ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 04, pp.67774-67779, April, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

GASTRO-RENAL INTERFACE IN PATHOPHYSIOLOGY OF HYPERTENSION

***Dr. Mohd. Nawaz, Dr. Ankita Prakash, Dr. Rashmi prakash and Dr. Nitin Ashok John**

Physiology, SR. Dr. Ram Manohar Lohia Institute of Medical Sciences Lucknow, India

ARTICLE INFO

Article History:
Received 11th January, 2018
Received in revised form
18th February, 2018
Accepted 13th March, 2018
Published online 30th April, 2018

Key words:
Hypertension: Gastro-Renal Axis,
GI Hormones,
Sodium Homeostasis,
Renal,
Autocrine.

ABSTRACT

There has been an increase incidence of hypertension and metabolic disorders in the community of people of both developed and developing countries. The complications of hypertension at times are coupled with those of patients of diabetes and obesity. Neuropathy, retinopathy, autonomic dysfunctions and nephropathy are the common complications in hypertension as well as diabetes mellitus. The changing life style and stress in jobs in this world of the surrival of the fitness further increase in incidence of hypertension in adult population is in evitable. In this context adequate preventive measures such as exercise, diet and life style modifications are in demanding state for management of these ailments. But understanding the root cause of especially causation of primary hypertension needs to be evaluated, understood and needs to be put into practice. Along with kidney there is increasing importance of the GI hormones in the regulation of sodium balance, and consequently on blood pressure as sodium homeostasis is the prime contributors towards raised Blood Pressure. The recent modern school of thought belief in the fact that the GI tract hormones and peptides regulate the autocrine functions of renal hormones and are critical in affecting renal functions including sodium excretion. Hence we decided to explore the literature and review the role of GI Tract hormones in regulating the blood pressure and its implication in management of blood pressure. Increased understanding of the role of the gastro-renal axis in the regulation of renal function may give us a novel insight into the pathogenesis of hypertension and provide a new treatment strategy for hypertension.

Citation: Dr. Mohd. Nawaz, Dr. Ankita Prakash, Dr. Rashmi prakash and Dr. Nitin Ashok John, 2018. "Gastro-renal interface in pathophysiology of Hypertension", *International Journal of Current Research*, 10, (04), 67774-67779.

INTRODUCTION

Hypertension is one of the most common and important health related problems in world. (first –Poulter and Prabhakaran, 2015) It has been estimated that around 29%of the world's adult population or 1.56 billion people will have hypertension by the year 2025 (Kearney *et al*., 2005). The prevalence of high blood pressure and its adverse consequences result in a large number of hypertensive patients in both developed as well as developing counties thereby resulting in financial burden for providing health care and thus affecting countries economy (Kearney *et al*., 2005). The exact cause of essential hypertension is still not known despite of very intensive research studies and moreover etiology requires further exploration as it is a complex disorder with environmental, genetic and epigenetic factors. However various monogenic causes of hypertension have been discovered. Specially role of GIT hormones in pathophysiology of hypertension is gaining importance for its imminent role.

****Corresponding author:*** **Dr. Mohd. Nawaz,**
Physiology, SR. Dr. Ram Manohar Lohia Institute of Medical Sciences Lucknow, India.

Among numerous environmental factors, sodium intake is thought to be a very important role in pathogenesis of hypertension. Sodium is very essential element for body fluid and cellular homeostasis. The mechanism of sodium absorption is sensed by various gastrointestinal hormones in regulation of blood pressure via excretion of sodium through kidney has been seen (Whelton *et al*., 2012; Farquhar, *et al*., 2015; Lambers Heerspink *et al*., 2012). Hence along with kidney there is increasing importance of the GI hormones in the regulation of sodium balance, and consequently on blood pressure. For example, GI tract hormones and peptides regulate the autocrine functions of renal hormones thereby affecting renal functions including sodium excretion. These facts gave us an impetus to explore the literature and review the role of GI Tract hormones in regulating the blood pressure and its implication in management of blood pressure.

Sodium homeostasis by kidney: Kidney play a crucial role in sodium homeostasis and body fluid and hence long term regulation of blood pressure (Herrera *et al*., 2012). Almost all parts of nephrons are involved in sodium regulation and therefore in regulation of blood pressure (Hall *et al*., 2012; Wadei and Textor, 2012; Burnier *et al*., 2006; Horita *et al*.,

2013; Wang *et al*., 2009; Gildea *et al*., 2015) This is achieved by various transporters like sodium glucose transporters, sodium hydrogen exchanger, sodium amino acid cotransporter, sodium bicarbonate cotransporter, sodium phosphate cotransporter and various other transporters which are present on luminal and basolateral side of tubular cells (Hall *et al*., 2012; Wadei and Textor, 2012; Burnier *et al*., 2006; Horita *et al*., 2013; Wang *et al*., 2009; Romero, 2005). These sodium cotransporters, exchangers, and pumps are influenced by numerous neural, hormonal, and humoral factors. These mediators broadly classified into two groups. One is causing natriuresis (example Dopamine) and second is causing retention of sodium and water example angiotensin. These two groups keep the body sodium and fluid in balance and maintain blood pressure in normal range. In hypertensive patient it has been found that natriuresis mediated by dopamine is also decreased (Zhang and Harris, 2015; Giani *et al*., 2014).

Mechanism of sodium absorption in GIT: GIT is first and most important organ in salt sensing and its absorption regulation. Other organs are also involved in salt sensing in body for maintenance of blood pressure. In GIT salt sensing and absorption starts from tongue, stomach, small and large intestine (Noda and Hiyama, 2007; Orlov and Mongin, 2007; Titze and Machnik, 2010; Jones *et al*., 2014; Benos *et al*., 2004). In case of excess of sodium in body, the GIT initiates mechanism that causes natriuresis and diuresis and little amount of salt is absorbed through the gut. In contrast to this in salt depleted state, tongue and stomach sense the need for salt intake and this enhances GIT hormone secretions especially involved in sodium reabsorption from kidney and other organs and this increases sodium level in the body (Fu and Vallon, 2014). Many studies have shown that sodium is excreted more faster if given orally than intravenous (Furness *et al*., 2013; Michell *et al*., 2008; Carey, 1978; Andersen *et al*., 2000; Mironova *et al*., 2015; Preston *et al*., 2012). Apart from gastro- renal reflex sodium sensors are also present in vascular smooth muscle that directs the kidney to decrease sodium transport (Drummond *et al*., 2008). In addition the recruitment of aversive taste pathways for example activation of sour and bitter taste sensing cells and taste receptors in kidney which also participate in sodium homeostasis (Oka *et al*., 2013; Liu *et al*., 2015; Rabin *et al*., 2009; Okoro *et al*., 1998; Arguelles *et al*., 2007). Therefore, the targeting of sodium sensors in different parts of the body, including those present in the GI tract, might be the new targets in future for anti-hypertensive therapy.

GIT Hormones secretion and modulation of renal handling of sodium: Studies regarding GIT hormones mediated natriuretic signalling mechanism is not completely understood but it is clear that various GI polypeptides and hormones play important role in regulation of blood pressure via renal sodium transport[10]. These GIT derived substances can be grouped in to three classes and these are GIT hormones, pancreatic hormones and GIT neuropeptides. On the basis of their ability for sodium excretion they can be classified into two groups and these are GIT derived substances involved in increasing sodium excretion and those decreasing sodium excretion.

Glucagon Like Peptide (GLP-1): GLP-1 is secreted by L cells in intestine and degraded by dipeptidy peptidase-4. It acts on receptor GLP-1R which is widely distributed all over body and over brush border of kidney. In rodents stimulation of GLP-1R suppresses the renal proximal tubule sodium transport and causes natriuresis. This is done by inhibition of sodium hydrogen exchanger 3 (NHE3) activity via a protein kinase-A mechanism (Farah *et al*., 2016). So GLP-1 has both activities; that is increase sodium excretion and vasodialator activity (Yu *et al*., 2003). The natriuretic effect of GLP-1 in humans is also associated with a decrease in plasma Ang II but not plasma, aldosterone, Renin or urinary excretion of angiotensinogen (Skov *et al*., 2013) In one study it has been foud that exenatide, a GLP-1 agonist, reduced systolic and diastolic blood pressure (Moretto *et al*., 2008) .In essential hypertension it is seen that decreased GLP-1Rs, and GLP-1-mediated renal arterial vasorelaxation is impaired (Liu *et al*., 2015). Hence decreased GLP-1 and renal GLP-1R expression may be involved in the pathogenesis of hypertension. These studies would suggest that GLP-1 would have an antihypertensive action.

Gastrin, cholecystokinin, and dopamoine interaction: Gastrin is major hormone secreted by G cells in stomach in pyloric region of stomach and upper part of small intestine. Other site inbody are cerebral and few peripheral neurons, pituitary glands and spermatocyte (Rehfeld *et al*., 1984; Schalling *et al*., 1990). CCK is secreted by I cells in upper intestine. Both hormones share common receptor CCK-A and CCK-B but CCK-A has high affinity for CCK while CCK-B is having more affinity for Gastrin. CCK-BR is mainly present in proximal convoluted tubule, distal tubule and collecting ducts (von Schrenck *et al*., 2000). Both Gastrin and CCK can act as hypertensive via natriuresis and dieresis (Rehfeld *et al*., 1984; von Schrenck *et al*., 2000; Chen *et al*., 2013). but Gastrin exerts more effect on renal proximal tubule (Melis *et al*., 2007). Food increases serum gastrin levels, and sodium given orally, even without food, also increases serum gastrin levels.[45] The role of Gastrin hormone in regulation of sodium excretion and blood pressurehas also been substantiated by animal experiment study in mice gastrin (Gast) gene-deficient mice in which it was found that there is no sodium excretion after ingestion of sodium and these mice developed salt-sensitive hypertension (Survé and Håkanson, 1998).

This might be related to the ability of gastrin to inhibit Na -K -ATPase and NHE3 activities in RPT cells (Chen *et al*., 2013; Liu and Jose, 2013; Liu *et al*., 2016). Gastrin also induces natriuresis and diuresis via Dpamine receptor specially D1 like receptor (D1 and D5) synergistically (Chen *et al*., 2013; Jiang *et al*., 2016). It has been seen that natriuresis produced by ingestion of high sodium in diet can be blocked by D1 like receptor agonist (Fenodopam) or CCK-BR antagonist (Jiang *et al*., 2016). Hence these data suggest that there is synergistic action between CCK-BR and DI-R/D5-R to increase sodium excretion. So any aberrant interaction between renal CCK-BR and both D-1 like receptor may lead to pathogenesis of hypertension.

Insulin and Renal Dopamine interaction: Insulin is a hormone secreted by beta cell of pancreas and regulates blood sugar level within normal range via its receptors which are widely present all over the body including nephron. Insulin acts on almost all parts of nephron and has anti natriuretic effect through specific sodium transporters, channels and exchangers. In insulin resistance patients compensatory hyperinsulinaemia leads to increased salt absorption and hence is attributable in genesis of hypertension (Baudrand *et al*., 2014). It has been found that high sodium diet causes increased

insulin resistance (Baudrand *et al*., 2014). Insulin and Dopamine have antagonistic action on renal sodium transport. Insulin acts on Dopaminergic system at two different levels in kidney. First insulin enhances uptake of hydroxylphenylanine, immediate precursor of catechcolamine, specially dopamine, through increase in transport in PCT[51]. Second Insulin increases expression of D5R and its mediated inhibition of Na-K ATPase activity on PCT which is an important counterbalance to increase sodium absorption (Ahmad Banday and Lokhandwala, 2006; Banday *et al*., 2007). Dopamine also regulates insulin receptor expression and functions (Li *et al*., 2015). It has been found that D-1 like receptor agonist Fenodopam increases the expression of insulin receptors in human PCT. Also activation of D2R regulates insulin secretion (Li *et al*., 2015). It has been found that acute administration of a D -like receptor agonist quinpirole or an agonist bromocriptine inhibits glucose-stimulated insulin secretion by D-R dependent or independent mechanism (Rubí *et al*., 2005; de Leeuw van Weenen *et al*., 2010). So disruption of D2R in mice shows impaired insulin secretion and glucose metabolism.

GIT Hormones and Renin Angiotensin system (RAS) Interaction: RAS plays important role in development and maintenance of Hypertension (Carey, 2015; Santos *et al*., 2012). Angiotensin 2(AT2) is main mediator of RAS and it is mainly present in renal tubular cells and interstitium of kidney. Angiotensin 2 acts via AT1 receptor in kidney. Recently various studies have been done on interaction between RAS and GIT hormones.

GLP-1 and RAS: GLP-1 can interact with RAS (Skov *et al*., 2013; Hirata *et al*., 2009; Kim *et al*., 2013). GLP-1R agonist counteract hypertensive action of AT2. It has been seen that GLP-1R agonist (Liraglutid) normalizes both systolic and diastolic blood pressure in AT2 induced hypertension. Same result was also found by Exanadin-4. (Hirata *et al*., 2009) Therefore beneficial role of combination of GLP-1R agonist with RAS inhibition has been seen (Kim *et al*., 2013). Combination of AT2R blocker (Telmisarton) and DPP-4 inhibitor (Linagliptin) reduces urinary excretion of albumin and renal oxidation stress in Diabetic endothelial Nitric Oxide synthase (NOS), indicating that these two might be new approach for patient with diabetic nephropathy (Alter *et al*., 2012).

Role of Ghrelin in Hypertension: Ghrelin is a hormone acts as endogenous ligand for growth hormone secretogouge receptor (GHS-R) 62. Ghrelin is secreted by mainly X/A type cells in stomach (Date *et al*., 2000) and also from small intestine, heart, liver, pancreas, brain64. Secretion of ghrelin is stimulated by fasting and inhibited by feeding (Date *et al*., 2000), resulting in pre-prandial rise of the plasma ghrelin level (Cummings *et al*., 2001). The plasma ghrelin level is also correlated inversely with body mass index (BMI), low in obese patients and high in patients with anorexia nervosa and cardiac cachexia (Ariyasu*et al*., 2001; Tschöp *et al*., 2001). Ghrelin stimulates GH secretion, promotes feeding (Nakazato *et al*., 2001), and decreases insulin secretion and increases blood glucose levels (Dezaki *et al*., 2004; Dezaki *et al*., 2006). GHS-R is expressed in a variety of tissues, including the heart, blood vessels and kidney. Suggesting possible cardiovascular effects of ghrelin. Recently it has been reported that plasma gherelin level is elevated and antagonist of the ghrelin receptor causes earlier onset of salt-sensitive hypertension in rats, indicating hat endogenous ghrelin serves as an anti-hypertensive hormone (Sato *et al*., 2011) .One study was done in 2013 on gherelin and they found that it significantly increases the urine volume and increase urine Na+ excretion. Furthermore, ghrelin increases urine nitric oxide (NO) excretion and tends to increase renal neuronal nitric oxide synthase (nNOS) mRNA expression. It has been also found that Ghrelin did not alter the plasma angiotensin II level and renin activity, nor urine catecholamine levels. Furthermore, ghrelin prevented the high salt-induced increases in heart thickness and plasma ANP mRNA expression. These results demonstrate that long-term ghrelin treatment counteracts salt-induced hypertension in rats primarily through diuretic action associated with increased renal NO production, thereby exerting cardio-protective effects (Hirotaka Aoki1 *et al*., 2013).

Role of gut Microflora in Hypertension: In recent years, various studies have been done regarding the influence of microflora of GIT and their effect on blood pressure. Although the mechanisms of gut microflora on regulation of blood pressure are complex, effects on gut or renal hormones/peptide synthesis or release might be involved. The gut flora, via various metabolites such as short chain fatty acids SCFA, can influence the number and function of enterochromaffin cells, thereby promoting the release of serotonin that would alter the physiology (Miyamoto *et al*., 2016). SCFA influence blood pressure via activating sensory receptors such as olfactory receptor 78 (Olfr78), GPR (Schalling *et al*., 1990), and GPR (Miyamoto *et al*., 2016; Afsar *et al*., 2016). Olfr78 is expressed well in the renal juxtaglomerular apparatus, where activation of Olfr78 induces renin secretion. Treatment with antibiotics reduces the biomass of the gut flora and elevates blood pressure in Olfr78 knockout mice [75].It is reported that gut flora affect the generation of free dopamine and norepinephrine in the gut lumen (Asano *et al*., 2012).

The levels of dopamine and norepinephrine in the lumen of the cecum are higher in control mice than the germ-free mice (Asano *et al*., 2012). Resistant starch is fermented to SCFAs by microflora in the large intestine. It is found that high-amylose resistant starch is associated with increased gene expression of proglucagon (gene for GLP-1) and PYY in the cecal and large intestine, and increased plasma levels of PYY and GLP-1, which play important roles in the regulation of blood ressure (Keenan *et al*., 2012) Dietary factors such as high fiber diet, and acetate supplementation change the gut microbiota, downregulate renal RAS, and prevent the development of hypertension in desoxycorticosterone acetate–salt hypertensive mice (Marques *et al*., 2017). These indicate that targeting the gut microbiota may be a potential and novel strategy for the regulation of gastro-renal axis and treatment of hypertension.

Conclusion

After these discussion, it is evident that increasing support of the concept of a gastro-renal communication in the excretion of a sodium load. GIT hormones and peptides released from the intestine into the circulation in response to sodium intake that interacts with dopamine and various other receptors in the kidney to regulate sodium excretion and keep the blood pressure within in the normal range. Any imbalance in gastro-renal natriuretic signaling axis may cause the

pathogenesis of hypertension. Increased understanding of the role of the gastro-renal axis in the regulation of renal function may give us a novel insight into the pathogenesis of hypertension and provide a new treatment strategy for hypertension.

REFERENCES

Afsar, B., Vaziri, N.D., Aslan, G., Tarim, K. and Kanbay, M. 2016. Gut hormones and gut microbiota: implications for kidney function and hypertension. *J Am Soc Hypertens*., 10:954–961.

Ahmad Banday, A. and Lokhandwala, MF. 2006. Defective renal dopamine D receptor function contributes to hyperinsulinemia-mediated hypertension. *Clin Exp Hypertens*., 28:695–705.

Alter, M.L., Ott, I.M., von Websky, K., Tsuprykov, O., Sharkovska, Y., Krause-Relle, K., Raila, J., Henze, A., Klein, T. and Hocher, B. 2012. DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for diabetic nephropathy. *Kidney Blood Press Res*., 36:119–130.

Andersen, L.J., Jensen, TU., Bestle, M.H. and Bie, P. 2000. Gastrointestinal osmoreceptors and renal sodium excretion in humans. *Am J Physiol Regul Integr Comp Physiol*., 278:R287–R294.

Arguelles, J., Diaz, J.J., Malaga, I., Perillan, C., Costales, M. and Vijande, M. 2007. Sodium taste threshold in children and its relationship to blood pressure. *Braz J Med Biol Res*., 40:721–726.

Ariyasu, H., Takaya, K., Tagami, T., Ogawa, Y., Hosoda, K., *et al*., 2001. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. *J Clin Endocrinol Metab.,* 86: 4753-4758

Asano, Y., Hiramoto, T., Nishino, R., Aiba, Y., Kimura, T., Yoshihara, K., Koga, Y. and Sudo, N. 2012. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *Am J Physiol Gastrointest Liver Physiol*., 303:G1288–G1295.

Banday, AA., Fazili, FR. and Lokhandwala, MF. I. 2007. nsulin causes renal dopamine D receptor desensitization via GRK2-mediated receptor phosphorylation involving phosphatidylinositol 3-kinase and protein kinase C. *Am J Physiol Renal Physiol*., 293:F877–F884.

Baudrand, R., Campino, C., Carvajal, CA., Olivieri, O., Guidi, G., Faccini, G., Vöhringer, PA., Cerda, J., Owen, G., Kalergis, AM. and Fardella, CE. 2014. Highsodium intake is associated with increased glucocorticoid production, insulin resistance and metabolic syndrome. *Clin Endocrinol (Oxf)*. 80:677–684.

Benos, DJ. 2004. Sensing tension: recognizing ENaC as a stretch sensor. *Hypertension*., 44:616–617.

Burnier, M., Bochud, M. and Maillard, M. 2006. Proximal tubular function and salt sensitivity. *Curr Hypertens Rep*., 8:8–15.

Carey, RM. 1978. Evidence for a splanchnic sodium input monitor regulating renal sodium excretion in man. Lack of dependence upon aldosterone. *Circ Res*., 43:19–23.

Carey, RM. 2015. The intrarenal renin-angiotensin system in hypertension. *Adv Chronic Kidney Dis*., 22:204–210.

Carranza, A., Musolino, PL., Villar, M. and Nowicki, S. 2008. Signaling cascade of insulin-induced stimulation of L-dopa uptake in renal proximal tubule cells. *Am J Physiol Cell Physiol*., 295:C1602–C1609.

Chen, Y., Asico, LD., Zheng, S., Villar, VA., He, D., Zhou, L., Zeng, C. and Jose, PA. 2013. Gastrin and D dopamine receptor interact to induce natriuresis and diuresis. *Hypertension*, 62:927–933.

Cummings, DE., Purnell, JQ., Frayo, RS., Schmidova, K., Wisse, BE., *et al*., 2001. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes,* 50: 1714-1719.

Date, Y., Kojima, M., Hosoda, H., Sawaguchi, A., Muhtashan, SM., *et al*., 2000. Ghrelin, a novel growth hormone releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology,* 141: 4255-4261.

de Leeuw van Weenen, JE., Parlevliet, ET., Maechler, P., Havekes, LM., Romijn, JA., Ouwens, DM., Pijl, H. and Guigas, B. 2010. The dopamine receptor D agonist bromocriptine inhibits glucose-stimulated insulin secretion by direct activation of the alpha2-adrenergic receptors in beta cells. *Biochem Pharmacol*., 79:1827–1836.

Dezaki, K., Hosoda, H., Kakei, M., Hasiguchi, S., Watanabe, M., *et al*., 2004. Endogenous ghrelin in pancreatic islets restricts insulin release by attenuating Ca2+ signaling in β-cells: implication in the glycemic control in rodents. *Diabetes,* 53: 3142-3151.

Dezaki, K., Sone, H., Koizumi, M., Nakata, M., Kakei, M., *et al*., 2006. Blockade of pancreatic islet-drived ghrelin enhances insulin secretion to prevent high-fat dietinduced glucose intolerance. *Diabetes* 55: 3486-3493.

Drummond, HA., Grifoni, SC. and Jernigan, NL. 2008. A new trick for an old dogma: ENaC proteins as mechanotransducers in vascular smooth muscle. *Physiology (Bethesda)*. 23:23–31.

Farah, LX., Valentini, V., Pessoa, TD., Malnic, G., McDonough, AA. and Girardi, AC. 2016. The physiological role of glucagon-like peptide-1 in the regulation of renal function. *Am J Physiol Renal Physiol*., 310:F123–F127.

Farquhar, WB., Edwards, DG., Jurkovitz, CT. and Weintraub, WS. 2015. Dietary sodium and health: more than just blood pressure. *J Am Coll Cardiol*., 65:1042–1050.

first –Poulter, NR., Prabhakaran, D. and Caulfield, M. 2015. Hypertension. *Lancet*, 2015;386:801–812.

Fu, Y. and Vallon, V. 2014. Mineralocorticoid-induced sodium appetite and renal salt retention: evidence for common signaling and effector mechanisms. *Nephron Physiol*., 128:8–16.

Furness, JB., Rivera, LR., Cho, HJ., Bravo, DM. and Callaghan, B. 2013. The gut as a sensory organ. *Nat Rev Gastroenterol Hepatol*., 10:729–740.

Giani, JF., Janjulia, T., Taylor, B., Bernstein, EA., Shah, K., Shen, XZ., McDonough, AA., Bernstein, KE. and Gonzalez-Villalobos, RA. 2014. Renal generation of angiotensin II and the pathogenesis of hypertension. *Curr Hypertens Rep*., 16:477

Gildea, JJ., Xu, P., Carlson, JM., Gaglione, RT., Bigler Wang, D., Kemp, BA., Reyes, CM., McGrath, HE., Carey, RM., Jose, PA. and Felder, RA. 2015. The sodium-bicarbonate cotransporter NBCe2 (slc4a5) expressed in human renal proximal tubules shows increased apical expression under high-salt conditions. *Am J Physiol Regul Integr Comp Physiol*., 309:R1447–R1459.

Hall, JE., Granger, JP., do Carmo, JM., da Silva, AA., Dubinion, J., George, E., Hamza, S., Speed, J. and Hall, ME. 2012. Hypertension: physiology and pathophysiology. *Compr Physiol*., 2:2393–2442.

Herrera, M. and Coffman, TM. 2012. The kidney and hypertension: novel insights from transgenic models. *Curr Opin Nephrol Hypertens*, 21:171–178.

Hirata, K., Kume, S., Araki, S., Sakaguchi, M., Chin-Kanasaki, M., Isshiki, K., Sugimoto, T., Nishiyama, A., Koya, D., Haneda, M., Kashiwagi, A. and Uzu, T. 2009. Exendin-4 has an anti-hypertensive effect in salt-sensitive mice model. *Biochem Biophys Res Commun*., 380:44–49.

Hirotaka Aoki1, Masanori Nakata1 and Katsuya Dezaki Ghrelin 2013. counteracts salt-induced hypertension via promoting diuresis and renal nitric oxide production in Dahl rats *Endocrine Journal*, 60 (5), 571-581

Horita, S., Seki, G., Yamada, H., Suzuki, M., Koike, K. and Fujita, T. 2013. Roles of renal proximal tubule transport in the pathogenesis of hypertension. *Curr Hypertens Rev*., 9:148–155.

Jiang, X., Chen, W., Liu, X., Wang, Z., Liu, Y., Felder, RA., Gildea, JJ., Jose, PA., Qin, C. and Yang, Z. 2016. The synergistic roles of cholecystokinin B and dopamine D receptors on the regulation of renal sodium excretion. *PLoS One*., 11:e0146641.

Jones A, Kainz D, Khan F, Lee C, Carrithers MD. Human macrophage SCN5A activates an innate immune signaling pathway for antiviral host defense. *J Biol Chem*. 2014;289:35326–35340.

Kearney, PM., Whelton, M., Reynolds, K., Muntner, P., Whelton, PK. and He, J. 2005. Global burden of hypertension: analysis of worldwide data. *Lancet*, 365:217–223.

Keenan, MJ., Martin, RJ., Raggio, AM., McCutcheon, KL., Brown, IL., Birkett, A., Newman, SS., Skaf, J., Hegsted, M., Tulley, RT., Blair, E. and Zhou, J. 2012. High-amylose resistant starch increases hormones and improves structure and function of the gastrointestinal tract: a microarray study. *J Nutrigenet Nutrigenomics*., 5:26–44.

Kim, M., Platt, MJ., Shibasaki, T., Quaggin, SE., Backx, PH., Seino, S., Simpson, JA. and Drucker, DJ. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med*., 2013;19:567

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., *et al*., 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature,* 402: 656-660.

Lambers Heerspink, HJ., Holtkamp, FA., Parving, HH., Navis, GJ., Lewis, JB., Ritz, E., de Graeff, PA. and de Zeeuw, D. 2012. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int*., 82:330–337.

Li, F., Yang, J., Jones, JE., Villar, VA., Yu, P., Armando, I., Felder, RA. and Jose, PA. 2015. Sorting nexin 5 and dopamine D1 receptor regulate the expression of the insulin receptor in human renal proximal tubule cells. *Endocrinology*, 156:2211–2221.

Liu, L., Liu, J., Gao, Y., Ng, CF., Yu, X., Dou, D. and Huang, Y. 2015. Protein kinase Cβ mediates downregulated expression of glucagon-like peptide-1 receptor in hypertensive rat renal arteries. *J Hypertens*., 33:784–790.

Liu, T. and Jose, PA. 2013. Gastrin induces sodium-hydrogen exchanger 3 phosphorylation and mTOR activation via a phosphoinositide 3- kinase-/protein kinase C-dependent but AKT-independent pathway in renal proximal tubule cells derived from a normotensive male human. *Endocrinology*, 154:865–875.

Liu, T., Konkalmatt, PR., Yang, Y., and Jose, PA. 2016. Gastrin decreases Na+, K+-ATPase activity via a PI3-kinase- and PKC-dependent pathway in human renal proximal tubule cells. *Am J Physiol Endocrinol Metab*., 310:E565–E571.

Liu, X., Gu, F., Jiang, L., Chen, F. and Li, F. 2015. Expression of bitter taste receptor Tas2r105 in mouse kidney. *Biochem Biophys Res Commun*., 458:733–738.

Marques, FZ., Nelson, EM., Chu, PY., Horlock, D., Fiedler, A., Ziemann, M., Tan, JK., Kuruppu, S., Rajapakse, NW., El-Osta, A., Mackay, CR. and Kaye, DM. 2017. High fibre diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in DOCA-salt hypertensive mice. *Circulation*. 2016. Accessed.

Melis, M., Krenning, EP., Bernard, BF., de Visser, M., Rolleman, E. and de Jong M. 2007. Renal uptake and retention of radiolabeled somatostatin, bombesin, neurotensin, minigastrin and CCK analogues: species and gender differences. *Nucl Med Biol*., 34:633–641.

Michell, AR., Debnam, ES. and Unwin, RJ. 2008. Regulation of renal function by the gastrointestinal tract: potential role of gut-derived peptides and hormones. *Annu Rev Physiol*., 70:379–403.

Mironova, E., Chen, Y., Pao, AC., Roos, KP., Kohan, DE., Bugaj, V. and Stockand, JD. 2015. Activation of ENaC by AVP contributes to the urinary concentrating mechanism and dilution of plasma. *Am J Physiol Renal Physiol*., 308:F237–F243.

Miyamoto, J., Kasubuchi, M., Nakajima, A., Irie, J., Itoh, H. and Kimura, I. 2016. The role of short-chain fatty acid on blood pressure regulation. *Curr Opin Nephrol Hypertens*., 25:379–383.

Moretto, TJ., Milton, DR., Ridge, TD., Macconell, LA., Okerson, T., Wolka, AM. and Brodows, RG. 2008. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*., 30:1448–1460.

Nakazato, M., Murakami, N., Date, Y., Kojima, M., Matsuo, H., *et al*., 2001. A role for ghrelin in the central regulation of feeding. *Nature* 409: 194-198.

Noda, M. and Hiyama, TY. 2015. Sodium sensing in the brain. *Pflugers Arch*., 467:465–474.

Oka, Y., Butnaru, M., von Buchholtz, L., Ryba, NJ. and Zuker, CS. 2013. High salt recruits aversive taste pathways. *Nature*., 494:472–475.

Okoro, EO., Uroghide, GE. and Jolayemi, ET. 1998. Salt taste sensitivity and blood pressure in adolescent school children in southern Nigeria. *East Afr Med J*., 75:199–203.

Orlov, SN. and Mongin, AA. 2007. Salt-sensing mechanisms in blood pressure regulation and hypertension. *Am J Physiol Heart Circ Physiol*., 293:H2039–H2053.

Pisegna, JR., Tarasova, NI., Kopp, JA., Asico, LD., Jose, P., Farnsworth, DW., Michejda, CJ., and Wank, SA. 1996. Postprandial changes in renal function are mediated by elevated serum gastrin acting at cholecystokinin type B receptors (CCKBR) in the kidney (Abstract). *Gastroenterology*, 110:1106A.

Preston, RA., Afshartous, D., Forte, LR., Rodco, R., Alonso, AB., Garg, D. and Raij, L. 2012. Sodium challenge does not support an acute gastrointestinal-renal natriuretic signaling axis in umans. *Kidney Int*., 82:1313–1320

Rabin, M., Poli de Figueiredo, CE., Wagner, MB. and Antonello, IC. 2009. Salt taste sensitivity threshold and exercise-induced hypertension. *Appetite*., 52:609–613.

Rehfeld, JF., Hansen, HF., Larsson, LI., Stengaard-Pedersen, K. and Thorn, NA. 1984. Gastrin and cholecystokinin in pituitary neurons. *Proc Natl Acad Sci USA*. 81:1902–1905.

Romero, MF. 2005. Molecular pathophysiology of SLC4 bicarbonate transporters. *Curr Opin Nephrol Hypertens*., 14:495–501.

Rubí, B., Ljubicic, S., Pournourmohammadi, S., Carobbio, S., Armanet, M., Bartley, C. and Maechler, P. 2005. Dopamine D -like receptors are expressed in pancreatic beta cells and mediate inhibition of insulin secretion. *J Biol Chem*., 280:36824–36832.

Santos, PC., Krieger, JE. and Pereira, AC. 2012. Renin-angiotensin system, hypertension, and chronic kidney disease: pharmacogenetic implications. *J Pharmacol Sci*., 120:77–88.

Sato, T., Nakashima, Y., Nakamura, Y., Ida, T. and Kojima, M. 2011. Continuous antagonism of the ghrelin receptor results in early induction of salt-sensitive hypertension. *J Mol Neurosci.,* 43: 193-199.

Schalling, M., Persson, H., Pelto-Huikko, M., Odum, L., Ekman, P., Gottlieb, C., Hökfelt, T. and Rehfeld, JF. 1990. Expression and localization of gastrin messenger RNA and peptide in spermatogenic cells. *J Clin Invest*., 86:660–669.

Sharmilee, G., Blerina, K., Stephen, AB., Damian, G.M., Patrick, M., *et al*., 2002. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. *J Clin Endocrinol Metab.,* 87: 88- 2991.

Survé, VV. and Håkanson, R. 1998. Evidence that peroral calcium does not activate the gastrin-ECL-cell axis in the rat. *Regul Pept*.,

Skov, J., Dejgaard, A., Frøkiær, J., Holst, JJ., Jonassen, T., Rittig, S. and Christiansen, JS. 2013. Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men. *J Clin Endocrinol Metab*., 98:E664–E671.

Titze, J. and Machnik, A. 2010. Sodium sensing in the interstitium and relationship to hypertension. *Curr Opin Nephrol Hypertens*., 19:385–392.

Tschöp, M., Weyer, C., Tataranni, PA., Devanarayan, V., Ravussin, E., *et al*., 2001. Circulating ghrelin levels are decreased in human obesity. *Diabetes,* 50: 707-09.

US Burden of Disease Collaborators. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*., 2013;310:591–608.

von Schrenck, T., Ahrens, M., de Weerth, A., Bobrowski, C., Wolf, G., Jonas, L., Jocks, T., Schulz, M., Bläker, M., Neumaier, M. and Stahl, RA. 2000. CCKB/gastrin receptors mediate changes in sodium and potassium absorption in the isolated perfused rat kidney. *Kidney Int*., 58:995–1003.

Wadei, HM. and Textor, SC. 2012. The role of the kidney in regulating arterial blood pressure. *Nat Rev Nephrol*., 8:602–609.

Wang, X., Armando, I., Upadhyay, K., Pascua, A. and Jose, PA. 2009. The regulation of proximal tubular salt transport in hypertension: an update. *Curr Opin Nephrol Hypertens*., 18:412–420.

Whelton, PK., Appel, LJ., Sacco, RL., Anderson, CA., Antman, EM., Campbell, N., Dunbar, SB., Frohlich, ED., Hall, JE., Jessup, M., Labarthe, DR., Mac Gregor, GA., Sacks, FM., Stamler, J., Vafiadis, DK. and Van Horn, LV. 2012. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*, 126:2880–2889.

Yu, M., Moreno, C., Hoagland, KM., Dahly, A., Ditter, K., Mistry, M. and Roman, RJ. 2003. Antihypertensive effect of glucagon-like peptide 1 in Dahl saltsensitive rats. *J Hypertens*., 21:1125–1135.

Zhang, MZ. and Harris, RC. 2015. Antihypertensive mechanisms of intra-renal dopamine. *Curr Opin Nephrol Hypertens*., 24:117–122.

****