Review Article

THE POSSIBLE MECHANISMS THROUGH WHICH DIETARY PROTEIN INCREASES RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

Abstract

Obesity has been associated with various disease conditions, particularly diabetes and heart diseases; this necessitates various weight management schemes to ensure a healthy weight. Diet is one of the major key factors that regulate the body weight and as such, various diets have been documented to aid weight loss and management. High protein, low carbohydrate and low fat diets are reported to be effective for weight management. As a result, most individuals have shifted to high protein diet in order to maintain a healthy weight. Conversely, dietary protein is well known to increase renal blood flow and glomerular filtration rate. Chronic high intake of protein diet may increase the risk of developing renal disease as a result of increased glomerular pressure and hyperfiltration. The mechanism by which protein diet acts on the kidney is not well known, however, various mechanisms have been postulated. This review therefore discusses the various possible mechanisms through which dietary protein act on the kidney.

Keywords: glomerular filtration rate, hyperfiltration, kidney, nephron, protein, renal blood flow,

INTRODUCTION

High protein, low carbohydrate and low fat diets have been documented to be an effective diet for weight management [1 – 4]. This has caused a shift from intake of high carbohydrate and fatty food to food rich in protein. This strategy may be helpful in weight loss and maintenance, but may have a detrimental effect on kidney function. The function of the kidney is not restricted to excretion of metabolic waste, but it also plays a major role in body homeostatic mechanism as well as hormone secretion [5]. Consequently, damage to the kidney affects every aspect of the body physiology.

Protein diet has been reported to increase glomerular filtration rate (GFR) and renal blood flow (RBF) and chronic intake of high protein diet may increase the risk of developing renal disease as a result of elevated glomerular pressure and hyperfiltration [6, 7]. Dietary protein's effect is basically increased GFR and RBF, which are regulated by various physiological mechanisms, suggesting that it may act through one or more of these mechanisms. Understanding the mechanism through which protein diet increase GFR and RBF may

provide models that can help in the study and prevention of hyperfiltration and accompanying hemodynamic abnormalities as well as glomerular structural damage. This review therefore discusses the possible mechanisms through which dietary protein induce elevated glomerular pressure and hyperfiltration.

PROTEIN'S EFFECTS AND MECHANISM OF ACTION ON RENAL FUNCTION

The kidneys play major role in the body homeostasis through regulating plasma volume, adjusting blood pH and excreting metabolic waste products. To effectively perform these functions, the kidneys receive a high blood flow (about 25% of cardiac output), which results in a high GFR (about 125 ml/min) and production of 1 – 2 L of urine each day [8]. The regulation of renal blood flow is mediated by changes in renal vascular resistance which is mainly a consequence of arteriolar tone in the afferent and efferent arterioles [9]. Many factors interact to maintain a consistent blood flow, allowing filtration and urine formation to continue despite systemic changes in blood pressure. Factors that impact on renal hemodynamics include; the auto-regulatory mechanism, the renin-angiotensin mechanism, eicosanoids, kinins, the sympathetic nervous system (SNS), catecholamines, antidiuretic hormone, endothelin, nitric oxide, atrial natriuretic peptide and dopamine [10]. Chronic intake of protein enhances the growth of the kidney and this has been reported to be partly responsible for increased RBF and GFR. However, RBF and GFR have been observed to increase in acute high protein intake [11], connoting that protein act through mechanism(s) which influence normal physiological function of the kidney. The regulations of RBF and GFR are grouped into two mechanisms; extrinsic and intrinsic control. The extrinsic involves the neural control (SNS) and hormonal control, while the intrinsic is the renal auto-regulation, which is achieved by tubuloglomerular feedback and myogenic mechanisms [12].

NEURAL CONTROL AND DIETARY PROTEIN

The neural control of the kidneys is through the SNS. Efferent renal sympathetic innervation and neuroeffector junctions have been identified along the renal vasculature, the tubules and the granular cells of juxtaglomerular apparatus [13, 14]. The action of sympathetic system is through the release the norepinephrine at sympathetic nerve terminals into the interstitial space. Unlike many other organs the kidneys have a low resting sympathetic tone, meaning that a decrease in sympathetic nervous system cannot effectively decrease the resistance. The main aim of the SNS is to compensate for a fall in blood pressure or to prepare the body for the fight or flight response. Studies have investigated sympathetic activities in relation to

protein restriction by measuring norepinephrine (NE) turnover in the heart and inter-scapular brown adipose tissue (IBAT), and reported an increase in sympathetic activity [15, 16]. Since the resting sympathetic activity has a very minimal effect on renal function, any influence on it by dietary protein/amino acid will have little or no effect on kidney function.

There are a number of autocrine and paracrine factors within the kidney that influence the release of neurotransmitter, the degree of its degradation as it crosses the synaptic cleft and its effectiveness at the postsynaptic junction. Dopaminergic nerve fibers have been reported to terminate in the kidney. However, the physiologic significance of these nerves is unclear [17]. Dopamine is synthesized within the kidney in the proximal tubule through the decarboxylation of circulating L-3,4-dihydroxyphenylalanine (L-DOPA) by the enzyme L-amino acid decarboxylase and discharged into the lumen, where it binds to and activates specific dopaminergic receptors [18]. It acts locally to exert its actions in a paracrine and autocrine fashion. The major effects include; increase in RBF and natriuretic response. Dopamine receptors are classified into the D1 and the D2 subtype families, dopamine D_1 receptor stimulation results in renal vasodilatation and natriuresis while dopamine D_2 receptors may play a synergistic role in the dopamine modulated natriuresis [19].

L-DOPA is derived from the amino acids L-phenylalanine and L-tyrosine and increased availability of these by protein diet intake will enhance intra-renal dopamine synthesis, thus it was hypothesised that the amino acid-induced glomerular hyperfiltration may be due to increased dopamine secretion. In line with this, studies in humans have demonstrated an increase in dopamine secretion after a high protein meal [20, 21], and administration of L-tyrosine in animal studies have also shown a similar effect [22, 23]. In another animal study, the infusion of amino acids containing L-tyrosine increased both GFR and renal dopamine excretion, but the same solution without L-tyrosine increased GFR but not urinary dopamine output. Also, the infusion of L-tyrosine alone increased renal dopamine excretion but not GFR [24]. This study suggested thus; urinary dopamine does not play a significant role in the regulation of kidney function, renal innervation is essential in the GFR response to systemic amino acid infusion, and a dopaminergic mechanism apart from tubular dopamine excretion is involved. In line with this, a study assessed the amino acid-induced glomerular hyperfiltration in association with dopaminergic mechanism in 12 healthy male volunteers. The subjects were administered with an electrolyte - balanced solution of mixed amino acid (10%), and their RBF and GFR were assessed by renal clearance of inulin and p-aminohippuric acid. The subjects were orally administered with either placebo or sulpiride; a

centrally and peripherally acting dopamine like receptor antagonist, or domperidone which affects only peripheral dopamine receptors, before amino acid infusion. It was observed that those that received the placebo, amino acid infusion significantly increased GFR and RBF, while those pre-treated with domperidone, the renal response to amino acid was marginally altered, while in those pre-treated with sulpiride, renal hemodynamic changes induced by amino acid were completely abolished. From their study, the authors suggested that dopaminergic mechanism was involved in the amino acid-induced glomerular hyperfiltration and may be mediated throupgh activation of D_2-like receptors [25]. Furthermore, a study in anesthetized rats demonstrated that dopamine D_2-receptor agonist caused an increase in GFR which corroborated to that provoked by infusion of a 10% amino acid solution and that D_2 receptor antagonist sulpiride which acts both centrally and peripherally completely abolished the renal hemodynamic response to amino acids, whereas domperidone, a peripherally acting D_2 receptor antagonist partly inhibits this hyperfiltration [26].

Méndez *et al,* [27] studied the renal hemodynamic response to intravenous infusion of a 10% mixed amino acid solution in anesthetized euvolemic Wistar-Furth rats in the presence or absence of specific dopamine D_1 [Sch 23390 (SCH)] and dopamine D_2 [S-sulpiride (S-SP)] receptor antagonists. This study showed that the infusion of amino acid in vehicle pre-treated rats resulted in an increase in GFR and RPF. Administration of amino acid in the presence of SCH also resulted in elevations in both GFR and RPF but amino acid infusion in the presence of S-SP completely prevented the rise in both GFR and RPF. Same study also examined whether the amino acid-induced hyperfiltration was due to dopamine release from renal nerves or enhanced renal tubule dopamine synthesis. Amino acid was administered to rats whose left kidney had been chronically denervated, while the right kidney remained intact. It was observed that the infusion of amino acid led to significant increase in GFR and RPF only in the intact control kidney, whereas GFR and RPF remained unaltered in the denervated kidney.

Nitric oxide (NO) is another paracrine factor that acts in the kidney to modulate neurotransmission activity. It is produced through the action of nitric oxide synthase (NOS) enzyme. This exist in three isoforms; neuronal (nNOS, NOSI), inducible (iNOS, NOSII), and endothelial (eNOS, NOSIII) and all are expressed within the kidney [14]. The eNOS isoform has been reported to be present in the endothelial cells of the renal vasculature and glomerular capillaries [28, 29]. The nNOS isoform has been identified within the renal

sympathetic nerves [30] and at low levels in the renal tubules, but at high levels in the macula densa region [31]. Nitric oxide has been reported to modulate the activity of renal sympathetic nerves. Nitric oxide has been demonstrated to act directly at the pre-junctional membrane to facilitate norepinephrine release [32] and at the post-junctional membrane, the vascular or tubular epithelial cells to depress norepinephrine mediated effects [33, 34]. Studies have shown that inhibition of NO synthesis prevents amino acid/dietary protein-stimulated renal vasodilation and hyperfiltration. A study investigated NO's participation in the renal vasodilatation and increased GFR induced by amino acid infusion in rat. In the study, NO synthesis was inhibited with JVG-monomethyl L-arginine (LNMMA) and it was that renal arterial infusion of LNMMA that resulted in a significant decrease in GFR and RPF. It was also observed that amino acid infusion resulted in a significant increase in GFR and RPF, which were completely inhibited by intra-renal infusion of LNMMA. From their results, they concluded that NO participates in regulation of basal renal hemodynamics and NO participates in amino acid induced hyperfiltration and renal vasodilatation [35]. Another study reported that intravenous infusion of L-NMMA in anesthetized euvolemic Munich-Wistar rats caused a modest reduction in RPF rate without a change in GFR. The pre-treated L-NMMA rats then received an intravenous infusion of either 10% glycine or 11.4% mixed amino acids. They observed that L-NMMA pre-treatment attenuated glycine-induced hyperfiltration and obliterated the renal hyperemic response, and in rats that received the mixed amino acid, L-NMMA caused modest blunting of the mixed amino acid-induced hyperfiltration, but failed to curtail the renal hyperemia [36]. Salazar *et al,* [37] studied renal hemodynamic response to a meat meal (10 g/kg) in conscious dogs with and without an intra-renal NO synthesis inhibition with NG-nitro-L-arginine methyl ester (L-NAME). They observed in those not treated with L-NAME a significant renal hyperemia after the meat meal, while those that were pre-treated with intra-renal infusion of L-NAME, the induced increase GFR and RPF by the meat meal was abolished. Same study also demonstrated that pre-treatment with L-arginine and L-NAME did not modify the meat meal-induced changes in GFR and RPF. A more recent study investigated the role of high protein intake on cortical COX-2 expression and whether cortical COX-2 contributes to hyperfiltration and increased intra-renal renin biosynthesis. They reported that cortical COX-2 increased after protein loading, but decreased after protein restriction. They also reported that COX-2 inhibition attenuated high protein-induced hyperfiltration, but had no effect on high protein-induced intra-renal renin elevation. Same study also examined the interactions between intra-renal nNOS and COX-2 systems. It was reported that cortical COX-2 elevation seen in salt

restriction was blocked by nNOS inhibition, and that cortical nNOS expression increased after protein loading. They also reported that inhibition of nNOS activity completely reversed high protein-induced cortical COX-2 elevation and hyperfiltration. From their results they concluded that NO is a mediator of high protein-induced cortical COX-2 elevation and suggested that both intra-renal nNOS and COX-2 systems appeared to regulate afferent arteriolar tone and subsequent hyperfiltration seen in high-protein intake [38]. Cyclooxygenase is the rate-limiting enzyme for prostaglandin production. Prostanglandin has been associated with protein induced vasodilation and hyperfiltration [39]. In contrast, a study by Sällström and colleague, [11] showed that in C57BL/6J male conscious mice, the inhibition of NO synthesis failed to abolish the high protein-induced glomerular hyperfiltration, thus concluded that protein-induced glomerular hyperfiltration is independent of NO synthase.

HORMONAL CONTROL AND DIETARY PROTEIN

Several vasoactive substances have been documented to regulate and influence RBF and GFR either by constricting or dilating the afferent and efferent arterioles of the kidney. Vasodilators cause a fall in afferent and efferent arteriolar resistances and consequently increasing RBF and GFR. Various vasodilators have been reported to increase RBF with proportionate increase in GFR. These include glucocorticoids, glucagons, growth hormone and dopamine [19, 40, 41], while others like prostaglandin E_1, bradykinin, acetylcholine and histamine have been reported to cause large increase in RBF, but the observed increase was not accompanied by elevated GFR [42]. The vasodilatory effect of amino acid is well documented, and studies have showed that increased GFR in response to amino acid infusion was associated with a reduction in afferent arteriolar resistance and a subsequent increase in single nephron plasma flow [43]. What however remain unclear is; if the effect of protein on renal functions is due to its direct effect on arterioles or indirectly through other vasodilators. The receptors of the various vasodilators have been identified, but researchers are yet to identify protein/amino acid receptor on kidney tissue. However, *N*-methyl-D-aspartate (NMDA) receptor is a diheteromeric receptor complex that functions as a membrane calcium channel in central nervous system tissue. *N*-methyl-D-aspartate activation results in calcium entry and the stimulation of nNOS activity and its major agonists are glutamate and glycine [44]. These NMDA receptors have been identified in the kidney and the Inhibition caused marked renal vasoconstriction and a reduction in RBF. The RBF/GFR response to one of the normal agonists, glycine, which normally increases RBF, was nearly abolished in rats pre-

treated with two different types of NMDA receptor antagonists [45]. Another study demonstrated that 2 weeks of low-protein diet (8% protein vs. 21% protein in control diet) down-regulated NMDA receptor in rats fed low-protein diet compared with control, and that low-protein feeding results in loss of glycine-induced vasodilation and GFR responses associated with decreased renal NMDA receptor expression. The study therefore concluded that the kidney NMDA receptor expression is conditioned by protein intake and this receptor may play an important role in the kidney vasodilatory response to glycine infusion and protein feeding in rats [44].

Furthermore, the vasodilatory effect of protein has been suggested to be mediated via release of vasodilatory hormones which could either be released into the systemic circulation in response to protein diet to cause vasodilation and increased GFR, or released within the kidney to initiate local vasodilatory action [46]. Several hormones have been postulated to mediate the protein/amino acid vasodilatory and hyperfiltration effects. Studies have ruled out Growth hormone, insulin, and atrial natriuretic peptide, but glucagon and local hormones such as prostaglandins, endotheliurn-derived relaxing factor and bradykinin have been suggested as possible mediators [47].

Plasma glucagon level has been shown to increase in response to protein meals and amino acid infusion [48, 49], but branched-chain amino acids which do not stimulate renal vasodilation does not stimulate the release of glucagon. Carbohydrate meals do not influence renal hemodynamics and has been shown not to cause increased plasma glucagon [50]. In line with this, glucagon has been demonstrated to cause increase in GFR and renal plasma flow. However, the glucagon required to cause comparable increase in RBF and GFR are much higher than the level observed due to protein and amino acid infusion [51 – 53]. This suggests that glucagon is not the sole mediator, but may be partly involved in the protein/amino acid induced hyperfiltration and vasodilatation. The study by Katherine and coworker [54] in diabetic patients failed to demonstrate glucagon as the primary mediator of the amino acid-induced glomerular hyperfiltration in diabetes, but in normal individuals, they observed that the response to amino acids was partly dependent on glucagon.

Prostaglandins are intra-renal hormones which have been reported to be involved in the regulation of vascular tone as well as salt and water homeostasis in the mammalian kidney. Prostaglandins (PG) such as PGE_2 and PGI_2 have been suggested to contribute to changes in

renal hemodynamics in response to a protein diet [38]. Renal prostaglandin production has been demonstrated to increase in response to protein load or amino acid infusion and decrease in response to protein restriction [38, 39, 55]. Inhibition of prostaglandin production by nonsteroidal anti-inflammatory drugs such as aspirin and meclofenamate has been reported to abolish the augmented GFR after a meat meal or during amino acid infusion in human subjects and animals [55, 56]. Study by Bing and coworker [38] demonstrated that COX-2 level increased after protein loading, but decreased after protein restriction in male Sprague-Dawley rats [57]. In the study, the animals were treated with either a low-protein diet (CA170595, 8% casein, Harlan Teklad, Madison, WI), normal-protein diet (TD 91352, 20% casein, control), or high-protein diet (CA170598, 50% casein) for 2 weeks and the rats on the high-protein diet were subsets and were treated with either COX-2 inhibitor (2 mg/kg, daily gastric gavage of SC-58236) or nNOS inhibitor (20 mg/kg daily of 7-nitroinidazole) during the second week of high-protein diet treatment. They observed that cortical COX-2 increased in rats treated with high-protein diet, but decreased in rats treated with low-protein diet compared with rats on normal-protein diet. In the subset group, it was observed that COX-2 inhibition attenuated high protein-induced hyperfiltration, but had no effect on high protein-induced intra-renal renin elevation suggesting that induction of cortical COX-2 contributed to high protein-induced hyperfiltration but not intra-renal renin elevation. Cortical nNOS expression also increased after protein loading, and inhibition of nNOS activity completely reversed high protein-induced cortical COX-2 elevation and hyperfiltration.

Bradykinin and kallidin are members of kallikrein-kinin system and are together classified as kinin [58]. They are formed from substrate kininogen through the action of the enzyme kallikrein, which has been reported to be present in the plasma and in several tissues, including kidneys, pancreas, intestine, sweat glands and salivary glands [59]. Kallikrein has been demonstrated to influence renal function, and kallikrein inhibitors and kinin antagonists have been observed to affect renal function [60]. Studies have suggested that Intra-renal bradykinin may be involved in the protein - induced increase in renal hemodynamics. A study on GFR, RPF and renal kallikrein in rats fed 9%, 25% or 50% protein (casein) diets for 8 to 13 days showed that GFR, RPF and renal synthesis of prokallikrein, as well as excretion of both active kallikrein and prokallikrei increased progressively with increasing dietary protein. The treatment of 50% protein-fed rats with aprotinin, a kallikrein inhibitor markedly lowered renal and urinary kallikrein, as well as GFR and RPF in aprotinin - treated rats compared to vehicle-treated. It was concluded that renal kallikrein and kinins participated in mediating the

renal vasodilatory effect of dietary protein [61]. Similarly, another study examined the role of tissue kallikrein and kinins in renal vasodilation produced by intravenous infusion of a 10% amino acid solution over 60 – 90 mins in rats fed with 9% protein diet for 2 weeks, reported an increase GFR and RPF, which was associated with a 2 – 3 fold increase in urinary kinin excretion rate [62]. Same study reported that pre-treatment with aprotinin abolished the rise in urinary kinins and prevented significant increase in GFR and RPF in response to amino acid infusion. Also, in rats pre-treated with a B2 kinin receptor antagonist - bradykinin, the amino acid infusion raised urinary kinins to a level similar to that of the untreated rats, but GFR and RPF responses were absent. It was reported that aprotinin or the kinin antagonist produced no consistent change in renal function in rats that were not infused with amino acid, and observed that the tissue active kallikrein level dropped to 50% in amino acid-infused rats, suggesting that amino acid-induced increase in kinins was not associated with an increase in renal kallikrein activity. From their results, the authors concluded that kinins generated in the kidney participated in mediating renal vasodilation during acute infusion of amino acid. A study by Jaffa and colleague [63] in moderately diabetic (MD) rats fed with low (9%), normal (25%) and a high (50%) protein diet respectively, reported that in MD rats fed with 9% protein diet, GFR, RPF and kallikrein excretion rate were significantly reduced, compared to MD 25% protein-fed rats and MD 50% protein-fed rats. From their findings, they suggested that the renal hemodynamic response to dietary protein manipulation in diabetic rats might be mediated via changes in renal kallikrein-kinin system activity.

TUBULOGLOMERULAR FEEDBACK AND DIETARY PROTEIN

Tubuloglomerular feedback (TGF) is an intrinsic feedback mechanism designed to protect against large fluctuations in GFR and solute excretion due to changes in renal perfusion pressure [64]. Tubuloglomerular feedback mechanism is mediated by the juxtaglomerular apparatus and links the changes in sodium chloride (NaCl) concentration at the macula densa with the control of renal arteriolar resistance [65]. The macula densa cells of the distal nephron sense changes in delivery of NaCl which changes with respect to renal perfusion pressure. Increase in renal perfusion pressure increases GFR, thereby increasing delivery of NaCl to the macula densa cells of the juxtaglomerular apparatus. The signalling from the macula densa cells to the adjacent afferent arterioles involves adenosine. This triggers an increase in afferent arteriolar resistance and a decrease in GFR towards normal [66]. Decrease in NaCl delivery causes macula densa cells to initiate response that decreases the afferent arteriolar resistance, consequently raising the glomerular hydrostatic pressure and

return GFR to normal and in addition, it initiates renin-angiotensin II system. Angiotensin II constricts the efferent arterioles, thereby increasing glomerular hydrostatic pressure and returns GFR towards normal [67].

Tubuloglomerular feedback mechanism has been proposed as a mediator of protein-induced vasodilation given that a high protein intake will increase the filtration of amino acid, consequently increasing tubular amino acid reabsorption at the proximal tubule. At the proximal tubule, amino acid is co-transported with Na^+ thus decreasing the NaCl delivery to the distal tubule. The macular densa senses this as a fall in GFR and thus reduce the degree of TGF signalling which results in vasodilatation of afferent arterioles and a consequent rise in GFR [68]. Studies have assessed this by observing the effect of high protein feeding on sodium-dependent amino acid reabsorption in the proximal tubules, and NaCl delivery to the distal tubules [69]. Woods and co-workers [69] infused a solution of four amino acids (Ala, Ser, Gly and Pro) intravenously into anesthetized dogs with either normal kidneys or with blunted tubuloglomerular feedback kidneys achieved by lowering renal artery pressure or blocked by making the kidneys non-filtering. They observed an increase in RBF, GFR and proximal tubular Na^+ reabsorption but the distal Na^+ delivery remained relatively constant after 90 min of amino acid infusion. The hemodynamic responses to amino acids were abolished in the blunted tubuloglomerular feedback kidneys induced by lowered renal artery pressure and non-filtration. In another study, it was observed that rats fed a high-protein diet had higher rates of Na^+ and Cl^- reabsorption between the late proximal and early distal tubules and a lower Na^+ and Cl^- concentrations in the early distal tubule than rats fed a low-protein diet [70]. It was also reported that TGF was diminished in rats fed with high-protein diet. From their findings, they deduced that dietary protein does not alter TGF system but influences the signal eliciting the TGF response [70]. In healthy human subjects, intravenous administration of amino acid resulted in a significant increase in RBF and GFR. However, the amino acid-induced renal hemodynamic effects were abolished when the healthy volunteers received a low sodium diet (20 mEq/day) for three days prior to amino acid infusion [71].

Increase proximal tubular NaCl reabsorption and fall in distal tubules NaCl concentration which elicit TGF response are likely to play an important role in protein-induced renal hemodynamics. However, a study by Sällström *et al,* [11] differed. In their study of high protein-induced hyperfiltration in conscious mice, the influence of TGF was studied using female adenosine A_1-receptor knockout mice and corresponding wild-type mice. The mice were given a low-protein diet (8% casein) for 10 days, followed by a high-protein diet (50%

casein) for 10 days. Glomerular filtration rate was measured after 10 days on a low-protein diet and in half of the animals the diet was switched to a high-protein diet, whereas the other half continued with low protein. After another 10 days, GFR was again measured. Adenosine A_1-receptor knockout female mice had a similar GFR and developed a similar hyperfiltration, as their corresponding wild-type controls. From previous studies above, the GFR in adenosine A_1-receptor knockout female mice lacking the TGF mechanism was expected to be less or not affected by dietary protein intake. However, the knockout mice treated with a high-protein diet exhibited a similar degree of hyperfiltration as wild-type mice having intact TGF mechanism. Thus, concluding that hyperfiltration occurs independently of the TGF mechanism.

The inconsistency recorded in these studies may be due to the technique used; the use of conscious animals which had an advantage in preventing possible influence of anesthetic agent, measurement of GFR via FITC-inulin clearance, a modified technique described by Qi *et al*, [72]. Seney *et al,* [70] directly observed the TGF system via micropuncture and microperfusion techniques, Woods and co-workers [69] blunted TGF by non-filtering kidneys or by lowering renal artery pressure, which might influence the normal response, whereas Sällström *et al,* [11] used adenosine A_1-receptor knockout mice lacking the TGF mechanism. Wang *et al,* [73] investigated the role of endogenous adenosine in glycine-induced hyperfiltration. Glomerular filtration rate and effective RPF in conscious chronically instrumented rats reported that glycine-induced-glomerular hyperfiltration and hyperemia were blunted in adenosine deaminase treated rats. However upon treatment with erythro-9-(2-hydroxy-3-nonyl) adenosine hydrochloride, an adenosine deaminase inhibitor, this effect of adenosine deaminase was reversed. Also, the injection of 8-phenyltheophylline an adenosine A1 receptor antagonist abolished the glycine-induced glomerular hyperfiltration and significantly decreased the effective RPF response to glycine. They inferred that endogenous adenosine, acting at adenosine A1 receptors, plays an important role in the glomerular hyperfiltration and hyperemia induced by glycine. A study design that takes into consideration the differences in these techniques might address the disparity.

Another interesting fact is that the fall in NaCl concentration in distal tubules influences the macula densa to stimulate renin secretion, making it possible that renin angiotenin II system may play a part in protein-induced hemodynamics. Studies have observed a rise in renin level in response to protein diet or amino acid infusion [74]. A study examined the effects of

dietary protein on angiotensin converting enzyme (ACE) in male Wistar Kyoto rats, which were fed with isocaloric diets containing 5, 16 or 50% protein for 3 weeks. Angiotensin converting enzyme activity was measured in the kidney medulla, cortex and proximal tubule brush border membrane. It was observed that renal cortex and brush border ACE activity increased in parallel with protein intake, whereas, kidney medulla ACE activity did not vary significantly and the increase in ACE activity in the brush border membrane corresponded to a similar increase in the maximum number of binding sites of 3H-ramiprilat, suggesting that the increase in ACE activity corresponded to an increase in ACE concentration [75]. Scabora *et al,* [76] investigated the impact of maternal protein restriction during whole pregnancy on the medial solitary tract nuclei (nTS) cytological pattern and expression of angiotensin II receptors (AT1R) and AT2R in 16-week-old offspring (LP). The study reported a decrease in the expression of AT1R in the entire nTS of 16-week-old LP rats compared with those of age-matched appropriate normal-protein ingestion, inferring that maternal protein restriction interfere with angiotensin activity in the offspring. However, a study in instrumented conscious dog fed with 10 g/kg of raw beef, designed to study the role of angiotensin system in protein-induce hemodynamic, observed that the normal renal hemodynamic responses to protein diet were not abolished by blockade of the renin angiotensin system with captopril, or by activation of this system by dietary salt restriction, or infusion of exogenous angiotensin II, suggesting that the renin-angiotensin system plays a relatively unimportant role in protein-stimulated renal vasodilation [46].

CONCLUSION

The precise mechanism by which protein induces hyperfiltration and vasodilation is still unclear, although several studies have inferred different mechanisms which include the role of NO, TGF and some vasodilators as potential causative factors. The variations of results reported in the studies reviewed were majorly dependent on the techniques used. The proposition that TGF mechanism could be the mediator of protein – induced hyperfiltration has been countered by a recent study that took into consideration the interference of anaesthetic agent on the observed response. This recent study used conscious adenosine A_1-receptor knockout mice model to nullify the role of TGF mechanism. In addition, the potential role of NO as a mediator of renal hyperfiltration and vasodilation by protein was queried by a knockout mice model for specific NOS isoforms expressed in the kidney, thus doubting the role of NO in protein – induced hemodynamics.

There are possibilities that the action of protein on renal functions may involve a synergy of the mechanisms highlighted, or that different amino acid constituents act through various mediators. This therefore warrants further investigations. More so, attention has been drawn to the role of NMDA receptors in the kidney, where pre-treatment with its antagonist abolished the normal protein/amino acid induced hyperfiltration and vasodilation and a low-protein diet down-regulates NMDA receptor. Further characterisation of the role of these receptors in protein/amino acid-induced hemodynamics needs to be investigated. Receptors might interestingly be the sole mediator of protein's effect on the kidney.

REFERENCES

1. Anne K, David AL, Barbara JS, Lauren L. Weight loss on a low-fat diet: consequence of the imprecision of the control of food intake in humans. *Am J Clin Nutr* l991;53:1124-9.
2. Astrup A, Meinert Larsen T, Harper A. Atkins and other low carbohydrate diets: hoax or an effective tool for weight loss? *Lancet*. 2004;364:897.
3. Kelly AM, Caitriona O, Dayna S. Comparison of a Low-Fat Diet to a Low-Carbohydrate Diet on Weight Loss, Body Composition, and Risk Factors for Diabetes and Cardiovascular Disease in Free-Living, Overweight Men and Women. *The Journal of Clinical Endocrinology & Metabolism*. 2004;89(6):2717-2723.
4. Iris S, Dan S, Yaakov H, Danit RS, Shula W, Ilana G, Rachel G, Drora F, Arkady B, Hilel V, Osnat T, Rachel Z, Benjamin S, Dov B, Ziva S, Einat S, Rachel M, Esther K, Joachim T, Georg MF, Matthias B, Michael S, Meir JS. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *The New England Journal of Medicine.* 2008:359 no. 3.
5. Linda SC. Saunders text and review series physiology. pg.110. 3rd ed. Toronto: W. B. Saunders Company 2003.
6. King AJ, Levey AS. Dietary protein and renal function. J Am Soc Nephrol.1993;3:1723–1737.
7. Metges CC, Barth CA. Metabolic consequences of a high dietary-protein intake in adulthood: assessment of the available evidence. *J Nutr*. 2000;130:886–889.
8. Persson P. Aspects of Regulation of GFR and Tubular Function in the Diabetic Kidney: Roles of Adenosine, Nitric Oxide and Oxidative Stress. *Acta Universitatis Upsaliensis*. 2013;871. 54 pp. Uppsala.

9. Just A. The mechanisms of renal blood flow autoregulation. Dynamics and contributions. *Am J Physiol Regul Integr Comp Physiol.* 2007;292:R1-R17.

10. Holechek MJ. Renal hemodynamics: an overview. *Nephrol Nurs J.* 2003;30(4):441-446.

11. Sällström J, Carlström M, Olerud J, Fredholm B, Kouzmine M, Sandler S, Persson A, Erik G. High-protein-induced glomerular hyperfiltration is independent of the tubuloglomerular feedback mechanism and nitric oxide synthases. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology.* 2010;299:R1263-R1268.

12. Prakasam LR. Fundamentals of medical physiology, Pg. 629-664. 4th ed., Hyderabad, India PARAS Medical publisher 2008.

13. Kate M. Denton, Susan E. Luff, Amany Shweta, Warwick P. Anderson. Differential neural control of glomerular ultrafiltration. *Proceedings of the Australian Physiological and Pharmacological Society*. 2004;34: 85-91.

14. Edward JJ, Ulla CK, Gerald F. Neural Control of Renal Function. *American Physiological Society. Compr Physiol*. 2011;1:731-767.

15. Laryssa NK, James BY, Lewis L. Effect of Protein on Sympathetic Nervous System Activity in the Rat;Evidence for Nutrient-specific Responses. *J. Clin. Invest.* 1986;77:551-558.

16. Martins CD, Chianca DA, Fernandes LG. Cardiac autonomic balance in rats submitted to protein restriction after weaning. *Clin Exp Pharmacol Physiol.* 2011;38, 89–93.

17. Sterns RH. Renal actions of dopamine. *Up To Date.* 2013;21:C21.

18. Carey RM. Theodore Cooper Lecture: Renal dopamine system: paracrine regulator of sodium homeostasis and blood pressure. *Hypertension*. 2001; 38:297.

19. Cheung PY, Barrington KJ. Renal dopamine receptors: mechanisms of action and developmental aspects. *Cardiovascular Research.* 1996;31:2-6.

20. Williams M, Young J, Rosa R, Gunn S, Epstein F, Landsberg L. Effect of protein ingestion on urinary dopamine excretion. Evidence for the functional importance of renal decarboxylation of circulating 3, 4-dihydroxyphenylalanine in man. *J Clin Invest* 1986;78:1687—1693.

21. Fukagawa NK, Bandini LG, Lee MA, Young JB. Effect of age on dopaminergic responses to protein feeding. American Journal of Physiology - Renal Fluid and Electrolyte Physiology. 1995;268(37-4):F613-F625.
22. Agharanya JC, Wurtman RJ. Studies on the mechanism by which tyrosine raises urinary catecholamines. *Biochem Pharmacol.* 1982; 31: 3577–3580.
23. Mühlbauer B, Mickeler C, Schenk F. Protein-induced increase in urinary dopamine in normal and diabetic rats: role of catecholamine precursors. *Am J Physiol* 1997a; 273: R80–R85.
24. Mühlbauer B, Spöhr F, Schmidt R, Osswald H. Role of renal nerves and endogenous dopamine in amino acid-induced glomerular hyperfiltration. *Am J physiol.* 1997b; 273: F144-F149.
25. Luippold G, Schneider S, Stefanescu A, Benöhr P, Mühlbauer B. Dopamine D_2 – like receptors and amino acid- induced glomerular hyperfiltration in humans. *BJCP*. 2001;51:415- 421.
26. Luippold G, Mühlbauer B. Dopamine D_2 receptors mediate glomerular hyperfiltration due to amino acids. *JPET*. 1998 vol. 286 no. 3 1248-1252.
27. Mendez R, Lopez R, Lopez G, Marti M, Martnez-Maldonado M. Effects of dopamine-receptor antagonists and renal denervation on amine acid-induced hyperfiltration. *Am J Physiol Renal Fluid Electrol Physiol* 1991;261:30:F70—F75.
28. Bachmann S, Bosse HM, Mundel P. Topography of nitric oxide synthesis by localizing constitutive NO synthases in mammalian kidney. *Am J Physiol Renal Physiol.*1995; 268: F885-F898.
29. Mattson DL, Wu F. Nitric oxide synthase activity and isoforms in rat renal vasculature. *Hypertension.* 2000;35: 337-341.
30. Liu GL, Liu L, Barajas L. Development of NOS-containing neuronal somata in the rat kidney. *J Auton Nerv Syst.* 1996;58: 81-88.
31. Wu F, Park F, Cowley AW Jr, Mattson DL. Quantification of nitric oxide synthase activity in microdissected segments of the rat kidney. *Am J Physiol Renal Physiol*. 1999;276: F874-F881.
32. Walkowska A, Badzynska B, Kompanowska-Jezierska E, Johns EJ, Sadowski J. Effects of renal nerve stimulation on intrarenal blood flow in rats with intact or inactivated NO synthases. *Acta Physiol Scand.* 2005;183:99-105.

33. Eitle E, Hiranyachattada S, Wang H, Harris PJ. Inhibition of proximal tubular fluid absorption by nitric oxide and atrial natriuretic peptide in rat kidney. *Am J Physiol Cell Physiol.* 1998;274:C1075-C1080.

34. Wu XC, Johns EJ. Interactions between nitric oxide and superoxide on the neural regulation of proximal fluid reabsorption in hypertensive rats. *Exp Physiol.* 2004;89: 255-261.

35. Tolins JP, Raij L. Effects of amino acid infusion on renal hemodynamics. Role of endothelium-derived relaxing factor. *Hypertension*. 1991;17(6 Pt 2):1045-51.

36. King AJ, Troy JL, Anderson S, Neuringer JR, Gunning M, Brenner BM. Nitric oxide: a potential mediator of amino acid-induced renal hyperemia and hyperfiltration. *J Am Soc Nephrol.* 1991;1(12):1271-7.

37. Salazar FJ, Alberola A, Nakamura T, Granger JP. Role of nitric oxide intherenalhemodynamic response to a meat meal. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*. 1994; 267: R1050-R1055.

38. Bing Y, Jie X, Zhonghua Q, Raymond CH, Ming-Zhi Z. Role of renal cortical cyclooxygenase-2 expression in hyperfiltration in rats with high-protein intake. *American Journal of Physiology - Renal Physiology.* 2006; 29: F368-F374.

39. Daniels BS, Hostetter TH. Effects of dietary protein intake on vasoactive hormones. *Am J Physiol Regul Integr Comp Physiol*. 1990;258:R1095–R1100.

40. Ahloulay M, Bouby N, Machet F, Kubrusly M, Coutaud C, Bankir L. Effects of glucagon on glomerular filtration rate and urea and water excretion. *American Journal of Physiology.* 1992;263, F24-36.

41. Ogle GD, Rosenberg AR, Kainer G. Renal effects of growth hormone on renal function and kidney growth. *Pediatr Nephrol*. 1992;6(4):394-8.

42. Valentina K, Iekuni I. Hormonal regulation of glomerular filtration. Ann. Rev. Med. 1985.36: 515-31.

43. Meyer TW, Ichikawa I, Zatz R, and Brenner BM. The renal hemodynamic response to amino acid infusion in the rat. *Trans Assoc Am Physicians.* 1983;96:76–83.

44. Larry AS, Francis BG, Ser J, Joseph S, Sonia T, Aihua D, Scott CT, Roland CB, Karen AM. Protein intake regulates the vasodilatory function of the kidney and NMDA receptor expression. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology.* 2004;287:R1184-R1189.

45. Deng A, Valdivielso JM, Munger KA, Blantz RC, and Thomson SC. Vasodilatory *N*-methyl-D aspartate receptors are constitutively expressed in rat kidney. *J Am Soc Nephrol*. 2002;13:1381–1384.

46. Woods LL. Mechanisms of renal hemodynamic regulation in response to protein feeding. *Kidney International*. 1993;44:659—675.

47. Woods, Lori L. Mechanisms of renal vasodilation after protein feeding: role of the renin-angiotensin system. *Am. J. Physiol. Regulatory Integrative Comp. Physiol.* 1993;264(33):R601-R609.

48. Fioretto P, Trevisan R, Valerio A, Avogaro A, Borsato M, Doria A, Semplicini A, Sacerdoti D, Jones S, Bognetti E, Viberti GC, Nosadini R. Impaired renal response to a meat meal in insulin-dependent diabetics: role of glucagon and prostaglandins. *Am J Physiol Renal Fluid Electrolyte Physiol.* 1990;258:F675–F683.

49. Wada L, Don BR, Schambelan M. Hormonal mediators of amino acid-induced glomerular hyperfiltration in humans. *Am J Physiol Renal Fluid Electrolyte Physiol*. 1991;260:F787–F792.

50. Ando A, Kawata T, Hara Y, Yaegashi M, Arai J, Sugin N. Effects of dietary protein intake on renal function in humans. *Kidney Int.* 1989;36(Suppl 27):S4—S67.

51. Parving HH, Christiansen JS, Noer I, Tronier B, Mogensen CE. The effect of glucagon on kidney function in short-term insulin-dependent juvenile diabetes. *Diabetologia*. 1980;19:350–354.

52. Friedlander G, Blanchet-Benque F, Nitenberg A, Laborie C, Assan R, Amiel C. Glucagon secretion is essential for amino acid-induced hyperfiltration in man. *Nephrol Dial Transplant.* 1990;5:110-117.

53. Smoyer WE, Brouhard BH, Rassin DK, Lagrone L. Enhanced GFR response to oral versus intravenous arginine administration in normal adults. *J Lab Clin Med.* 1991;118:166—175.

54. Katherine RT, Mark EP, Sheryl KC, Robert AS. Effects of amino acids and glucagon on renal hemodynamics in type 1 diabetes. *American Journal of Physiology - Renal Physiology*. 2002;282:F103-F112.

55. Vanrenterghem YF, Verberckmoes RK, Roels LM, Michielsen PJ. Role of prostaglandins in protein-induced glomerular hyperfiltration in normal humans. *Am J Physiol Renal Fluid Electrolyte Physiol.* 1988;254: F463–F469.

56. Levine MM, Kirschenbaum MA, Chaudhari A, Wong MW, Bricker NS. Effect of protein on glomerular filtration rate and prostanoid synthesis in normal and uremic rats. *Am J Physiol Renal Fluid Electrolyte Physiol*. 1986;251: F635–F641.

57. Harris RC, Breyer MD. Physiological regulation of cyclooxygenase-2 in the kidney. *Am J Physiol Renal Physiol*. 2001;281: F1–F11.

58. Yousef GM, Diamandis EP. The New Human Tissue Kallikrein Gene Family:Structure, Function and Association to Disease. *Endocri Rev.* 2007;22: 184-204.

59. Sharma JN, Al-Banoon A. The role of inflammatory mediators bradykinin in cardiovascular and renal diseases. *Scientific Reports.* 2012;1:142.

60. Wang D, Yoshida H, Song Q, Chao L, Chao J. Enhanced Renal Function in Bradykinin B2 Receptor Transgenic Mice. *Am J Physiol Renal Physiol.* 2000;278:484-491.

61. Jaffa AA, Harvey JN, Sutherland SE, Margolius HS, Mayfield RK. Renal kallikrein responses to dietary protein: a possible mediator of hyperfiltration. *Kidney Int.* 1989;36(6):1003-10.

62. Jaffa AA, Vio CP, Silva RH, Vavrek RJ, Stewart JM, Rust PF, Mayfield RK. Evidence for renal kinins as mediators of amino acid-induced hyperperfusion and hyperfiltration in the rat. *J Clin Invest*. 1992;89(5):1460–1468.

63. Jaffa AA, Silva RH, Kim B, Mayfield RK. Modulation of renal kallikrein production by dietary protein in streptozotocin-induced diabetic rats. JASN. 1996;7:721-727.

64. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy.*Hypertension*. 2004;44: 1–7.

65. Castrop H, Huang Y, Hashimoto S, Mizel D, Hansen P, Theilig F, Bachmann S, Deng C, Briggs J, Schnermann J. Impairment of tubuloglomerular feedback regulation of GFR in ecto-5′-nucleotidase/CD73-deficient mice. *J Clin Invest.* 2004;114:634–642.

66. Sun D, Samuelson LC, Yang T, Huang Y, Paliege A, Saunders T, Briggs J, Schnermann J. Mediation of tubuloglomerular feedback by adenosine: evidence from mice lacking adenosine 1 receptors. *Proc Natl Acad Sci USA* 2001;98:9983–9988.

67. Carey RM, Siragy HM. Newly recognized components of the renin–angiotensin system: potential roles in cardiovascular and renal regulation. *Endocr Rev*. 2003;24:261–271.

68. Gonska T, Hirsch JR, Schlatter E. Amino acid transport in the renal proximal tubule. *Amino Acids.* 2000;19:395–407.

69. Woods LL, Mizelle HL, Montani JP, Hall JE. Mechanisms controlling renal hemodynamics and electrolyte excretion during amino acids. *American Journal of Physiology - Renal Physiology.* 1986;251;F303-F312.

70. Seney FD Jr., Persson EG, Wright FS. Modification of tubuloglomerular feedback signal by dietary protein. *Am J Physiol Renal Fluid Electrolyte Physiol.* 1987;252: F83–F90.

71. Ruilope LM, Rodicio J, Robles RG, Sancho JM, Blanca G, Joey P, Romero JC. Influence of a low sodium diet on the renal response to amino acid infusions in humans. *Kidney International*. 1987;31(4):992-999.

72. Qi Z, Whitt I, Mehta A, Jin J, Zhao M, Harris RC, Fogo AB, Breyer MD. Serial determination of glomerular filtration rate in conscious mice using FITC-inulin clearance. *Am J Physiol Renal Physiol*. 2004;286:F590–F596.

73. Wang YX, Brooks DP. The role of adenosine in glycine induced glomerular hyperfiltration in rats. *J Pharmacol Exp Ther*. 1992;263(3):1188-94.

74. Rosenberg ME, Chmielewski D, Hostetter TH. Effect of Dietary Protein on Rat Renin and Angiotensinogen Gene Expression. *J. Clin. Invest.* 1990;85:1144-1149.

75. Bruno M, Michele G, Catherine C, Corinne W, Mariette B, Jean-Louis IM. Effects of dietary protein and uninephrectomy on renal angiotensin converting enzyme activity in the rat. *Kidney International*. 1994:45:1587—1592.

76. Scabora JE, de Lima MC, Lopes A, de Lima IP, Mesquita FF, Torres DB, Gontijo JAR. Impact of taurine supplementation on blood pressure in gestational protein-restricted offspring: Effect on the medial solitary tract nucleus cell numbers, angiotensin receptors, and renal sodium handling. *Journal of Renin-Angiotensin-Aldosterone System*, 2013;1470320313481255.