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Transforming growth factor beta1 and aldosterone

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Abstract

Purpose of review—It is well established that blocking renin-angiotensin II-aldosterone system (RAAS) is effective for the treatment of cardiovascular and renal complications in hypertension and diabetes mellitus. Although the induction of transforming growth factor beta1 (TGFbeta1) by components of RAAS mediates the hypertrophic and fibrogenic changes in cardiovascular-renal complications, it is still controversial as to whether TGFbeta1 can be a target to prevent such complications. Here we review recent findings on the role of TGFbeta1 in fluid homeostasis, focusing on the relationship with aldosterone.

Recent findings—TGFbeta1 suppresses adrenal production of aldosterone and renal tubular sodium reabsorption. We have generated mice with TGFbeta1 mRNA expression graded in five steps from 10% to 300% normal, and found that blood pressure and plasma volume are negatively regulated by TGFbeta1. Notably, the 10 % hypomorph exhibits primary aldosteronism and sodium and water retention due to markedly impaired urinary excretion of water and electrolytes.

Summary—These results identify TGFbeta signaling as an important counterregulatory system against aldosterone. Understanding the molecular mechanisms for the suppressive effects of TGFbeta1 on adrenocortical and renal function may further our understanding of primary aldosteronism as well as assist in the development of novel therapeutic strategies for hypertension.

Keywords

Corticosteroids; Collecting ducts; Epithelial sodium channel; Na⁺/K⁺-ATPase

Introduction

Renin-angiotensin-aldosterone system (RAAS) functions as an endocrine and autocrine/paracrine system to play an integral role in cardiovascular and renal physiology by regulating blood pressure, fluid volume, and electrolyte balance[1,2] as well as the development of fibrosis and remodeling in heart and kidney tissue. Its excessive activation is associated with the induction and progression of hypertension, atherosclerosis, cardiac

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Conflicts of Interest

The authors have no conflicts of interest.

hypertrophy, heart failure, cardiovascular events including myocardial infarction and stroke, and chronic kidney disease. Therefore, blocking RAAS provides beneficial effects for the treatment of cardiovascular and renal disease. Experimental and clinical evidence indicates that pharmacological inhibition of RAAS with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, and mineralocorticoid receptor antagonists is effective in treating hypertension, heart failure, and chronic kidney diseases, including diabetic renal injury. The results show a reduction in morbidity and mortality by cardiovascular diseases worldwide. However, many patients are unable to benefit from these therapies to due contraindications from taking RAAS modulators such as allergic reactions or severely diminished renal function. Therefore, novel therapeutic agents that could bypass these contraindications would be clinically important.

Transforming growth factor beta1 (TGFbeta1), the prototypic member of the TGFbeta superfamily, is a potent pleiotropic cytokine with effects on a broad range of biological processes including apoptosis[3], cell proliferation[4], tumor suppression[4], senescence[5], differentiation[6], migration[7], immunity[8], osteogenesis[9], adipogenesis[10], and wound healing[11]. In addition, a growing number of convincing evidence indicates that both angiotensin II and aldosterone activate TGFbeta signaling, which mediates many of the complications of RAAS-related hypertension including progressive renal dysfunction[2] and cardiac hypertrophy[12]. As such, development of therapeutic strategies targeting TGFbeta signaling may be a way to effectively treat hypertension, heart failure, and chronic kidney disease in patients who cannot tolerate RAAS modulators.

However, whether TGFbeta1 plays a role in the control of blood pressure and/or of RAAS has not yet been clearly demonstrated. In humans, the 915C allele of a single nucleotide polymorphism in the TGFbeta1 gene (*TGFB1*), which leads to proline at residue 25 within the signal peptide sequence, has been associated in a population with a reduced risk of hypertension[13]. The 869C allele of a second polymorphism, which leads to proline at residue 10 within the signal peptide sequence, has been associated in a population with an increased risk of hypertension[14,15], but how the changes in the functional effects of TGFbeta1 affect blood pressure remains undetermined. Since they are polymorphisms in the coding region which presumably result in functional changes of the protein, it remains unclear whether they cause loss-of-function or gain-of-function.

Recently, a set of C57BL/6 mice having 5 different *Tgfb1* mRNA expression of ~10%, 50%, 200%, and 300% normal levels have been generated, and it has been found that blood pressure is negatively regulated by TGFbeta1[16]. It is noteworthy that the mice with 10% normal TGFbeta1 expression develop hypertension, primary aldosteronism and markedly impaired diuresis and natriuresis without developing renal excretory dysfunction.

These *in vivo* findings, together with previous *ex vivo* and *in vitro* findings that TGFbeta1 suppresses the adrenocortical synthesis of mineralocorticoids and their activation of renal tubular sodium reabsorption, suggest that TGFbeta1 plays a critical physiological role in controlling blood pressure and maintaining fluid homeostasis. In the present review, we will focus on the relationship between TGFbeta1 and aldosterone in RAAS in the pathophysiology of hypertension.

Activation of the TGFbeta signaling by aldosterone

Previous studies have demonstrated that most components of the renin-angiotensin-aldosterone system (RAAS) can up-regulate TGFbeta signaling independently of blood pressure. For example, renin via the (pro)renin receptor[17–19], angiotensin II via the AT1 receptor[20–22], and aldosterone via the mineralocorticoid receptor[23–25] all increase TGF-beta1 expression, and angiotensin II also stimulates expression of TGF-beta receptors leading to a further amplification of the effects by TGF-beta1[2].

TGFbeta1 mRNA expression was increased in cultured HL-1 cardiomyocytes receiving aldosterone[26], and in cultured renal fibroblast cells exposed to aldosterone[27]. In mice treated with a NOS inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) and angiotensin II, genetic deficiency of the mineralocorticoid receptor in myeloid cells significantly attenuated inflammation, fibrosis and the mRNA levels of TGFbeta1 in the heart and aorta[28]. Aldosterone also increased the secretion of TGFbeta1 in dendritic cells[29].

However, the mechanism(s) whereby aldosterone increases TGFbeta1 expression is not fully understood. Han et al. have reported that the stimulation of TGFbeta1 mRNA expression by aldosterone is significantly inhibited by an extracellular-signal regulated kinase 1/2 inhibitor PD98059, a c-Jun N-terminal kinase inhibitor SP600125, or an activator protein-1 inhibitor curcumin in rat mesangial cells[30]. On the other hand, Juknevičius et al. have shown that aldosterone provokes urinary excretion of TGF-beta1 without influencing renal TGFbeta1 transcripts, suggesting posttranscriptional enhancement of renal TGFbeta1[31].

Increased renal production of TGFbeta1 is associated with various diseases related to the activation of RAAS such as hypertension and diabetes mellitus. Additionally, urinary TGFbeta1 has been found to be associated with increasing interstitial fibrosis as well as proteinuria and mesangial expansion in patients with certain glomerulonephritides[32]. Urinary TGFbeta1 excretion reflects renal TGFbeta1 production. As such, urinary TGFbeta1 excretion is a useful marker to assess the efficacy of treatment with RAAS inhibitors in clinical settings. For example, losartan, an angiotensin II type 1 receptor blocker, and spironolactone, a mineralocorticoid receptor antagonist, were reported to reduce urinary TGFbeta1 excretion[33,34].

These data indicate that TGFbeta signaling is intimately associated with chronic kidney disease. Additionally, it is closely tied into the RAAS, which leads to cardiorenal complications. TGFbeta signaling is known to play an integral role in fibrosis, and these data demonstrate that TGFbeta1 plays a pivotal role in the development of cardiorenal complications due to its interplay with the RAAS.

TGFbeta1 negatively regulates aldosterone synthesis

In contrast to the stimulatory effect of aldosterone on the expression of TGFbeta1, TGFbeta1 has been shown to exert potent inhibitory effects on aldosterone synthesis in cultured adrenocortical cells[35–37].

Hotta et al. have shown that TGFbeta1 inhibits the formation of the delta 4-steroids including cortisol, corticosterone, aldosterone, and androstenedione in cultured bovine adrenocortical cells[35]. TGFbeta1 significantly decreased the activity of cholesterol side-chain cleavage, which is the first enzymatic step of steroidogenesis, and reduced the protein levels for cytochrome P450 side-chain cleavage (P450scc), adrenodoxin and adrenodoxin reductase in cultured sheep adrenal cells[38]. TGFbeta1 also decreases the transcript levels of steroidogenic acute regulatory protein (StAR), which assists transport of cholesterol from the outer mitochondrial membrane to the inner membrane where P450scc resides, in bovine adrenocortical cells[39]. Le Roy et al. reported that TGFbeta1 reduced adrenocorticotropin-induced cortisol production and decreased the transcript levels of steroid 17-alpha-monooxygenase (Cyp17a1), hydroxyl-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (Hsd3b1), and StAR in the bovine adrenocortical cells[40]. These results demonstrate that TGFbeta1 suppresses multiple enzymatic steps of steroidogenesis that are upstream of the aldosterone synthesis in the adrenal cortex.

Recently, Liakos et al. have reported that TGFbeta1 reduced forskolin-induced production of cortisol and 11-hydroxyandrostenedione by 85% and angiotensin II-induced aldosterone production by 80%. TGFbeta1 strongly inhibits forskolin-induced steroid 11beta-hydroxylase (Cyp11b1) activity and *Cyp11b1* mRNA levels, as well as angiotensin II-induced aldosterone synthase (Cyp11b2) activity and *Cyp11b2* mRNA levels in the human adrenocortical tumor cell line NCI-H295R[36]. The promoter activity of *Cyp11b1* studied with the luciferase assay was suppressed by TGFbeta1, but the responsible site was different from Smads-binding sequences, suggesting that the repression of promoter activity of *Cyp11b1* by TGFbeta1 is indirect[36]. Indeed, TGFbeta1 inhibits transcription of steroidogenic factor 1[41], which plays an important role in the development of adrenal and gonadal steroidogenic cells[42] and enhances transcription of steroidogenic enzymes including Cyp11a1, steroid 21-hydroxylase (Cyp21a1), Cyp11b1 and Cyp11b2[43] by binding a shared promoter element[44].

These findings in cultured adrenocortical cells have been reproduced in mice having TGFbeta1 mRNA expression graded in five steps from 10% normal to 300% normal[3]. Higher than normal levels of TGFbeta1 lead to reduced plasma aldosterone levels despite the plasma volume being decreased, due to reduced expression of *Cyp11b1*, *Cyp11b2*, *Hsd3b1*, and *Star*, whereas lower than normal levels of TGFbeta1 lead to increased plasma aldosterone levels despite the plasma volume being expanded, due to increased expression of these genes.

In addition to the alteration in plasma aldosterone levels, corticosterone levels were also significantly higher than normal in TGFbeta1 hypomorphic mice, whereas in hypermorphic mice plasma aldosterone levels were significantly lower than normal[16]. The plasma active renin and angiotensin II levels were lower than normal in hypomorphic mice and higher than normal in hypermorphic mice. Additionally, the hypomorphic mice had a markedly higher systolic blood pressure and less natriuresis than WT mice, which was normalized by administration of spironolactone, a mineralocorticoid receptor antagonist, or amiloride, an epithelial sodium channel (ENaC) blocker. This suggests that TGFbeta signaling plays an

important role in regulating fluid homeostasis at least partly via suppression of corticosteroid synthesis and ENaC activity[16].

Microscopic examination of the adrenals showed no structural abnormalities, such as nodular hyperplasia, in any of the mice, but the adrenal weight normalized to body weight was doubled in the hypomorphic mice. Therefore, the hypomorphic mice can reasonably be classified as having secondary hypertension due to primary aldosteronism comparable to that seen in humans with idiopathic bilateral adrenal hyperplasia.

TGFbeta1 regulates adrenal development and can induce apoptosis in human adrenocortical H295R cells[45]. Interestingly, TGFbeta signaling pathway may be associated with development of adrenocortical tumors in human[46]. The expression of SMAD3 that is one of the components of TGFbeta signaling was low in malignant adrenocortical carcinomas.

Although molecular targets of TGFbeta1 in adrenocortical cells may differ between species and further investigation is needed, evidence has shown that TGFbeta1 regulates adrenal development and inhibits steroidogenesis in adrenal cortex. Furthermore, recent reports suggest interactions between TGFbeta signaling and adrenocortical tumorigenesis.

TGFbeta1 and aldosterone differentially regulate renal sodium reabsorption

In addition to the suppressive effect of TGFbeta1 on adrenocortical function, TGFbeta1 also directly inhibits ENaC activity stimulated by aldosterone in the kidney. Aldosterone exerts its pressor effect via expanding extracellular fluid volume through stimulating the activity of ENaC, which is located in the “aldosterone-sensitive distal nephron” including late distal convoluted tubules 2, connecting tubules, and collecting ducts in the kidney[47,48]. In the collecting duct, principal cells contain the machinery to respond to aldosterone and to absorb Na^+ . Three molecular complexes are necessary for this aldosterone response: mineralocorticoid receptors, ENaC, and Na^+/K^+ -ATPase. All of these 3 components are present along the aldosterone-sensitive distal nephron. The activity of ENaC is positively regulated by plasma aldosterone levels and correlates with dietary sodium intake. The effect of aldosterone on Na^+ transport appears to be greater on ENaC than on the Na^+/K^+ -ATPase. Interestingly, the effect of aldosterone on the ENaC activity is rapid (< 2 min) and mediated by plasma membrane steroid receptors, which is not inhibited by cycloheximide, an inhibitor of protein synthesis, suggesting the presence of non-genomic mechanisms[49,50] (Figure).

Although regulation of ENaC by aldosterone is extremely important to Na^+ homeostasis and blood pressure control, variety of other hormones including TGFbeta1 regulate ENaC activity either in parallel with aldosterone or independently[48]. Husted et al. reported that TGFbeta1 inhibits the increase of Na^+ entry across the apical membrane in the rat inner medullary collecting duct cells due to mineralocorticoid activity [50,51]. Peters et al. reported that TGFbeta1 promotes internalization of betaENaC and destabilizes the whole ENaC complex in the epithelial cell surface[52]. We also reported that the open probability, functional expression and total activity of ENaC in the collecting duct cell microdissected from TGFbeta1 hypomorphic mice are significantly greater than those from WT mice[16]. In addition, collecting duct specific overexpression of TGFbeta1 partly restores natriuresis in

mice with low *Tgfb1* expression (unpublished observation). These findings indicate that TGFbeta1 prevents Na⁺ absorption via ENaC even when the channel is fully activated by aldosterone.

Recently, protease nexin-1 (PN-1) was identified as an endogeneous inhibitor for prostatic which has been shown to increase ENaC activity[53]. PN-1 belongs to the serpin (serine protease inhibitor) family and is known to be an endogeneous inhibitor for alpha-thrombin, plasmin, and plasminogen activators. PN-1 inhibited prostatic-induced ENaC activation in *Xenopus* oocytes, and knock down of PN-1 gene expression increased baseline sodium current in M-1 cells; a mouse cortical collecting duct cell line[54]. Moreover, prostatic and PN-1 appear to be reciprocally regulated by aldosterone (increased prostatic and decreased PN-1) and TGFbeta1 (decreased prostatic and increased PN-1) [54]. TGFbeta1-induced PN-1 overexpression is associated with an increase in Smad2 binding to the promoter of PN-1 in human vascular smooth muscle cells[55]. In another study, TGFbeta1 inhibited the transepithelial electrical current, which is mainly amiloride sensitive and relies on the alphaENaC expression, in mpkCCDcl4 cells; a mouse cortical collecting duct cell line[56]. Removal of the N-terminus of Smad4 not only abolished the inhibitory effects of Smad4 on sodium current but also prevented the inhibition of sodium current by TGFbeta1. It suggests that TGFbeta1 decreases the ENaC functionality via a Smad4-dependent pathway.

It has been demonstrated that TGFbeta1 and aldosterone differentially regulate renal sodium reabsorption in proximal tubules as well. Human, rat, and mouse proximal tubular cells express mineralocorticoid receptors and Na⁺/K⁺-ATPase alpha1 subunits[57]. In human kidney proximal tubule HKC11 cells, aldosterone increases Na⁺/K⁺-ATPase-mediated ⁸⁶Rb uptake[57]. In primary human proximal tubule epithelial cells, aldosterone stimulates Na⁺/H⁺ exchange activity with an increase in cell surface expression of Na⁺/H⁺ exchanger 3[58]. In contrast, TGFbeta1 induces dose dependent decrease in the activity of Na⁺/K⁺-ATPase[59] and the expression of alpha and beta subunits of Na⁺/K⁺-ATPase in rabbit primary proximal tubule cells[60].

The precise molecular mechanism by which TGFbeta1 reduces the renal actions of aldosterone is still poorly understood. However, it's probably multifactorial and likely involves differential metabolic effects of aldosterone and TGFbeta1 on mitochondrial oxidative phosphorylation[59].

Conclusion

It is well established that blocking RAAS provides beneficial effects for the treatment of cardiovascular and renal complications in hypertension and diabetes. Although the induction of TGFbeta1 by angiotensin II and aldosterone mediates the fibrogenic changes in these complications, TGFbeta1 inhibition alone is unlikely to be a successful target to inhibit the fibrogenic complications in renal and cardiac disease due to its role in salt retention and hypertension. More research is needed to further tease out the molecular mechanisms between TGFbeta1 and adrenocortical function, and this might lead to enhanced understanding about the pathophysiology of primary aldosteronism and allow for new therapeutic strategies for patients with hypertension.

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Key points

- Recent evidence demonstrates that TGFbeta1 has an inhibitory role in adrenal production of corticosteroids including aldosterone.
- TGFbeta1 antagonizes renal tubular reabsorption of sodium by aldosterone via inhibiting the activity of ENaC and Na⁺/K⁺-ATPase.
- Phenotype of the TGFbeta1 hypomorphic mice indicates that TGFbeta1 is physiologically important for normal natriuresis and protects against the development of primary aldosteronism.

Figure.

A diagram depicting the effects of transforming growth factor-beta1 (TGF-1) on the adrenal production of corticosteroids and on the natriuretic function in collecting duct principal cells. PN-1, protease nexin-1; MR, mineralocorticoid receptor; ENaC, epithelial sodium channel.