Chapter

Connexin-Based Channels and RhoA/ROCK Pathway in Angiotensin II-Induced Kidney Damage

Gonzalo I. Gómez, Victoria Velarde and Juan C. Sáez

Abstract

The incidence of chronic kidney diseases is increasing worldwide, and there is no efficient therapy to reduce this phenomenon. The main therapies currently available focus on the control of blood pressure and the optimization of the blockade of the renin-angiotensin system (RAS). In addition, it is known that in several models of kidney damage, the amounts of connexins are altered. On the other hand, fasudil, a selective ROCK blocker, has shown renoprotective effects. The beneficial effects of blocking the RhoA/ROCK pathway in renal function may be related to its action of reducing macrophage infiltration, inflammation, and oxidative stress (OS), its expression of extracellular matrix genes and proteinuria, or to its effects on connexin abundance. Even though a correlation has been found between renal damage, caused by an increase in the RAS activity, connexins, and the RhoA/ROCK signaling pathway, it has not yet been possible to clearly determine its functional significance. Moreover, it has not been possible to identify the preponderance of this signaling pathway in the development of chronic kidney diseases. Here, we describe the advances in this subject.

Keywords: hypertensive nephropathy, oxidative stress, fibrosis, inflammation, Cx43, fasudil

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem whose prevalence is persistently increasing. It is estimated that about 10% of adults in developed countries suffer some degree of kidney damage [1]. Patients with CKD usually develop a progressive kidney damage characterized by glomerular sclerosis and/or tubulointerstitial fibrosis, which eventually leads to end-stage renal disease, the last stage of this condition [2]. The detrimental effect of this process includes the progressive reduction of glomerular filtration rate (GFR) given by an increase in damaged nephrons, which eventually leads to organ failure [3]. CKD has different etiologies, including diabetic nephropathy, hypertensive nephrosclerosis, and glomerulonephritis. However, regardless of the initial cause, the morphological characteristics, such as tubular necrosis and glomerular sclerosis, are similar [4, 5]. This condition induces the partial destruction of nephrons and the progressive failure of renal function [4, 5].

2. Hypertensive nephropathy

Hypertension is the second cause of end-stage renal disease (ESRD) [6, 7]. Hypertensive nephropathy starts in the glomeruli due to an increase in intraglomerular pressure. These initial events activate and damage mesangial cells, epithelial cells, and podocytes within the glomerulus. In turn, these cells produce vasoactive and pro-inflammatory mediators, which increase cell damage and favor fibrosis, reducing renal blood flow and glomerular filtration rate [8]. The renal corpuscle, formed by Bowman's capsule and glomerulus, is the fundamental structure in the filtration process. The glomerulus is formed mainly by blood capillaries, podocytes, and the mesangium. The mesangium plays a key role in the structural and functional stability of the glomerulus, allowing it to successfully fulfill its filtering function [9]. The mesangial cells (MCs) constitute 30–40% of the cellular population of the glomerulus, and their function is to support the glomerulus and participate in the maintenance of the opening of its capillaries, regulation of the glomerular filtration rate, and synthesis and degradation of extracellular matrix proteins [9].

The renin-angiotensin system (RAS) is the prototype of a classic systemic endocrine network whose actions in the kidney and adrenal gland include regulation of blood pressure, intravascular volume, and electrolyte balance [10]. The RAS plays an integral role in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. This pathway is initiated by the regulated secretion of renin from the kidney, the rate-limiting processing enzyme [11]. RAS begins with the biosynthesis of renin by the juxtaglomerular (JG) cells. Active renin secretion is regulated mainly by (1) the renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pressure; (2) changes in delivery of NaCl (sensed as changes in Cl concentration) to the macula densa cells of the distal tubule, which lie close to the JG cells and form the JG apparatus; (3) sympathetic nerve stimulation via beta-1 adrenergic receptors; and (4) negative feedback by a direct action of angiotensin II (AngII) on the JG cells [11]. Renin secretion is stimulated by a fall in perfusion pressure or in NaCl delivery and by an increase in sympathetic activity [11, 12]. Angiotensinogen is secreted constitutively by the liver and reacts with renin, ending transformed into the inactive decapeptide angiotensin I (AngI) [11]. AngI is hydrolyzed by angiotensin-converting enzyme (ACE), which removes the C-terminal dipeptide to form AngII, a potent vasoconstrictor [11, 12]. AngII is the primary effector of a variety of RAS-induced physiological and pathophysiological actions [11]. AngII, via the AT1 receptor, stimulates the production of aldosterone by the zona glomerulosa in the adrenal gland [11]. Aldosterone is a major regulator of sodium and potassium ion (Na^+ and K^+, respectively) balance and thus plays a major role in regulating extracellular volume [11, 12]. It enhances the reabsorption of Na^+ and water in the distal tubules and collecting ducts (as well as in the colon and salivary and sweat glands) and thereby promotes K^+ (and hydrogen ion) excretion [11, 12].

The vasoconstriction and the increase in blood pressure mediated by AngII represent only part of the pleiotropic actions of this peptide. AngII stimulates aldosterone secretion, cell infiltration, proliferation and migration, thrombosis, superoxide ion production, and other factors involved in nephropathy [8]. When MCs are stimulated with AngII, the synthesis of extracellular matrix is increased and accumulates in the extracellular space [13]. Activated MCs produce more reactive oxygen species (ROS) [14, 15] and synthesize and release more pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) and chemokines, such as the macrophage chemoattractant protein (MCP-1) and transforming growth factor β (TGF-β) [13, 15–17]. In addition, high concentrations of AngII maintained for long periods of time in mice induce an inflammatory response characterized by the expression of pro-inflammatory cytokines such as IL-1β and

TNF-α [18], infiltration of macrophages (positive ED-1) [19], tubular overexpression of osteopontin (OPN) [19], and the expression of other pro-inflammatory cytokines, chemokines, and adhesion molecules [8, 20]. AngII also increases the expression of nicotinamide adenine dinucleotide phosphate oxidase (NOX), one of the main enzymes in the generation of ROS, contributing to the onset of oxidative stress (OS), independent of the action of pro-inflammatory cytokines [21, 22]. The sum of these alterations leads to an activation of the transcription factor nuclear factor-NF-κB, which increases the synthesis and release of extracellular matrix protein, such as type IV collagen, laminin, and fibronectin [13, 16], inducing the formation of mesangial nodules with lesions that extend to the interstitial areas, hindering the adequate function of the glomerulus [9, 13, 15, 16]. In summary, intrarenal RAS is an important factor in the pathophysiology of hypertension and hypertensive nephropathy [23].

2.1 Angiotensin II and RhoA/ROCK pathway in renal damage

Two receptors, AngII II receptor type 1 (AT1R) and type 2 (AT2R), both coupled to different G proteins, mediate the actions of AngII. The AT1 receptor activates small G proteins, including Ras, Rac1, RhoA, and the Rho kinase system (ROCK) [24], while the AT2 receptor inhibits RhoA [25]. The Rho family of small GTPases (Rho GTPase) is constituted by monomeric G proteins of 20–40 kDa considered as molecular switches, which cycle between two conformational states, an active state bound to GTP and an inactive state bound to GDP. In mammals, this family is composed of 20 members, of which the most studied are Rac1, Cdc42, and RhoA. The latter being the most studied member of this family [26]. ROCK, an effector downstream of RhoA, is a serine–threonine kinase of around 160 kDa, which in mammals is present in two isoforms, ROCK1 and ROCK2 [27, 28]. ROCK is composed of an amino terminal kinase domain, followed by a super-coiled helix region, which contains the Rho-GTP binding site and a carboxy-terminus, which contains an internal domain rich in cysteine residues [27]. ROCK1 and ROCK2 are highly homologous, sharing an identity of approximately 65% in their amino acid sequences and approximately 92% homology in their amino terminal kinase domain [27, 28].

The RhoA/ROCK pathway has received considerable attention because of its implication in a wide variety of pathophysiological states present in cardiovascular diseases, pulmonary hypertension, Alzheimer's disease, and glaucoma [27]. The RhoA/ROCK pathway plays an important role in renal pathophysiology, where RhoA/ROCK participates in the regulation of pro-inflammatory cytokines (e.g., TNF-α and IL-1β) [24, 29] and increases the amount of TGF-β and NFκB [27]. On the other hand, great interest has been generated in the use of fasudil, a selective ROCK inhibitor, as regulator in a wide variety of animal models of kidney damage, including unilateral ureteral obstruction, hypertensive glomerulosclerosis, acute renal failure induced by ischemia–reperfusion or by contrast-induced acute kidney injury, and renal failure induced by AngII [27, 30]. Fasudil, a ROCK inhibitor, prevents kidney damage by reducing the expression of extracellular matrix genes, OS, pro-inflammatory cytokines, and macrophage infiltration and inhibiting the cascade of events that leads to these effects. Thus, both RhoA and ROCK could be considered as therapeutic targets to prevent hypertension and kidney damage [24, 27, 29, 31].

2.2 Connexins in hypertensive nephropathy

Gap junctions (GJs) are conglomerates of intercellular channels that result from docking of two HCs or connexins, each one contributed by one of the cells in contact and formed by six connexins (Cxs). GJs allow direct ion exchange (explaining the

electrical coupling), small metabolites (e.g., nicotinamide adenine dinucleotide: NAD^+, glucose, lactate, and glutamate), and second messengers (e.g., cyclic adenosine monophosphate [cAMP] and inositol trisphosphate [IP_3]) between adjacent cells (explaining metabolic coupling) [32, 33]. There are 21 isoforms of Cxs in humans and 20 in rodents. Each Cx is named according to its approximate molecular weight, and its transmembrane structure identifies four transmembrane domains connected by two extracellular loops and one intracellular loop, which implies that the C and N terminals are in the intracellular space [34]. HCs are fundamental pathways for the exchange of ions and small molecules between the intra- and extracellular compartments. These structures can be opened under physiological and pathophysiological conditions, allowing the release of paracrine and autocrine signaling molecules to the extracellular medium (e.g., adenosine triphosphate [ATP], glutamate, NAD^+, and prostaglandin E2 [PGE2]) [35]. Each type of channel formed by the Cxs has unique gate properties, in addition to a characteristic conductance and permeability features [36–38].

The kidney regulates blood pressure mainly through excretion of Na^+ and water, depending on the hormonal action of the RAS and other hormone systems with renal action [39]. However, in order to fulfill this function, the kidney requires the coordinated action of different cell types, including vascular and tubular cells [39]. This intrarenal coordination has not yet been well established, but, since connexins (Cxs) are present in the kidney, the existence of direct communication between the different cell types of the nephron has been proposed to occur through gap junctions (GJs) and/or hemichannels (HCs) [39]. In mammalian kidneys, nine types of Cxs have been detected (Cx26, Cx30.3, Cx31, Cx32, Cx37, Cx40, Cx43, Cx45, and Cx46), which are located in the vasculature or in different segments of the renal tubule, where most likely fulfill different functions [39].

In cortical astrocytes, it has been demonstrated that two pro-inflammatory cytokines, TNF-α and IL-1β, reduce intercellular communication mediated by GJs and increase the permeability of the membrane through HCs formed by Cx43 (Cx43 HCs) [40]. This opposed regulation of Cx43 GJs and HCs also occurs in cultures of proximal tubule cells treated with metabolic inhibitors or pro-inflammatory cytokines, where an increase in the activity of Cx HCs has been demonstrated in response to these stimuli [41, 42]. In pathological conditions such as hypertension, the amount of renal Cxs is altered. For example, in the two-kidney one-clip model (2K1C), an increase in the amount of Cx43 mRNA and protein in the glomerulus was observed [43]. Recently Oliveira et al. showed for the first time that bone marrow mononuclear cell (BMMC) transplantation in clipped kidney of the 2K1C rats significantly increased N-cadherin, E-cadherin, connexin40, and nephrin expression accompanied by improved renal morphology and function and decreased fibrosis [44]. This cell-based therapy, especially using the mononuclear cell fraction, has shown to improve regeneration of multiple tissues under pathological conditions [44]. A recent study provided evidence that both Cx40 and Cx37 participate in endothelial nitric oxide synthase (eNOS) regulation in vivo, where in mice subjected to the 2K1C procedure, the interaction of Cx40 and Cx37 with eNOS was enhanced, resulting in increased nitric oxide (NO) release [45]. Mice lacking Cx40 featured decreased levels of eNOS [45], and in different models of hypertension, Cx37 selectively participates from an altered expression of AT2R [46]. In addition, the amount of Cx43 is increased in inflammatory processes in damaged renal tubules and in interstitial cells in human kidneys [47]. Toubas et al. observed in three different models of CKD (i.e., the transgenic renin [$Ren^{+/+}$] model, the administration of antibodies against the glomerular basement membrane [α-GMB], and the unilateral obstructive uropathy) an increase in the amount of renal Cx43. Consequently, they postulated that this change in Cx43 was

altered by the development of inflammation in the damaged kidney [36]. Therefore, Cx43 is considered a new mediator of renal disease involved in central processes of inflammation and fibrosis, while its inhibition even after the initiation of the disease attenuates renal damage and preserves renal function in animal models of vascular, tubular, and glomerular CKD [48]. Although renal tissue expresses several Cxs, only a few studies have described the involvement of GJs and HCs in kidney damage, and no signaling pathway has been clearly associated with these changes [36, 41, 42]. Therefore, the role of Cx-based channels in normal renal tissue or in the development and progression of kidney damage remains largely unknown.

2.3 Connexin43 and the RhoA/ROCK pathway participate in angiotensin II-induced kidney damage

The main therapies for CKD currently available focus on the control of blood pressure and the optimization of the blockade of the renin-angiotensin system (RAS) [49]. The renal afferent arterioles are primarily responsible for regulating preglomerular resistance, renal blood flow, and GFR. Elevated renal vascular resistance and preglomerular reactivity are observed in AngII-induced hypertension [50]. Although many systemic, neural, paracrine, and autoregulatory mechanisms contribute to afferent arteriolar dynamics, in AngII-dependent hypertension, a direct effect has been observed between the RhoA/ROCK pathway and the endogenous production of AngII [50]. In our studies we have observed that, although treatment with fasudil does not reduce systolic blood pressure (SBP), the establishment of irreversible renal damage is prevented (**Figure 1**, **Table 1**), reducing inflammation, OS, and fibrosis, and also kept the amount of Cx43 and phosphorylated myosin phosphatase target subunit-1 (MYPT-1) at normal levels [51] (**Figure 2**). We have also identified the timepoint when renal damage turns irreversible and, as such, independent of the cause [51]. We considered that kidney damage became irreversible after 4 weeks of treatment with AngII since SBP, inflammation, OS, fibrosis, the amount of Cx43, and phosphorylation status of MYPT-1 remained high even after 2 weeks of AngII withdrawal [51]. On the contrary, these parameters were reversed in animals infused with AngII for 3 or less weeks, which indicates that AngII can generate alterations that can be compensated by kidney tissue that was not affected by AngII and/or recovery thanks to the small regeneration capacity of kidney tissue [51].

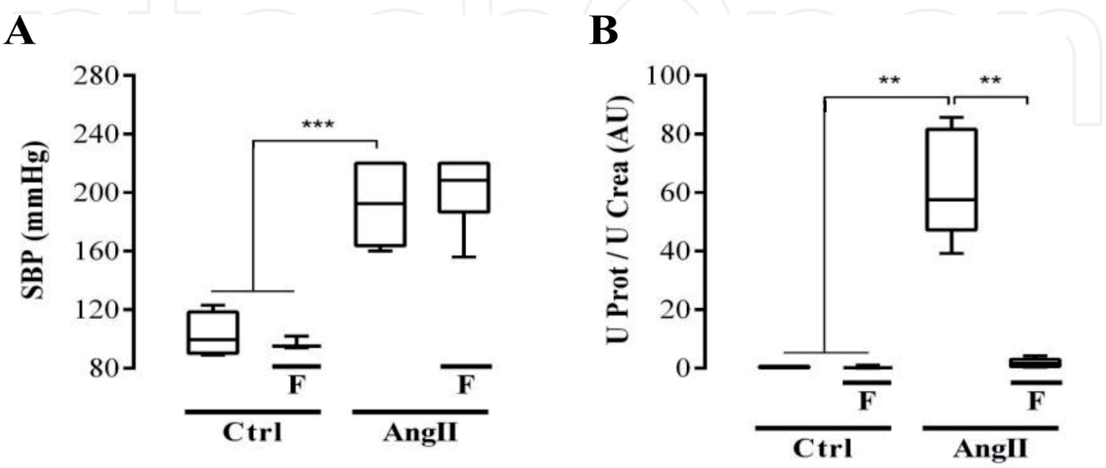

Figure 1.
*Fasudil does not modify the SBP in rats treated with AngII for 4 weeks but prevents the decrease in renal function. (A) Protein (UProt) and creatinine (UCrea) were measured in urine samples to assess renal function from ratio UProt/UCrea. (B) The bars represent the means ± SE of a n ≥ 4 rats per experimental group. The differences between the subgroups of each of the three groups were evaluated by an ANOVA followed by a Tuckey test. ***p < 0.001, **p < 0.01, and * p < 0.05 vs. AngII group.*

Groups	Weight (gr)	Proteinuria (mg/day)	Creatinine clearance (ml/min)	FE Na + (%)	FE K+ (%)
Ctrl	482 ± 31	2.7 ± 1.1***	1.4 ± 0.3***	0.2 ± 0.0***	12.0 ± 2.7***
Ctrl+fasudil	480 ± 36	3.6 ± 1.1***	2.1 ± 0.1***	0.1 ± 0.0***	12.5 ± 0.3***
AngII	364 ± 42	214.0 ± 19.0	0.7 ± 0.0	2.2 ± 0.4	162.0 ± 23.0
AngII+fasudil	368 ± 17	19 ± 7.2***	1.9 ± 0.2***	0.5 ± 0.1***	30 ± 7.2***

*** *p< 0.001 vs. AngII groups (n≥4/all groups).*

Table 1.
Values for weight, proteinuria, creatininuria, creatininemia, creatinine clearance, and fractional excretion (FE) for Na^+ and K^+ in the experimental groups.

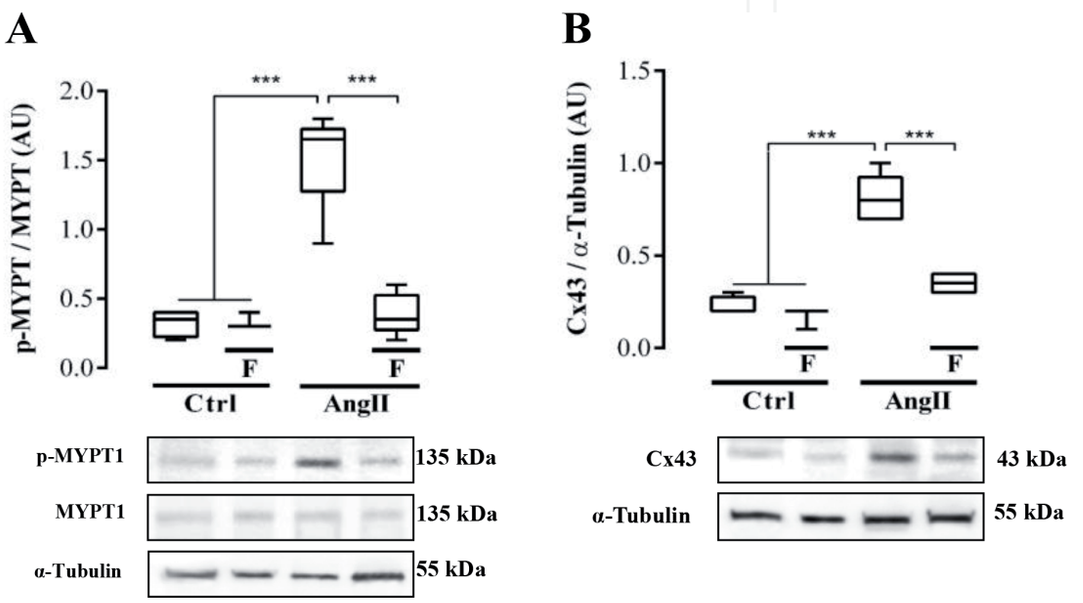

Figure 2.
*The increase in the amounts of phosphorylated MYPT and Cx43 is prevented with fasudil in rats treated with AngII for 6 weeks. Four groups of animals, two control groups (Ctrl and Ctrl+fasudil) and two experimental groups (AngII administered for 6 weeks and AngII+fasudil administered for the last 4 weeks), were studied. Fasudil (100 mg/kg/day) was given in the drinking water. Graphs show phosphorylation of MYPT-1 (A) and the relative amount of Cx43 (B). Under the graph representative pictures of phosphorylated MYPT (p-MYPT), unphosphorylated MYPT and Cx43 positive bands and its loading control (α-tubulin) are shown. The bars represent the means ± SE of n ≥ 4 rats per experimental group. The differences between the subgroups of each of the three groups were evaluated by an ANOVA followed by a Tuckey test. ***p < 0.001 vs. AngII group.*

The activity of the RhoA/ROCK pathway has been widely investigated in the pathogenesis of hypertension, where this pathway would fulfill an important role in the regulation of smooth muscle contraction. Other cellular processes such as proliferation, hypertrophy, adhesion, and migration of vascular cells are also mediated by the RhoA/ROCK pathway. These changes could lead to an increase in peripheral vascular resistance, which is one of the critical characteristics of several models of hypertension [52]. Therefore, inhibition of the RhoA/ROCK pathway represents a new approach in the prevention and treatment of hypertension [52]. The protective effect of fasudil in vivo is partly explained by its pleiotropic action in different systems. Therefore, considering that ROCK inhibitors were developed as antihypertensive drugs, it is striking that in our model of rats treated with AngII for 6 weeks, fasudil did not affect SBP, but did reduced the progression of kidney damage [51]. Similar to our observations, several studies have established that fasudil is renoprotective without affecting blood pressure, establishing a

controversy regarding the use of fasudil and its antihypertensive action [53–56]. In view of these results, it would be interesting to develop a line of research that could explain why fasudil does not prevent the increase in SBP, even when it prevents kidney damage.

Hypertensive nephropathy begins in the glomerulus by increasing intraglomerular pressure. These early events activate and damage mesangial cells, epithelial cells, and podocytes in the glomerulus [42]. In turn, these cells produce vasoactive and pro-inflammatory agents, which increase cell damage and promote fibrosis, reducing renal blood flow and glomerular filtration [8]. In afferent arteriolar cells from rats treated with AngII, the activation of NF-κB is mediated by the RhoA/ROCK pathway, and the ROCK/NF-κB axis contributes to the upregulation of angiotensinogen, leading to an increase in the amount of intrarenal AngII [50]. We found that AngII increases the membrane permeability of MES cells, a mesangial glomerular cell line via AT1 receptors, as well as the activation of a RhoA/ROCK-dependent intracellular signaling pathway, followed by the upregulation of three nonselective channels, and the generation of OS and pro-inflammatory cytokines [42]. In MES-13 cells, AngII promotes a feedforward mechanism in which three nonselective channels (Cx43 HCs, Pannexin 1 channels, and $P2X_7$ receptors) maintain or even amplify inflammatory and oxidative responses, causing damage to kidney cells [42].

Xie et al. explored the mechanism of the reduction in the amount of Cx43 induced by RhoA/ROCK signaling in high glucose-treated glomerular mesangial cells (GMCs) [57]. Their results indicate that activated RhoA/ROCK signaling induced Cx43 degradation in GMCs cultured in high glucose via a pathway dependent on F-actin regulation that promoted the association between ZO-1 and Cx43 [57]. Interestingly, we found changes in RhoA/ROCK activity and also found that ROCK inhibitors prevented increases in the amount of Cx43 induced by AngII [51]. Since the expression and activation of RhoA/ROCK and Cx43 HCs, respectively, occur in the same direction, it is likely that they are regulated by the same transduction mechanism and intracellular signaling pathway activated by AngII. Therefore, it was postulated that changes in RhoA/ROCK pathway and Cx43 precede renal damage in this model of hypertensive nephropathy [51]. A comparable response has been found in fibroblasts, and a direct relationship has been demonstrated between the activation of the RhoA/ROCK pathway and the increase in the amount of Cx43. In these cells, the expansion mechanisms in response to stretching involve the release of ATP to the extracellular medium through the RhoA/ROCK pathway and the activation of Cx HCs [58]. In addition, treatment with Y-27632, another inhibitor of the RhoA/ROCK pathway, or with blockers of Cx HCs, such as octanol or carbenoxolone, inhibits the increase of ATP in the extracellular medium and the growth of fibroblast [58]. Nevertheless, this direct relationship is not observed in all cell types. For instance, in corneal epithelial cells, where a RhoA/ROCK-dependent pathway is involved in the formation of Cx43 GJs, inhibition of RhoA/ROCK-dependent pathway results in greater cell–cell communication mediated by Cx43 GJs [59].

Therefore, we propose that blocking AngII-induced damage progression in mesangial cell could be accomplished by inhibiting the RhoA/ROCK as previously demonstrated. Moreover, the effective reduction of initial AngII-induced alterations in cell membrane permeability leading to activation of several metabolic pathways that promote OS and generation of pro-inflammatory cytokines can be accomplished with selective and potent inhibitors of nonselective channels [42, 51].

The differences between the subgroups in each of the three groups were evaluated by an ANOVA followed by a Tuckey test. $^{**}p < 0.01$, $^{***}p < 0.001$ vs. AngII groups ($n \geq 4$/all groups).

3. Conclusions

In conclusion in the hypertensive nephropathy, inflammation, oxidative stress, fibrosis, changes in amount and cell membrane permeability of Cx43 HCs, and activity of the RhoA/ROCK pathway are important in the progression of damage induced by AngII. These alterations are prevented by fasudil, revealing a close relationship between activation of a RhoA/ROCK-dependent pathway and Cx43 in CKD.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Notes/thanks/other declarations

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Appendices and nomenclature

CKD	chronic kidney diseases
RAS	renin-angiotensin system
ESRD	end-stage renal disease
GFR	glomerular filtration rate
MCs	mesangial cells
JG	juxtaglomerular cells
AngI	angiotensin I
ACE	angiotensin-converting enzyme
AngII	angiotensin II
IL-1β	interleukin-1β
TNF-α	tumor necrosis factor-α
MCP-1	macrophage chemoattractant protein
TGF-β	transforming growth factor-β
ED-1	infiltration of macrophages
OPN	osteopontin
NOX	nicotinamide adenine dinucleotide phosphate oxidase
ROS	reactive oxygen species
OS	oxidative stress
AT1	angiotensin II receptor type 1
AT2	angiotensin II receptor type 2

ROCK	Rho kinase system
Rho GTPase	Rho family of small GTPases
NFκB	nuclear factor-κB
GJs	gap junctions
Cxs	connexins
HCs	hemichannels
BMMC	bone marrow mononuclear cell
2K1C	two-kidney and one-clip rat model
eNOS	endothelial nitric oxide synthase
SBP	systolic blood pressure
MYPT-1	myosin phosphatase target subunit-1
MES-13	mesangial glomerular cells line

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