Journal of Biosciences and Medicines, 2020, 8, 26-44
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Association of Acid-Base Balance in the Renal Proximal Tubule and Blood Pressure Alterations: Potential Role of Local Mediators

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How to cite this paper: Aryal, D. and Jackson, K.E. (2020) Association of Acid-Base Balance in the Renal Proximal Tubule and Blood Pressure Alterations: Potential Role of Local Mediators. *Journal of Biosciences and Medicines*, **8**, 26-44.
https://doi.org/10.4236/jbm.2020.84003

Received: February 22, 2020
Accepted: March 29, 2020
Published: April 2, 2020

Abstract

Disturbances in acid-base balance leading to the development of hypertension are currently gaining increased attention among researchers. Perturb acid-base balance characterized by metabolic acidosis has been demonstrated in hypertensive animals and humans. Research suggests that acid-base changes are not only the consequences of elevated blood pressure but can precede the development of hypertension. However, no exact mechanism has been identified to link acid-base imbalance with alterations in blood pressure. The kidney proximal tubule is the major site for maintaining normal bicarbonate concentrations which is an important component of acid-base balance. Acid-base transporter proteins in the renal proximal tubule such as Na^+/HCO_3^- cotransporters, Na^+/H^+ exchangers, and anion-exchangers play important roles in controlling acid secretion, ammonia production and bicarbonate reabsorption for maintaining acid-base balance. It is well known that sodium retention in the renal tubules leads to increase in blood volume and consequently increases in blood pressure. Therefore, it is the purpose of this review to discuss the role of sodium-coupled acid-base transporters in regulating proximal tubular sodium retention and controlling blood pressure homeostasis. We will also focus on the capacity of local mediators; angiotensin II, cortisol, prostaglandin and aldosterone, to regulate acid-base and blood pressure homeostasis.

Keywords

Acid-Base Transporters, Hypertension, Proximal Tubule, Angiotensin II

1. Introduction

The kidney plays a crucial role in maintaining acid-base homeostasis, which is

important for proper functioning of several physiological processes in the body. The kidneys also regulate extracellular fluid volume (ECFV) homeostasis by controlling sodium and water balance, which is a key component of blood pressure control [1]. Kidneys have two significant roles in maintaining acid-base balance; namely, they reabsorb bicarbonate from urine and excrete hydrogen ions in the form of ammonium into urine. The association of bicarbonates and hydrogen ions with sodium-linked transporter proteins such as Na^+/HCO_3^- cotransporters, Na^+/H^+ exchangers, and anion-exchangers plays a significant role in both acid-base balance and blood pressure regulation [2]. Since the proximal tubule is the major site for sodium reabsorption in the kidney, it is the purpose of this review to examine the current literature in regards to the relationship between acid-base imbalance and hypertension as well as to explore the possible biological pathways underlying the linkage between these health conditions.

The renin-Angiotensin Aldosterone System (RAS) has been widely studied for its role in the pathogenesis of hypertension and associated renal injury. In recent years, focus has been shifted to the importance of tissue specific local RAS components and their activation, contributing to the regulation of renal hemodynamics, maintenance of extracellular fluid volume, regulation of sodium reabsorption and the control of blood pressure [3]. In the kidney, angiotensin II (Ang II) is one of the components of the RAS system compartmentalized in the renal interstitial fluid and the proximal tubular (PT) compartments with much higher concentrations than those existing in the systemic circulation [4]. Local Ang II signaling in the kidney regulates acid-base transport and metabolism [5]. Under acidic conditions, proximal tubule cells upregulate the expression of type 1 Ang II receptors, hence enhancing the ammonia genesis action of Ang II to counter the acid-base imbalance [6]. Since, intrarenal Ang II signaling via AT1a receptors in the renal proximal tubule is a major regulator of blood pressure and sodium homeostasis [7], the increasing effect of Ang II during acid challenge might have a significant role in sodium homeostasis. No studies to date have provided a clear insight upon the independent role of Ang II inside the tubule cell to lead to disturbed acid-base balance and affect blood pressure regulation. This review will explore the effect of disturbed acid-base balance in the proximal tubule that may eventually contribute to the pathogenesis of increased blood pressure. The focus will be on the potential role of local mediators like Ang II.

Endogenous elevations of angiotensin II could stimulate several pathophysiological mechanisms, which contribute to hypertension. Recent studies show that, chronically elevated Ang II augments sympathetic nerve outflow directly, probably by inhibiting the reflex decrease in sympathetic nerve activity following an increase in arterial pressure [8]. Involvement of reactive oxygen species (ROS) as second messengers in Ang II-mediated signaling in the CNS could be the novel signaling mechanism important in hypertension triggered by Ang II acting in the CNS [9]. Inflammation has recently emerged as an important mechanism in

the progression of Ang II-dependent hypertension [10]. Intrarenal Ang II has been studied for its role in altering proximal tubule sodium (Na^+) transport, which consequently affects blood pressure homeostasis [11] [12].

It is well documented that renal Na^+ retention leads to hypertension. Acid-base transporters in the renal tubules play a significant role in mediating renal Na^+ retention as most of the acid-base transporters are coupled with Na^+. Hence there might exist a direct linkage between acid-base balance and the mechanism involved in hypertension which needs to be further elucidated [13]. Over the last few decades, several investigators including genetic based studies have proposed that alterations in the expression and function of acid-base transporters can be involved in blood pressure deregulation [14] [15]. In one of the studies, oral administration of sodium bicarbonate containing mineral water for seven days to hypertensive subjects resulted in a decreased systolic blood pressure (by 5 mmHg). Similarly, in some salt-sensitive, but not in salt-resistant patients, oral loading with sodium bicarbonate ($NaHCO_3$) increases blood pressure, but the pressor effect of $NaHCO_3$ is half that of sodium chloride (NaCl) [16]. These alterations in blood pressure regulation have been demonstrated genetically in several animal models with disrupted expression of acid-base transporters. The human SLC4A5 gene encoding NBCe2 (Na^+/HCO_3^- -cotransporter) has been identified as a hypertensive susceptible gene based on the association of a single nucleotide polymorphisms with blood pressure (BP) levels and hypertension status [17]. However, controversy still exists as to the exact functional characteristics and within which section of renal tubule leads to hypertension.

2. Acid-Base Transport in Renal Proximal Tubule: Role of Ang II

The renal proximal tubule (RPT) is a mutual site for acid-base transport, which promotes regulation of blood pH as well as sodium and water transport to maintain renal fluid dynamics. The ability of RPT acid-base transporters to affect blood pressure regulation has been hypothesized [18]. In this light acid-base transporters are expressed in all segments of the nephron and collecting duct; and since the actions of many acid-base transporters involve co- or counter-transport of Na^+ and/or Cl^-, they can directly influence renal NaCl handling and eventually pressure natriuresis [19]. Few would argue the importance of pressure natriuresis in the regulation of normal blood pressure.

The kidneys have the predominant role of regulating systemic bicarbonate (HCO_3^-) concentration and hence, the metabolic components of acid-base balance. This function of the kidneys has two components: reabsorption of virtually all the filtered HCO_3^- and production of new HCO_3^- to replace that consumed by normal or pathologic acids. This production or generation of new HCO_3^- is done by net acid excretion. Net acid excretion by the kidneys occurs by two processes: the excretion of titratable acid and the excretion of ammonium (NH_4^+) [20]. We briefly summarize in this review, the ammonia excretion from

proximal tubule and its effect on sodium bicarbonate reabsorption.

Interstitial angiotensin II stimulates H^+ secretion and HCO_3^- reabsorption in both proximal and distal tubules. In proximal tubules, Ang II at low concentrations ($<10^{-9}$ M) stimulate bicarbonate reabsorption, Na^+/H^+-exchange, and Na^+/HCO_3^- cotransport, while inhibition of bicarbonate reabsorption has been documented with concentrations higher than 10^{-8} M [21]. A study on human subjects claimed that Ang II regulates acid-base balance, as administration of Losartan (AT1 blocker) exacerbates acidosis by significantly decreasing net acid excretion [22]. However, there are not enough studies to corroborate whether the above mentioned action of Ang II is via a renal mechanism. Nagami, 2004 confirmed that Ang II stimulates ammonia production and secretion at the S3 segments of proximal tubule in acidotic mice [23]. Ang II receptors are present both on the luminal and the basolateral membranes of the proximal tubule. Acid secretion, bicarbonate reabsorption and ammonia production are stimulated by Ang II binding to either luminal or basolateral membrane receptors. However, to promote ammonia secretion, the Ang II must bind with luminal membrane receptors. This site-specific activity of Ang II may regulate the other sodium-linked transporters that are present on the membrane of the PT which ultimately can influence the concentration of sodium and fluid volume inside the cell [7] [24].

In this review, we will briefly summarize the potential role of acid-base transporters mainly, Na^+/H^+-exchanger (NHE3), Na^+/HCO_3^- cotransporters (NBCe1, NBCe2, NBCn1), Cl^-/HCO_3^- -exchanger and Na^+/K^+ ATPase pump on alterations in blood pressure (**Figure 1**). We will also discuss the role of intrarenal angiotensin II in acid-base transport across the proximal tubule leading to blood pressure disturbances.

2.1. Na^+/H^+ Exchanger

The Na^+/H^+ Exchanger is a transporter present mostly on the apical side of the proximal tubule which functions to secret H^+ in exchange for Na^+ promoting regulation of acid-base homeostasis. NHE3 is the major isoform of this transporter which is encoded by the SLC9A3 gene [25]. The proximal tubule reabsorbs at least 70% - 80% of the approximately 4500 mEq/d of filtered HCO_3^-. Most (probably > 70%) of this HCO_3^- reabsorption is stimulated by H^+ secretion on the apical membrane by the sodium-hydrogen exchanger (NHE3). In addition to reabsorption of filtered HCO_3^-, the kidneys also produce additional HCO_3^- beyond that which has been filtered at the glomerulus. This process occurs by the excretion of acid into the urine. The net acid excretion of the kidneys is quantitatively equivalent to the amount of HCO_3^- generation by the kidneys [20] [26] [27]. Previous studies have shown; blood pressure is lower in renal NHE3-deficient than in wild type mice on a normal sodium chloride diet but is normalized when fed a high sodium chloride diet [28]. This suggests that cellular H^+ secretion plays a potential role in the observed dietary blood pressure lowering effects. In addition, angiotensin II increases luminal H^+ secretion in exchange for

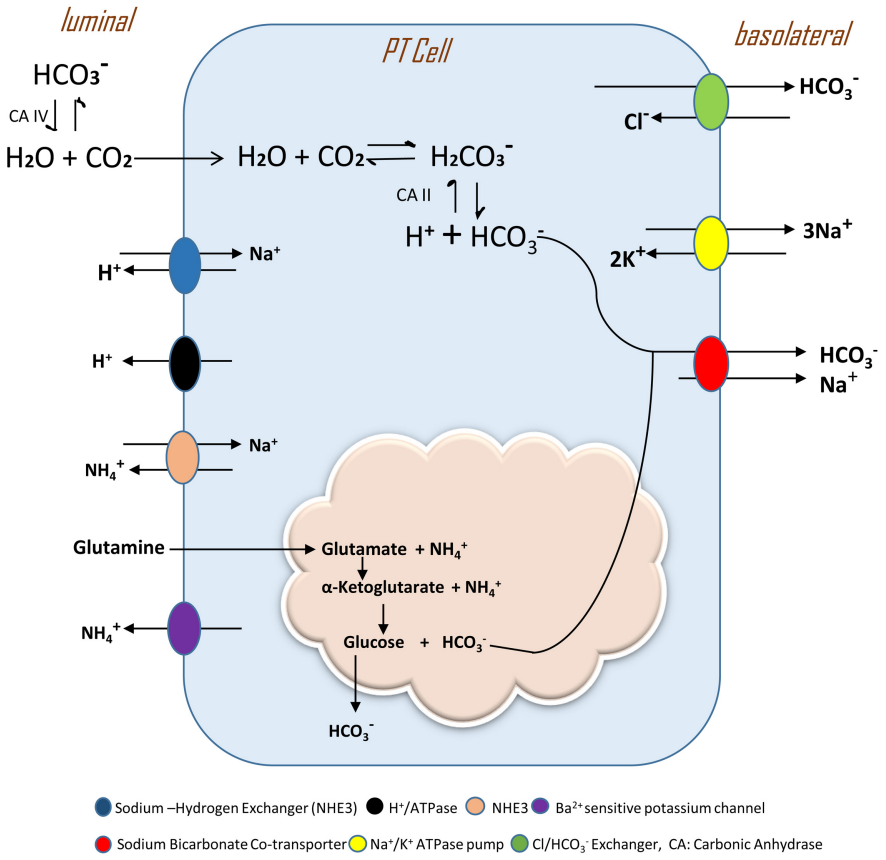

Figure 1. Sodium transport, bicarbonate reabsorption and ammonia metabolism across proximal tubule.

Na^+ into the cell via AT1 receptors because it does not affect the exchange in AT1R knockout mice and renal proximal tubule cells in which the AT1R is blocked or silenced. This provides evidence for intrarenal angiotensin II mediated NHE3 activity [29].

2.2. Na^+/HCO_3^- Cotransporter

Proximal tubule cells in the kidney transport HCO_3^- into the interstitial fluid and ultimately to the blood, mainly via the renal splice variant of the electrogenic Na^+/HCO_3^- co-transporter NBCe1-A; however, other isoforms namely, NBCe2 and NBCn1 are also present [30]. NBCe1-A is located on the basolateral membrane of PT cells and is responsible for $3HCO_3^-$ ions transport into the blood for each Na^+ ion whereas, NBCe2 is present mostly on the luminal membrane of the proximal tubule [31]. In the collecting duct, mutation in the SLC4A5 gene encoding NBCe2 induces hypertension because of the stimulation of 1:1 Na^+ to HCO_3^- stoichiometry of other transporters like NBCn1 rather than the 1:2 stoichiometry of the NBCe2. Therefore, for every HCO_3^- reabsorption there is equal Na^+ reabsorption from NBCn1 as compare to NBCe1-A, which ultimately results in blood pressure elevation [32]. However, in case of the proximal tubule, NBCe2 is present on the apical membrane so there may be

some other transporters activated, which could promote Na^+ reabsorption. Another study showed an increase in NBCe1-A expression reported in the renal cortex of spontaneously hypertensive rats as compared to Wistar Kyoto rats [33]. However, it is unclear whether these changes in acid-base transporter expression and function are causative, compensatory or unrelated to the blood pressure alterations. It is well observed that AT1 receptors are expressed in renal PT cells and regulate the uptake of local Ang II, therefore local Ang II may control the NBCe1-A and NBCe2 independently, while maintaining normal bicarbonate concentrations and Na^+ homeostasis. Ang II has the greatest stimulatory effect on the reabsorption rate of HCO_3^- when applied at a low dosage to either the luminal or the basolateral surface (Figure 2). When applied at a high dosage to either surface, however, Ang II reduces HCO_3^- reabsorption [34] [35]. The stimulatory effects of Ang II on HCO_3^- reabsorption may be mediated by a decrease in intracellular cyclic AMP levels or by activating a PKC pathway [36] [37]. Taken together, there is need of further research to explore the role of acid-base transporters on activation of local mediators influencing the blood pressure homeostasis.

2.3. Cl^-/HCO_3^- Exchanger

Among human bicarbonate transporters, two major gene families encode Na^+ independent Cl^-/HCO_3^- exchangers: the SLC4 anion exchanger (AE) family, and the SLC26 "sulfate permease" anion transporter family. The most extensively studied among them are the Na^+-independent anion exchangers, AE1, AE2, and AE3, all of which are expressed in the kidney [38] [39]. HCO_3^- generated intracellularly exits the basolateral membrane through a chloride-bicarbonate exchanger, a truncated version of the anion exchanger 1 (AE1), which is the

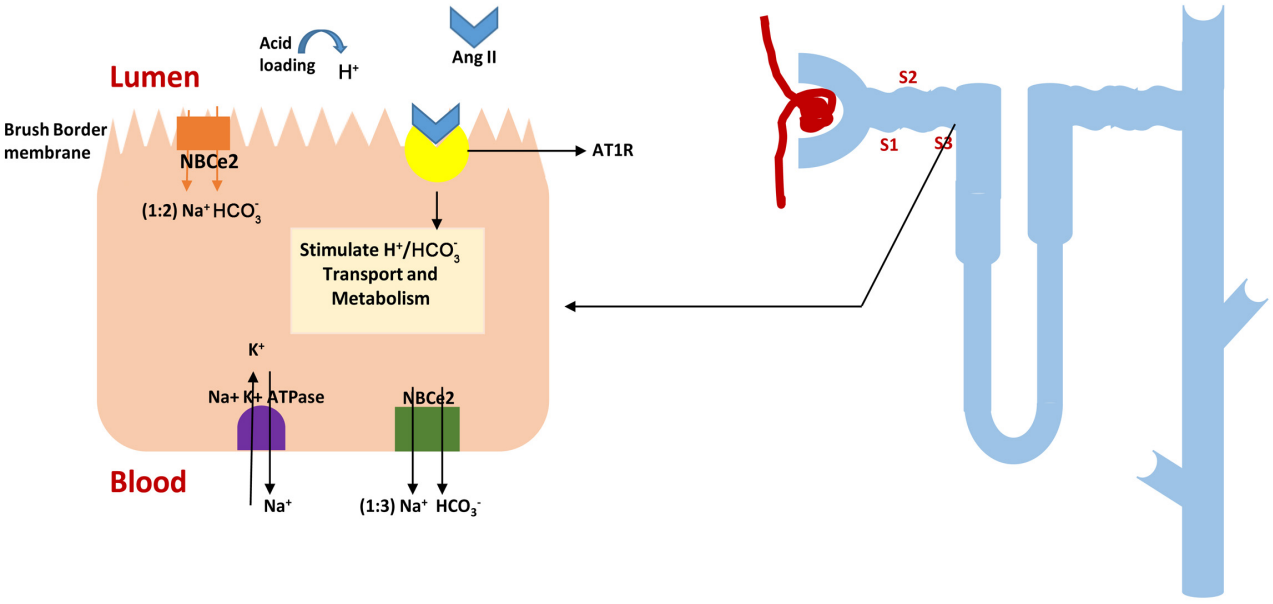

Figure 2. Angiotensin II regulated sodium-bicarbonate transport across S3 segment of renal proximal tubule cell in nephron.

Cl^-/HCO_3^- exchanger in red blood cells that facilitates CO_2 transport [40]. The Cl^-/HCO_3^- exchanger is stimulated by oxidative stress and by α1-adrenoceptors in immortalized proximal tubular epithelial cells of spontaneous hypertensive rats [41]. Angiotensin II also increases Cl^-/HCO_3^- exchanger activity in immortalized renal proximal tubules from spontaneous hypertensive rats as compared to proximal tubules from normotensive WKY rats [42]. Furthermore, bicarbonate reabsorption is independent of the presence of luminal chloride in isolated rabbit medullary collecting duct, although it is completely abolished in the absence of basolateral chloride, presumably due to impairment of peritubular bicarbonate exit in exchange for Cl^- via the Cl^-/HCO_3^- exchanger AE1 [43].

2.4. Na^+/K^+ ATPase Pump

Na^+/K^+ ATPase pumps are active transporters, which are localized mostly on the basolateral side of proximal convoluted tubules second only to distal convoluted tubules [44]. The major role of these pumps is to balance the concentration of Na^+ and K^+ on the tubular and luminal sites of nephrons. These pumps function by ATP mediated transport of three sodium ions out of cells for two potassium ions into cells, both against their concentration gradients [45]. Although, less has been explored about the role of Na^+/K^+ pump in acid-base balance, Na^+/K^+ ATPase stimulates several other Na^+-dependent cotransporters such as Na-glucose, Na-phosphate, Na-amino acids and exchangers like Na^+/H^+ on the luminal membrane. One such active transporter is the H^+/K^+ ATPase, which is expressed in the renal tubules, where it may function in potassium reabsorption and in the maintenance of acid-base balance [46]. Overexpression of Na^+/K^+ ATPase transporters in the renal proximal tubule of hypertensive rats in previous studies has been identified. The overexpression of Na^+/K^+ ATPases was regulated by local hormones like Ang II and aldosterone [47]. Ang II acutely stimulates Na^+/K^+ pump expression in plasma membranes of rat proximal tubules by approximately 33%. Phosphorylation at the Ser 938 residue of the Na^+/K^+ ATPase is responsible for the overexpression of the pump [48]. Also, Ang II stimulates the renal proximal tubule Na^+/K^+ ATPase activity via activation of Protein Kinase C (PKC) [49]. In contrast, Ang II activates NADPH oxidase which inhibits the activity of the Na^+/K^+ pump in cardiac myocytes via a PKC dependent pathway [50]. Furthermore, aldosterone increases Na^+/K^+ ATPase activity in the proximal tubule via classical mineralocorticoid receptor activation [51]. Prostaglandins role in renal ion-transport has been previously shown. An acute study showed that one of its isoform PGE1, when incubated with rabbit kidney PT cells, increases the expression of Na^+/K^+ ATPase [52]. These results provide the mechanistic insight for involvement of Na^+/K^+ ATPase pump for controlling other transporter proteins for regulating acid-base balance along with maintaining blood pressure.

3. Ammonia Transport in Renal Proximal Tubule

Renal ammonia metabolism is crucial for maintaining acid-base balance. In the

proximal tubule, ammonium (NH_4^+) is generated from glutamine. Glutamine is first converted to glutamate by glutaminase. Then glutamate dehydrogenase converts glutamate to α-ketoglutarate and two ammonium ions. The α-ketoglutarate can be oxidized or converted to glucose (which is used for gluconeogenesis), both processes release bicarbonate. The ammonium is transported into the renal lumen in exchange for sodium by a luminal exchanger. The ammonium is then excreted into the urine with filtered chloride as its anion. The bicarbonate is returned to the blood via the basolateral sodium/bicarbonate cotransporter. This process generates new bicarbonate, while excreting an acid (ammonium chloride). Hypokalemia and acidemia stimulate ammonia genesis, promoting hydrogen excretion and bicarbonate retention [53]. Angiotensin II stimulates the basolateral sodium/bicarbonate cotransporter, facilitating absorption of the generated bicarbonate. In the proximal tubules, ammonia generation is linked to sodium absorption. Hence, increased ammonia production may stimulate sodium reabsorption and volume expansion, which could ultimately lead to rise in blood pressure. Ammonia production and transport are regulated by a variety of factors, including extracellular pH and potassium (K^+) concentration, and by several hormones, such as mineralocorticoids, glucocorticoids and angiotensin II. This coordinated process of regulated ammonia production and transport is critical for the effective maintenance of acid-base homeostasis. Ang II stimulates ammonia production and secretion in proximal tubule segments through intracellular calcium-mediated signaling. In contrast, a concentration-dependent effect of angiotensin II on total ammonia production in the proximal tubule of the micro-perfused mouse was observed. The ammonia genesis is stimulated in lower concentration ranges but inhibited at high concentrations. The increased intracellular calcium mediates the stimulatory effect of angiotensin II [54] [55] [56] [57].

During metabolic acidosis, Ang II stimulates the ammonia genesis and secretion of ammonia from the proximal convoluted tubules with an upregulation of NHE3 transporters on the brush border membrane [58]. Current literature supports the involvement of Rh glycoproteins in the transport of ammonia. Chronic metabolic acidosis in animals was shown to increase basolateral plasma membrane Rhcg expression [59]. These critical facilitators of ammonia transport in the kidney could mark a new approach for studying the mechanism of ammonia transport and its consequence on acid-base homeostasis, which ultimately affects blood pressure regulation.

4. Disturbed Acid-Base Balance and Its Consequences on Renovascular Function

Metabolic acidosis can be the common cause of disturbing acid-base balance which is characterized by decreased blood pH because of a reduction in bicarbonate reabsorption and acid accumulation in the blood. The excessive consumption of acid precursor foods (mainly sources of phosphorus and proteins)

commonly associated with a western-type diet may lead to a chronic imbalance in acid-base regulation eventually resulting in cardio-metabolic dysfunction. Metabolic acidosis is known to cause insulin resistance in the skeletal muscle [60] [61]. The acute form of metabolic acidosis has a profound effect on kidney function, promoting a progress decline in the Glomerular Filtration Rate (GFR) [62]. However, there are only a few studies investigating the molecular pathway of acidosis related hypertension, and whether acidemia can induce local mediators promoting hypertension remains unclear. One of those studies suggests, chronic metabolic acidosis may stimulate intrarenal renin-angiotensin system components (*i.e.*, Angiotensinogen, Ang II, Angiotensin Converting Enzyme) along with proteinurea, which is a marker of kidney injury [63]. Hence, more studies are required to confirm the association of acid loading with the activation of a vasoconstrictor like Ang II in renal tubules, which could ultimately be responsible for promoting hypertension.

Furthermore, the impact of intracellular acid-base disturbances on the contractile and relaxant functions of the arterioles has been studied for its effect on hypertension. As hypertension is characterized by increased contraction of the vascular wall, an increase in intracellular acid load has been associated with an ability to induce contraction of vascular smooth muscle cells [64] [65]. A decrease in intracellular pH via acid loading in vascular smooth muscle cells causes contractions, and during the contraction, an acid-base transporter NBCn1 is activated in a calcineurin-dependent pathway leading to an increase in intracellular Ca^{2+} [66] [67]. Hence, the acid-base imbalance activates Ca^{2+} signaling in vascular smooth cells and may have an important role in the pathogenesis of increased peripheral resistance in the arteries. Although, this review focuses on renal mechanism of blood pressure regulation during altered acid-base balance, the above described studies cannot be disregarded for its potential mechanism whereby acid-base imbalance leads to sustained hypertension. Since, the exact mechanism of essential hypertension remains to be elucidated, one cannot rule out the possibility of diet induced alterations in acid-base balance leading to activation of local mediators, such as angiotensin II or prostaglandins, which activate cellular pathways, such as calcineurin-dependent pathways, or PKC dependent pathways to increase sodium reabsorption and volume expansion which consequently promote hypertension.

5. Possible Renal Mechanisms Linking Metabolic Acidosis and Increased Blood Pressure

5.1. Insulin Resistance

Insulin resistance is a pathological condition characterized by impaired response to insulin stimulation in target tissues *i.e.*, liver, muscle and adipose tissues [68]. Apart from these classical insulin target tissues, insulin receptors are also expressed in kidney tubules and arterial vasculature. In the vasculature, insulin acts via phosphoinositide-3-kinase (PI3K) pathway to produce NO and hence dilate

the vessels. During impaired insulin function (insulin resistance), the vasodilator action is impeded, consequently rising the blood pressure. On the other hand, insulin action upon renal tubular sodium reabsorption is preserved during insulin resistance hence contributing to reduce natriuresis and rise in blood pressure [69] [70].

DeFronzo *et al.*, initially observed that disturbed acid-base balance could develop insulin resistance in humans [71]. Also, correction of the acid-base imbalance, improves insulin resistance in patient with chronic kidney disease [72]. A recent study inferred that, reduced insulin receptor expression during insulin resistance in renal proximal tubule give rise to the development of albuminuria which is markedly higher in hypertensive individuals [73] [74]. Angiotensin II plays an important role in regulating insulin signaling by blocking insulin mediated NO production and promoting vasoconstriction via MAPK pathway [75]. These studies suggest that impact of disturbed acid-base balance in renal tubules could alter insulin signaling which might play a role in pathogenesis of hypertension. Further studies are needed to explore various acid-base transporters in renal tubular compartment and their effect on insulin resistance-mediated rise in blood pressure.

5.2. Aldosterone Secretion

Acidosis induced aldosterone secretion is unique in that it doesn't follow classical biosynthesis methods involving increase plasma potassium levels, adrenocorticotropic hormone (ACTH) stimulation and angiotensin II activation. However, plasma hydrogen ion concentration could be the regulator of aldosterone secretion during metabolic acidosis [22] [76] [77]. Genetic mutation of gene, CYP11B2 encoding aldosterone synthase (an enzyme responsible for biosynthesis of aldosterone) has produced low blood pressure effect and metabolic acidosis in human subjects [78]. Therefore, there might exist an independent mechanism which interlink the metabolic acidosis-induced aldosterone secretion and blood pressure regulation. Less has been studied of the effect of aldosterone on proximal tubule, as mostly aldosterone act via mineralocorticoid receptors predominantly expressed in distal convoluted tubules and collecting tubules of nephron, which promotes Na^+ retention and increases blood volume ultimately increasing the blood pressure [79]. However, some studies conferred that aldosterone inhibits urinary ammonium excretion by impairing ammonia genesis in the proximal tubule cellular compartments [80]. Further studies can be designed to see the independent effect of aldosterone on various sodium linked acid-base transporters in the proximal tubules and its consequences on sodium homeostasis leading to blood pressure regulation.

5.3. Cortisol Production

A study showed, diet induced mild metabolic acidosis could lead to rise in blood pressure possibly by the increase production of cortisol by adrenal cortex [81].

The primary mechanism behind this cortisol-induced hypertension is the over-stimulation of the non-selective mineralocorticoid receptors abundant in distal convoluted tubules and the collecting ducts of the nephron which results in Na+ reabsorption, volume expansion and finally rise in blood pressure [82]. However, during systemin acidosis, the rise in production of cortisol promotes, ammonium excretion, increase titratable acid production and increase proximal tubule Na^+/H^+ exchange [83]. Hence, cortisol mediated physiological alterations in acid-base transporters and ammonia metabolism could be the novel mechanism yet to be explored to support the acidosis-induced hypertension. Cortisol has demonstrated variable effects on renin-angiotensin system. The renin substrate (angiotensinogen) maybe increase during cortisol stimulation but no significant change in plasma Ang II concentration has been observed. Hence, systemic Ang II is less likely to be a part of mechanism involved in cortisol induced hypertension [84]. Whether, the activation of local renin angiotensin system in metabolic acidosis-induced cortisol production must be addressed before conferring the RAS independent effect of cortisol in hypertension.

5.4. Heme Oxygenase Induction

Heme Oxygenase (HO) is an enzyme that degrades heme to free iron, biliverdin and carbon mono-oxide (CO) [85]. HO-1 is stress induce isoform of HO, concentrated mostly in spleen, liver and kidneys [86]. Researchers have reported that, disturbed acid-base physiology during metabolic acidosis is associated with increased expression of HO-1 in kidney [87]. Also, there exists an increase HO-1 expression in vascular smooth muscle cells exposed to the acidic medium (pH 6.8) [88]. Our lab has previously demonstrated that, Ang II infusion promotes hypertension via induction of HO-1, which produces a marked increase in endogenous CO, which elicit vasoconstriction by inhibiting nitric oxide synthase (NOS) [89]. Since, kidney proximal tubule has been implicated as a major site for heme synthesis [90], proximal tubule HO-1 induction during metabolic acidosis may have possible influence to regulate sodium-linked acid-base transporters for sodium handling by the proximal tubule and eventual hypertension.

5.5. Prostaglandins

Prostaglandins (PGs) are recognized as intrarenal vasodilators which function as endocrine-antihypertensive agents during its existence in kidney [91]. PGE2, PGF2α and PGA have been extensively studied for their role in regulating renal blood flow, electrolyte balance and essential hypertension [92]. PGA has been identified as a potential regulator of blood pressure homeostasis, as its concentration is seen to be reduced in hypertensive patients [93]. The effect of acute acidosis on prostaglandin levels was previously evaluated in rats, and the data revealed, serum PGF2α is increased over eight minutes of time with the increase in degree of acidosis [94]. However, kidney being major site for metabolism of PGs [92], the renal mechanism of various PG isoforms on blood pressure regula-

tion hasn't been studied much. Hence, acidosis-induced PG production in renal tissues can be a novel approach to examine the mechanism of acidosis induced hypertension. Since, PGA being the regulator of antihypertensive action and being itself metabolized in kidney cortex [95], the effect of chronic or acute metabolic acidosis, on levels of PGA might provide some ideas about its fate in renal tissues. Furthermore, an *in vitro* study suggests that, PGF2α when subjected to LLC-PK1 cells of proximal tubule origin [96] in acidic condition, inhibits the ammonia production [97]. As we already discussed, ammonia metabolism is linked to sodium homeostasis and blood pressure regulation, the ultimate effect of PGF2α can influence the renal mechanisms altering blood pressure.

Taken together, various local mediators of renal hemodynamics and metabolic functions can have important mechanistic link associated with acid-base imbalance and the hypertension (**Figure 3**). Hence, identification of specific mechanism could lead to novel insight to find the cause of hypertension.

6. Conclusion

Studies evaluating the role of a disturbance in acid-base balance leading to the pathogenesis of hypertension are scarce. The involvement of various sodium-dependent transporters in the kidney tubules specifically in the proximal tubule is responsible for the maintenance of normal concentrations of bicarbonates and the secretion of ammonia. Local production of Ang II, aldosterone, cortisol, prostaglandins and heme oxygenase in the kidney is a key regulator of these transporters. Hence, study of mechanisms involved in altered acid-base balance and their ability to promote an elevation in blood pressure could reveal novel therapeutic targets for the treatment of hypertension.

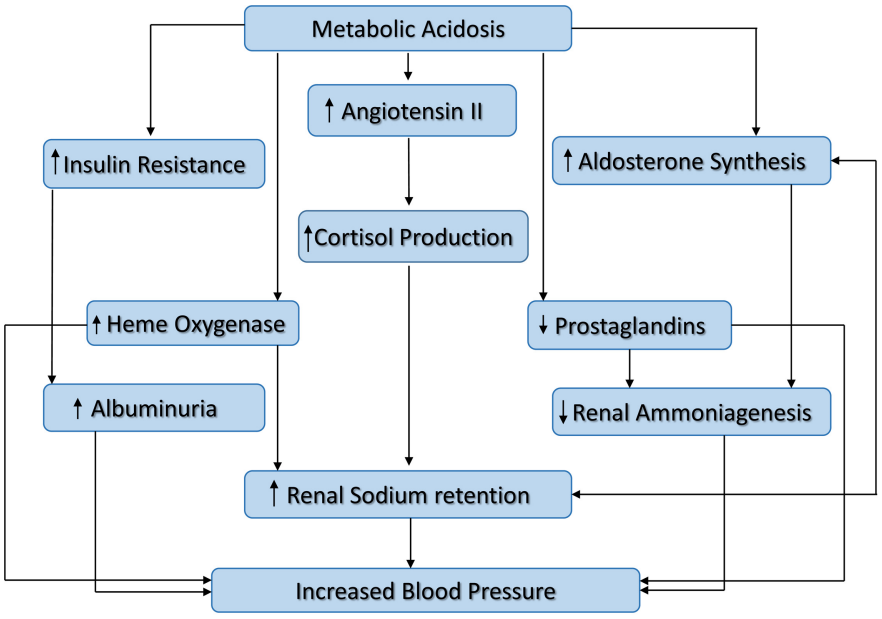

Figure 3. Possible linking mechanisms for the association between hypertension and metabolic acidosis.

Conflicts of Interest

The authors declare no conflicts of interest.

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