be determined. The knowledge of the primary structure of several elements of the aldosterone response system (e.g., mineralocorticoid receptor and Na⁺,K⁺-ATPase) allows us to understand abnormal regulation of Na⁺ balance at the molecular level and, potentially, to identify genetic alterations responsible for these defects. (Hypertension 1992;19:221–227)

KEY WORDS • mineralocorticoid hypertension • sodium transport • aldosterone • carrier proteins • genes

Aldosterone was the first described hormone involved in the regulation of sodium and potassium balance. Isolated deficit of the aldosterone action leads to sodium wasting and hyperkalemia, whereas mineralocorticoid excess induces sodium retention and potassium wasting, although rare, causing hypertension in humans. Chronic mineralocorticoid treatment is also a useful model of animal hypertension. Aldosterone now appears as only one element of a complex homeostatic mechanism allowing the preservation of the sodium balance and consequently the stability of the extracellular fluid volume and the maintenance of blood pressure. In addition, it also has an important role in regulating the potassium balance. These controls are achieved by adjusting the transport rate of electrolytes across the epithelia lining the distal parts of excretory systems (e.g., distal nephron, colon, and ducts of excretory glands). The scope of the present review will be restricted to the action of aldosterone on these epithelia, the classic target tissues of aldosterone. It should be noticed, however, that high affinity mineralocorticoid receptors have been demonstrated in several nonepithelial cell types. The physiological role of these receptors is not yet completely understood, and for some of these effects, the mechanism of action appears to be completely different from that observed in epithelial cells. However, concerning the regulation of sodium balance, evidence has been provided for a direct involvement of central nervous system receptors in the pathogenesis of mineralocorticoid-induced hypertension.

Mineralocorticoid Effects

The aldosterone-responsive epithelia are able to control the composition of the fluids leaving the organism by establishing large ionic gradients between the interstitial milieu and the fluid to be excreted. This is possible because they are highly impermeant to passive diffusion of ions (for which reason they are called “tight” epithelia). The effects of aldosterone in mammals have been mostly studied on the cortical collecting tubule of the kidney and on the colon. In these tissues, aldosterone induces both an increase of Na⁺ reabsorption and of K⁺ secretion. The molecular mechanisms of action have been extensively studied in amphibian tight epithelia, for example, the urinary bladder of the toad and more recently in cell cultures originating from these tissues. The amphibian experimental models demonstrate primarily the Na⁺ transport response. The general mechanism by which Na⁺ and K⁺ ions are actively transported across these epithelial cells is represented in Figure 1.

Three phases can be distinguished in the time course of the effect of aldosterone. First, a latent period (30–60 minutes) in which no modification of the Na⁺ transport occurs. Second, an early response (2–3 hours) in which there is a large increase of Na⁺ transport and
FIGURE 1. Schematic diagram shows mechanism of trans-
epithelial Na⁺ and K⁺ transport in "tight" epithelia. The
primary active process, the Na-K pump (P) is specifically
located in the basolateral membrane (bl m), the membrane
facing the blood. It transports Na⁺ ions out of the cell toward
the blood and K⁺ ions into the cell. Because of the low
intracellular Na⁺ concentration maintained by the Na-K
pump, Na⁺ ions enter the cell passively through the Na⁺
channels located in the apical (ap) membrane, facing the
luminal fluid. Thus, Na⁺ ions are transported across the cell
from the lumen to the blood. K⁺ ions accumulated in the cell
by the Na-K pump recirculate across the basolateral mem-
brane through K⁺ channels and, in K⁺-secreting epithelia, also
across the apical membrane. In these epithelia, the lumen
negative transepithelial potential ( —), created by Na⁺ trans-
port, favors the exit of K⁺ into the lumen. The tight junctions
(t j) prevent the back-leak of transported ions.

a parallel decrease of the transepithelial resistance;
both effects can be explained by an increase of the Na⁺
permeability of the apical membrane, although other
modifications are not excluded. Third, a late response
where Na⁺ transport continues to increase for 6-12
hours while the transepithelial resistance is stable. This
phase can be followed for about 24 hours in amphibian
epithelia in vitro, but morphological and functional
changes continue to occur over a much longer period
when experimental animals are chronically exposed to
mineralocorticoid hormones.11,12

In addition to their effect on Na⁺ and K⁺ transport,
mineralocorticoid hormones promote the net secretion
of H⁺ ions by the distal nephron and the colon. The
mechanism of the increased acid net secretion may
result from direct effects such as the stimulation of an
N-ethylmaleimide-sensitive H⁺-ATPase13,14 or of a
H,K-ATPase,15 or be the consequence of the physiolog-
ical modifications associated with a higher Na⁺ and K⁺
transport rate such as an increase in luminal negative
potential or decrease of the paracellular ionic perme-
ability. The effect of mineralocorticoid on acid secretion
can hardly be considered as a regulatory mechanism
since blood pH has not been shown to be a stimulus to
aldosterone secretion.16

The main steps in the mechanisms of action of aldo-
sterone are described in Figure 2 and will be reviewed in
the following sections. Similar to other steroid hormones,
the first step of aldosterone action is binding to intracel-
lar receptors, and then the hormone-receptor complex
interacts with DNA (see "Receptors"). Thereby, it modifies
the expression of a number of genes, inducing or
repressing the synthesis of several proteins (see "From
Receptors to Effectors"). The final effect on electrolyte
transport is produced by modification of the function of
several membrane transport systems, the effector mecha-
nisms (see "Effector Mechanisms").

Receptors

Binding studies in aldosterone target tissues reveal
two distinct binding sites, a type I with a high affinity
(Kₐ around 1 nM) and a low capacity and a type II with
a lower affinity (Kₐ, around 50 nM) and a larger number
of binding sites. Because the type I binding site was
found specifically in the aldosterone target tissues, it has
also been designated as the mineralocorticoid receptor
(MR). A MR complementary DNA (cDNA) has been
identified and cloned by low-stringency hybridization
using a lymphoid glucocorticoid receptor (GR) cDNA
as a probe.17 A new gene encoding a 107 kd protein was
found. When expressed in COS cells, the protein en-
coded by the MR gene had the ability to bind aldoste-
rone and other steroids with affinities similar to those
observed for the type I aldosterone receptor. The MR
protein is part of a large family of intracellular hormone
receptors (e.g., steroid hormone receptor, thyroid hor-
mone receptor, vitamin D receptor, and retinoic acid

FIGURE 2. Schematic diagram shows molecular mecha-

Isms of action of aldosterone. Aldosterone (A) binds to an
intracellular receptor (R), and the active hormone-receptor
complex interacts with hormone-responsive elements (HRE)
of the DNA to modulate the transcription of specific genes,
leading to the expression of specific proteins, the aldosterone-
induced proteins (AIP). The candidate targets for the action
of these AIP are listed below the figure. The Na-K pump (P)
known to be itself induced by aldosterone. The mechanism
by which the other effectors are regulated are still conjectural
as discussed in the text. mRNA, messenger RNA.

receptor) that share a common general structure, including a central highly conserved (more than 90% homology between members of the family) DNA binding region of about 70 amino acid residues and a C-terminal steroid recognition region.18

Tissue-specific expression of the MR protein is generally restricted to organs in which high affinity aldosterone binding sites have been demonstrated (i.e., the organs including tight epithelia), but MR expression is also observed in the brain (mostly the hippocampus), in the heart, and in blood vessels. The role of the MR in these nonepithelial cells is not yet understood.

The type II aldosterone binding site is generally designated as the GR because its steroid binding characteristics are similar to the GR identified in other tissues.

Both type I and type II demonstrate a poor selectivity between natural glucocorticoid and mineralocorticoid hormones. The MR has a similar affinity (Kₘ around 1 nM) for both aldosterone and cortisol (or corticosterone, the naturally occurring glucocorticoid in the rat),17,19 whereas the GR has only a slightly higher affinity for cortisol (Kₘ, 10–50 nM) than for aldosterone (50–100 nM).18 Considering that total circulating levels of cortisol are usually several orders of magnitude higher than those of aldosterone, and even if cortisol is heavily bound to plasma proteins while aldosterone is mostly free, the free hormone plasma level of cortisol is still many times higher than that of aldosterone. Then how is a mineralocorticoid-specific response to aldosterone possible?

This question has only recently received a satisfactory answer. Aldosterone-responsive epithelia express a high activity of the 11β-hydroxysteroid dehydrogenase (11β-OHSD), an enzymatic complex that catalyzes the transformation of cortisol into the much less active cortisone (Figure 3). Two clinical situations are known in which the activity of this enzyme is reduced. First, the congenital apparent mineralocorticoid excess (AME) syndrome,20 in which 11β-OHSD is deficient. Second, the acquired AME syndrome, which is caused by inhibition of the 11β-OHSD such as glycyrrhetinic acid, found in licorice, or its derivative carbenoxolone, a drug used in the treatment of peptic ulcer.21,22 In both cases, signs of an excessive mineralocorticoid stimulation are observed (e.g., Na⁺ retention, hypertension, and hypokalemia) in spite of low levels of circulating aldosterone and renin. From these observations and the replication of these phenomena in experimental models using carbenoxolone, a new hypothesis has been put forward. In the aldosterone target tissue, the intracellular level of cortisol is maintained at a very low level by rapid metabolism of cortisol into the relatively inactive cortisone by the 11β-OHSD22 (Figure 3). Corticoid receptors are consequently free to interact with aldosterone, a molecule resistant to the 11β-OHSD activity. Aldosterone is thus allowed to control specifically electrolyte transport through a nonselective receptor, even in the presence of high and variable circulating levels of a potent agonist, cortisol, because this agonist is specifically excluded from the target tissues by enzymatic metabolism. If this mechanism is now well recognized to explain the hypertension of the rare AME hereditary syndrome, the possible role of alteration of the function of the 11β-OHSD in other forms of hypertension has still to be explored.

The designation of the aldosterone type I as mineralocorticoid receptors and the type II as glucocorticoid receptors in target tissues appears somewhat misleading for several reasons. First, there is the absence of a clear selectivity of the isolated receptor for natural glucocorticoid or mineralocorticoid hormones. Second, occupancy of both types of receptor is necessary for the expression of the full physiological mineralocorticoid response,24 and a mineralocorticoid type response can be elicited in several tissues by specific type II agonists.25,26 Third, if the 11β-OHSD hypothesis is true, type II receptors in aldosterone target tissues would not be exposed to the circulating glucocorticoid hormones unless the capacity of the 11β-OHSD is overcome by high levels of steroids. Until we get a better understanding of the role of each type of receptor, it seems wise to use the "type I" and "type II" aldosterone receptor nomenclature, instead of "mineralocorticoid" and "glucocorticoid" receptor, in aldosterone target tissues.

**From Receptors to Effectors**

Similar to the other steroid hormones, once aldosterone is bound to its receptor (or receptors), the hormone–receptor complex is able to interact with specific sequences of DNA, the so-called hormone-responsive elements (HRE) to activate or repress specific genes.18,27 Such HRE have been identified for glucocorticoid, progesterone, and estrogen receptors. By analogy, the exis-

**FIGURE 3.** Schematic diagram shows mechanisms of aldosterone selectivity in target tissues. Cortisol is circulating at a concentration higher than aldosterone and has a roughly similar affinity for type I and type II receptors. However, in the "classic" epithelial aldosterone target tissues, cortisol is prevented from binding to mineralocorticoid receptors (for the sake of simplicity only one receptor [R] is drawn in the figure) by rapid metabolism through the 11β-hydroxysteroid dehydrogenase (11β-OHSD). The cortisol metabolite, cortisone, has a much lower affinity for the aldosterone receptors. Conversion of cortisone into cortisol occurs in other tissues, mostly in the liver. Deficient function or inhibition of the 11β-OHSD leads to higher intracellular cortisol concentrations in epithelial target tissues. Cortisol is then able to bind to type I and type II receptors, inducing the signs and symptoms of hyperaldosteronism in the absence of increased aldosterone levels.
tence of analogous mineralocorticoid-responsive elements has been suspected, and mineralocorticoid receptor–hor-
mone complexes can activate transcription of a reporter
gene by binding to the DNA of the glucocorticoid
HRE.28–29 However, the presence of specific mineralocor-
ticoid response elements in aldosterone-controlled genes
of target tissues has still to be demonstrated.

There remains a wide gap in our understanding of the
mechanisms that transmit the information from the
control of transcription to the effectors; most of them
are still hypothetical. The natrieric effect of aldoste-
ronle on amphibian tight epithelia is dependent on the
synthesis of new proteins, as shown by the inhibition of
this effect by protein synthesis inhibition.30 In mamma-
lian kidney both the natriuretic and the kaliuretic effects
can be prevented by protein synthesis inhibitors.31

In principle, any of the various membrane transport
systems involved in the Na+ and K+ translocation could
be an aldosterone-induced protein (AIP); however, except
for the Na,K-ATPase (see below), no other "effectors"
protein has been characterized as an AIP. Several
AIPs have been identified by two-dimensional
m garbage or by direct protein modifications; indeed, evidence
is still hypothetical. The natriferic effect of aldoste-
onle is responsive to cyclic AMP 38–40 and cyclic GMP, 41 but
there is no proof that these mechanisms are involved in
the response to aldosterone. Similarly, intracellular
Ca2+ is known to inhibit the apical Na+ channel,42,43 but
the effect of aldosterone on intracellular Ca2+ in epithe-
lial cells is not known. Another interesting mechanism,
the control of intracellular pH, has been well investi-
gated in the amphibian early distal tubule, the physio-
logical equivalent of the mammalian thick ascending limb.44
In these epithelial cells, aldosterone induces an
intracellular alkalization through the activation of a
Na-H exchanger, and since the apical membrane of
these segments contains K+ channels that can be acti-
vated by cytoplasmic alkalization,45 this results in an
increase of the K+ secretion into the tubule lumen. This
tubule segment is not a classic tight epithelium aldoste-
ronle target; however, aldosterone binding studies46 as
well as immunolocalization studies47 have revealed min-
eralocorticoid receptors, although at a comparatively
low level. Since physiological studies have been
performed with large doses of aldosterone, it is not pres-
ently known whether intracellular pH modulation and
K+ secretion in this segment is mediated by type I or
II receptors, or both. Although intracellular pH
also modifies the Na+ conductance of tight epithelia,48 it
is not known whether pH mediates the effect of aldos-
terone in these classic target epithelia.

In addition, aldosterone has been shown to induce an
increase of enzyme involved in the generation of ATP,
particularly citrate synthase.49,50 However, in several
amphibian cell lines, a natriergic response could be
observed in the absence of detectable change of citrate
synthase activity.51 Whether this metabolic effect of
aldosterone is direct or indirect (related to increased
Na+ transport) is still a matter of debate.

**Effector Mechanisms**

As outlined in Figure 1, at least four basic elements
are involved in the vectorial active transport of Na+ ac-
cross a tight epithelium. First, the apical Na+ channel
provides a regulated permeation pathway of Na+ ac-
cross the apical membrane. Second, the basolateral Na,K-
ATPase, or Na,K pump, constitutes the Na+ pathway
across the basolateral membrane and, using the meta-
abolism energy supplied in the form of ATP, maintains
the low intracellular Na+ concentration that drives this ion
from the lumen into the cell. Third, because the Na+
ions are pumped by the Na,K-ATPase in exchange for
K+ ions, a pathway must exist to allow K+ to exit the cell.
K+ channels are present in the basolateral membrane of
tight epithelia. In some tight epithelia (for which the
main function is Na+ reabsorption), these basolateral
K+ channels constitute the main pathway of K+ recircu-
lation. In other tight epithelia, those involved in the
secretion of potassium (the cortical collecting tubule and,
to a lesser extent, the distal colon), K+ channels are also
present in the apical membrane, allowing K+ to exit the
cell toward the apical compartment. Finally, the tight
junctions, the structure controlling the paracellular path-
way, must be impermeant to Na+ ions to prevent the back
leak of Na+ from the basolateral to the apical compart-
ment. The effects of aldosterone on each of these ele-
ments will be reviewed in the following paragraphs.

Entry of Na+ across the apical membrane through
Na+ channels is the rate-limiting step of transepithelial
Na+ transport in tight epithelia. The control of the
number of active Na+ channels in the apical membrane
thus appears as the first possible target for a min-
eralocorticoid hormone. The epithelial amiloride-sensi-
tive Na+ channel is a complex protein structure: the
 purified amiloride binding membrane protein isolated
from bovine kidney medulla is composed of six distinct
subunits ranging in molecular weight from 40 to 315
kd.52,53 Although amiloride seems to bind to a 150-kd
polypeptide,52,54 the function of each subunit has yet to
be determined. The physiological characteristics of sin-
gle amiloride-sensitive Na+ channels have been studied
by the patch clamp technique, and they appear similar
in mammalian55 and amphibian56 tight epithelia: the
channel has a small conductance of about 5 pico-
siemens and slow kinetics (mean open time in the second
range). In contrast with the Na+ channel of excitable cells,
the epithelial Na+ channel is poorly voltage-sensitive, with
a slight activation by membrane hyperpolarization.55,57
A number of studies have identified the increase of the
apical membrane Na+ permeability as the main
event of the early response to aldosterone (see Refer-
ce 9 for review). This effect is due to an increase of
the number of active channels without change of the
conductance of each channel.58 Recent data indicate
that the kinetics of opening and closing of the channel
could be modulated by aldosterone.59 Although the Na+
channel may seem a likely candidate for an AIP, it
appears that at least part of the proteins constitutive
of the channel are already present in the apical membrane
before aldosterone action. Previous exposure of the apical membrane to proteolytic enzymes or carboxylre- active agents prevents the subsequent effect of aldoste- rone (in contrast with the effect of ADH, which is thought to act by addition of new membrane-containing Na" channels and is not prevented by the same maneu- ver), and the composition of Na⁺ channels is not altered by aldosterone. This is confirmed by the absence of an effect of aldosterone on the amount of messenger RNA (mRNA) coding for amiloride-sensitive Na⁺ channels in Na⁺ transporting A6 cells. Asher and Garty have been able to demonstrate two phases in the effect of aldosterone on the apical membrane Na⁺ conductance in the toad bladder. During the early phase (3 hours), although aldosterone induced a more than twofold increase of the apical membrane permeability to Na⁺, vesicles isolated from the epithelium do not demon- strate an increase of Na⁺ transport; thus, this early effect is lost in the process of isolating the membrane. In contrast, after a longer exposure to aldosterone (6 hours), resulting in an additional increase of apical membrane permeability, an increase of amiloride-sen- sitive Na⁺ transport was observed in the vesicles; this later change apparently results from a permanent altera- tion of the Na⁺ channel.

The Na-K pump has the best characterized structure of these four elements. Its primary structure has been determined in humans and in several species. The functional Na,K-ATPase is composed of two subunits. The first is a 100-kd α-subunit that contains the catalytic sites of ATP hydrolysis, the Na⁺ and K⁺ transport binding sites, and the binding site for the specific inhibitors the cardiac glycosides. The second is a 40-60-kd glycosylated β-subunit, the function of which is not entirely determined, but it is at least involved in the maturation and expression to the surface of the α-subunit. Of the three known isoforms (α1, α2, α3), only the α1 isoform is expressed in significant amounts in epithelial cells. Two β isoforms are present in amphibian tight epithelial cells, but only the β1 isoform expression is induced by aldosterone.

The Na,K-ATPase has been definitely identified as one of the AIPs in amphibian tight epithelia. Aldoste- rone induces a rapid (detectable within 15 minutes) increase of the transcription of both the α- and the β-subunit genes. This leads to a twofold to fourfold accumulation of the mRNA coding for both subunits. The rapidity of this effect favors the hypothesis that both genes are directly regulated by a corticosteroid- responsive element, although a more complex mecha- nism cannot be excluded. At the protein level, it was shown that the synthesis of both α- and β-subunits was increased after exposure to low doses of aldosterone corresponding to occupancy of type I receptors, although maximal effect can be obtained only by using large concentrations of aldosterone corresponding to occupancy of type II receptors. This effect is not apparent before the third hour of aldosterone exposure and thus appear to be an event of the late response.

Because this response occurs even after inhibition by amiloride of Na⁺ entry through the apical membrane, it is not only a consequence of an increase Na⁺ load to the cell. On the other hand, several investigators have observed that preventing Na⁺ entry by blocking apical membrane Na⁺ channels reduced the effect of aldoste- rone on the activity of the basolateral Na-K pump whereas others found opposite evidence. These apparently contradictory results may be reconciled by the recent observation by Blot-Chabaud et al and Barlet-Bas et al that aldosterone controls a latent pool of Na-K pump and that active Na-K pump are recruited from this pool when the sodium load to the cell is increased. Thus, although aldosterone induces directly the synthesis of new Na,K-ATPase units, an increase of active Na-K pump at the plasma membrane might be observed only if an adequate Na⁺ loading of the cell is allowed.

Aldosterone effects may include an activation of both apical and basolateral K⁺ channels. An increase of the basolateral K⁺ conductance has been reported both in mammalian and in amphibian tight epithelia. Although the type of K⁺ channels involved in this response has not been determined, they appear to be lidocaine-sensitive. In toad bladder cells, the increase of the basolateral K⁺ conductance occurred during the early response and was independent of the increase of Na⁺ transport.

In the K⁺-secreting epithelia such as the cortical collecting tubule, the stimulation of K⁺ secretion by aldosterone can be explained by several mechanisms. First, the apical membrane is depolarized by the increased Na⁺ permeability, leading to an increase of the driving force for K⁺ exit from the cell to the lumen. Second, the increase of the basolateral Na-K pump activity hyperpolarizes the basolateral membrane potential preventing K⁺ exit to the basolateral side and accumulates more K⁺ into the cell, thereby also increasing the driving force for K⁺ exit across the apical membrane. Third, an activation of apical membrane K⁺ channels would amplify the secretory K⁺ flux due to the increased driving force. Such an increase of the apical K⁺ conductance has been well demonstrated in the cortical collecting tubule of the rabbit. In this model, this effect was part of the late response and appeared to be dependent on Na⁺ transport. The relative importance of the change of driving force versus change of conductance for K⁺ across the apical mem- brane is still a matter of debate and may be species specific.

The tight junctions may also be a target of the action of aldosterone. Several investigators have reported an increase of the paracellular resistance of the rabbit cortical collecting tubule or the colon after exposure to mineralocorticoid. In contrast, aldosterone increased the paracellular permeability in A6 cells, an effect that was dependent on Na⁺ transport. These effects were relatively small, and their physiological significance is not known.

Perspectives and Conclusions

Blood pressure is a quantitative trait that varies continuously in the whole population. Blood pressure and its regulation are controlled by a variety of mechan- isms involving probably several genetic loci and environ- mental and other factors, such as diet, body weight, stress, and physical exercise. The hereditary nature of hypertension has been demonstrated in both human and animal models. As pointed out by Corvol and colleagues, two main approaches have been used to
study the genetic factors involved in arterial hypertension. One approach is to test a series of genetic markers distributed throughout the genome to carry a link between increased blood pressure and specific genes. The other approach is to study candidate genes that are known to participate in blood pressure regulation, such as hormonal factors (e.g., renin-angiotensin-aldosterone axis, catecholamines, and vasopressin), factors involved in target cells (e.g., heart and blood vessels), or as described in this short review, the distal segments of the nephron, which play a critical role in the fine control of sodium metabolism. It is quite evident that the control of sodium reabsorption in the distal nephron could be one of the first factors in the establishment of hypertension. The link between sodium metabolism and hypertension has been often discussed, and in most physiological models that have been proposed, a “kidney factor” has been postulated to explain the genesis of high blood pressure.

We believe that the identification of the sodium transport protein involved in sodium reabsorption in the distal nephron and the identification of the molecular mechanisms by which these transporters are controlled should lead to the identification of candidate genes playing a role in the genesis of hypertension. Among other congenital diseases, the congenital deficiency in 11beta-OHSD is a recent example of a possible candidate gene involved in essential arterial hypertension. In the future, it will be of special interest to understand in molecular terms the entry of sodium at the apical membrane through amiloride-sensitive sodium channels, which is the limiting factor in the sodium transport function of tight epithelia. In 1963, Liddle and his colleagues described a familial hypertension disorder simulating primary aldosteronism but with negligible aldosterone secretion. This disorder could be corrected by treatment with low doses of a sodium channel inhibitor, suggesting that the sodium channel itself (or its regulation) was involved. In this context, we believe that the understanding of the molecular mechanism by which aldosterone controls sodium reabsorption is a prerequisite in defining the most important candidate genes involved in the genesis of hypertension linked to renal sodium retention.

References


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