Af17 Deficiency Increases Sodium Excretion and Decreases Blood Pressure

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ABSTRACT
The putative transcription factor AF17 upregulates the transcription of the epithelial sodium channel (ENaC) genes, but whether AF17 modulates sodium homeostasis and BP is unknown. Here, we generated Af17-deficient mice to determine whether deletion of Af17 leads to sodium wasting and low BP. Compared with wild-type mice, Af17-deficient mice had lower BP (11 mmHg), higher urine volume, and increased sodium excretion despite mildly increased plasma concentrations of aldosterone. Deletion of Af17 led to increased dimethylation of histone H3 K79 and reduced ENaC function. The attenuated function of ENaC resulted from decreased ENaC mRNA and protein expression, fewer active channels, lower open probability, and reduced effective activity. In contrast, inducing high levels of plasma aldosterone by a variety of methods completely compensated for Af17 deficiency with respect to sodium handling and BP. Taken together, these data identify Af17 as a potential locus for the maintenance of sodium and BP homeostasis and suggest that a particular histone modification is directly linked to these processes. Af17-mediated regulation of BP is largely, but not exclusively, the result of modulating ENaC, suggesting it has potential as a therapeutic target for the control of BP.


Abnormal regulation of BP leads to hypertension or hypotension. Hypertension is a major risk factor for cardiovascular diseases such as heart attack, congestive heart failure, stroke, peripheral vascular disease, and ESRD. Hypotension can deprive the brain and other vital organs of oxygen and nutrients, leading to shock, a life-threatening condition.

Enhanced Na⁺ reabsorption is long thought to increase blood volume and thus systemic arterial BP. Molecular characterization of monogenic forms of hypertension has confirmed this idea. These disorders are exemplified by mineralocorticoid excess, glucocorticoid-remedial aldosteronism, pseudohypoaldosteronism type II (PHAII), and Liddle’s syndrome. They result from inactivated 11β-HSD2,† fused 11-hydroxylase/aldosterone (aldo) synthase (AS),2 gain-of-function mutations in the mineralocorticoid receptor (MR),3 or in the with-no-lysine (K) kinases WNK1 and WNK44,5 or gain-of-function mutations in β and γ subunits of the epithelial sodium channel (ENaC),6,7 respectively. All of these mutations impinge on salt
absorptive mechanisms in the kidney. WNK1 and WNK4 have been shown to regulate ENaC.8,9

A number of inherited disorders characterized by salt wasting and hypotension are caused by loss-of-function mutations impairing salt homeostasis. Examples include Bartter’s and Gitelman’s syndromes, with defects in six genes encoding renal tubular transporters and ion channels (reviewed in ref.10), and autosomal recessive PHAI, with loss-of-function mutations in the three subunits of ENaC.11,12

However, the etiology of abnormal BP is not completely defined. First, BP is a complex trait determined by the interactions of multiple genetic and environmental factors. Epigenetic regulation through chromatin modifications should be important in BP control. To date, a direct link between a particular gene impinging histone modifications to BP has not been clearly established. Second, numerous mouse models lacking ENaC and their direct or indirect regulators such as AS,13 angiotensinogen (Agt),14 angiotensin-converting enzyme (ACE),15 MR,16 Sgk1,17 WNK1,18 WNK4,19 and Period20 have been reported. However, the role of these models in showing the epigenetic control of BP is still unclear. This is because, to our knowledge, the function of these genes in chromatin regulation remains unknown. Finally, ENaC is tightly regulated at multiple levels by aldo. Most studies concerning ENaC and aldo focus of determining if and how AF17 regulates BP. Here, we use

RESULTS

Af17−/− Mice Fed a Normal Na+ Diet Have Impaired Renal Water and Electrolyte Retention and Decreased BP

Generation of Af17−/− mice has been described.25 As shown in Supplementary Figure S1, analyses of 37 Af17−/− and 34 Af17+/+ mice on a normal Na+ diet showed subtle, but non-

significant differences in body weight, urinary osmolality, [Na+], [K+], [creatinine], [Na+]creatine, and [K+]/[creatinine] between the two groups. The mutant urine volume and excretion of Na+, K+, and creatinine were significantly increased by 15 to 38% versus control, respectively (Figure 1, A–D). These changes were associated with a significant decrease in plasma osmolality and [Na+] and a nonsignificant reduction in plasma [K+] and [creatinine] (Figure 1, E–H). Extensive BP measurements with 57 Af17−/+ mice and 67 mutants showed that the mutants display significantly lowered diastolic, systolic, and mean BP by 11 to 12 mmHg (Figure 1I), which was coupled with increased plasma [aldo] from 176 pg/ml in Af17−/+ mice to 385 pg/ml (Figure 1I). The increased [aldo] is possibly caused by reduced BP.26 Obviously, such [aldo] was not high enough to fully compensate for the loss of Af17 (see below). These results suggest that Af17−/− mutants show impaired renal function and decreased BP, a phenotype observed in several of other knockout mice under the same dietary conditions (see Discussion).

Active Channel Number, Open Probability, and Effective Activity of ENaC Were Lower in Af17−/− than Af17+/+ Mice on the Normal Na+ Diet

To determine whether the Na+ disturbance is a result of attenuated ENaC function, we performed cell-attached experiments to directly assess the basal ENaC activity on the apical plasma membrane of principal cells in split-open aldo-sensitive distal nephron. Figure 2A contains representative current traces. In parallel with dramatically decreased ENaC open probability (Po) and the number of active channels within a patch (N), Af17−/− mice on the normal Na+ diet have markedly reduced effective ENaC activity (fNPo), which is defined as NPo multiplied by the probability of observing patches with at least one active channel (f) (Figure 2, B–D). Although the decrease in N can be attributed to the impaired ENaC transcription (see below), the decrease of the Po points to an unexpected new role of Af17 in regulating ENaC activity.

Af17−/− Mice Fed the Normal Na+ Diet Display Impaired ENaC Expression and Increased H3 K79 Methylation in Whole Kidney Lysate

To investigate whether the decreased active channel number of ENaC results from impaired ENaC expression in kidney, we performed real-time RT-qPCR and Western blot analyses. Af17−/− mice display decreased expression of α, β, and γENaC to about 19, 67, and 76% of control at the mRNA level and to about 19, 42, and 37% of control at the protein level, respectively (Figure 3). As predicted,23 histone H3 K79 dimethylation (me2K79) was increased to 157% of control, and H3 K9 dimethylation (me2K9) remained constant with Af17 deletion (Figure 3).

Af17 Is Expressed in Aqp2-Expressing Renal Collecting Duct Principal Cells

To test whether Af17 is expressed in aldo-sensitive distal nephron, we analyzed the expression of β-geo reporter driven
by the Af17 promoter in the Af17−/− kidney,25 with Aqp2 as a marker of principal cells. X-gal staining was detected in Aqp2-expressing and many other cells (Figure 4). Therefore, Af17 is expressed in the principal cells, providing a molecular basis for directly regulating ENaC expression and activity.

Af17−/− Mice Fed a Normal Na+ Diet Display H3 K79 Hypermethylation at the αENaC Promoter

To show that Af17 regulates αENaC transcription through modulation of H3 K79 methylation in vivo, chromatin immunoprecipitation (ChIP) assay coupled with real-time qPCR was conducted with primers specific for amplification of the αENaC promoter regions (Figure 5A and refs. 22,27,28). ChIP with anti-me2K79 detected no substantial signals in Ra and R1 regions but robust signals from R0, R2, and R3 in wild-type (WT) mice (Figure 5B). Despite no difference in Ra, Af17−/− mice significantly enhanced me2K79 in all four other regions, with >170-fold in R1 versus WT control (Figure 5B). No obvious differences in total H3 or H3 me2K9 between the two groups over the entire αENaC 5′-flanking region were observed (Figure 5C). Furthermore, ChIP with normal rabbit IgG yielded barely detectable background signals. In brief, deletion of Af17 causes specific changes in H3 me2K79 associated with the αENaC promoter, but not a generalized effect on histone H3 in vivo in mouse kidney, indicating that Af17 upregulates αENaC mRNA expression by modulating H3 me2K79 at the αENaC promoter.

Aldo-Perfused Af17−/− Mice Display Similar Renal Physiology and BP to Af17+/+ Control

To directly test the hypothesis that high levels of aldosterone antagonizes the effect of Af17 deletion on H3 K79 methylation and thus ameliorates the renal dysfunction of Af17−/− mice, Af17+/+ and Af17−/− (n = 10 to 11 mice/genotype) animals fed the normal Na+ diet showed impaired renal function and decreased BP, despite mildly increased plasma aldosterone. Af17+/+ (n = 34) and Af17−/− (n = 37) mice fed the normal Na+ diet in metabolic cages were analyzed for the parameters as indicated. For BP measurement, n = 57 mice for Af17+/+ and n = 65 mice for Af17−/−. For all other parameters, n = 6 to 37 mice/group. For additional parameters, see Supplemental Figure S1. In all cases, *P < 0.05 versus Af17+/+.
were perfused with aldosterone at 10 μg/100 g per day. Urine collection and BP measurements were conducted on days 0, 4, and 7. For convenience, animals were treated one more day before tissue harvest.

Although Af17−/− mice had significantly higher urine volume, excretion of Na⁺, K⁺, and creatinine, and lower diastolic, systolic, and mean BP than control at day 0 (Figure 6 and Supplementary Figure S2), these parameters were no longer significantly different between the two groups after 4- or 7-day aldosterone perfusion (Figure 6). Other urinary values ([Na⁺], [K⁺], [creatinine], [Na⁺]/[creatinine], and [K⁺]/[creatinine]) were similar at all of these three time points (Supplementary Figure S2). The plasma [Na⁺], [K⁺], and [aldosterone] at day 8 showed no significant difference between the two groups except WT Po to various degrees ranging from 16 to about 600% (Figure 2, A–D). However, all of these parameters were no longer significantly different between the two groups. Consistently, no significant difference in protein expression of α, β, and γENaC and H3 m2K79 was observed between Af17−/− and Af17+/+ mice (Supplementary Figure S3).

**Figure 2.** Impairment and restoration of ENaC activity in Af17−/− mice. (A) Representative current traces from cell-attached patches monitoring ENaC activity under conditions as indicated. Dashed lines indicate the respective current state with a c denoting the closed state. (B–D) Summary graph of ENaC Po (B), active channels within a patch (C), and effective ENaC activity (D). In all cases, *P < 0.05 versus Af17+/+.

On a Low Na⁺ Diet, Af17−/− Mice Exhibited Similar Renal Physiology and BP to Af17+/+ Control in a Time-Dependent Manner

Low Na⁺ diet is known to increase [aldosterone]. To test whether low Na⁺ diet-induced aldosterone excess also rescues Af17 phenotype, we challenged Af17+/+ and Af17−/− (n = 6 to 20 mice/group) animals with a low Na⁺ diet (0.02% Na⁺). Urine was collected at 12 hours and then every 24 hours. After 72 hours, urinary Na⁺ was barely detectable. Therefore, additional urinary analyses beyond this time point were omitted. BP was measured for 7 days. At day 8, mice were terminated for further analyses. All mice survived the treatment, eliminating the possibility of biased data because of differences in the animal tolerance to the challenge.

Both groups had greatly decreased urine volume and excretion of Na⁺, K⁺, and creatinine to levels ranging from 17 to 69% of their pretreatment values at 12 hours. For these parameters, Af17−/− mice maintained significantly higher levels than control (Figure 7 and Supplementary Figure S4). However, such differences became nonsignificant as the treatment proceeded. No differences were also observed in urinary [Na⁺], [K⁺], [creatinine], [Na⁺]/[creatinine], and [K⁺]/[creatinine], except [Na⁺] at 12 hours and [creatinine] at 12 and 24 hours (Supplementary Figure S4). The diastolic, systolic, and mean BPs in the Af17−/− were normalized in all days examined (Figure 7 and Supplementary Figure S4). Similar to aldosterone perfusion, dietary salt re-
AF17 regulates mRNA and protein expression of ENaC. (A) Real-time RT-qPCR for expression of ENaC genes in kidney of mice fed the normal Na\(^+\) diet, with \(\beta\)-actin as internal control. Restriction for 8 days caused a pronounced elevation of ENaC activity for both genotypes compared with those on the normal Na\(^+\) diet (Figure 2). Importantly, we no longer observed an inhibitory effect of AF17 deletion on ENaC Po, the functional channel numbers, and the effective ENaC activity (fNPo) for AF17\(^{+/+}\) and AF17\(-/-\), respectively. The plasma [Na\(^+\)], [K\(^+\)], and [aldo] were statistically indistinguishable between the two genotypes (Figure 7 and Supplementary Figure S4). However, the [aldo] was 750 pg/ml in AF17\(-/-\) and 650 pg/ml in AF17\(^{+/+}\) mice (Figure 7E), which was significantly higher than that on the normal Na\(^+\) diet (Figure 1J).

**High Dietary Potassium Attenuated the Effect of AF17 Deletion on Renal Function and BP**

High KCl diets are also known to significantly increase plasma aldol in mice and rats,\(^{29}\) so we fed AF17\(^{+/+}\) and AF17\(-/-\) (\(n = 7\) to 26 mice/group) with a 6% K\(^+\) diet for 5 days. Although the urine volume and excretion of Na\(^+\), K\(^+\), and creatinine at day 0 on the normal Na\(^+\) diet was significantly higher in the mutant mice than the AF17\(^{+/+}\) control, these differences were blunted after 2 and 4 days of K\(^+\) loading, with only two exceptions (Figure 8 and Supplementary Figure S5). The urine volume and creatinine excretion were still significantly higher in AF17\(-/-\) than AF17\(^{+/+}\) mice at day 2 (Figure 8 and Supplementary Figure S5). Similar to the normal Na\(^+\) diet, the high K\(^+\) diet did not differentiate the two groups in all other urinary parameters ([Na\(^+\)], [K\(^+\)], [creatinine], [Na\(^+\)]/[creatinine], and [K\(^+\)]/[creatinine]; Supplementary Figure S5). However, it should be noted that, compared with the normal Na\(^+\) diet at day 0, in both genotypes, the treatment for 2 and 4 days led to a more than two-fold increase in urine volume, no significant changes in Na\(^+\) excretion, a more than four-fold increase in K\(^+\) excretion, and a two-fold increase in urinary [K\(^+\)] (Figure 8 and Supplementary Figure S5). In contrast, the urinary [Na\(^+\)] was significantly decreased to about 40% of the pretreatment in the two genotypes (Supplementary Figure S5). Consistently, the significant differences between the two genotypes in diastolic, systolic, and mean BP at day 0 were diminished at day 2 and day 4 (Figure 8 and Supplementary Figure S5). Plasma analyses unearthed comparable levels of [Na\(^+\)], [K\(^+\)], and [aldo] at day 5, with [aldo] being dramatically increased to 723 pg/ml in the AF17\(^{+/+}\) and 725 pg/ml in the AF17\(-/-\) mice (Figure 8).

**DISCUSSION**

Strong evidence suggests the presence of BP loci at 17p11–21 around marker D17S250 on human chromosome 17.\(^{24,31}\) Mutations in WNK4 within this interval are the causative factor for PHAII.\(^5\) AF17 also lies in this segment only 290 kb away from D17S250 on human chromosome 17.24,31 Mutations in WNK4 within this interval are the causative factor for PHAII.\(^5\) AF17 also lies in this segment only 290 kb away from D17S250 on human chromosome 17.24,31 Mutations in WNK4 within this interval are the causative factor for PHAII.\(^5\) AF17 also lies in this segment only 290 kb away from D17S250 on human chromosome 17.24,31 Mutations in WNK4 within this interval are the causative factor for PHAII.\(^5\) AF17 also lies in this segment only 290 kb away from D17S250 on human chromosome 17.24,31 Mutations in WNK4 within this interval are the causative factor for PHAII.\(^5\) AF17 also lies in this segment only 290 kb away from D17S250 on human chromosome 17.24,31...
from D17S250. The rat and mouse syntenic fragments on chromosomes 10 and 11, respectively, contain an AF17 homolog and are strongly linked to hypertension. It is worthy of note that the expression of AF17 in the distal nephron is consistent with its role in sodium transport.

**Figure 4.** Af17 is expressed in aldosterone-sensitive distal nephron. (A and B) Sections of Af17−/− kidney were stained with X-gal and an antibody against the principal cell marker Aqp2. Boxed regions in A and B were amplified in C and D, respectively. The arrowheads indicate cells apparently expressing Aqp2 and β-geo reporter driven by the Af17 promoter.

**Figure 5.** Af17 deletion causes H3 K79 hypermethylation at the αENaC promoter in kidney. (A) Diagram of the αENaC promoter. (B and C) ChIP assay showing increased H3me2K79 associated with R0-R3, but not with Ra subregion of the αENaC promoter. Kidney chromatin was prepared from four WT and four mutant mice, pooled into two groups according to genotype, and analyzed by ChIP with the antibodies indicated, and followed by real-time qPCR with primers amplifying the subregions of αENaC promoter as shown in A. Relative H3me2K79 abundance was set to 1 in R0 from WT kidneys and was calculated accordingly for all other samples. *P < 0.05 versus Af17+/−. n = 4 mice/group (B). Representative agarose gel analyses of the final qPCR products were shown to verify the specificity of qPCR for each sample (C).
to see whether mutations of Af17 occur and account for BP variation in the general population.

The observed renal phenotype in Af17−/− mice is not simply caused by a defect in feeding and drinking behavior, but at least partially results from decreased ENaC activity. Under basal conditions, Af17 may downregulate H3me2K79 and upregulate ENaC by multiple mechanisms, ranging from expression of mRNA, protein, and active channels to Po (Figure 9). Although the mechanism is elusive at this moment, identification of Af17 as an ENaC Po regulator is a surprise and points to a new aspect of Af17 function. Sgk1 can upregulate ENaC Po,34 possibly by phosphorylating inducible nitric oxide synthase (iNOS) to limiting NO production and its inhibitory effect on ENaC activity through SGK1 and Nedd4−2.8,9 Although the BP phenotype of Period−/− mice has not been reported, these mice fed the standard diet also had higher Na+ excretion and lower αENaC expression than WT controls.20

Another feature not limited to Af17−/− mice is that the changes in Na+ reabsorption are not accompanied by an inverse effect on K+, indicating that the impaired ENaC function cannot account for the complete panoply of the renal dysfunction. Indeed, such coupling was not observed in Sgk1−/−,17,37 AS−/−,13 αENaC(−/−)Tg,38 and ßENaCmm/m mice.39 Although Sgk1+/+ and Sgk1−/− mice did not display a significant difference in urinary Na+ excretion on a normal Na+ diet, their
Supplemental Figure S4. In all cases, * indicates a low Na\(^+\) in the urinary excretion of Na\(^+\), but not the low BP in mice.\(^{40,41}\)

A high intake of dietary NaCl can largely restore Na\(^+\) absorption, but not the low BP in mice.\(^{40}\)

Af17\(^{-/-}\) and Af17\(^{+/+}\) mice show similar renal physiology and BP in a time-dependent manner on the low Na\(^+\) diet. Af17\(^{+/+}\) (solid line or dark bar) and Af17\(^{-/-}\) (dotted line or gray bar) mice were fed the low Na\(^+\) diet (0.02% Na\(^+\)) in metabolic cages and analyzed for the parameters before (day 0) and after treatment at various time points as indicated. For BP measurement, \(n = 17\) to 21 mice/group. For all other parameters, \(n = 4\) to 14 for Af17\(^{-/-}\) mice and \(n = 6\) to 14 for Af17\(^{-/-}\) mice. For additional parameters, see Supplemental Figure S4. In all cases, \(*P < 0.05\) versus Af17\(^{+/+}\).

![Graphs showing renal physiology and BP in Af17\(^{-/-}\) and Af17\(^{+/+}\) mice](www.jasn.org)

**CONCISE METHODS**

**Reagents**

Antibodies against dimethyl histone H3 K79 and dimethylated histone H3 K9 were purchased from Millipore. Antibodies specific for \(\alpha\), \(\beta\), or \(\gamma\)ENaC were either purchased from SantaCruz or kindly provided by Dr. Ryoichi Teruyama, who purified these antibodies originally generated by Dr. Mark Knepper’s group. The chicken anti-Aqp2 antibody is a generous gift from Dr. James Wade (University of Maryland, College Park, MD).

**Serum, Plasma, and Urine Measurements**

The concentrations of Na\(^+\), K\(^+\), and creatinine in urine or serum were measured with an analyzer (Roche Cobas Integra 400 plus) in the Clinical Pathology Laboratory, Department of Veterinary Medicine and Surgery, University of Texas MD Anderson Cancer Center. This analyzer measures Na\(^+\) and K\(^+\) using ion selective potentiometry and creatinine by absorbance photometry. Plasma aldosterone was specifically measured using a \(^{125}\)I-Coat-A-Count RIA kit (Siemens, Los Angeles, CA). Because the aldosterone-specific antibody used in this kit was generated in rabbit, mouse...
samples can be directly measured, eliminating large variations and possible aldosterone loss created from additional extraction steps. Plasma and urine osmolarity was measured by vapor pressure (Wescor Vapro Vapor Pressure Osmometer 5520; Scimetrics, Houston, TX).

Metabolic Balance Studies
Two- to 4-month-old Af17−/− and Af17+/+ mice and their mutant littermates were used for the study. They were acclimated for 3 to 7 days in Tecniplast metabolic cages with free access to water and normal laboratory diet containing 0.4% Na+. After that, mice were continued on the same normal Na+ diet for at least 3 more days. During these days, systolic, diastolic, and mean BPs were measured daily with the CODA tail-cuff BP system (Kent Scientific, Torrington, CT) as reported.43 All mice were subjected to at least one cycle of measurement containing 20 to 30 individual readings for each parameter each day. Twenty-four-hour urine was collected daily unless otherwise indicated. For each mouse, data from multiple days were pooled to calculate the final average to represent that mouse and counted as 1 (n = 1). To minimize circadian effects, BP measurements and urine collection were conducted around 5:00 p.m. each day. In other experiments, mice examined as above with the normal Na+ diet were subsequently implanted subcutaneously with ALZET 1007D micro-osmotic pumps preloaded with aldosterone. The infusion was conducted for 8 days at 10 µg/100 g per day.29 Alternatively, the mice were challenged with the low Na+ diet (0.02% Na+) for 8 days or the high potassium diet (6% K+) for 5 days.

In all cases, urine volume and urinary electrolyte excretion were normalized to two parameters: (1) body weight at the start point of collection and (2) 24 hours based on actual hours between the two collection time points. The ethics of all animal experiments were reviewed and approved by the Animal Welfare Committee, The University of Texas Health Science Center at Houston.

Electrophysiology, Real-Time RT-qPCR, X-gal Staining, and IHC
These assays have been described previously22,25,44 and are detailed in Supplemental Information.

Figure 8. On the high K+ diet, Af17−/− and Af17+/+ mice had similar renal physiology and BP on the high K+ diet. Af17+/+ and Af17−/− mice were fed the high K+ diet (6% K+) for up to 5 days in metabolic cages and analyzed for the parameters before (day 0) and after treatment as indicated. n = 8 to 26 for Af17+/+ mice and n = 7 to 25 for Af17−/− mice. For additional parameters, see Supplemental Figure S5. In all cases, *P < 0.05 versus Af17+/+.
Figure 9. Model for impairment and restoration of Na\(^+\) balance and BP in Af17\(^{-/-}\) mice. Under basal conditions such as the normal Na\(^+\) diet, deletion of Af17 leads to significantly increased H3 K79 methylation, and subsequently impaired ENaC activity, disturbance of Na\(^+\) balance, and decreased BP. The mildly increased plasma [aldo] is not sufficient to antagonize the effect of Af17 loss on H3 K79 methylation and thus fails to rescue the Af17\(^{-/-}\) phenotype. Under aldo excess such as aldo perfusion or Low Na\(^+\) diet dramatically increased aldo levels efficiently disturbance of Na\(^+\) balance and a renal physiology and BP phenotype indistinguishable in the absence of Af17, leading to comparable levels of H3 K79 methyl-

AChiastic by which Af17 and aldo22 inhibit H3 K79 methylation are low Na\(^+\) between

all comparisons, with the statistical significance set at


BP

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