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Endocannabinoid system: An untold story in hypertensive nephropathy

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ABSTRACT

Prognosis of hypertension leads to organ damage by causing nephropathy, stroke, retinopathy and cardiomegaly. Kidney, retinopathy and blood pressure (BP) have been discussed in plenty in relation with catecholamines of autonomic nervous system (ANS) and angiotensin II of renin angiotensin aldosterone system but very little have been told about the role of endocannabinoid system (ECS) in the regulation of kidney function, retinopathy and BP. ECS is a unique system in the body, which can be considered as master regulator of body functions. It encompasses endogenous production of its cannabinoids, its degrading enzymes and functional receptors, which innervate and perform various functions in different organs of the body. Kidney, retinopathy and BP pathologies arise normally due to elevated catecholamine and ang II, which are vasoconstrictor in their biological nature. Question arise which system or agent counterbalances the vasoconstrictors effect of noradrenaline and ang II in normal individuals? This review will not only try to illustrate the significance of ECS in the kidney and BP regulation but also establish the connection of ECS with ANS and ang II. This review will also explain that ECS, which is vasodilator in its action either independently counteract the effect produced with the vasoconstriction of ANS and ang II or by blocking some of the common pathways shared by ECS, ANS, and ang II in the regulation of kidney and BP regulation. This article conclude that persistent control of BP and normal functions of kidney is maintained either by decreasing systemic catecholamine, ang II or by up regulation of ECS, which will result in the regression of nephropathy, stroke, retinopathy, and cardiomegaly induced by hypertension.

Keywords: hypertension, nephropathy, retinopathy, endocannabinoids

INTRODUCTION: ENDOCANNABINOID SYSTEM AND ITS AGONISTS

Endocannabinoid system (ECS) is the poorly studied system in human body as it contains stigma word “cannabis”. It has been documented that ECS is directly involved in apoptosis, levels of neurotransmitter and homeostasis [1]. Similar to renin angiotensin system (RAS) and autonomic nervous system (ANS) (autonomic system), ECS has wide distribution throughout the human body in different organs like gut [2], kidney [3], brain [4], heart [5], and eyes [6]. Similar to RAS and ANS, this system possess its own receptors and ligands, which are involved in many human body functions like antiproliferative, anti-inflammatory and antimetatstic effects [7].

ECS consists of the two endogenous agonists of cannabinoid receptor agonists, anandamide (AEA) and 2-arachidonylglycerol (2-AG) [8], their respective hydrolyzing enzymes, fatty acyl amide hydrolase (FAAH) [9] and monoacylglycerol lipase (MAGL) [10], and the cannabinoid receptors, CB1 [11] and CB2 [12]. AEA is synthesized mostly by release from N-arachidonoyl phosphatidylethanolamine (PE) mediated by N-arachidonoyl PE-specific phospholipase D, and its agonist effect on CB receptors is controlled by FAAH-mediated metabolism to inactive arachidonic acid and ethanolamine [12]. In contrast, 2-AG is synthesized from membrane phospholipids by phospholipase C beta and diacylglycerol lipase (DAGL), and it undergoes hydrolysis by MAGL to form arachidonic acid and glycerol [13].

Although AEA and 2-AG are well known endogenous representatives of ECS but there are some other endogenous agonists, which are not well known as N-arachidonoylethanolamine (anandamide, AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonyl glyceryl ether (noladin ether), N-arachidonoyl dopamine (NADA), and O-arachidonoyl-ethanolamine (virodhamine) [14]. The first endocannabinoids was AEA, which was found in procine brain which was later found to be member of family known as N-acylethanolamine (NAE) [15] while other well know 2-AG was identified in rat brain and canine gut [16]. After the discovery of Noladin ether, which is synthesized analogue of 2-AG, which was later found to present endogenously in porcine brain [17].

Biosynthesis of Endocannabinoids and Their Hydrolysis

AEA synthesis take places from lipid membranes precursor PE to N-acylphosphatidylethanolamine (NAPE) by the activation of N-acetyletransferase (NAT). NAPE produce AEA by the involvement of phospholipase D (NAPE-PLD) [18] (**Figure 1**).

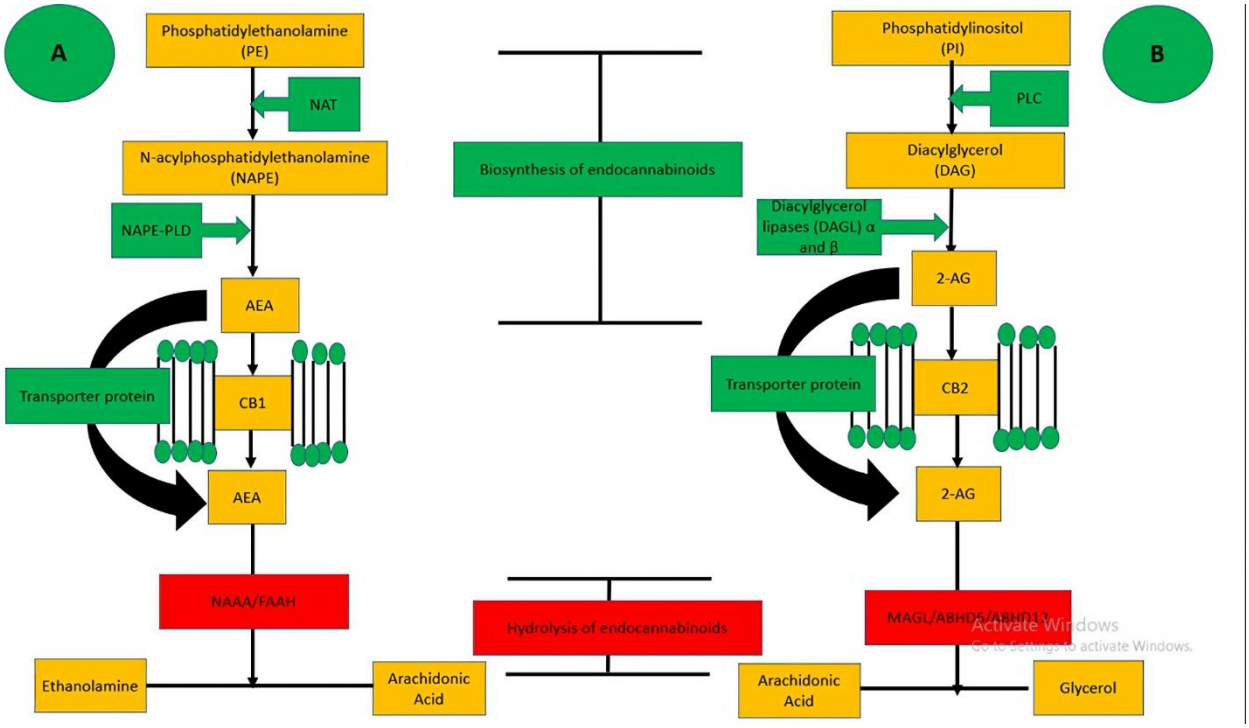

Figure 1. Biosynthesis & hydrolysis steps of AEA (A): PE was converted to NAPE by help of an enzyme called as NAT. NAPE is further converted to AEA by involving one enzyme NAPE-PLD. AEA follow two pathways either attached to CB1 receptor & elicit pharmacological response or it is hydrolyzed by enzyme FAAH & NAAA-mediated hydrolysis to ethanolamine and arachidonic acid. Biosynthesis & hydrolysis steps of 2-AG (B): PI is converted to DAG with help of an enzyme phospholipase C (PLC). DAG is converted to 2-arachidonoylglycerol (2-AG) by an enzyme diacylglycerol lipase (DAGL α & β). 2-AG follows two pathways either attached to CB2 receptor & elicit pharmacological response or it is hydrolyzed by three enzymes MAGL, α & β-hydrolase-6 (ABHD-6), & ABHD-12 into glycerol & arachidonic acid (Source: Author's own elaboration, using [18-21])

Biosynthesis of 2-AG begins with the hydrolysis of lipid membrane mediated by phospholipase C, which results in the production of diacylglycerol (DAG) from phosphatidylinositol (PI), which later converted to 2-AG by an enzyme diacylglycerol lipases DAGL α and DAGL β [19], as shown in **Figure 1**.

After endogenous production of both agonists are released into the extracellular space, bind to specific receptor, and produce biological response. As these are produced on demand to produce biological effects but in pathological situations or to terminate effects of endogenous agonists are terminated by catalytic enzymes [20]. AEA is hydrolyzed into arachidonic acid (AA) and ethanolamine by a well-known enzyme FAAH and lesser known N-acylethanolamine-hydrolyzing acid amidase (NAAA) [21].

Innervations of RAS, ANS, and ECS in these vital organs have been discussed a lot in literature but cross talk has not done to understand the linkage of these systems with each other and regulation of functions of these organs by using three systems. As mentioned above RAS and ANS are potent vasoconstrictors while the presence and role of ECS must be justified as vasodilator and regulator of RAS and ANS. It would be interesting to know the onset of hypertension and its prognosis by keeping in view the role of potential vasoconstrictor systems RAS and ANS and a vasodilator ECS system. Apparently, it seems that vasoconstrictor systems RAS and ANS are opposed by a vasodilator ECS, which helping these vital organs to main homeostatic environment. It can be assumed that vasoconstriction/vasodilation equation in physiological situation is disrupted and lead to pathological situations. It would also be interesting to know the status of all three systems in physiological and pathological situations. It can be deduced that role of endocannabinoids has not been addressed properly when compared to RAS and ANS while a story of three is explained by two systems.

HYPERTENSION AND RESISTANT HYPERTENSION

Hypertension is one of the leading causes of nephropathy, retinopathy, stroke and cardiopathy. According to new recommendation by American College of Cardiology/ American Heart Association (AHA) for the detection, evaluation and management of high blood pressure (BP) in adult the goal of BP treatment was reduced for systolic and diastolic BPs to >130/80 mmHg [22]. Hypertension managed at baseline level does not harm the vital organs but when hypertension becomes persistent and turn to resistant hypertension it can cause organ damge nephropathy, retinopathy, stroke and cardiopathy. Resistant hypertension can be defined as BP of hypertensive patients that remains elevated above the base line even concurrent use of three different classes of antihypertensive drugs at their maximally tolerated dose. These classes are mostly calcium channel blocker (CCB), a blocker either from angiotensin converting enzyme (ACE) or angiotensin receptor blockers (ARBs) and a diuretic [23]. In a retrospective study of >200,000 patients with incident hypertension, those with RH were 47% more likely to suffer the combined outcomes of death, myocardial infarction, heart failure, stroke, or CKD [24]. Persistent, uncontrolled elevated BP may be an early sign of resistant hypertension. Better control of BP will lead to the poor prognosis of hypertension and vice versa.

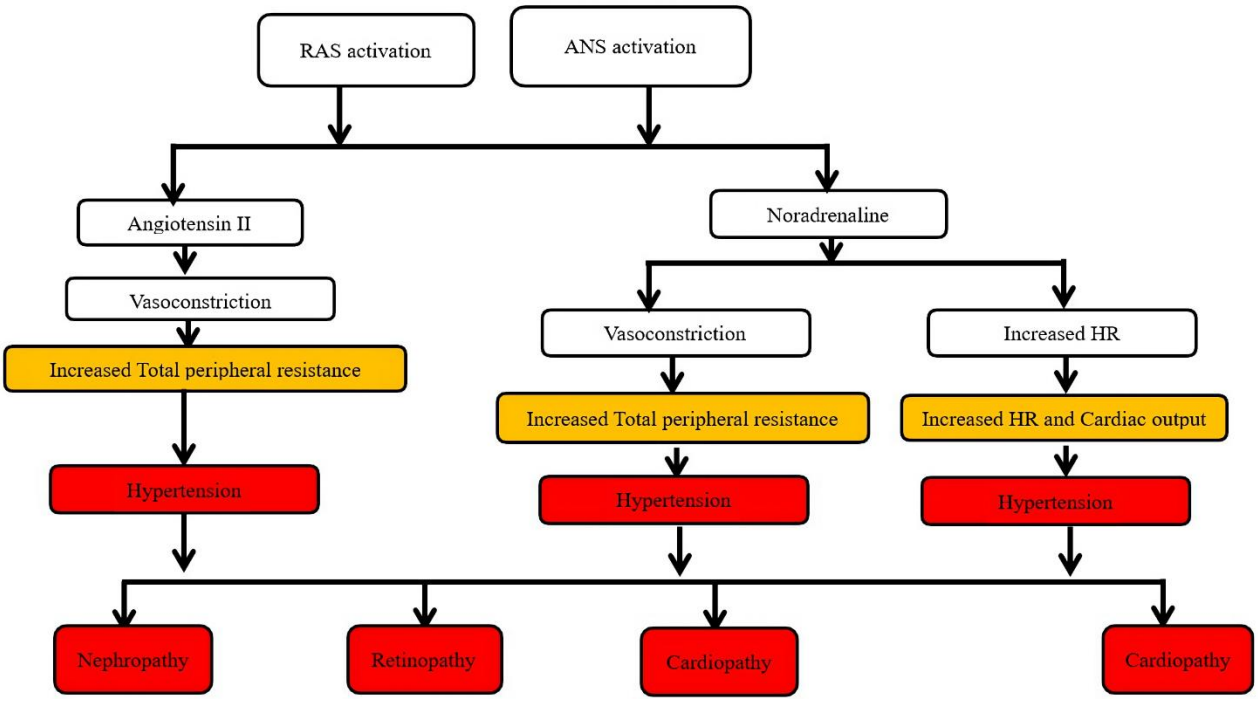

Figure 2. Role of RAS & ANS in pathogenesis of different disease in body. Both noradrenaline & ang II produce systemic vasoconstriction, which increase peripheral vascular resistance. This increased resistance in globally & regionally result in disease of regional organ like nephropathy, retinopathy, & cardiopathy (Source: Author's own elaboration, using [24-28])

Pathophysiology of Hypertension

Maintenance of BP is balance between cardiac output and peripheral resistance. A person with normal cardiac output may have high peripheral resistance, which can be manifested not only in large arteries but also in capillaries and arterioles. Many factors have been accounted for raised BP and among these renin-angiotensin system, sympathetic nervous system, salt intake, insulin resistance and obesity while minor factors are genetics, endothelial dysfunction due to change in endothelin and nitric oxide [24]. Apparently vasoconstriction of arterial bed seems to be a major reason for hypertension and sympathetic nervous system [25, 26] and renin angiotensin aldosterone system (RAAS) seems major factors involved in the pathogenesis hypertension [27, 28]. In pathological state both systems RAS and ANS dominate and produce their effect through various mechanisms as shown in **Figure 2**.

Another minor factor, which can induce vasoconstriction may be endothelin. At present, most of the classes (angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), alpha blockers, calcium channel blockers and direct vasodilators) used for the management of hypertension are aimed to offset the arterial vasoconstriction while only beta blockers are aimed to normalize the heart rate by blocking β1 receptors on heart. Only prominent vasodilator in the body that causes vasodilation in endothelial cells and vascular smooth muscle is nitric oxide pathway [29]. Nitric oxide is endothelium derived relaxing factor [30] an intermediate pathway, which produces its effect by upregulating NO/CGMP pathways. In case of essential hypertension, reduced levels of NO in the plasma [31] and impaired endothelium dependent vasodilation are observed [32]. This can be deduced that up regulation of noradrenaline and ang II (vasoconstrictor pathway) results in down regulation of NO/CGMP pathway (vasodilator pathway).

Question arises, as follows:

1. What control these vasoconstrictor systems in persons having normal BP?
2. Is there any vasodilator system in the body, which counterbalances vasoconstrictor system?
3. Hypertension is either dominance of these vasoconstrictor systems or absent of vasodilator system?

Indeed, hypertension is a story of two systems that cause vasoconstriction, but which system is remained unexplained that counter act both systems. We assumed that unexplained system is ECS that causes vasodilation and counterbalances vasoconstriction of both RAS and ANS in normal individual.

Role of Endocannabinoid and Exogenous Cannabinoids in Hypertension

Massive amount of data is witness for therapeutic role of ECS in hypertension [33-37]. Main reasons that support substantial role of ECS in hypertension is based upon three aspects:

(1) vasodilatory effect of endocannabinoids [38],

(2) overactivation of endocannabinoid tone in hypertension [39], and

(3) dominant hypotensive action in hypertensive animals when compared to normotensive animals [39].

Antihypertensive activity of ECS is also attributed to vasculo-protective action [38, 40]. The well-known mechanisms attributed to relaxant properties of ECS are,

(1) stimulation of classical CB1 and/or CB2 receptors,

(2) TRPV1 receptors,

(3) calcium channels activation, and

(4) inhibition of calcium entry, along with

(5) endothelium-dependent mechanisms [40].

The effect of ECS on BP and heart rate (HR) is complex and depends upon the status of animal whether anesthetized or not and response on BP was triphasic [41]. This study made conclusion that activation of CB1 receptors downstream the mechanism inhibits the release of norepinephrine, negative ionotropic effect on heart and stimulation of endothelial hypothetical receptor.

AEA and 2-AG have different effects in conscious animals. AEA when given to conscious animals resulted in increased plasma norepinephrine level, increased renal sympathetic tone and increased in BP when given intracerebroventricular to both conscious and anesthetized animals [41]. Same study observed monophasic effects of 2-AG on circulatory system when given to rats anesthetized either with urethane or pentobarbital. The ECS seems does not play a significant role in cardiovascular physiological system, which can be argued with result of AEA and MethAEA when given intravenously in spontaneously hypertensive rats (SHR) and different animal models of secondary hypertension induce hypotension when compared normotensive rats. Another evidence of ECS effectiveness can be argued by action of CB1 receptors antagonist, rimonabant and AM251, 2 FAAH inhibitors, URB597 and AM3506, reduce elevated BP and cardiac contractility while these parameters remain unchanged in normotensive rats. Prolonged hypotension was observed after acute administration of EC agonist like AEA and inhibitors of FAAH, URB 597, in hypertensive rats while such convincing results were never observed in chronic administrations. AEA decreased BP in SHR [42] but increases BP in salt sensitive rats [43]. Differences in observed effects may be unrelated dose, treatment duration, frequency, and route of administrations.

Keeping in view the significance of ECS agonists, attempts were made to synthesize exogenous cannabinoids to mimic the effects of endocannabinoids either by facilitating biosynthesis of EC agonists or avoiding their degradation by inhibiting hydrolyzing enzymes as shown in **Figure 1**. latest research focused on blocking the receptors of ECS like rimonabant (SR141716) [44], AM6545 and AM4113 [45] antagonists for CB1 and SR144528 antagonist for CB2 [46] while AM1241 have been employed as agonists for CB2 receptors to get therapeutic responses. Other than synthesized agonists and antagonists for CB1 and CB2 receptors, researchers also focused the inhibition of endocannabinoids degrading enzymes like FAAH [47-49] and MAGL [50, 51]. Interestingly, inhibition of EC receptors and degrading enzyme lead to the hypotensive effects, which point out the usefulness of ECS in cardiovascular system ailments.

Prognosis of Hypertension to Hypertensive Nephropathy

Hypertension or resistant hypertension is associated with worse clinical outcome and comorbidities. Hypertension is an established risk factor for target organ death and comorbidities these include nephropathy [28, 52], retinopathy [53-55], cardiomegaly [27], and brain [56].

HYPERTENSIVE NEPHROPATHY

Increase in pressure load to the kidney vasculature as result of elevated BP causes mechanical stretch to the capillaries of glomerulus and mesangial cells, which initiate repair response that is mediated by fibrogenic cytokines and angiotensin II. Proximal tubule is the primary target of injury and progression of kidney disease [57]. Repetitive injuries and repair response can result in glomerulosclerosis, which is further worsen by local factor proteinuria [58]. Proteinuria is a strong and independent promotors of progression of renal disease as demonstrated in no diabetic renal disease by the modification of diet in renal disease study [59]. Important factors in genesis of CKD includes activation of RAS, oxidative stress, and NADPH ox and ET-1 [60].

Renal impairment is a frequent problem in cardiovascular diseases including hypertension [61]. The destructive renal function contributes to tubular interstitial fibrosis, vascular sclerosis and glomerular sclerosis [62]. Activation of renin-angiotensin-aldosterone system, inflammation, oxidative stress, endoplasmic reticulum stress, apoptosis and mitochondrial dysfunction are vital contributors in hypertensive nephropathy (HN) [63-65]. The renal inflammation, tubular interstitial fibrosis, proteinuria and glomerular sclerosis are valuable markers for evaluation of renal dysfunction in chronic kidney disease [66]. Application of angiotensin-converting enzyme inhibitor can reverse hypertension-induced proteinuria and renal damage [67]. It is well accepted that antihypertensive therapy can retard the decrease in renal function [59]. It is now well established that people with CKD are several times more likely to die from cardiovascular causes than those without CKD [68]. A major component of this relationship can be safely attributable to development of hypertension and its complications [69]. Therefore, treatment of hypertension is the most important lifesaving intervention in the management of all forms of CKD.

Role of SNS and RAS in the Pathogenesis of Hypertensive Nephropathy

RAS-blocking agents are the standard therapy for renoprotection in patients with diabetic and nondiabetic CKD [70, 71]. Last, regarding sympathetic hyperactivity, the use of the sympatholytic agent moxonidine in multidrug therapy seems to be a promising strategy to achieve optimal BP levels in patients with CKD. Vaccarin isolated from vaccaria segetalis seed on the right kidney in renovascular hypertension are possibly due to downregulation of fibrosis, inflammatory molecules, oxidative stress, ang II, and AT1 receptor levels [72]. Furthermore, both lowering BP and inhibiting the RAS are specific goals for cardiovascular protection in CKD. Nephropathy can be established by measuring the podocin and nephrin expression in kidney, glomerulosclerosis, albuminuria, and proteinuria.

Seminal studies demonstrating the link between vascular perfusion to the kidney and the development of hypertension remain fundamental to the field of BP research [73]. It has been reported in massive number of research papers that targeted blockade of RAS or its activation without angiotensin receptors arrest the hypertension to renovascular hypertension [74, 75].

RAS significantly affects the renal blood flow in the kidney and increase in ang II to lead to decreased renal blood flow, which can be supported by previously reported data [76]. Ang II not only induce renovascular vasoconstriction but also reduced the renal blood flow by reducing renal oxygen delivery [75]. This decrease in renal oxygen delivery in the kidney lead to cell injury and loss of function [77]. It can be great strategy to increased oxygen supply to the kidney and improve function by blocking angiotensin receptors. In laboratory experiments has improved renal cortical oxygenation in rats with [78] or without kidney disease [79].

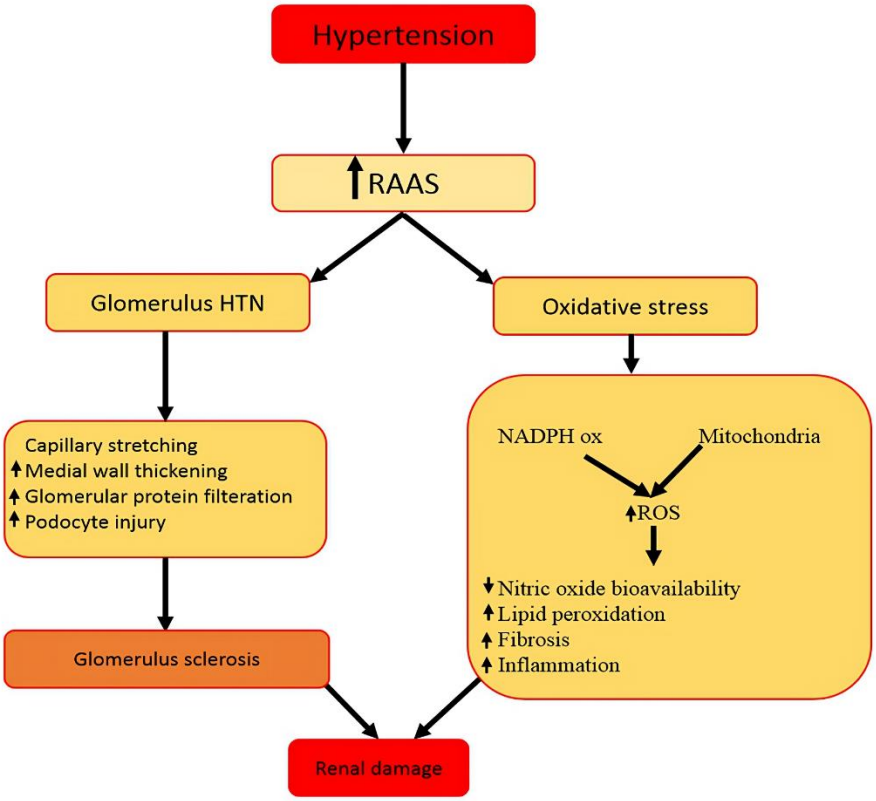

Figure 3. Role of RAS in pathogenesis of hypertensive nephropathy. After RAAS activation systemically and in kidney 2 separate pathways glomerulus hypertension & oxidative stress start in kidney. Glomerulus hypertension led to changes in Bowman's capsule by capillary wall stretching, medial wall thickening, & podocyte injury. All these factors contribute to glomerulus sclerosis, which result in disturbance of kidney excretory & reabsorption functions led to renal damage. Second pathway as result of RAS activation is oxidative stress in kidney, which cause lipid peroxidation, fibrosis, & inflammation. All these factors contribute in establishment of renal damage (Source: Author's own elaboration, using [70-80])

It is always not the vasoconstriction or decreased oxygenation to the renal tissue leads to renal complication. Elevated levels of ang II leads to the number of complications like increased oxidative stress and glomerulus hypertension, as shown in **Figure 3**.

Increased oxidative stress in the kidney lead to the increased inflammatory mediator and loss of renal function in normotensive and hypertensive rats [80]. Hydrogen sulphide is well known gaseous transmitter with known ang II blocking effects [81-83] have been found to reduce the degree of renal IRI by potentiating its antioxidant and anti-inflammatory mechanism, as evidenced by decreased NF-kB concentration and downregulation of ICAM-1 expression in normotensive and hypertensive rats [80]. Reversal of oxidative stress locally in the kidney and globally can minimize the injury produced by elevated levels of ang II. It is believed that ACE inhibitors like hydrogen sulphide can protect kidney by reversing oxidative stress.

Activation of sympathetic nervous system results in the release of neurotransmitters like noradrenaline in systemic and renovascular circulations. Noradrenaline (NA) is responsible for the elevation of BP and involved in the pathogenesis of HN as shown in **Figure 2**. Noradrenalin in the kidney are friends or foe [84] or both [85]. Noradrenaline raises BP by increasing total peripheral resistance by acting on alpha 1 adrenergic receptor. Noradrenaline induces vasoconstriction to generate a net filtration pressure to perfuse the organ. However, due to underlying pathology the increased levels of NA will increase total peripheral resistance, which will ultimately increase perfusion pressure than required. In nutshell, increased perfusion pressure will lead to the reduction in blood flow to the organs like spleen [86], mesenteric [87] and in kidney [88]. Normally levels of noradrenaline are taken as predictor of SNS activity [89]. Renal sympathetic nerve activity has gained lot of interest of researcher in past decade, and it make sense that kidney is densely populated with sympathetic innervations, which directly communicate sympathetic nervous system with the kidney. Evidence have been provided that sympathetic denervation in the kidney has resulted in the reduction of BP in patients with resistant hypertension [90, 91]. Renal sympathetic nerve activity (RSNA) have been found to play a key role in the regulation of BP [92]. It is logical to raise the question that reduction of RSNA can reduce BP then increased RSNA can also induce renal hypertension, which is called as HN. An increase in systemic BP may lead to increased sympathetic nerve activity globally and locally in the kidney, which may lead to HN.

It is interesting to know that both RAS and SNS are regulator of BP in normal circumstances, but it is equally important to know which system in the body is controlling both systems (RAS and SNS) to keep them in equilibrium in physiological state. When this equilibrium is disturbed or disrupted due to onset of disease then immediately both systems go on to rise. Is that ECS in the body, which is third system to control RAS and SNS?

Role of ECS in the Pathogenesis of Hypertensive Nephropathy

Unfortunately, little is known about ECs in hypertension and hypertension induced nephropathy. In addition to its well-documented role in obesity and its metabolic complications [93], the ECS has been implicated in the pathogenesis of CKD, including DN [94]. Both CB1R and CB2R are expressed in the human and rodent kidney [94], particularly in mesangial cells [95], podocytes [96], and proximal tubular cells [97, 98]. ECs mostly produces their biological effects by using CB1 and CB2 receptors, which are G-protein coupled receptors [99, 100]. Type one cannabinoid receptor agonists have been shown to exhibit a vasodilatory effect [101], inhibit the release of neurohormonal factors [102], improve myocardial energy metabolism [103], and suppress vasopressin-induced vasoconstriction [104]. AEA has anti-inflammatory properties, protecting podocytes from Hcys-induced injury by inhibition of NLRP3 inflammasome activation through its COX-2 metabolite, PGE2-EA [105]. CB1 receptors antagonists increased the acute mortality after myocardial infarction [106]. AEA decreases the GFR, increases renal blood flow independent of changes to BP [107]. AEA vasodilates juxtamedullary afferent arterioles via CB1, which was blocked by nitric oxide synthase inhibitors [108]. Mechanistically this might be due to endothelial cells and mesangial cells that have ability to produce and metabolize AEA [108]. Dual inhibition of FAAH and MAGL in the kidney of C57 BL mice not only have ameliorated MAP but also increased urinary excretion along with natriuresis [47, 50].

OEA is PPAR-α (peroxisome proliferator-actiavted receptor-α) agonist and there is evidence of renoprotctive and antiproteinuric effects of PPAR-α activation in various animal models of kidney injury including DN [58, 82, 109]. Furthermore, in cultured podocyte, PPAR-α activation reduce apoptosis and increase nephrin expression [109-111].

Role of Endocannabinoids in Hypertensive Nephropathy

Although limited literature is available to establish the role of ECS and DN but none of the study has explained the role of ECs and their role in nephropathy. None of the study investigated the role of eondocannabinoids in HN. Nephropathy can be established by measuring the albuminuria and proteinuria along with podocin and nephrin expression in kidney, glomerulosclerosis, **Figure 3** illustrates the mechanism of development of nephropathy associated hypertension. Chronic increase in MAP is the reason of elevated either NA, ang II or both, which has deleterious effects on kidney and lead to organ damage manisfested by albuminuria [112]. This elevated levels of ang II causes podocyte injury [96] either by nephrin loss or activation of CB1 receptors, which magnify the effects of ang II [113]. AEA in medulla resulted in diuresis, tubular sodium and potassium excretion [50]. However, study showed that endogenous ECs can improved the function of kidney but did not explain the role of ECs in HN. Study reported that selective inhibition of FAAH and dual inhibition of endocannabinoids enzymes FAAH and MAGL in medulla of the kidney can lower BP and promote diuresis and natriuresis [47, 50]. Invitro data provides a mechanism that insult to podocyte in glomerulus either increases hyperglycemia or glomerular capillary hypertension that enhances CB1 receptor and lower CB2 receptors respectively [114]. This will imbalance the signaling of CB1 and CB2 pathways in ECs. This podocyte damage due to CB1 and CB2 imbalance will result in albuminuria, which is marker of malfunction of kidney and at the same time loss of podocin and nephrin, which are crucial component of glomerular filtration barrier. Studies have suggested direct role of podocyte CB1 and CB2 receptors in glomerular perm-selectivity [115]. Imbalance between CB1 and CB2 signalling on the other side activate proinflammatory macrophages that releases inflammatory cytokines like TNF-α and inflammasome, which causes nephrin loss and overexpression of elastic collagen membranes (ECM), which will cause renal fibrosis in the same mechanism as CB1 receptors does on mesangial cell (MC) and myofibroblast (MF) by overexpressing ECM [116]. This increased albuminuria, loss of podocin and nephrin lead to glomerulosclerosis and nephropathy induced by hypertension. Some of the commercially prepared CB1 receptor antagonists, AM6545 and AM4113, possess reno-protective effects by interfering with TGFβ1-mediated renal inflammation and fibrosis, via peripheral action [45]. In nutshell, up regulation of CB2 receptor or utilizing the CB1 receptor can be a therapeutic strategy to reverse HN.

CONCLUSION AND FUTURE DIRECTIONS

Synthesis of synthetic cannabinoids can increase therapeutic use and reduced adverse effect profile. Synthetic selective inhibitors of CB1 and CB2 receptors antagonists, selective inhibitors of ECs enzyme FAAH and MAGL and selective agonists for CB1, CB2, and TRPV1 receptors will lead to increased therapeutic efficacy and decreased negative health impact on public. Both sympathetic nervous system and RAS play a pivotal role in the pathogenesis of HN. We propose a future direction that upregulation of ECs will not only downregulate SNS and RAAS but also will arrest the progression of HN and regulate kidney functions.

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Declaration of interest: No conflict of interest is declared by the author.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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