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Differential Effects of Glucocorticoids and Mineralocorticoids on the mRNA Expression of Colon Ion Transporters in Infant Rats

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ABSTRACT

Several epithelial ion transporters are developmentally regulated in the preweaning period, at the time when the circulating levels of glucocorticoid and mineralocorticoid hormones increase. The specific role of glucocorticoids and mineralocorticoids in the maturation of epithelial ion transport is still disputed. In this study, we investigated the effect of corticosteroids on the mRNA expression of ion transporters in the infant rat colon, a glucocorticoid- and mineralocorticoid-sensitive organ. The expression of the Na,K-ATPase, the H,K-ATPase and the amiloride-sensitive Na^+ channel mRNA was investigated in control rats from fetal to adult life. We found that the mRNA of the three transporters is temporarily up-regulated in the preweaning period. Rats were then injected with a single dose of betamethasone or aldosterone at 10 d of age. The main effect was the glucocorticoid stimulation of the Na,K-ATPase mRNA within 6 h (4-fold). Glucocorticoids did not alter H,K-ATPase nor Na^+ channel mRNA within 6 h. Aldosterone moderately (1.7-fold) stimulated Na^+ channel within 6 h, but did not alter Na,K-ATPase nor H,K-ATPase mRNA. Twenty-four hours after injection, both glucocorticoids and mineralocorticoids had less pronounced and distinct effects. In tissue with lower aldosterone receptor abundance (renal cortex) or with no aldosterone receptor (stomach), glucocorticoids induce a similarly rapid increases in Na,K-ATPase mRNA (4-fold within 6 h), whereas aldosterone had no effect within 6 h. However, glucocorticoids did not stimulate Na,K-ATPase mRNA in the brain, a tissue rich in glucocorticoid receptors.

This study indicates that Na,K-ATPase is a primary target for glucocorticoids in the preweaning period, and suggests that glucocorticoid induction of Na,K-ATPase mRNA may play an important role in the maturation of epithelial ion transport capacity. The effect is probably mediated by glucocorticoids and not by mineralocorticoid receptors. However, it seems that an auxiliary factor is required for glucocorticoid-dependent stimulation of Na,K-ATPase mRNA. (***Pediatr Res* 38: 164–168, 1995**)

Abbreviations

GC, glucocorticoid hormone
MC, mineralocorticoid hormone
11β-HSD, 11β-hydroxysteroid dehydrogenase
PCR, polymerase chain reaction

It is well established that corticosteroid hormones have an important influence on normal growth and differentiation. Several studies have suggested that such effects are mediated by modulating the level or the activity of certain key enzymes involved in metabolic and physiologic processes (1, 2). The maturation of several ion transporters is developmentally regulated in the kidney and the intestine during the preweaning period, at the time when the circulating levels of both GC and MC hormones increase (3, 4). A deficiency of corticoids (*e.g.* adrenalectomy) delays tissue differentiation, and treatment with exogenous GC causes the premature appearance of normal events of development (5). The mechanisms by which corticosteroid hormones stimulate the maturation of epithelial ion transport is still disputed. GC may directly alter the transcription rate of key enzymes for cell metabolism, such as Na,K-ATPase (6). On the other hand, it has been suggested that GC may alter the phospholipid composition of the cell membrane (7). In the latter study, the alteration in phospholipids was accompanied by a change in the activity of membrane-bound ion transporters, such as the Na-dependent phosphate, glucose, and proline carriers.

Several studies have shown that the activity of Na,K-ATPase is low in a variety of infant tissues, such as the kidney, lung, intestine, and heart, and that GC stimulate enzyme maturation (8–12). In the infant kidney, the transcription rate of Na,K-ATPase is directly increased by GC (6). GC do not regulate Na,K-ATPase mRNA in adults (13, 14). In adults, Na,K-ATPase mRNA is regulated by MC, at least in aldosterone-sensitive cells (13). The role of aldosterone in the maturation of Na,K-ATPase is less well defined. Adrenal corticosteroids are known to have pronounced effects in the mammalian colon (15–18). The activity of colon Na,K-ATPase

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is low in infancy, and both aldosterone and GC have been shown to stimulate maturation of the enzyme activity (4, 19). The rat distal colon contains abundant MC and GC receptors which are expressed in epithelial surface and crypt cells (20, 21). Thus, the colon is an excellent model in which to study the specific role of GC and MC in the maturation of epithelial ion transporters. This study was therefore designed to determine the ontogeny of the basolateral Na,K-ATPase, the luminal H,K-ATPase (22), and the amiloride-sensitive Na^+-channel (23) in the rat colon and to evaluate the role that GC and MC play in their maturation.

MATERIAL AND METHODS

Animals. Experiments were performed on male Sprague-Dawley rats aged 10 d (ALAB, Sollentuna, Sweden). The rats were injected intraperitoneally with betamethasone (60 μg/100 g body wt), aldosterone (80 μg/100 g body wt), or vehicle. These doses were chosen because, in previous experiments, we found that they maximally accelerate the maturation of renal Na,K-ATPase (8, 24). The rats were then anesthetized after 6 or 24 h with thiobutabarbital (8 mg/100 g body wt), and the organs were immediately removed. The distal colons (one-third part from the colorectal junction) were then cut open, emptied of all contents, and washed in ice-cold saline. In one protocol, control rats of various ages (20-d gestational age, 10, 20, and 50 d postnatally) were used. We pooled the organs from three to five fetuses before homogenization.

Northern and RNA dot blot hybridization. Total RNA was isolated from tissues, as previously described (3). The integrity of the RNA was routinely evaluated by Northern blot (Fig. 1). To quantify the mRNA level, 4 μg of total RNA were denatured in ice-cold 10 mM NaOH and blotted in triplicate under vacuum onto a nylon filter, as previously described (10). Probes were random-prime labeled with ^{32}P (Megaprime DNA Labeling system, Amersham, Buckinghamshire, UK). Prehybridization (20 min) and hybridization (3 h) were performed at 65°C with Amersham Rapid Hybridization buffer. Filters were washed at 65°C to a final stringency of 0.1 × SSPE, 0.1% SDS. The filters were subjected to autoradiography at −70°C and the results analyzed by laser densitometry. Data were corrected by the intensity of an internal standard (pooled mRNA from control rats) to which an arbitrary value of 1 is given. Expression of actin mRNA was also routinely determined to evaluate appropriate loading. The Na,K-ATPase α1 and α2 probes are full-length cDNAs, α3 is the *PstI-SmaI* fragment (278 bp) and β1 is the *Hin*dIII- *Pst*I fragment (271 bp). Actin cDNA was purchased from Clontech Labs, Palo Alto, CA. The colon H,K-ATPase α subunit and the Na-channel α subunit probes are 421- and 223-bp fragments (53–473 and 86–308 nucleotides, respectively) which were synthetized from rat colon and renal mRNA by reverse transcriptase-PCR. PCR primers (20 mer) were designed according to the published sequence (23, 25). RNA (2 μg) was reverse transcribed in a 20-μL reaction containing 50 mM Tris-HCl, 75 mM KCl, 3 mM $MgCl_2$, 1 mM DTT, 2 mM dNTP, 25 mg/mL oligo(dT), 30 U RNasin, and 100 U Moloney murine leukemia virus reverse-transcriptase. After incubation for 30 min at 42°C, the samples were used for PCR amplification. Reactions were performed in 10 mM Tris-HCl, 50 mM KCl, 1.5 mM $MgCl_2$, 50 pM of each primer and 2 U *Taq* DNA polymerase. The following temperature profile was used: 1 min at 94°C, 1 min at 55°C, and 2 min at 72°C (35 cycles). Gel analysis of the PCR products showed unique bands of the predicted size.

Statistical analysis. Six rats were studied in each group. Values are given as means ± SD. The statistical analysis was performed with the *t* and analysis of variance test.

RESULTS

In the colon, the expression of the Na,K-ATPase α1 and β1 subunits, the H,K-ATPase α subunit, and Na-channel α subunit was ontogenically regulated. For clarity of presentation, only the Na,K-ATPase β1 subunit mRNA is shown throughout this report, because α1 and β1 mRNA always changed in parallel. The mRNA of all three ion transporters are expressed in the fetal colon (Fig. 2). Postnatally, the mRNA of all three ion transporters increased to a maximal level in the preweaning period (≈20 d of age) and then declined to the adult level ($p < 0.05$ for all mRNA, analysis of variance test).

It is well established that the circulating levels of GC and MC increase during the 3rd wk of life (3, 4). To evaluate whether the temporary up-regulation of the Na,K-ATPase, H,K-ATPase, and Na-channel mRNA is due to corticoids, rats

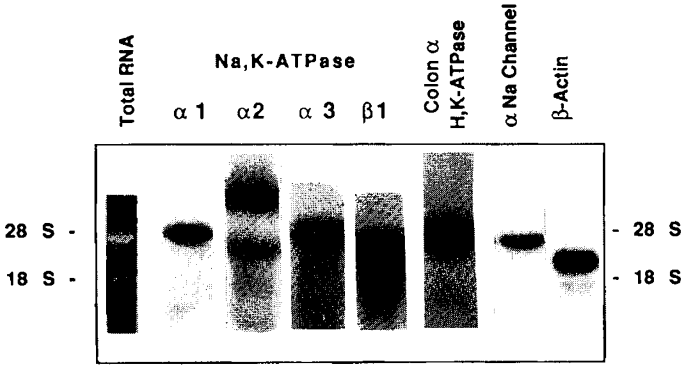

Figure 1. Representative Northern blot analysis. Ten micrograms of total RNA were loaded in each lane and probed with α1, α2, α3, and β1 Na,K-ATPase, colon α H,K-ATPase, α Na-channel, and β-actin cDNAs, respectively. Positions of ribosomal 18S and 28S are indicated. Ethidium bromide staining of total RNA is also illustrated.

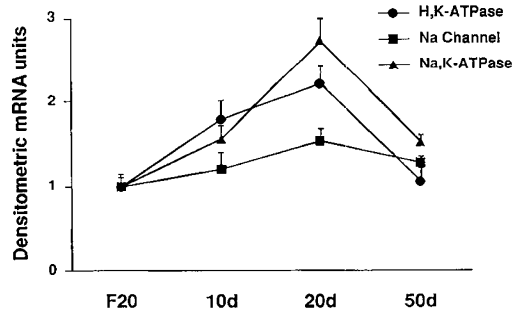

Figure 2. Ontogenic changes of colon β1 Na,K-ATPase, α H,K-ATPase, and α Na-channel mRNA in normal rats from fetal life (20-d gestational age, *F20*) to adult life (10, 20, and 50 d postnatally). An arbitrary value of 1 has been assigned to mRNA abundance in F20 rats.

were given a single injection of betamethasone or aldosterone at 10 d of life—*i.e.* before the physiologic surge of corticosteroids occurs. GC had different effects on the mRNA of the three ion transportrers in the colon (Fig. 3). The Na,K-ATPase mRNA increased rapidly after GC injection. The effect was greater after 6 h (≈4-fold increase over sham-injected animals) than after 24 h. GC also stimulated the H,K-ATPase mRNA. However, the effect was moderate and occurred only after 24 h (1.6-fold). GC did not alter the Na-channel mRNA at 6 or at 24 h. The injection of aldosterone caused less distinct effects (Fig. 3). Na,K-ATPase mRNA was not altered 6 h after the treatment. Twenty-four hours after injection, the expression of Na,K-ATPase mRNA was moderately but significantly increased in aldosterone-treated rats (1.9-fold). The H,K-ATPase mRNA showed a similar pattern; the mRNA was not alterd after 6 h but moderately increased after 24 h (1.8-fold). The Na-channel mRNA was moderately but significantly increased after both 6 and 24 h (≈1.7-fold).

To further exclude that GC might activate Na,K-ATPase by cross-binding to MC receptors, we studied the effects of corticosteroid treatment in tissue with a low level of MC receptor (renal cortex) and in aldosterone-independent tissue (stomach). After 6 h, GC but not aldosterone injection resulted in a significant increase in renal and gastric Na,K-ATPase mRNA (≈4-fold in both tissues) (Fig. 4). The effects of GC was greater after 6 h than after 24 h. The effects of GC were also studied in brain, a tissue rich in GC receptors and Na,K-ATPase (Fig. 5). Six hours after injection, GC had no effect on brain α1, α2, α3, and β1 Na,K-ATPase mRNA.

DISCUSSION

This study suggests that the GC stimulation of Na,K-ATPase mRNA may play a central role in the postnatal maturation of colon function. The function of the intestine matures most rapidly during the transition from ingestion of milk to solid food (26, 27), and corticosteroids play an important role in this process (1, 2). The activity of several enzymes involved in transepithelial ion transport undergoes a postnatal maturation regulated by circulating GC (5). Both direct and indirect mechanisms have been suggested to explain the effect of steroids on epithelial ion transporter maturation. It has been shown that GC induce a change in the phospholipid composition of the cell membrane and, therefore, may indirectly influence the transport of phosphate, glucose, and amino acids (7). Changes in the composition of phospholipids alter the membrane fluidity and therefore the activity of membrane-bound enzymes (28).

On the other hand, GC may directly affect enzymes that play a key role in transepithelial ion transport. In this study, we investigated the maturation of the basolateral Na,K-ATPase,

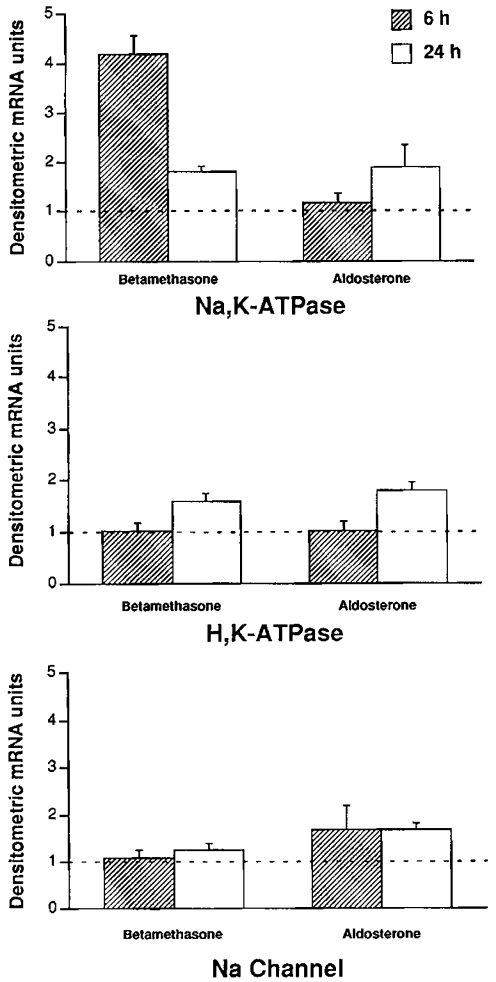

Figure 3. Effects of corticosteroid treatment on β1 Na,K-ATPase, α H,K-ATPase, and α Na-channel mRNA in colon from 10-d-old rats. Rats were given injections of betamethasone 6 or 24 h before the experiment. An arbitrary value of 1 has been assigned to mRNA abundance in control rats (*dotted line*).

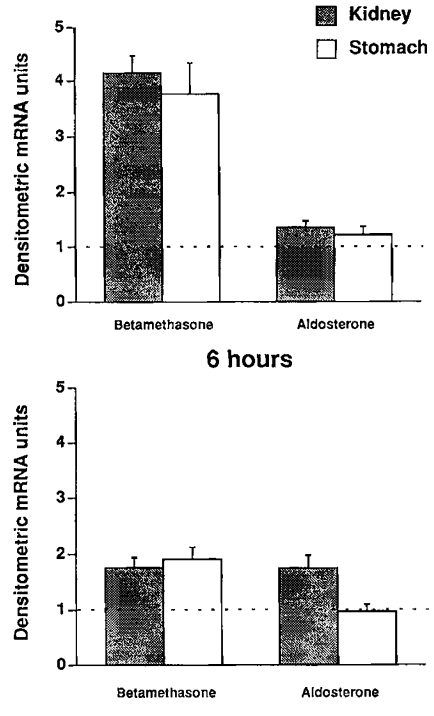

Figure 4. Effects of betamethasone and aldosterone on β1 Na,K-ATPase mRNA in kidney and stomach from 10-d-old rats. Rats were given injections of betamethasone or aldosterone 6 and 24 h before the experiment. An arbitrary value of 1 has been assigned to mRNA abundance in control rats (*dotted line*).

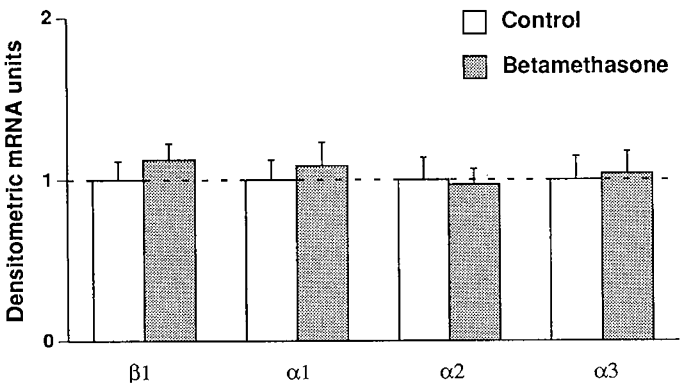

Figure 5. Effect of betamethasone treatment on α1, α2, α3, and β1 Na,K-ATPase mRNA in brain from 10-d-old rats. Rats were given injections of betamethasone 6 h before the experiment. An arbitrary value of 1 has been assigned to mRNA abundance in control rats.

the luminal H,K-ATPase, and the amiloride-sensitive Na-channel. We found that the mRNA of these ion transporter are temporarily up-regulated in the preweaning period. A similar up-regulation of Na,K-ATPase mRNA has been found in other tissues, corresponding to the period of their most rapid maturation (29). These results suggest that an increased synthesis of ion transporters occurs during weaning. In the rat, the circulating level of GC and MC increases in the preweaning period (3, 4), and it has been shown that the maturation of colon Na,K-ATPase activity can be accelerated by GC and MC (4, 11). To determine whether the up-regulation of the colon transporter mRNA is due to corticosteroids, betamethasone, and aldosterone were injected into 10-d-old rats—*i.e.* before the upsurge in circulating corticosteroids occurs. Inasmuch as the levels of endogenous hormones are very low during the first 2 postnatal wk, a maximal response to injected hormones can be expected in these infant rats. Nevertheless, only the Na,K-ATPase mRNA was rapidly and markedly stimulated by GC in the infant colon (4-fold over controls). GC induced no change in Na-channel mRNA and only moderate and late changes in H,K-ATPase mRNA. Aldosterone had only moderate and late effects on Na,K-ATPase and H,K-ATPase mRNA. The effect of aldosterone on Na-channel mRNA was also moderate. The finding that the strong GC effect on Na,K-ATPase occurs at an earlier stage than the moderate effect on other ion transporters may indicate that Na,K-ATPase is a primary target for GC in the preweaning period.

Na,K-ATPase is an integral membrane protein that is present in all mammalian cells. By actively pumping $3Na^+$ out of the cell and $2K^+$ into the cell, the Na,K-ATPase generates a Na^+ gradient that is used by the cell to run a variety of "secondary" Na^+-dependent transporters (30). Glucose, amino acids, and other essential ions, such as hydrogen and phosphates, are moved across the cell membrane by these carriers. Na,K-ATPase enzyme is therefore the key enzyme for normal cell homeostasis and for fluid movement across epithelial layers. Becaue the enzyme provides the driving force for a variety of ion transporters, it is highly likely that the limited availability of Na,K-ATPase activity is a rate-limiting step for cellular function in immature cells. The activity of Na,K-ATPase is low in most infant tissues. It has been suggested that hyperkalemia in preterm babies may be due, in part, to a shift of potassium from the intracellular space to the extracellular space with low Na,K-ATPase activity (31). The maturation of the concentrating capacity closely follows the maturation of renal Na,K-ATPase (5). The present study therefore suggests that GC induction of Na,K-ATPase mRNA may play an important role in the maturation of tissue function.

The mechanisms whereby corticosteroids regulate Na,K-ATPase mRNA are still debated. We have recently found that the transcription rate of Na,K-ATPase gene is increased by GC in the infant kidney and that infant GC receptors bind to the Na,K-ATPase promoter (6). The effect of GC is tissue-specific and occurs only in tissues that are rapidly maturing (9). GC do not seem to be necessary for Na,K-ATPase transcription in the adult renal cortex, because adrenalectomy does not affect the abundance of Na,K-ATPase mRNA in proximal tubules (13, 14), nor does GC treatment in control rats alter renal Na,K-ATPase mRNA (3). In the adult colon, it has been reported that GC but not aldosterone increase Na,K-ATPase mRNA. However, the effect of GC was almost completely abolished by cycloheximide, suggesting an indirect effect (32). Some data indicate that aldosterone may regulate Na,K-ATPase mRNA in the adult rat colon through a thyroxine-dependent pathway (33). *In situ* hybridization studies show that in adrenalectomized adult rats the Na,K-ATPase mRNA abundance is reduced in MC-sensitive segments of the nephron—*i.e.* the distal tubule and the collecting duct (13). The effect of aldosterone on the biosynthesis of Na,K-ATPase has been studied in cultured amphibian A6 renal cells. In these cells, there is evidence of a direct aldosterone-dependent enhancement of the Na,K-ATPase transcription rate (34). However, it has recently been shown that the aldosterone stimulation of Na^+ transport in A6 cells is mediated by GC receptors and not by MC receptors (35). The present study clearly indicates that GC have a more direct effect on infant colon Na,K-ATPase mRNA than aldosterone does, suggesting that, in infant colon cells, aldosterone does not directly regulate Na,K-ATPase gene transcription. The GC and MC receptors are very abundant and homogeneously expressed in colon surface and crypt cells (20, 36), and therefore compartimentalization of the receptors should not account for this differential response. In the present paper, aldosterone seems to activate the Na-channel mRNA. Amiloride-sensitive Na^+ channels mediate the first step of active Na^+ reabsorption in numerous epithelia, such as the distal nephron and the distal colon (37). Aldosterone is the major regulator of Na^+ reabsorption, acting via an increase in the apical Na^+ permeability (38). It has been suggested that the cytoplasmic Na^+ concentration serves as a mediator for the action of aldosterone because a correlation between intracellular Na^+ and the amount of Na,K-ATPase has been established (39). It therefore seems possible that aldosterone may contribute to maturation of the colon by increasing Na^+ entry and secondarily stimulating Na,K-ATPase mRNA.

Steroid hormones bind to cytoplasmic receptors which, after ligand binding, are transported into the nucleus where they regulate the transcription of target genes by binding to specific DNA sequences (40). It is a paradox that GC and aldosterone have very similar receptors, bind to both receptors with a very

similar affinity, recognize the same DNA binding element, and yet have different physiologic functions. The presence of 11β-HSD in aldosterone-sensitive tissues has been thought to mediate the specificity (19). The enzyme protects these tissues from the circulating levels of GC, because it rapidly metabolizes cortisol and corticosterone to inactive metabolites. Therefore only aldosterone can bind to its receptor and activate gene transcription. Besides the ubiquitously distribution of the receptors for MC and GC, the 11β-HSD is also expressed in the colon (20). The results of the present study seem to indicate that mechanisms besides 11β-HSD mediate the specificity of corticosteroid action. Similar doses of GC and MC were used, yet the specificity was preserved. The finding that, in tissue with low MC receptors (kidney) (41) or aldosterone-independent tissue (stomach) (42), the Na,K-ATPase mRNA increased rapidly after GC in a similar manner seems to indicate that the GC receptor and not the MC receptor mediates the response. However, the observation that, in a tissue such as the brain where both Na,K-ATPase and GC receptors are abundant and ubiquitous (43, 44), GC did not stimulate an increase in Na,K-ATPase mRNA seems to indicate that other factors are necessary in addition to the GC receptor. It has been recently demonstrated that the specificity of GC and MC hormones can be mediated by the interaction of the receptors with other nuclear proteins (45). The promoter of Na,K-ATPase appears to interact with both the GC (6) and the MC receptors (46). The Na,K-ATPase gene could therefore be an useful model for studying the molecular mechanisms preserving the specificity of GC and MC action.

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