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Blood pressure regulation by the angiotensin type 1 receptor in the proximal tubule

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Abstract

Purpose of review—The renin–angiotensin system (RAS) plays a critical role in the pathogenesis of hypertension. Homeostatic actions of the RAS, such as increasing blood pressure (BP) and vasoconstriction, are mediated via type 1 (AT₁) receptors for angiotensin II. All components of the RAS are present in the renal proximal tubule, which reabsorbs the bulk of the glomerular filtrate, making this segment of the nephron a location of great interest for solute handling under RAS influence. This review highlights recent studies that illustrate the key role of renal proximal tubule AT₁ receptors in BP regulation.

Recent findings—A variety of investigative approaches have demonstrated that angiotensin II signaling via AT_{1a} receptors, specifically in the renal proximal tubule, is a major regulator of BP and sodium homeostasis. Reduction of proximal tubule AT_{1a} receptors led to lower BPs, whereas overexpression generally caused increased BPs.

Summary—AT_{1a} receptors in the proximal tubule are critical to the regulation of BP by the kidney and the RAS. The pattern of BP modulation is associated with alterations in sodium transporters. As a key site for sodium homeostasis, the renal proximal tubule could hence be a potential target in the treatment of hypertension.

Keywords

angiotensin type 1 receptor; hypertension; proximal tubule; renin–angiotensin system

INTRODUCTION

Hypertension affects more than 1 billion people worldwide. In the United States, one-third of adults suffer from hypertension, and only half of these patients have their blood pressure

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Conflicts of interest

There are no conflicts of interest.

(BP) under control. Ideal targets for BP control are complex [1], yet poorly controlled hypertension increases risk for cardiovascular disease, characterizing it as a condition with a high disease burden and huge healthcare costs [2–4].

A key pharmacologic target in the treatment of hypertension is blockade of the renin–angiotensin system (RAS) with use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs). Both drugs improve morbidity and mortality associated with several cardiovascular diseases [5–8] by effectively reducing effects of angiotensin II (AngII) [9,10]. As a major effector molecule of the RAS, angiotensin II acts via the type 1 (AT₁) receptor; activation of AT₁R in kidney is an integral part of the BP regulation [11]. Under normal circumstances, the goal of the RAS is to maintain effective circulating volume and tissue perfusion but in pathological conditions, RAS activation can be deleterious to cardiovascular function and BP regulation. Recent studies have characterized the essential and varied functions of AT₁ receptors in specific cell types. This review focuses on recent studies of BP regulation by AT₁ receptors in the renal proximal tubule and underscores their role in this region as key regulators of BP and sodium homeostasis (Fig. 1).

BLOOD PRESSURE REGULATION BY THE KIDNEY AND THE RENIN–ANGIOTENSIN SYSTEM

Decades ago, Guyton *et al.* [12] concluded that regulation of sodium excretion by the kidney was a key determinant of intraarterial pressure and suggested that when BP increases, activation of the pressure natriuresis mechanism facilitates excretion of sodium, which functions as a compensatory system to reduce effective circulating volume and thus lowers BP to normal levels [13]. They described the renal BP regulation as a pressure system of infinite gain, thus, defective handling of sodium by the kidney and consequent dysregulation of body fluid volumes provide a common pathway in pathogenesis of hypertension [13]. Furthermore, Guyton *et al.* [13] originally suggested a role for RAS in short-term BP regulation, yet the exact role of the RAS in arterial BP regulation was still evolving. Hall *et al.* [14] showed that infusion of AngII into the renal artery increased BP and that activation of the RAS shifted the pressure–natriuresis curve to the right, that is, where a higher systemic pressure is required to balance sodium output to input. Administering RAS inhibitors restored this relationship between systemic pressure and urinary sodium excretion back to the starting point [14–16]. The dependence of BP upon intact urinary sodium excretion and the pronounced effect of AngII provided insight into a role of the RAS in BP regulation by the kidney.

The kidney contains all components of the RAS, making it an important organ for BP regulation and sodium homeostasis. Renin is produced by the juxtaglomerular apparatus [17] and distal nephron [18,19], angiotensin-converting enzyme (ACE) and ACE2 are highly expressed in the proximal tubule [20] and angiotensin receptors (type 1 and type 2) are localized throughout the kidney [21,22]. Angiotensinogen (Agt) is largely produced in the liver; however, it can be synthesized in the proximal tubule and secreted into the tubular lumen [19,23,24]. Matsusaka *et al.* [25] recently described the relationship between

hepatically derived and renally derived Agt. Their data provide evidence that production is coordinated, and that liver-derived Agt is an important source of renal AngII generation. Furthermore, involvement of intrarenal Agt in mediating hypertension and modulating sodium balance was suggested [26]. Studies of the angiotensin receptors in BP regulation are described below. Our understanding of actions of the RAS has expanded with growing evidence for an intrarenal RAS which can cause hypertension independent of the systemic, circulating RAS [27]. As all RAS components are present in the kidney, it serves to reason that they perform vital functions within this excretory organ. Recent studies, largely in rodents, have shown that there is a renal feed-forward mechanism in AngII-dependent hypertension that stimulates intrarenal AngII generation, with suppression of the systemic RAS [28]. This feed-forward mechanism is caused by AT₁ receptor mediated AngII uptake and stimulation of additional renal tubular Agt. Increased renin formation by principal cells of the collecting ducts then convert Agt to AngI, creating even more AngII which exacerbates the sodium retention and hypertension [28]. A fundamental role for intrarenal ACE in the intrarenal RAS was shown in a recent study in which mice lacking ACE in the kidney were unable to produce AngII in the kidney resulting in a blunted hypertensive response to chronic AngII infusion [29]. Taken together, these studies demonstrate the considerable contribution of the intrarenal RAS to sodium handling and BP control.

BLOOD PRESSURE REGULATION BY THE ANGIOTENSIN 1A RECEPTOR IN THE KIDNEY

Throughout the body, AT₁ receptors mediate several effects contributing to BP and fluid homeostasis [30,31]. This is best exemplified by the phenotype of mice lacking the AT_{1a} receptor, the dominant AT₁ receptor isoform in rodents (AT_{1b} is the other isoform). AT_{1a} receptor-deficient mice demonstrate hypotension and profound sodium sensitivity [32], mimicking the pharmacologic effects of ARB use. In the vasculature, smooth muscle cell AT_{1a} receptors cause vasoconstriction [30]. The direct actions of AT_{1a} receptors contribute to pathogenesis of AngII-induced hypertension by reducing renal blood flow, thereby enhancing sodium retention [33]. When the AT₁ receptors are activated in the adrenal cortex, aldosterone is released and drives increased sodium reabsorption in the distal nephron [34]. In the central nervous system, AngII acts on both subtypes of the type 1 receptor, according to their relative cellular distribution, and AT_{1a} receptors exert a predominant effect on cardiovascular function and BP [35,36]. Like in the central nervous system, the relative contribution of AT_{1b} receptors to overall BP regulation is minimal compared with the AT_{1a} receptor. The other major category of the AngII receptors, AT₂ receptors, is generally thought to have the opposite effects of AT₁ receptors, inducing vasodilatation and natriuresis [37,38] and are described in a recent review by Steckelings *et al.* [39].

To demonstrate the central role of the kidney AT₁ receptor pools in BP regulation, Crowley *et al.* [11] utilized a kidney cross-transplantation strategy in AT_{1a} knock out and wild-type littermates. This experimental paradigm led to four experimental groups, each with only a single functioning transplanted kidney: kidney knock out, systemic knock out, total knock out, and wild type. Mice lacking AT_{1a} receptors only in the kidney (kidney knock out) presented with lower BP (~20 mmHg), without affecting aldosterone levels. Mice with

systemically absent AT_{1a} receptors (systemic knock out, renal AT_{1a} intact) also had similar BP reduction, suggesting AngII actions in extrarenal tissues are also important in determining BP set point. ‘Wild-type’ and ‘knock out’ surgical controls in this experiment had normal and reduced BPs, respectively.

In follow-up studies, with the same cross-transplant strategy, this same group [40] showed that when AT_{1a} receptors are absent from kidneys during AngII-mediated hypertension, the extrarenal AT_{1a} receptors cannot induce the same level of hypertension and cardiac hypertrophy. Importantly, during AngII infusion, sodium excretion was higher in mice lacking renal AT_{1a} receptors or having no AT_{1a} receptors at all (kidney knock out and total knock out groups) compared with mice with normal expression of AT_{1a} receptors in the kidney (wild type and systemic knock out). These studies support the notion that AT_{1a} receptors in the kidney are primary determinants of hypertension in AngII-dependent hypertension by promoting sodium retention and counteracting pressure natriuresis.

The kidney cross-transplant experiments suggest that AngII induces hypertension mainly through activating renal AT_{1a} receptors. However, there are a vast array of renal cell types and the specific cell lineage responsible (renal epithelia or vasculature) was unknown. We hypothesized that AngII signaling in each segment and/or cell type may exert distinct effects, based on the distinct physiological functions, hormonal control, and expression of RAS components. The proximal tubule was viewed as having high relevance, because two-third of the filtrate is reabsorbed here, it contains all the components of the RAS under local control [41–43], and it is a key locus of the pressure-natriuresis response [44]. Years ago it was shown that AngII in the proximal tubule stimulated fluid and sodium reabsorption by activating AT₁ receptors [45,46]. Schuster *et al.* [45] showed that AngII directly stimulated volume reabsorption in microperfused rabbit proximal convoluted tubules. Beyond effects in the proximal tubule, AT_{1a} receptors in the distal nephron might play a different role. In a recent study by our group, cell-specific deletion of the AT_{1a} receptor from intercalated cells in the collecting duct had no effect on baseline BPs, but exhibited an exaggerated hypertensive response to AngII infusion, indicating quite an opposite effect of these AT_{1a} receptors from those in the proximal tubule [47]. Additionally, knocking out AT_{1a} receptors from principal cells in the collecting duct, the locus of aldosterone stimulation of sodium reabsorption, had no effect on baseline BPs, however, it did attenuate the hypertensive response to AngII [48]. These studies highlight the increasing complexity of the actions of AngII along the nephron.

BLOOD PRESSURE REGULATION BY THE ANGIOTENSIN 1A RECEPTOR IN THE PROXIMAL TUBULE

Multiple investigators have sought to clarify the physiological significance of the proximal tubule RAS in sodium and fluid homeostasis, and together this body of work strongly supports a critical role for proximal tubule AT_{1a} receptors in a complex renal and systemic RAS. Some of the key studies will be reviewed here.

Thomson *et al.* [49] examined the complex relationship between dietary sodium intake and proximal tubular fluid reabsorption in rats using micropuncture. They discovered that high-

sodium diet suppressed systemic AngII, as expected, but unexpectedly increased tubular AngII; consistent with this finding, the effect of the ARB losartan on proximal tubule fluid reabsorption was unaffected by a high-salt diet. One conclusion from these studies is that the proximal tubule plays an important role in stabilizing end proximal flow rate rather than effecting natriuresis during high-salt diet. The role of the distal nephron was not directly addressed but is examined in subsequent studies using new mouse models (below).

In 2004, Le *et al.* [50] reported that in mice with transgenic expression of AT_{1a} receptors under control of the proximal tubule specific γ -glutamyl trans-peptidase promoter (Table 1). Transgenic AT_{1a} receptor expression was applied to mice of a wild-type background with intact receptors and to mice with targeted disruption of one or both of the AT₁ receptor genes (*Agtr1a* and *Agtr1b*) [51,57]. The transgene did not restore BP or abolish sodium sensitivity in *Agtr1a*^{-/-} *Agtr1b*^{-/-} mice but did attenuate the elevated renin expression, a characteristic of AT receptor-deficient mice, and significantly reduced cortical cyst formation in *Agtr1a*^{-/-} *Agtr1b*^{-/-} mice. In summary, this model did not demonstrate an effect of proximal tubule-specific AT_{1a} receptors on BP homeostasis, but did demonstrate that partial restoration of proximal tubule AT_{1a} receptors stabilizes renin expression and structural integrity of the renal cortex.

Gurley *et al.* [54] developed a mouse model specifically lacking AT_{1a} receptors in the renal proximal tubule with cre-loxp technology (Table 1). Mice bearing a conditional *Agtr1a* allele [55,52] were generated by the Coffman Laboratory (Duke University), inbred onto the 129/SvEv genetic background, and were crossed with 129/SvEv mice bearing a phosphoenolpyruvate carboxykinase-Cre recombinase transgene (Haase Laboratory, Vanderbilt University, Nashville, Tennessee, USA). Mice lacking AT_{1a} receptors in the renal proximal tubule knock out (PTKO) had significantly lower baseline BPs than controls (~10 mmHg). BPs in both wild-type and knock out groups responded similarly during high and low-sodium diets, indicating that proximal tubule AT_{1a} receptors do not regulate sodium sensitivity. However, at baseline, proximal tubule fluid resorption was significantly lower in PTKO mice compared with controls and protection against hypertension was evident during chronic infusion of AngII. Accompanying this reduced hypertensive response was increased natriuresis in the PTKOs along with reduced expression of key sodium transporter proteins: AngII caused a 30% reduction in the sodium hydrogen exchanger (NHE3) in the wild-type mice and more than 50% reduction in the PTKO group ($P < 0.05$). In addition to NHE3, the sodium phosphate cotransporter 2 (NaPi2) protein levels, unaffected in the wild-type mice, decreased by 36% in the PTKOs ($P = 0.005$). These transporter reductions during AngII are viewed as responses to the elevated BP associated with AngII hypertension and are amplified when there is reduction in signaling through AT_{1R}. Vasoconstrictive responses to acute infusion of AngII were nearly identical in both wild-type and PTKO groups indicating preserved vascular responses in PTKOs. Eliminating the proximal tubule AT_{1a}R prevented the AngII-mediated opposition of the proximal tubule pressure natriuresis response, thus, lower levels of BP are able to bring the mouse into sodium balance. These in-vivo findings highlight the critical role of proximal tubule AT_{1a} receptors and suggest that effectively targeting epithelial functions and sodium reabsorption of the proximal tubule of the kidney could be a useful and promising therapeutic strategy in hypertension.

Li *et al.* [56] utilized a different molecular approach to examine the effect of AngII on BP in the proximal tubule. Mice with either overexpression or deletion of constitutively active AT_{1a} receptors were generated [53]. This innovative model allowed examination of both gain and loss of function of the AT_{1R}. Androgen administration to female transgenic mice induced the transgene, causing, as expected, overexpression of AT_{1a} and raised BPs compared with the response in nontransgenic mice; Cre recombinase-mediated deletion of proximal tubule AT_{1a} receptors reduced BPs to a level similar to that reported by Gurley *et al.* [54]. A normal response to AngII was evident in the over-expression model and not examined in the deletion model. There were no apparent changes in expression of NHE3, NaPi2, or the epithelial sodium transporter in this proximal tubule-depletion model.

Work from Li and Zhuo sought to determine the role of proximal tubule intracellular AngII on BP [58[■]]. Wild-type AT_{1a} receptors were expressed in AT_{1a} deficient mice with or without an intracellular AngII fusion protein (AngII–ECFP). Transfer of only the receptors provoked higher SBP (12 mmHg) indicating a role for systemic AngII, whereas transfer of both receptors and AngII–ECFP protein led to higher proximal tubule AngII levels, even higher BP, and lower sodium excretion. This pattern suggests that, in proximal tubule, both AT_{1a} receptors and intracellular AngII impact BP regulation. The higher BP and signaling responses were prevented by losartan.

Regulation of the AT₁ receptor and potential mechanisms

Additional mechanisms by which AT_{1a} receptors are regulated include a role for the AT₁ receptor-associated proteins, angiotensin II receptor associated protein (ATRAP) and ARAP1, that determine the density of AT₁ receptors by interacting with the carboxylterminus. ATRAP selectively suppresses AngII-mediated pathological activation of the AT₁ receptor by inhibiting intracellular AngII signaling [59]. Overexpression of ATRAP can attenuate the effects of chronic AngII on the severity of hypertension by both an increase in natriuresis and suppression of the epithelial sodium transporter [60]. ARAP1 has the opposite effect as it increases AT₁ receptor expression by recycling it to the cell membrane, a response we predict would raise BP as over-expression (of AT_{1R}) causes salt-sensitivity and AngII-dependent hypertension [27]. These studies highlight how regulation of the receptor abundance and trafficking could control function.

Several studies, including those highlighted in this review, also examined sodium transport as a downstream function of AngII signaling in the renal proximal tubule. Reduced sodium retention during AT_{1A} receptor blockade or deletion provides potential mechanisms for BP lowering. Additionally, studies by Riquier-Brison *et al.* [61] illustrate how natriuretic stimuli (angiotensin-converting enzyme inhibitors inhibition of AngII, hypertension, high salt diet,) decrease proximal tubule sodium reabsorption. Modulation of abundance and cellular location of the NHE3 and NaPi2 in the renal proximal tubule are highly likely targets [61,62], as well as distribution of NHE3 and NaPi2 along the apical microvilli of the proximal tubule [61,63]. Finally, we should also consider additional effects of the fine control of sodium handling along the distal nephron and cortical collecting duct as additional agents for integrated sodium homeostasis along the nephron [44,49], for example, mediated by proximal production of AngII induced by proximal tubule AT_{1a} receptors.

CONCLUSION

Several experimental models have demonstrated a nonredundant role for AT_{1a} receptors in the epithelia of the renal proximal tubule to impact and regulate BP and fluid homeostasis. The regulation of systemic BP by the kidney is accomplished by modulation of sodium transporter proteins and sodium and fluid reabsorption. Targeting the proximal tubule may enhance natriuresis to balance elevated distal nephron sodium reabsorption and, thus reduce the BP at which sodium homeostasis can be maintained.

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KEY POINTS

- AngII acts via the type 1 angiotensin receptor to execute many of the actions of the RAS.
- The renal PT contains all of the components of the RAS and is a key site for the regulation of BP through modulation of tubular fluid reabsorption and regulated expression of sodium transporter proteins via proximal tubule AT_{1a} receptor-stimulated production of AngII.
- Reduced AngII signaling in the proximal tubule is associated with lower BP, protection from hypertension, and reduced sodium reabsorption by the nephron.
- Targeting the epithelial functions of the proximal tubule could be a useful therapeutic strategy in hypertension.

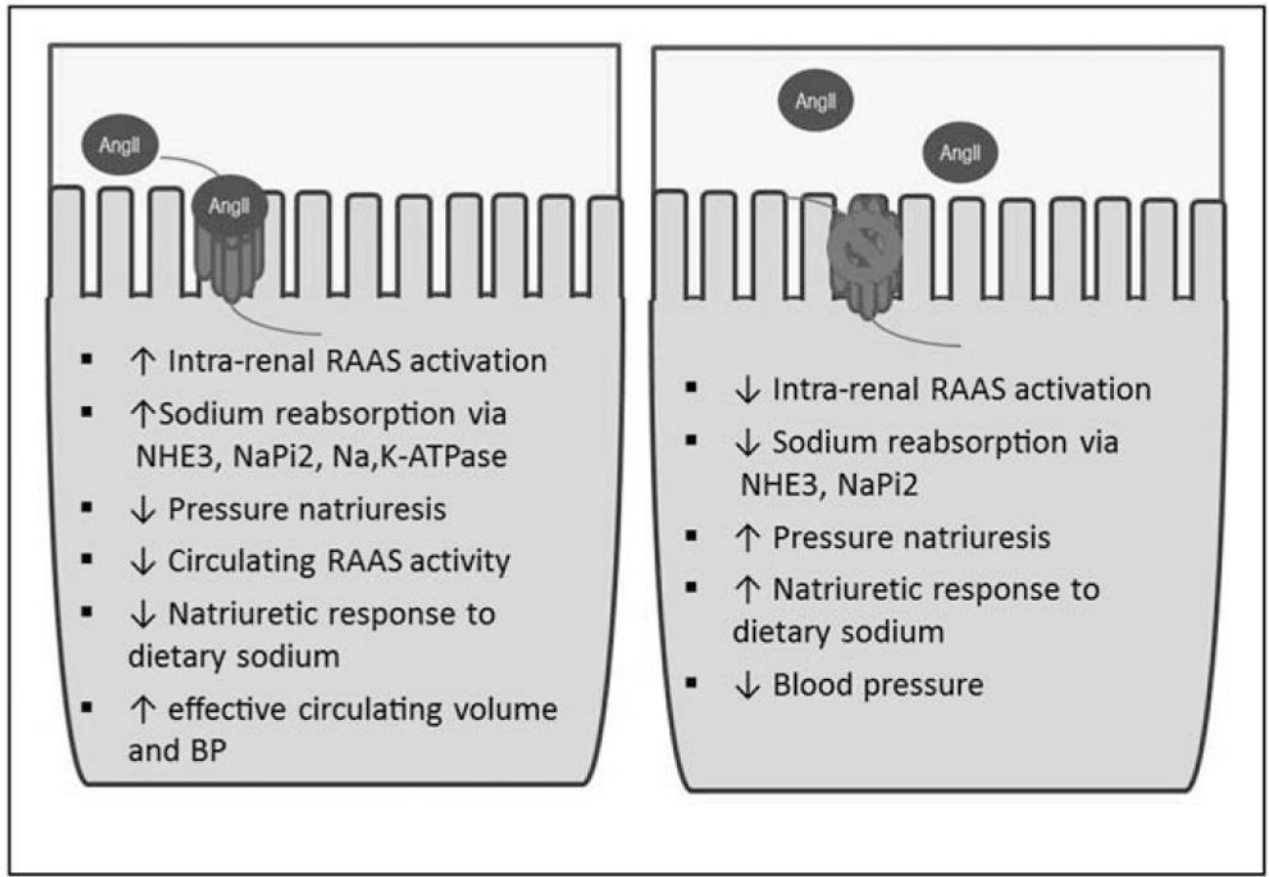


FIGURE 1.

Impact of AT_{1a} receptors in the proximal tubule. Summary of actions of AT_{1a} receptors in BP regulation by the proximal tubule. Left: The presence of AT_{1a} receptors leads to a set of responses culminating in increased BP. Right: The absence or blockade of AT_{1a} receptors results in the opposite phenotype. AngII, angiotensin II; BP, blood pressure; NaPi2, sodium phosphate cotransporter; NHE3, sodium-proton antiporter 3.

Table 1Summary of phenotypes: mouse models with targeted alterations in proximal tubule AT_{1a} receptors

Model	PT AT _{1a} R deletion (PTKO) ^a Gurley <i>et al.</i> 2011 [54]	PT AT _{1a} R overexpression (Tg) or deletion (KO) ^b Li <i>et al.</i> 2011 [56]	AT _{1a} R Tg expression in WT and AT ₁ R-deficient mice ^c Le <i>et al.</i> 2004 [50]	AT _{1a} R transfer ± ECFP/AngII in AT ₁ R deficient mice ^d Li <i>et al.</i> 2013 [58 ^{***}]
Baseline SBP	Radiotelemetry: PTKO <controls	Tailcuff: Tg >NT Radiotelemetry: Tg >NT >KO	Tailcuff: WT Tg ⁺ =WT Tg ⁻ KO Tg ⁺ =KO Tg ⁻	Tailcuff: AngII >AT _{1a} receptor alone >AT _{1a} KO
AngII hypertension	PTKO <controls (AngII 1000 ng/kg/min × 13d)	Tg >NT (AngII 800 ng/kg/min × 10d)	Not examined	Not examined
Sodium handling	Radiotelemetry SBP: PTKO =controls Ur Na excretion during AngII: PTKO >controls	Ur Na excretion: TG >NT =KO	Tailcuff SBP: KO Tg ⁻ =KO Tg ⁺	Not examined
Sodium transporters	Protein levels Baseline: PTKO had normal NHE3, NaPi2, NKCC, ENaC, NKA AngII infusion: PTKO had lower NHE3, NaPi2a but similar NKCC2.	mRNA levels Baseline: Tg had normal NHE3, NKCC2, NCC, NaPi2, ENaC, NKA KO had ↓NKCC2 and ↓NCC AngII infusion: NE	Not examined	Protein levels Baseline: AT _{1a} R-ECFP/AngII mice had higher NHE3 levels
Other	Male mice	Female and male mice	Male mice ↓Cortical cyst formation in Tg ⁺	Male mice

^aPhosphoenolpyruvate carboxykinase-Cre recombinase transgene crossed with a line with conditional *Agtr1a* allele.^bPT-specific, androgen-dependent, promoter construct (kidney androgen regulated protein 2).^cγ-glutamyl transpeptidase-driven transgene in WT mice and in mice with disruption of one or both of the murine AT₁ receptor genes (*Agtr 1a*, *Agtr 1b*)^dAT_{1a} receptor transfer with or without ECFP/AngII in AT_{1a}R deficient miceAngII, angiotensin II; ECFP/AngII, intracellular AngII fusion protein; KO, knock out; NaPi2, sodium phosphate cotransporter; NCC, sodium chloride cotransporter; NE, not examined; NHE3, sodium-proton antiporter 3; NKA, sodium potassium ATPase; NKCC2, Na-K-2Cl cotransporter; NT, nontransgenic controls; PT, proximal tubule; PTKO, proximal tubule knock out (AT_{1a}); Tg, transgenic; WT, wild type.

Adapted with permission [50–57].