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Crosstalk between renin and arachidonic acid (and its metabolites)

Undurti N. Das[1,2*], Ahmet Hacimüftüoglu[2], Erol Akpinar[2], Mustafa Gul[3] and A. M. Abd El-Aty[2,4]

Abstract

Renin plays a significant role in the regulation of blood pressure and fluid volume by modulating the renin–angiotensin–aldosterone (RAAS) system. Renin suppression reduces serum aldosterone levels and lowers blood pressure in addition to preserving renal function. However, exactly how renin synthesis and action are regulated and how renin suppression preserves renal function are not clear. We propose that arachidonic acid (AA) and its metabolites control renin synthesis, secretion, and action by virtue of its (AA) anti-inflammatory, cytoprotective actions and ability to regulate the secretion of renin. These findings suggest that direct renin suppression results in changes in AA metabolism. This proposal implies that AA and its metabolites may be developed as potential drugs to prevent and manage hypertension and preserve renal function.

Keywords Renin, Renin-angiotensin-aldosterone system, Inflammation, Arachidonic acid, Nitric oxide, Neurotransmitters

Introduction

The renin–angiotensin–aldosterone system (RAAS) is critical for the maintenance of normal blood pressure and blood volume. Renin is the rate-limiting step in the RAAS. This finding implies that suppressing renin secretion controls hypertension. Long-term suppression of renin has been shown to significantly decrease blood pressure and reduce serum aldosterone levels. In addition, direct renin suppression resulted in increased mean estimated glomerular filtration rate (eGFR) levels and significant preservation of renal function. The exact cause for this beneficial action is not clear.

*Correspondence:
Undurti N. Das
undurti@hotmail.com
[1] UND Life Sciences, 2221 NW 5th St, Battle ground, WA 98604, USA
[2] Department of Medical Pharmacology, Medical Faculty, Ataturk University, Erzurum 25240, Turkey
[3] Department of Physiology, Faculty of Medicine, Ataturk University, Erzurum 25240, Turkey
[4] Department of Pharmacology, Cairo University, Giza 12211, Egypt

Juxtaglomerular (JG) cells (also called granular or renin cells) secrete renin. Some of the important factors that regulate renin secretion include salt intake, blood pressure, angiotensin II, sympathetic nerves, renal eicosanoids and nitric oxide (NO). Cyclic AMP (cAMP) is a major controller of renin synthesis and release. The intrarenal sympathetic nerves and circulating catecholamines, the intrarenal baroreceptor, and the macula densa regulate renin synthesis and release by modulating cAMP [2].

The juxtaglomerular apparatus (JGA) contains macula densa cells that monitor intratubular salt concentrations and thus regulate renal blood flow by controlling afferent arteriole constriction and dilation. The renin granules present in JG secrete renin (see Figs. 1 and 2). Thus, the JGA serves as an intrarenal baroreceptor. The JGA is innervated by β−1 adrenoreceptors that regulate renin release. Renin converts angiotensinogen (formed in the liver) to angiotensin I, which, in turn, is converted to angiotensin II by angiotensin-converting enzyme (ACE), a potent vasoconstrictor and stimulator of aldosterone secretion from the adrenal cortex. β-Blockers decrease renal blood flow and the GFR by reducing renin release, which stimulates the release of antinatriuretic hormone

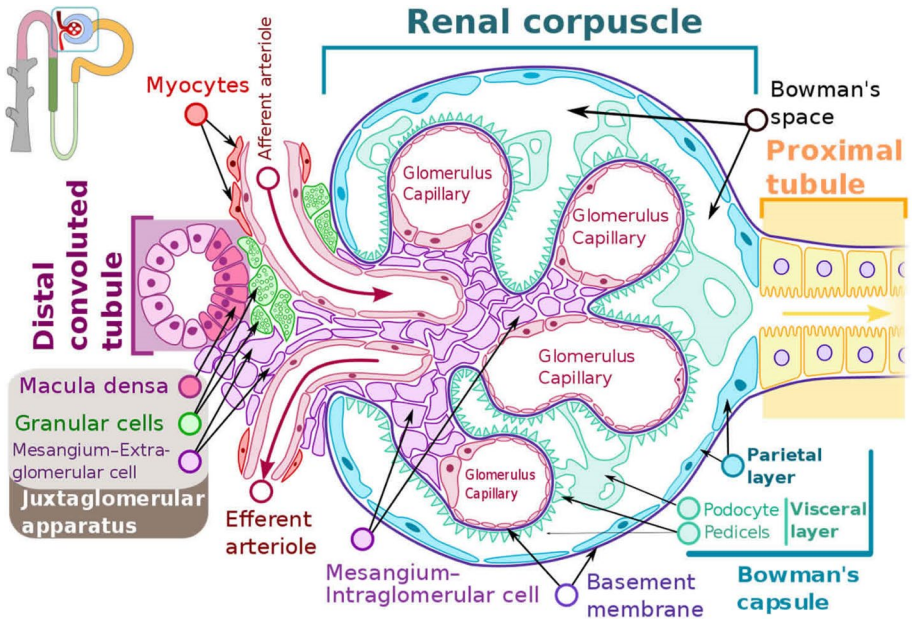


Fig. 1 The structure of the glomerular apparatus (JGA)

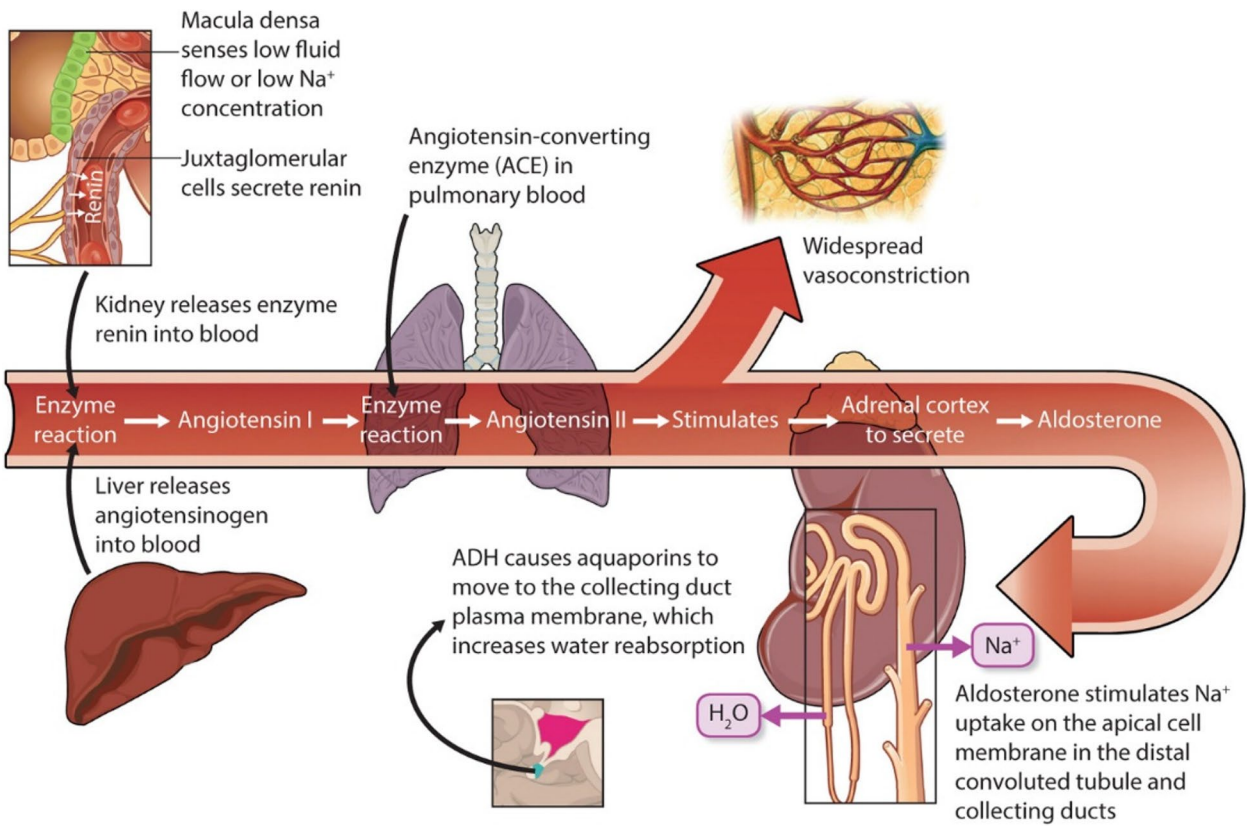


Fig. 2 Scheme showing the close relationships among the kidney, liver, lungs, adrenal cortex and vascular tissue and their relevance to the renin–angiotensin–aldosterone system (RAAS)

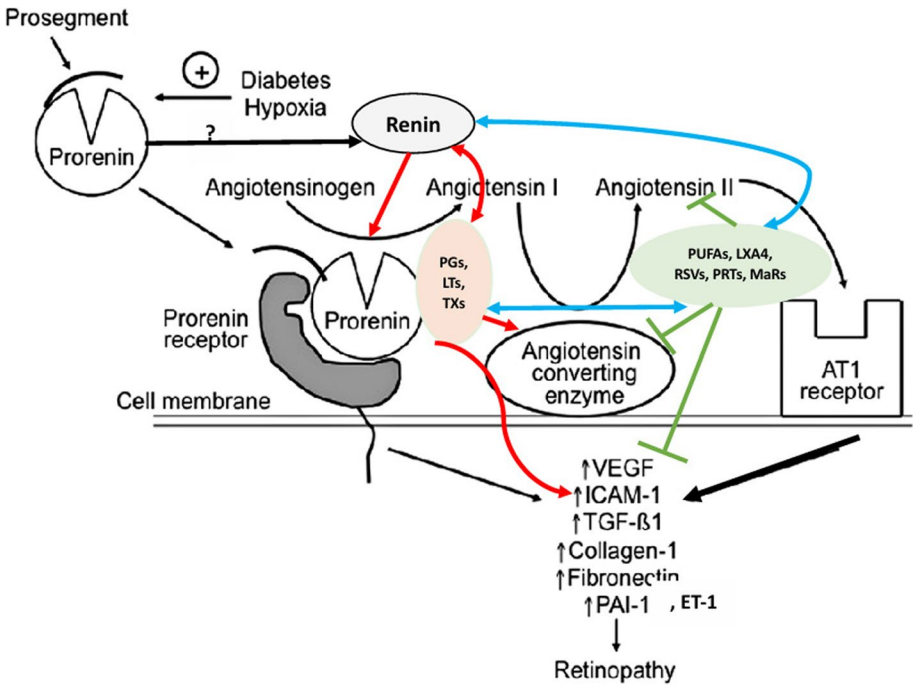


Fig. 3 Scheme showing the potential relationships among prorenin, renin, angiotensin II and EFAs and their metabolites and their relevance to some diseases. Polyunsaturated fatty acids (PUFAs: DGLA, AA, EPA and DHA) and their metabolites, such as PGs, LTs, TXs, LXA4, resolvins, protectins and maresins, can alter (suppress) the activities of renin and angiotensin-II and thus influence renal function, blood pressure, and blood volume. In contrast, PGs, LTs and TXs may increase the activities of renin, ACE, and angiotensin-II. Under physiological conditions, there is a balance between PGs, LTs and TXs vs. LXA4, RSVs, PRTs, and MaRs. PUFAs can alter cell membrane fluidity and thus alter the expression and binding of various growth factors and hormones to their receptors. LXA4 = Lipoxin A4; RSVs = Resolvins; PRTs = Protectins; MaRs = Maresins

(ADH) or vasopressin from the posterior pituitary. ADH is formed in the hypothalamus and is then transported to the posterior pituitary for secretion into the blood stream (see Fig. 2).

JG (renin) cells serve as baroreceptors to sense and transmit extracellular physical forces to chromatin, which, in turn, modulates renin gene expression and renin secretion. Renin cell integrin β1 senses changes in perfusion pressure and is transmitted to the renin cell nucleus via lamin A/C, which ultimately results in alterations in renin gene expression [3]. How exactly renin gene expression is modulated is not clear.

Renin and prorenin

Renin and prorenin are related to the renin–angiotensin system. Renin is the rate-limiting enzyme that converts angiotensinogen to angiotensin-1 (Ang-I). On the other hand, prorenin is an inactive precursor of renin with a prosegment covering the active center (see Figs. 3 and 4). Renin is an enzyme belonging to the aspartic protease family. The renin precursor prorenin has a prosegment consisting of 43 amino acids at the N-terminus, which covers the active center of renin called prorenin and is an inactive precursor [4, 5]. The human renin receptor is a 350-amino acid protein with a single transmembrane domain, and it shows renin- and prorenin-specific binding. The binding of renin results in a fourfold increase in its catalytic efficiency of angiotensinogen conversion to angiotensin I and can induce an intracellular signal with phosphorylation of serine and tyrosine residues associated with the activation of the MAP kinases ERK1 and ERK2. High levels of the renin receptor mRNA are detected in the heart, brain, and placenta, and lower levels are detected in the kidney and liver. The receptor is localized in the mesangium of glomeruli and in the subendothelium of coronary and kidney arteries, where it is associated with smooth muscle cells and colocalizes with renin [5].

Notably, prorenin and renin levels are highly correlated but do not change in parallel under all circumstances [6]. Acute stimuli of renin do not affect prorenin levels, whereas chronic stimuli lead to both increased renin and prorenin levels [6, 7], suggesting that renin is stored as an active enzyme and released immediately upon stimulation of the juxtaglomerular apparatus. In contrast, prorenin is released constitutively. Importantly, chronic stimulation causes more prorenin to be converted to renin, leading to an increased renin/prorenin

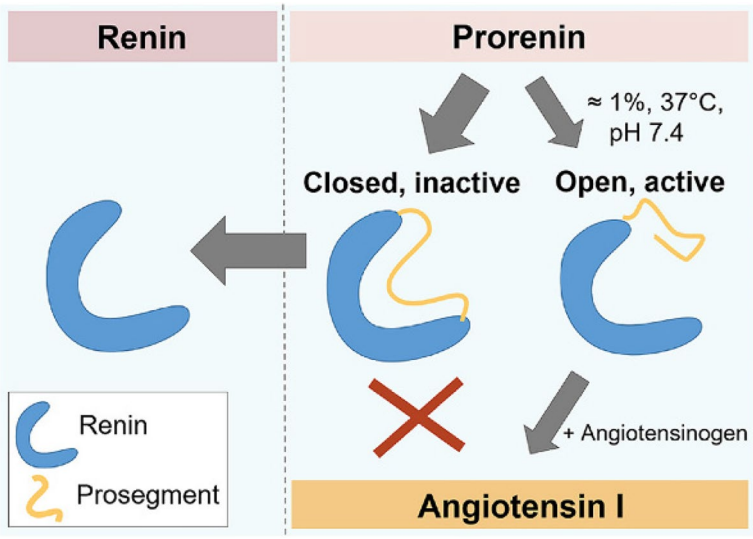


Fig. 4 Scheme showing the Renin and prorenin conformations. Under physiological conditions (pH 7.4, 37 °C), only ≈ 1% or less of prorenin occurs in the so-called 'open' conformation, i.e., a conformation where the prosegment has moved out of the enzymatic cleft, thus allowing it to react with angiotensinogen to yield angiotensin I. However, the majority of prorenin is closed and inactive. This 'proteolytic' activation occurs exclusively in the kidney, and the enzyme responsible for this activation is not yet known

ratio in plasma, although some exceptions exist for this assumption. The best example for this is diabetes mellitus complicated by retinopathy and nephropathy, wherein prorenin is increased many-fold compared with renin [8]. Pregnant women have high plasma prorenin levels, which are derived from the ovaries [9, 10], although the function of prorenin is not clear.

Prorenin in pregnancy

Pregnancy results in complex changes in various organs and systems, including but not limited to the endocrine, cardiovascular and renal systems. This is essential to ensure the smooth progress of pregnancy, appropriate growth and development of the fetus and the safety and health of the mother. Starting from the luteal phase of the menstrual cycle, these changes peak at the end of the first trimester of pregnancy (see Figs. 5, 6 and 7). These changes include systemic vasodilation; a decrease in peripheral vascular resistance; a reduction in maternal systolic, diastolic and mean arterial blood pressure; and a return to nonpregnant levels during the last month of pregnancy [11–15]. The increased heart rate in early pregnancy with increased cardiac output and left atrial dimension from preconception to midgestation decreases after 32–35 weeks of gestation. During pregnancy, a reduction in renal afferent and efferent arteriolar resistance leads to an increase in renal plasma flow (by 50–80%) and the glomerular filtration rate {GFR; by 40–65%}. As a result of these changes in renal blood flow, creatinine and urea clearance are increased. These adaptive changes are due to changes in the renin–angiotensin–aldosterone system (RAAS). Paradoxically, the levels of the renin precursor prorenin are also increased in pregnant women. This is unexpected since prorenin is inactive since a so-called prosegment covers its active site (see Fig. 4). This raises the important question as to why prorenin would rise at all.

It has been suggested that, possibly, prorenin contributes to the generation of angiotensin in nonrenal tissue(s) by binding to its receptor without the necessity for a prosegment-cleaving enzyme. Despite this interesting proposal, there is no evidence for this idea in humans. Notably, high prorenin levels are observed in those with diabetes. This so-called (pro)renin receptor [16] has been suggested to display Ang I-generating activity and to act as an angiotensin-independent agonist. However, there is no evidence for this hypothesis. This implies that (pro)renin and its receptor may have RAAS-independent functions [17, 18].

Given the increased levels of prorenin noted during pregnancy released from the corpus luteum, it (prorenin) may play a role in the modulation of maternal hemodynamic adaptation during gestation. Studies performed in animals indicate that prorenin produced and released by the placenta could play a role in the development of hypertension, proteinuria and growth restriction, which are hallmarks of preeclampsia [15]. Since there is no evidence for the conversion of ovarian/placental prorenin to renin, and under normal physiological conditions, only a very small amount of prorenin displays Ang I-generating

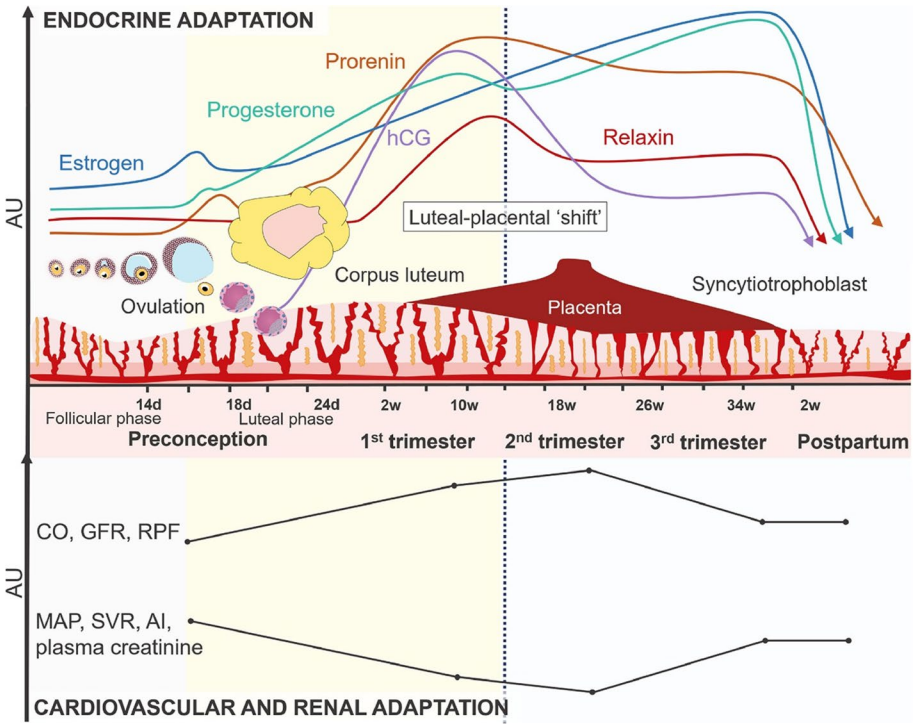


Fig. 5 Scheme showing the changes in various hormones **s**tarting from the luteal phase of the menstrual cycle, during pregnancy and during the postpartum period. These chnages include systemic vasodilation; a decrease in peripheral vascular resistance; a reduction in maternal systolic, diastolic and mean arterial blood pressure; and a return to nonpregnant levels during the last month of pregnancy

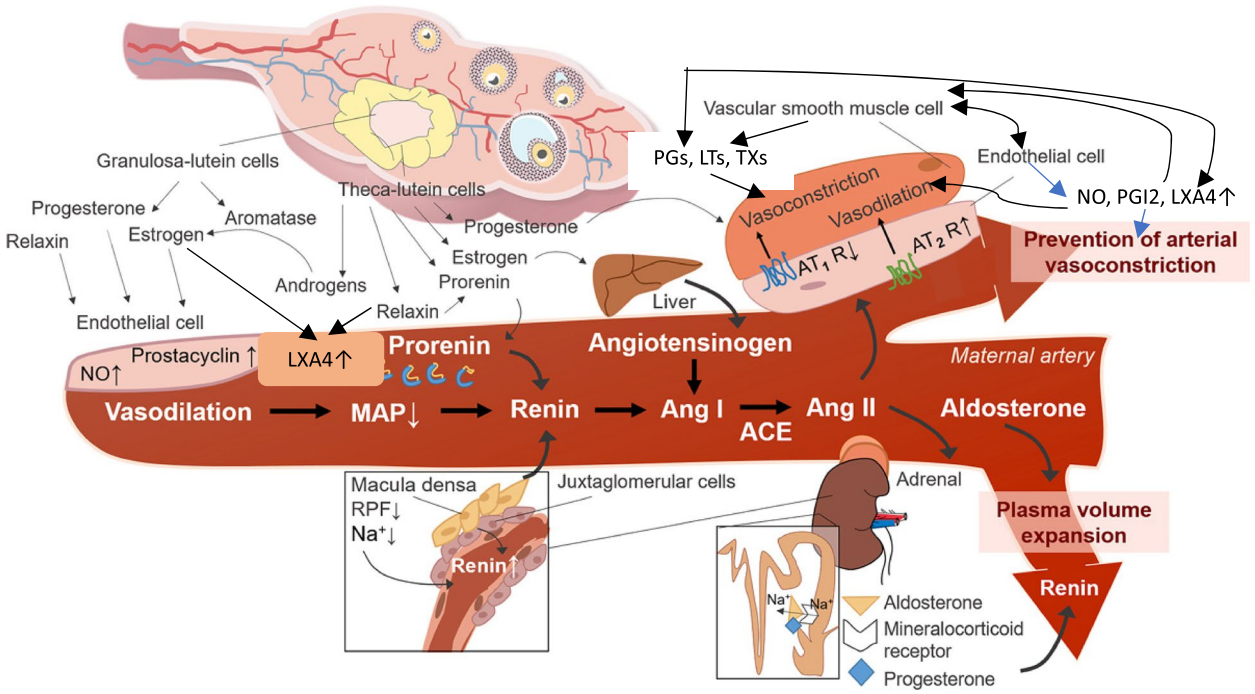


Fig. 6 Scheme showing the interaction of multiple factors secreted by the corpus luteum and their modulatory effects on the RAAS in human pregnancy. Progesterone acts as a mineralocorticoid receptor antagonist and thus blocks the effect of aldosterone. Ang. = angiotensin; AT_1R = angiotensin-II type 1 receptor; AT_2R = angiotensin-II type 2 receptor; GFR = glomerular filtration rate; MAP = mean arterial pressure; Na^+ = sodium; NO = nitric oxide; RPF = renal plasma flow

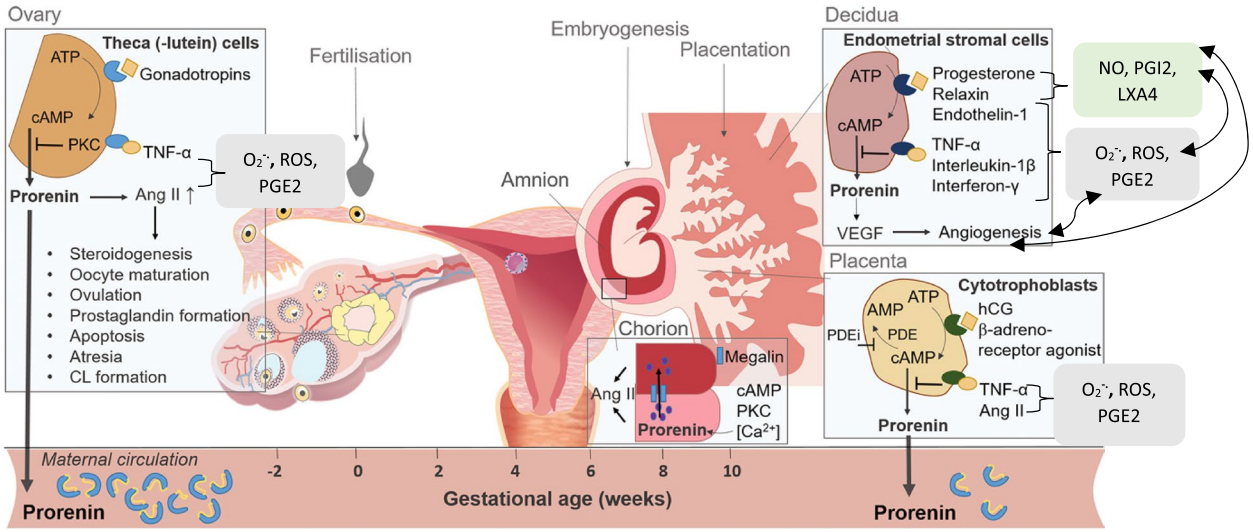


Fig. 7 Scheme showing local prorenin synthesis in the ovaries, uteroplacental unit and fetal membranes, known stimulators and inhibitors of prorenin synthesis, and possible functions (local and systemic) of prorenin. ATP = adenosine triphosphate; Ca 2 + = extracellular calcium; cAMP = cyclic adenosine monophosphate; hCG = human chorionic gonadotropin; PDE = phosphodiesterase; PDEi = phosphodiesterase inhibitor. PKC = protein kinase C; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

activity without prosegment removal, which implies that only under some very special conditions where prorenin formation and release are well beyond normal levels does prorenin lead to the formation of substantial amounts of Ang II. Such a scenario is expected to occur only when prorenin levels are > 1000-fold greater than those in blood. This is possible only in the immediate surroundings of the decidua and placenta, which are known to synthesize prorenin. However, both preeclampsia and FGR (fetal growth retardation) are characterized by low RAAS activity. Ang II derived from the ovary and uteroplacental unit seems to play a role in oocyte maturation and decidualization, angiogenesis and regional blood flow modification. It has been suggested that increased plasma levels of prorenin observed during pregnancy may be a direct vasodilator, although the exact underlying mechanism is not clear. In this context, the interaction between relaxin and endothelin-1 (ET-1) needs to be noted. Preeclampsia is characterized by low or absent relaxin levels, whereas ET-1 is upregulated. Both relaxin and ET-1 upregulate prorenin. This finding suggests that a second messenger that unifies the interaction among prorenin, Ang II, relaxin and endothelin-1 could exist. It has been proposed that second messengers could be AA and its metabolites (see Fig. 3).

AA as a potential second messenger unifying the interaction(s) among prorenin, renin, angiotensin-II, relaxin and endothelin-1

Prorenin is produced by mature ovarian follicles and the corpus luteum in response to gonadotropin stimulation. Relaxin is exclusively produced by the corpus luteum. causes relaxation via NO and prostacyclin (PGI2), and its deficiency is observed in preeclampsia. Relaxin stimulates prorenin production. Estrogens promote vasodilation via NO and PGI2 by stimulating endothelial NO synthase (eNOS) and cyclooxygenase-1 (COX-1), respectively. Estrogen additionally upregulates angiotensinogen and increases Ang II levels. Simultaneously, estrogens stimulate 11β-hydroxysteroid dehydrogenase 2 (11β-HSD-2) and thus prevent glucocorticoids from increasing blood pressure by binding to mineralocorticoid receptors. Like 17β-estradiol, progesterone causes vasodilation via eNOS and COX-1 and thus antagonizes Ang II-induced vasoconstriction. Although these factors are derived from the corpus luteum, it is not clear why it produces prorenin. It is likely that prorenin exerts its effects locally in the ovaries, uterus and/or placenta without any systemic effects [15].

Endothelin-1 (ET-1), a 21-amino acid peptide, is a vasoconstrictor produced by endothelial cells, vascular smooth muscle cells (VSMCs), macrophages, and the renal medulla. ET-1 acts on the receptors ETA and ETB, which are G protein-coupled cell-surface receptors. ETA is present on smooth muscle cells, whereas ETB receptors appear on endothelial and renal epithelial cells. Both ETA and ETB are present in the lungs. ET-1 is a potent vasoconstrictor with proliferative, profibrotic, pro-oxidative, and proinflammatory properties and maintains the tone of VSMCs. ET-1 is involved in postmenopausal hypertension, preeclampsia, and pulmonary hypertension, and its actions are antagonized by NO. Thus, the

balance between ET-1 and NO is important in maintaining normal hemodynamics.

ET-1 suppresses renal renin synthesis while stimulating decidual prorenin production. In contrast, TNF α, interleukin-1β and interferon-γ inhibit prorenin production [15, 19–22]. It has been suggested that decidual prorenin production stimulates vascular endothelial growth factor (VEGF) expression by stimulating local RAAS activation; thus, prorenin may facilitate decidualization [15].

In summary, prorenin is released by the corpus luteum to determine maternal hemodynamic adaptation in early gestation but is not converted to renin. Animal studies have suggested that excessive prorenin release by the placenta may lead to hypertension, proteinuria and growth restriction. However, there is no support for such an action of prorenin in humans. Despite this evidence, it has been argued that prorenin may have direct vasodilator effects, but the underlying mechanism is not clear. In view of the interactions among prorenin.

In view of the interactions among prorenin, renin, angiotensin-II, relaxin and endothelin-1, which are known to act on the COX, LOX and PGI2, and NO systems, it can be argued that AA is the crucial factor that acts as a second messenger at the center of these interactions. These findings suggest that when ET-1, angiotensin-II, and relaxin act on their respective cell membrane receptors, they activate phospholipases (PLAs), inducing the release of AA from the cell membrane lipid pool. The released AA will be utilized for the formation of its COX and LOX metabolites. ET-1 and angiotensin II induce the formation of proinflammatory and vasoconstrictor metabolites such as PGE2/leukotrienes (LTs)/thromboxanes (TXs), whereas relaxin stimulates the formation of NO, PGI2, and LXA4 (lipoxin A4), which are potent vasodilators. Even VEGF is known to act via AA metabolism [23].

It is likely that prorenin, renin, VEGF, Ang-II, relaxin, ET-1, estrogen, and progesterone bind to their respective receptors on the cell membrane, resulting in phospholipase A (PLA) activation, which results in the release of AA, EPA and DHA from the membrane lipid pool. This leads to the activation of the COX and LOX enzymes, which convert AA/EPA/DHA to form their respective metabolites. Notably, when ET-1, renin, TNF-α, IL-6, and Ang-II act on the COX and LOX enzymes, they induce the formation of PGs (especially PGF2α), LTs and TXs that have proinflammatory and vasoconstrictor actions, resulting in increased blood pressure. On the other hand, when relaxin, estrogen, and progesterone act on the COX and LOX enzymes AA, EPA and DHA are preferentially converted to form PGI2, PGE2 and LXA4, resolvins, protectins and maresins that are anti-inflammatory and vasodilators in nature, resulting in a reduction in blood pressure. How exactly this preferential conversion of AA (and EPA and DHA) to form pro- and anti-inflammatory compounds occurs on the basis of the stimulus (renin, VEGF, ET-1, and estrogen) is not clear. However, each stimulus can likely preferentially activate a specific PLA2 (since there are more than 20 types of phospholipases) that are able to induce the formation of a specific metabolite from AA/EPA/DHA such that either a vasoconstrictor or a vasodilator or a pro- or anti-inflammatory compound is formed. Notably, under some very specific conditions, the same stimulus can induce the formation of a vasoconstrictor or vasodilator or antiangiogenic or angiogenic compound(s) on the basis of the local conditions and requirements. For example, in diabetic retinopathy (DR), the infusion of AA may result in a reduction in the formation of VEGF (which is increased in DR). However, in CHD (coronary heart disease), AA induces the production of VEGF (which is deficient in CHD) to augment angiogenesis and the generation of collateral vessels to prevent further ischemic events. This ability of tissues/cells to induce the formation of compounds that have diametrically opposite actions from the same precursor, such as AA, suggests that we have yet to identify other factors that process the stimulus in the cells/tissues in a specific fashion that controls the metabolism of AA/EPA/DHA. The same argument may be extended to the action of ET-1, VEGF, renin, Ang-II, estrogen and progesterone to increase or reduce superoxide, ROS and NO generation (see Figs. 3, 6, 7 and 8).

It is evident from the preceding discussion that prorenin is not a direct precursor of renin but may have actions that are important in the regulation of blood volume and blood pressure since relaxin enhances prorenin production, and relaxin augments the production of NO and PGI2, which have potent vasodilators and the ability to regulate blood pressure. This interaction of prorenin with relaxin may explain its (prorenin) involvement in preeclampsia, hypertension, proteinuria and growth restriction.

When ET-1, renin, VEGF, Ang-II, estrogen, progesterone and other hormones and growth factors act on their respective receptors on the cell membrane to increase or suppress the expression of relevant genes to promote their activity, it is suggested that the release of AA (EPA/DHA) from the cell membrane lipid pool and the formation of their respective metabolites occur. Thus, AA, EPA, DHA and their metabolites (including but not limited to PGs, LTs, TXs, LXA4, resolvins, protectins and maresins) function as second messengers of various growth factors, such as the hormones ET-1, renin, VEGF, Ang-II, estrogen and progesterone. On the basis of these observations, we propose that the nuclear mechanotransduction

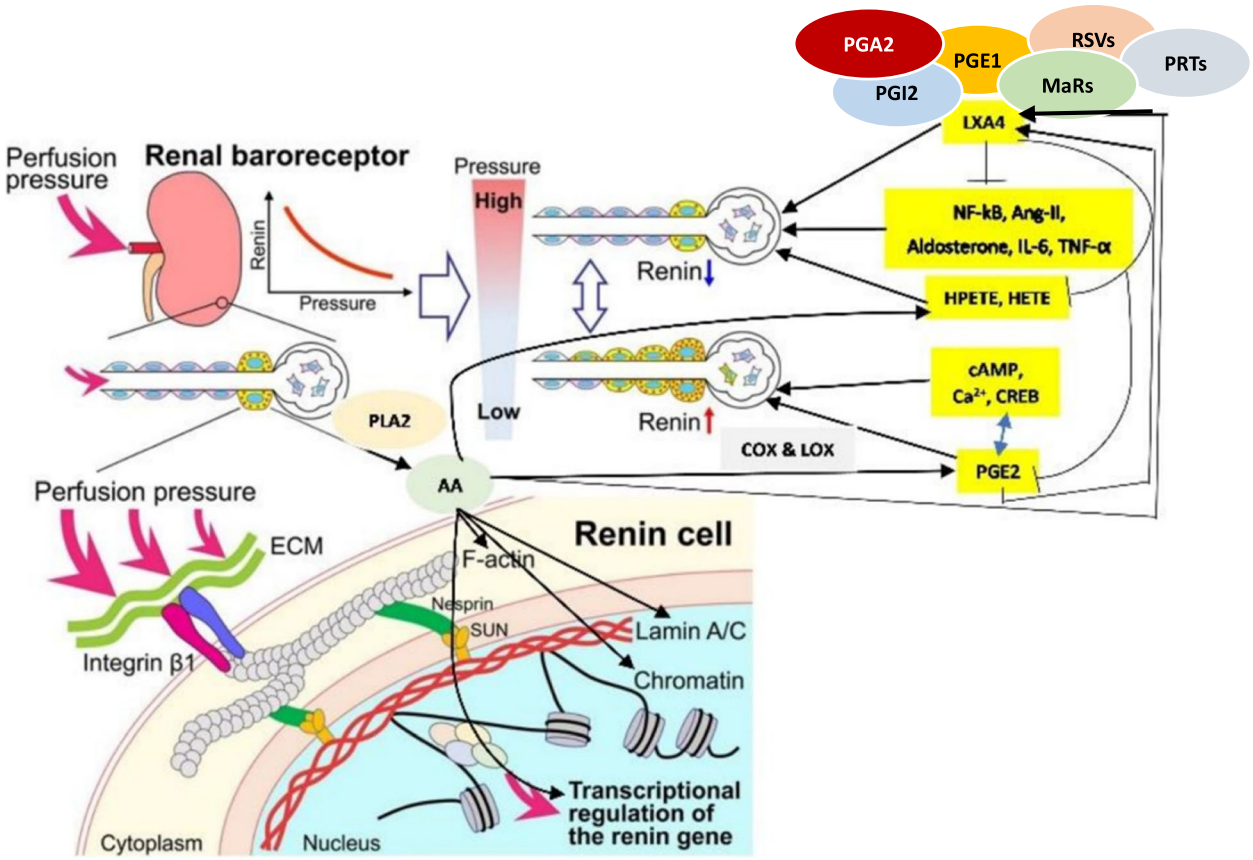


Fig. 8 Scheme showing how AA functions as a mechanotransducer and regulates renin synthesis and release. ECM = Extracellular matrix AA = Arachidonic acid; PGE2 = prostaglandin E2; LXA4 = lipoxin A4; NF-kB = Nuclear factor-kappa B; IL-6 = Interleukin-6; TNF = Tumor necrosis factor; HPETE = Hydroperoxyeicosatetraenoic acid; HETE = Hydroxyeicosatetraenoic acid; CREB = cAMP-binding protein. AA itself or its metabolites act on F-actin, lamin A/C and chromatin to regulate renin gene expression. Metabolites of AA, PGE2, LXA4, HPETE and HETE can either increase or decrease renin formation in response to changes in perfusion pressure. PGE2 can either increase or decrease renin synthesis, depending on its concentration, and bind to its various receptors. When PGE2 reaches its optimum level, it triggers the synthesis of LXA4 from AA and LXA4, which in turn inhibits PGE2 formation. NF-kB, angiotensin-II, aldosterone, IL-6 and TNF-α stimulate PLA2 to induce the release of AA from the cell membrane and enhance the formation of PGE2 and other metabolites of AA. LXA4 suppresses the expression of NF-kB and inhibits the synthesis of IL-6 and TNF-α. HPETE and HETE are proinflammatory molecules formed from AA that inhibit renin synthesis. AA and LXA4 increase the synthesis of nitric oxide (NO), a potent vasodilator. This positive and negative feedback regulation among AA, PGE2, LXA4, NF-kB, IL-6, TNF-α, angiotensin-II and cAMP can fine-tune renin synthesis and exocytosis to regulate perfusion pressure and blood pressure. These findings suggest that direct renin suppression enhances the release of AA, which is converted to LXA4 and PGI2, and enhances the formation of NO, which lowers blood pressure and protects renal tissue, thus preserving renal function. Although the emphasis has been on AA and its metabolites, other unsaturated fatty acids, such as GLA (gamma-linolenic acid), DGLA (dihomo-GLA), EPA and DHA, may also have similar beneficial effects. This figure has been modified from reference no. 24

mechanism of various cells (especially renin cells) is regulated by AA/EPA/DHA and thus modulates cellular function.

The hypothesis

Herein, we propose that the nuclear mechanotransduction mechanism of renin cells is regulated by arachidonic acid (AA) and its metabolites [4], which, in turn, modulates the secretion and action of the RAAS [24–29]. Although this hypothesis has been discussed with a focus on renin secretion and action, it has not escaped our attention because it may also have implications for the action of several growth factors, hormones, and other stimuli/factors.

Evolution of the hypothesis

A recent report revealed the existence of an elaborate network of major and minor cell processes called maculapodia projecting from the macular dense cell base toward other macula dense cells and the glomerular vascular pole that are upregulated by low dietary salt intake. The dynamic nature of renin cells (maculopodia) emphasizes

their critical role in the response of renin cells to salt and water changes in the body [29–31]. The maculapodia project into the extraglomerular mesangium and afferent and efferent arterioles to regulate cell-to-cell communication, especially between the JGA and other cells. It is possible that AA and its metabolites function as signaling molecules in this cell–cell communication to produce changes in renin cell morphology and motility, as AA is an important component of the cell membrane [31–33].

Crosstalk between the cell membrane and the nucleus

The cell membrane plays an important role in conveying messages from the external environment of the cell to its nucleus and vice versa [34, 35]. Mechanical pressures that produce changes in the cell shape are sensed by the nucleus to produce relevant alterations in cell behavior [34, 35]. Pressures exerted on the cell are conveyed to its nucleus, which serves as a ruler to tailor cell responses. Such pressure-induced changes in cell shape activate the enzyme cPLA2 (cytosolic phospholipase 2), which, in turn, recruits myosin II, leading to actin–myosin cytoskeleton contractility (see Figs. 9 and 10). The mechanical forces generated within a cell due to surrounding tissue stiffness, cytoskeletal reorganization, and changes in the physical surroundings of the cell can impose mechanical tension within the intracellular protein network (both cytosolic and nuclear). This mechanical tension may lead to a series of protein–protein interactions facilitated by membrane lipids to generate a signal(s) that drive cellular processes, including but not limited to cell differentiation, polarity, growth, adhesion, movement, and survival. The molecular mechanism of this mechanical signal transduction pathway is called "mechanotransduction". Thus, mechanical tension induced on the cell's membrane is transmitted to the cell interior, resulting in alterations in the cytoskeletal arrangement, which results in the transmission of these signals to the nucleus through the cytoskeleton and nucleoskeleton. These signals, in turn, lead to the activation of chromatin modifiers and the modulation of the epigenetic landscape, inducing chromatin reorganization and gene expression regulation and changes in chemical messengers such as transcription factors that are conveyed to the nucleus.

We hypothesize that alterations in perfusion pressure (because of changes in water and salt, exercise, alterations in cardiac function due to diseases, drugs, etc.) in the renal afferent arterioles lead to cPLA2 activation of the renin cell (which ultimately results in the formation of various metabolites of AA), resulting in changes in the actin–myosin cytoskeleton contractility of the renin cell membrane and parallel changes in renin release [24, 36–39].

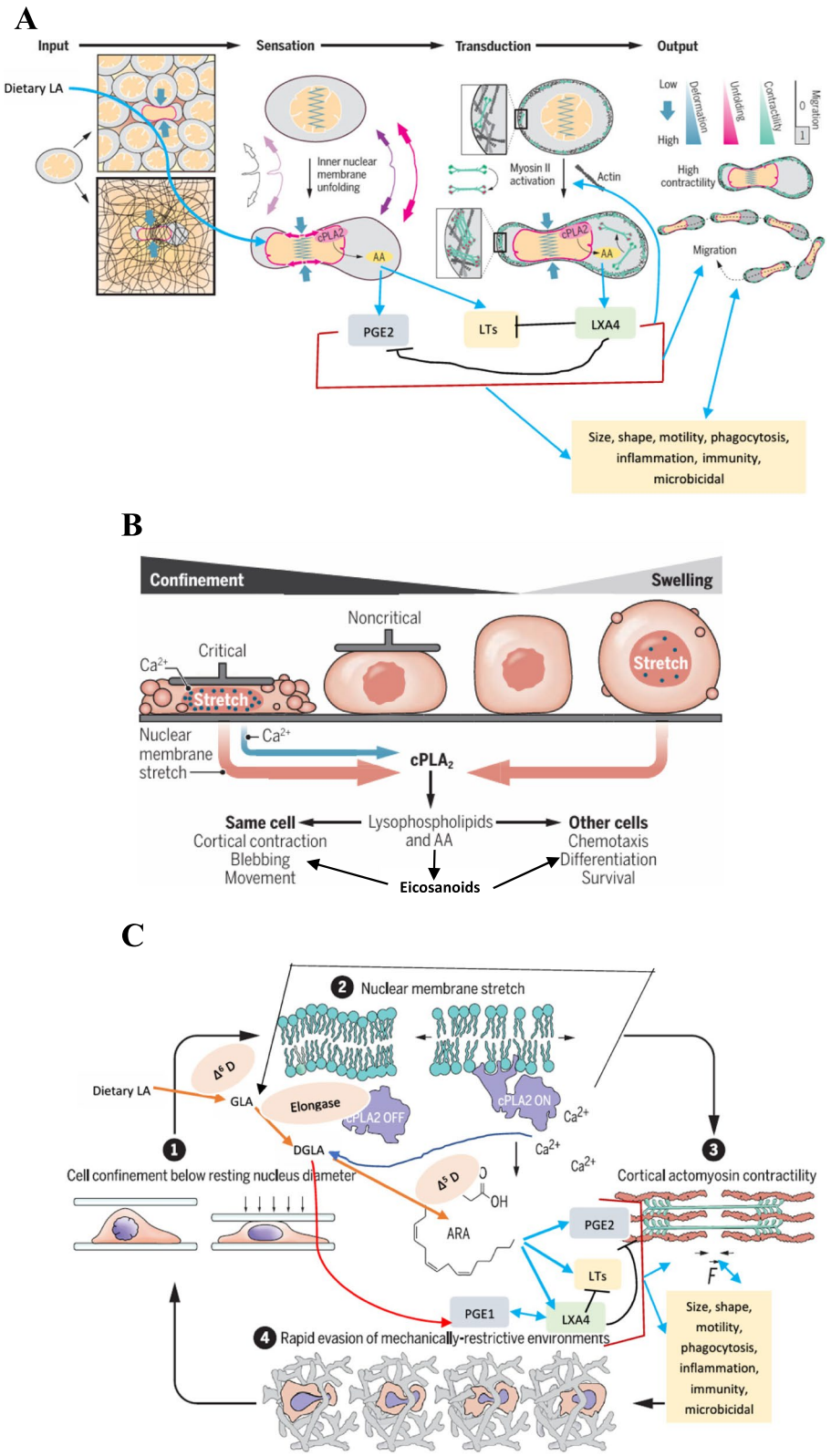
Activated cPLA2 releases AA (and possibly other unsaturated fatty acids EPA, DHA and DGLA) from the renin cell membrane. AA changes the behavior of the actin cytoskeleton (including lamin and integrin β1), and thus, the signals are transmitted to the nucleus through the nuclear pores and translocate the YAP-TAZ and MRTF-TFs. This change in the cytoskeleton and the translocation of the transcription factors YAP-TAZ and MRTF activate chromatin to change the expression of the renin gene. AA (and other unsaturated fatty acids) are precursors to several biologically active eicosanoids that can change the cell size and shape and alter cell motility and (cell) phagocytic and secretory (including exocytosis) properties. In addition, AA and other PUFAs and their eicosanoids influence inflammation and the immune response. Thus, AA of the cell membrane functions as a mechanotransducer [24]. Furthermore, AA and its products regulate the release of renin through their action on the transient receptor potential vanilloid type 1 (TRPV1) expressed in renal sensory nerves [27]. PGE2, PGI2, PGE synthase and the PGE2 receptors EP2 and EP4 have been shown to regulate renin secretion by controlling renal vascular tone [28–33, 36–39].

Regulation of renin secretion

Several factors regulate renin gene expression. The cAMP and Ca^{2+} pathways, cAMP-binding protein (CREB), and PPAR-γ (peroxisome proliferator-activated receptor-γ) increase, whereas NF-κB, IL-6, and TNF-α suppress renin gene expression and secretion [36–41]. AA and its metabolites (as well as EPA and DHA and their metabolites)

(See figure on next page.)

Fig. 9 **A** The nucleus acts as an elastic mechanotransducer of cellular shape and controls the dynamic behavior of the cell. In response to pressure, the cell shape changes, leading to inner nuclear membrane unfolding and the activation of the cPLA2-AA pathway. AA is the precursor of various eicosanoids that have several physiological and pathological actions. The unfolding of the inner nuclear membrane transduces myosin II to the cell cortex, where it regulates actin cytoskeleton contractility, which results in cell motility as needed. **B** Nuclear membrane transduction. In response to pressure or stretch stimuli, stretch in the nuclear membrane occurs in conjunction with calcium, which activates cPLA2 release and the release of AA. Eicosanoids formed from AA mediate cell autonomous and paracrine effects. **C** In response to physical pressure, cell nuclear deformation and unfolding and stretching of the nuclear envelope (2) trigger calcium release, cPLA2 activation and AA release, the precursors of several eicosanoids. These events lead to actomyosin force generation (3) and increased cell migratory capacity (4). **A**, **B** and **C** were created and modified from references 34 and 35



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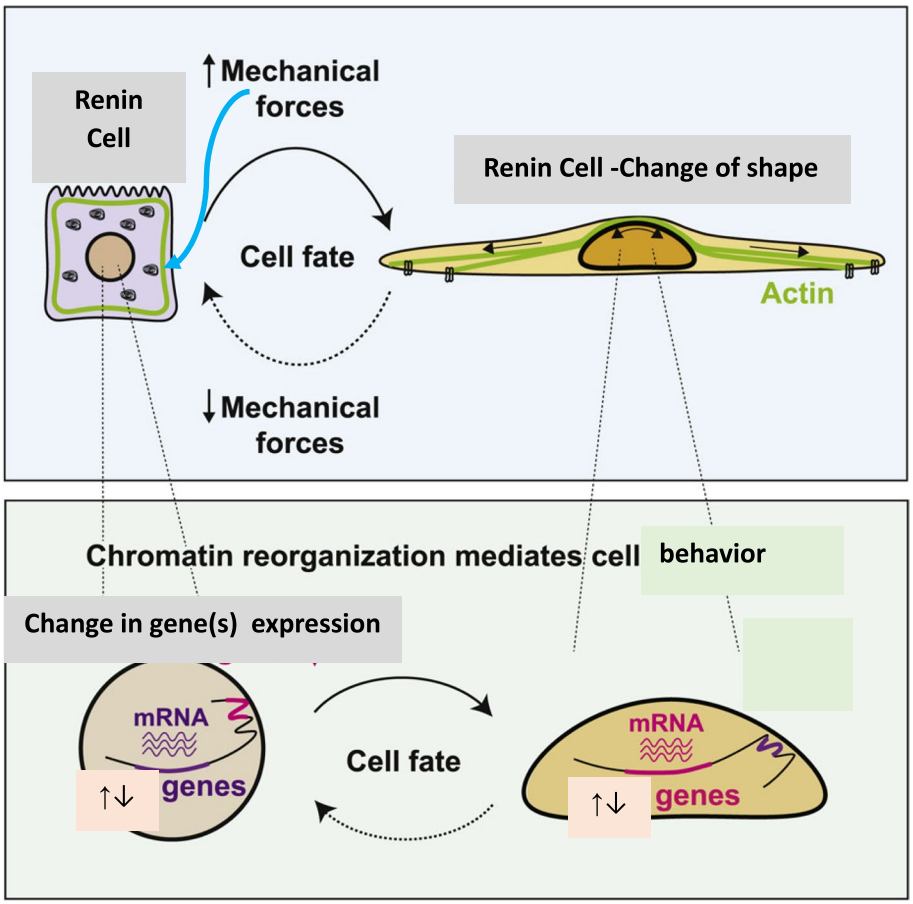

Fig. 10 A scheme showing the effect of mechanical forces (including blood flow shear stress in endothelial cells, which could be transmitted to renin cells) that modulate the actin–myosin cytoskeletal system and consequently alter the cell shape and eventually lead to chromatin reorganizations and mRNA expression and cell fate

play regulatory roles in renin gene expression [36–43] (see Fig. 11 for the metabolism of EFAs). AA (and EPA and DHA) regulate exocytosis and thus control renin secretion by interacting with syntaxin [44]. Catecholamines increase cAMP formation (via β1-receptors), and PGI2 and PGE2 suppress cAMP degradation and thus increase and suppress renin secretion [45] respectively. Nitric oxide augments renin secretion by enhancing cyclic GMP (cGMP) formation [46], whereas angiotensin-II and endothelin suppress renin release by increasing the cytosolic Ca^{2+}concentration [47]. Changes in afferent arteriole perfusion pressure (increases in perfusion pressure decrease whereas decreases in perfusion pressure increase) produce corresponding changes in the ability of JGA cells to release renin [42, 43, 48–60]. Notably, cAMP, cGMP, Ca^{2+}, CREB, PARPs, IL-6, TNF-α and NF-kB may have both inhibitory and stimulatory effects on renin and prorenin gene expression, depending on the concentration and duration of exposure of the cells to these molecules. Furthermore, each type of cell/tissue may have a different response. Thus, their actions (cAMP, cGMP, Ca^{2+}, CREB, PARP, IL-6, TNF-α and NF-kB) are cell- and tissue-specific and depend on the local concentration and exposure time.

Testing the hypothesis

The regulatory role of AA in renin secretion, action and renal function can be tested by performing relevant studies both in vitro and in vivo, as outlined below.

In vitro studies

Renin cells in culture can be exposed to various concentrations of AA, and their effects on renin synthesis (looking at renin gene expression) and secretion may be ascertained. In these studies, it will be interesting to measure the amount of prorenin, aldosterone and angiotensin-II formed and the activity of angiotensin converting enzyme (ACE). The effects of renin on AA metabolism may also be tested. It is possible that when various concentrations of renin are supplemented to

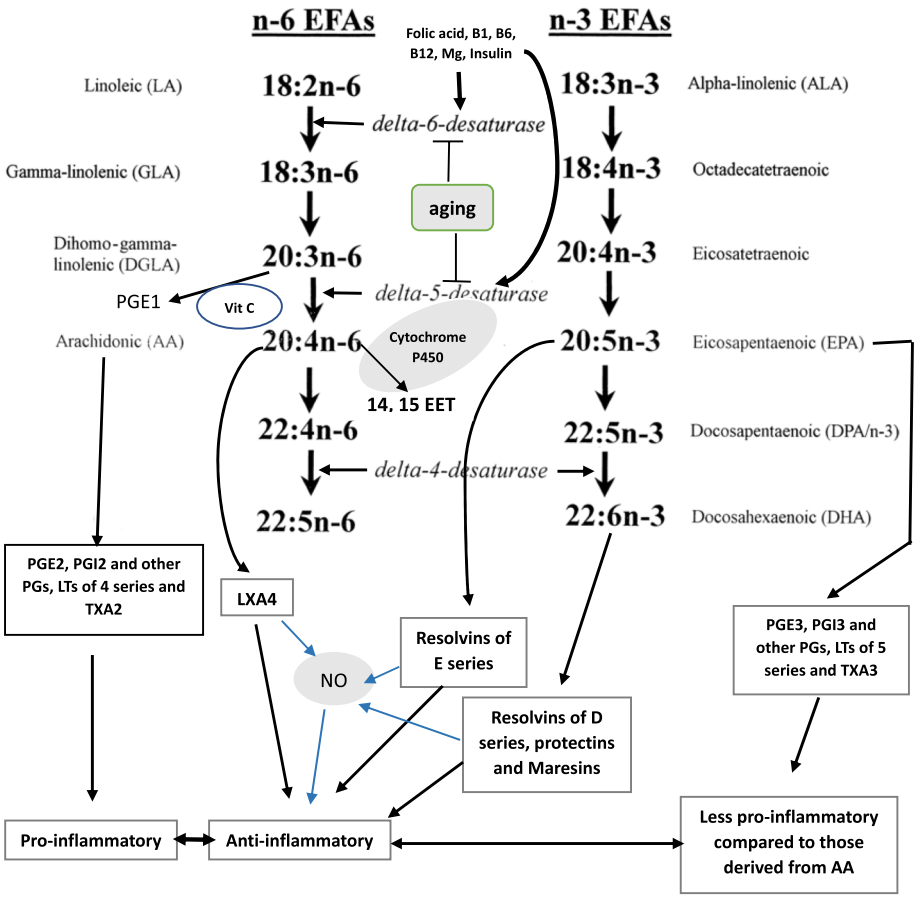

Fig. 11 Metabolism of essential fatty acids (EFAs)

renin cells, there are distinct changes in the metabolism of AA. These changes may include changes in the amounts of various PGs, LTs, TXs, and lipoxins (including resolvins, protectins and maresins) formed and secreted. In addition, it is important to measure the activities of desaturases and the enzymes COX and LOX in response to renin. Similarly, the effects of AA on the expression of the prorenin and renin genes and their protein content and the potential conversion or formation of renin from prorenin may also be measured. Dose and time (exposure to various time intervals of −24, 48, 72 and 96 h response) course studies need to be performed. In addition, the possibility that renin may alter the expression of PLA2, which is needed for the release of AA from the cell membrane lipid pool, needs to be assessed. However, various PGs, LTs, TXs, lipoxins, resolvin, protectins and maresins may have different actions and sometimes diametrically opposite actions on the basis of the concentration of the compounds and time and duration of incubation. Thus, it has been shown that the actions of eicosanoids mimic those of a bell-shaped curve, implying that the actions at lower doses may be opposite to those seen with higher doses of the compounds [61].

In vivo studies

To determine whether the results of in vitro studies reflect the in vivo situation, it is necessary to perform relevant in vivo studies. In mice, rats and rabbits, various doses of renin and prorenin may be infused into the renal artery, and in the perfusate, the concentrations of AA/EPA/DHA metabolites (PGs, LTs, TXs, lipoxins, resolvins, protectins and maresins) may be measured. Similarly, when various doses of AA/EPA/DHA are infused for different durations, the amount of renin/prorenin that is secreted can be measured. In addition to the effect of renin, the effects of AA infusion on the amount of aldosterone, angiotensin-II and ACE activity have also been measured. In these animal studies, renal blood flow, blood pressure, the amount of urine formed and the composition of urine (such as its sodium, potassium and other minerals; renin, aldosterone, and angiotensin-II) can also be assessed.

The results of the in vitro and in vivo studies outlined above may help elucidate the potential interaction between renin and AA. In vitro studies may reveal the local effects of AA (EPA/DHA) and its metabolites, whereas in vivo studies may delineate the systemic actions of AA and its metabolites. While performing these studies, one needs to pay attention to the potential interactions among various metabolites formed from them, as some metabolites may have diametrically opposite actions compared with certain other metabolites.

Implications

It is evident from the preceding discussion that AA and its metabolites, various neurotransmitters, catecholamines, angiotensin-II and endothelin and neuropeptides play regulatory roles in renin synthesis and release and its actions [62–67]. Hence, the long-term beneficial action of direct renin inhibitors in those with high renin levels, which are associated with well-preserved renal function, could be attributed to the increased formation and release of vasodilators and platelet antiaggregatory and anti-inflammatory metabolites of AA, such as PGI2, lipoxin A4, resolvins, protectins, maresins, and NO. In addition, the inhibition of renin can result in the reduced formation of angiotensin-II, aldosterone, and the proinflammatory cytokines IL-6 and TNF-α. This suggestion can be verified by measuring the plasma and urine concentrations of various PGs (especially PGI2 and PGE2), LXA4, HETEs and HPETEs, and NO in addition to plasma angiotensin-II, aldosterone and catecholamines.

Endothelial dysfunction plays a role in the pathogenesis of hypertension. Patients with essential hypertension have high levels of superoxide anion and hydrogen peroxide and low NO, with concomitant decreases in vitamin E and superoxide dismutase (SOD) and increases in lipid peroxides [62], which revert to normal after the control of hypertension [62]. An increase in the circulating levels of IL-1ra (IL-1 receptor antagonist) and IL-1 and IL-6 has been reported in patients with uncontrolled hypertension, suggesting that hypertension is an inflammatory condition [62–68]. Increased sympathetic activity may further aggravate the inflammatory milieu in hypertension since epinephrine and norepinephrine are proinflammatory in nature [69]. In contrast, acetylcholine, the vagal neurotransmitter has anti-inflammatory effects [70] and enhances endothelial NO generation. Acetylcholine is an anti-inflammatory molecule [70]. Acetylcholine is also a potent stimulator for lipoxin A4 (LXA4) generation. Patients with hypertension have low plasma concentrations of AA, the precursor of LXA4, implying that LXA4 deficiency could occur in essential hypertensive patients [71, 72]. Patients with hypertension have increased plasma levels of asymmetrical dimethyl arginine (ADMA), an inhibitor of NO generation [73]. Angiotensin-II is proinflammatory in nature [74]. LXA4 enhances eNO generation [75]. Previously, it was shown that AA enhances the formation of LXA4 [76] and inhibits angiotensin-converting enzyme (ACE) activity [77]. Because of these actions, AA is considered an anti-inflammatory and antihypertensive molecule. Furthermore, AA augments eNO generation [78]. These results suggest that renin secretion and action are regulated by AA and its metabolites and that the beneficial action of long-term suppression of renin may be attributed to increased formation of beneficial AA/EPA/DHA metabolites (see Fig. 11).

Although it is strongly believed that prorenin is unlikely to be converted to renin, there is some evidence to suggest that this could indeed occur [79]. However, paradoxically, prorenin circulates in human plasma in excess of renin, sometimes 100 times higher. Notably, bolus infusions of recombinant human prorenin do not increase the levels of renin, suggesting that there is little evidence for prorenin–renin conversion in the circulation [80].

The strong support for the regulatory role of essential fatty acids and their metabolites in the regulation of renin is derived from the observation that dietary unsaturated fatty acids inhibit renin secretion in the isolated perfused rat kidney [81, 82]. More studies are certainly needed to prove that this is indeed the case in humans.

Limitations and conclusions

Despite the evidence that an interaction exists between AA, EPA and DHA and their metabolites and renin (and RAAS), several other factors that influence such an association need to be considered. The fluidity of the cell membrane and consequently the transfer of signals from the membrane to the nucleus can be influenced not only by unsaturated fatty acids but also by cholesterol content. Thus, the ratio of unsaturated fatty acids (especially AA) to cholesterol needs serious consideration when the mechanotransducer function of AA and other unsaturated fatty acids is considered. The amount of AA/EPA/DHA released from the cell membrane is dependent on the activity of PLA2 and the subtypes of PLA2. There are several isomers of PLA2 (more than 12). The type of eicosanoid generated from the released AA/EPA/DHA is determined by the type of PLA2 activated.

Furthermore, the concentrations of AA and other unsaturated fatty acids in the cell membrane depend on the activities of desaturase enzymes that are essential for the conversion of dietary linoleic and alpha-linolenic acids to AA and eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, respectively (see Fig. 11 for the metabolism of essential fatty acids). Several endogenous and exogenous factors regulate the activities of

desaturases. Similarly, several factors regulate the conversion of AA, EPA and DHA to their respective eicosanoids by altering the activities of the COX and LOX enzymes. In addition, the activity of 15-PGDH (15-prostaglandin dehydrogenase), the enzyme that degrades eicosanoids, is important since it affects the plasma and local tissue concentrations of various prostaglandins (PGs).

AA, EPA and DHA are relatively stable and have much longer half-lives than eicosanoids, which are highly unstable and have much shorter half-lives (a few seconds to minutes). This implies that AA, EPA and DHA and their eicosanoid metabolites that possess different and at times opposite actions may interfere with each other's actions, so dissecting their differential actions may prove to be difficult, if not impossible, at times. Thus, while the roles of AA/EPA/DHA and their metabolites in the regulation of renin/prorenin are being studied, all these variables need to be taken into consideration, especially the diametrically opposite actions shown by some of their metabolites, as already discussed above. This contention is supported by our previous work [83] where we noted that PGE2 can both increase and suppress the activity of normal human leukocyte alkaline phosphatase activity, depending on the dose employed. This study revealed that high ($10^{-}3$ M) and low (10^{-11} M) PGE2 concentrations have the same effect on some biological systems.

If the proposal presented here is correct, it implies that the administration of AA/EPA/DHA (orally or parenterally) modulates the synthesis, release and activity of renin/prorenin. These findings suggest that AA/EPA/DHA may have antihypertensive and renoprotective properties that could be exploited and explored in the prevention and management of hypertension. The metabolites of AA/EPA/DHA that may have these beneficial effects include PGE1 (formed from DGLA); PGI2, LXA4, and PGA2 (formed from AA); and resolvins, protectins and maresins (formed from EPA and DHA). To delineate the specific metabolites that could have the most dominant or beneficial action, various metabolites of AA/EPA/DHA should be measured in the in vitro and in vivo studies suggested above.

Abbreviations

ACE	Angiotensin converting enzyme
AA	Arachidonic acid
cAMP	Cyclic AMP
cGMP	Cyclic GMP
CREB	Cyclic AMP-response element-binding protein
cPLA2	Cytosolic phospholipase 2
DHA	Docosahexaenoic acid
EP2 and EP4	PGE2 receptors
EPA	Eicosapentaenoic acid
GFR	Glomerular filtration rate
HETE	Hydroxyeicosatetraenoic acid
HPETEs	Hydroperoxyeicosatetraenoic acid
IL-6	Interleukin-6
IL-1	Interleukin-1
JGA	Juxtaglomerular apparatus
JG cells	Juxtaglomerular cells
LXA4	Lipoxin A4
MRTF	Myocardin-related transcription factor
NF-κB	Nuclear factor-κappa B
NO	Nitric oxide
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PGI2	Prostacyclin
PGE2	Prostaglandin E2
PGs	Prostaglandins
RAAS	Renin-angiotensin-aldosterone system
TRPV1	Transient receptor potential vanilloid type 1
TNF-α	Tumor necrosis factor-α
TAZ	PDZ-binding motif
TEAD	TEA domain family member–binding domain
YAP	Yes-associated protein
MRTF-YAP	is an activator of the YAP/TAZ–TEAD target gene, and these 2 pathways act to respond to extracellular stimuli to produce a context-dependent switch during mechanical or chemical signaling

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Authors' contributions
UND originated the idea and wrote the draft and final manuscript. AH, EA, MG, AE collected the data, and drafted the initial manusxript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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The authors declare no competing interests.

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