Multilayered Interplay Between Fructose and Salt in Development of Hypertension

What Has Been Revealed So Far

Ozgur C. Eren, Alberto Ortiz, Baris Afsar, Adrian Covic, Masanari Kuwabara, Miguel A. Lanaspa, Richard J. Johnson, Mehmet Kanbay

The prevalence of hypertension escalated over the past decades reaching an epidemic level worldwide.[1] Currently, the prevalence of hypertension is ≈30% of the adult US population, according to the National Health and Nutrition Examination Survey data, with many of these subjects having insulin resistance and or other features of the metabolic syndrome.[2]

In this regard, dietary fructose from sucrose or high-fructose corn syrup (HFCS) in food and beverages has been convincingly linked with hypertension in large epidemiological studies.[3] One of the largest report is the INTERMAP (International Study of Macro/Micronutrients and Blood Pressure), a cross-sectional epidemiological study on cross-cultural blood pressure (BP) differences analyzing 4680 men and women, aged 40 to 59 years, from Japan, China, United Kingdom, and the United States. INTERMAP has previously reported that intakes of vegetable protein, glutamic acid, total and insoluble fibers, total polyunsaturated fatty linoleic acid and n-3 fatty acids, phosphorus, calcium, magnesium, and nonheme iron were inversely related to BP. Direct positive associations of sugars (fructose, glucose, and sucrose) and sugar-sweetened beverages (especially combined with high sodium intake) were reported by the INTERMAP study.[4] In subjects whose 24-hour urinary sodium excretion was over the median, high-fructose intake (>2 SD, or 5.6% kcal) was associated with increased systolic/diastolic BP of 2.5/1.7 mm Hg.[5] Some studies have not reported an association of fructose intake with increased BP,[6,7] and this may relate to diets that are high in fruit (a major source of fructose), as fruits contain substances such as potassium, vitamin C, flavonols, and other components that block fructose-mediated metabolic effects.[8–11] However, when epidemiological studies evaluate the relationship of fructose from added sugars on BP, the findings are strong,[3] as noted by a recent meta-analysis.[12] Furthermore, when fructose is provided as a liquid, either alone or as part of an HFCS or sucrose-containing beverage, there is an acute BP raising effect.[13–15] Likewise, studies suggest that lowering sugar intake can reduce BP in hypertensive individuals.[16]

Several articles have summarized the effects of fructose on BP.[17] One important finding is that fructose does not raise BP simply as a consequence of weight. Indeed, pair-feeding studies have shown that rats fed fructose will develop hypertension, as well as hypertriglyceridemia, hyperuricemia, hyperinsulinemia, and mild renal injury despite no difference in weight with control animals.[18–20] Furthermore, we have not observed metabolic effects from artificial sugars,[21] although one group did report that saccharin might induce insulin resistance in mice.[22] Rather, animals studies suggest fructose may induce hypertension by a variety of mechanisms, including fructose-induced salt and water retention,[23–25] insulin resistance,[26] increased serum uric acid levels,[27] decreased renal nitric oxide availability,[28] and, recently, in utero programming of hypertension.[29]

Here we review more recent studies, particularly focusing on the complex synergism between sugar and salt in the development of hypertension (Figure 1). Excess dietary fructose may contribute to the development of sodium-induced hypertension through recruitment of several mechanisms known to increase BP (Figure 2). These include promotion of salt and water retention, sensitization to the renin-angiotensin system, and promotion of insulin resistance and nitric oxide (NO) deficiency.[30–34]

Effect of Fructose on the Development of Sodium-Induced Hypertension

The potential synergy between fructose and salt is becoming increasingly appreciated. While fructose intake does increase BP in rats[18] and humans,[15] many species show relatively little BP response to fructose, and the rise in BP does not result in hypertension as noted by radiotelemetry.[35] In this regard, the dietary salt content had a permissive effect for hypertension in rats fed 20% fructose for 7 days. The combination of high-fructose and high-salt in the diet was required for the hypertensive response, which did not develop in rats fed either alone.[23,24] This raises the question of whether dietary fructose might enhance the effects of high salt diet on BP.

From the Division of Nephrology (M. Kanbay), Department of Medicine (O.C.E., M. Kanbay), Koç University School of Medicine, Istanbul, Turkey; Dialysis Unit, School of Medicine, IIS-Fundacion Jimenez Diaz, Universidad Autónoma de Madrid, Spain (A.O.); Division of Nephrology, Department of Medicine, Suleyman Demirel University School of Medicine, Isparta, Turkey (B.A.); Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. PARHON' University Hospital, and 'Grigore T. Popa' University of Medicine, Iasi, Romania (A.C.); Department of Cardiology, Toranomon Hospital, Tokyo, Japan (M. Kuwabara); and Division of Renal Diseases and Hypertension, School of Medicine, University of Colorado Denver, Aurora (M.A.L., R.J.J.).

Correspondence to Mehmet Kanbay, Division of Nephrology, Department of Medicine, Koç University School of Medicine, Rumelifeneri Yolu, Sariyer 34450, Istanbul, Turkey. Email mkanbay@ku.edu.tr

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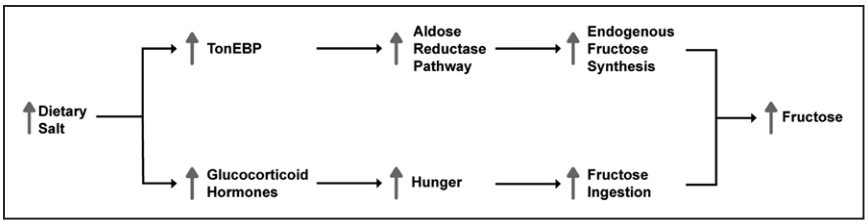

Figure 1. Salt intake increases fructose endogenous production.

Dietary Fructose Enhances Salt Absorption in the Gut

Dietary fructose, generated either from the breakdown of sucrose by the enzyme sucrose or from fructose present in foods or HFCS, is absorbed in the small bowel (especially the jejunum) via the Glut5 (glucose transporter 5; Slc2a5 [solute carrier family 2, facilitated Glut5]) transporter. Fructose enters the enterocyte by facilitated diffusion via Glut5, and the level of Glut5 expression is regulated in part by dietary fructose and sucrose.[36,37] Low doses of fructose are ≈90% cleared by the intestine, with only trace fructose but extensive fructose-derived glucose, lactate, and glycerate found in the portal blood.[38] High doses of fructose (≥1 g/kg) overwhelm intestinal fructose absorption and clearance, resulting in fructose reaching both the liver and colonic microbiota.[38,39] In turn, the fructose metabolized by the intestine can lead to a gut leak syndrome[40] in which endotoxin escapes from the gut into the portal system, enhancing the effects of fructose to induce fatty liver and metabolic syndrome.[41] While part of the gut leak likely relates to the effect of fructose metabolism in the enterocyte to induce local oxidative stress via the fructokinase pathway,[40] studies suggest that high-fructose diets may alter the gut microbiota, resulting in an enhancement of Firmicute and Proteobacteria with a reduction in Bacteroidetes, consistent with a more obesogenic phenotype.[42,43] Interestingly, similar findings were observed with diets with liquid glucose,[43] possibly because glucose is also converted to fructose in the body.[44]

The development of hypertension in response to fructose and salt requires an intact Glut5 system, as elevated BP does not occur in Glut5 knockout mice.[45] Furthermore, the fructose-driven hypertension was dependent on increased jejunal salt absorption in response to increased luminal fructose absorption.[45]

Indeed, the absorption of sodium chloride from the gut modulated by dietary fructose. PAT1 (putative anion transporter 1, Slc26a6, CFEX [chloride/formate exchanger]) is a major chloride transporter[46–52] in the gut, and, like Glut5, is regulated by dietary fructose, resulting in increased mRNA and protein levels of PAT1 in the apical membrane of jejunum.[36] Increased chloride absorption through PAT1 facilitates salt uptake and the development of increased BP. Thus, Slc26a6$^{-/-}$ mice (ie, mice lacking PAT1) failed to develop hypertension while on a fructose-rich diet, whereas wild-type (Slc26a6$^{+/+}$) mice did not develop hypertension when dietary chloride content was low.[36] In addition to the effects of fructose on PAT1, a high-dietary fructose intake also increases the jejunal expression of the sodium transporter NHE3 (sodium/hydrogen exchanger 3), which also contributes to intestinal sodium absorption.[39]

Kidney Involvement in Fructose-Related Hypertension

Excess dietary fructose leads to local renal renin-angiotensin system activation and increased proximal tubular sodium reabsorption (Figure 3). After glomerular filtration, fructose is partially reabsorbed in the proximal tubules via transporters SGLT5 (sodium-glucose linked transporter 5; SLC5A10), GLUT2 (SLC2A2), and GLUT5.[36,53–56] Tubular internalization and subsequent metabolism remain a pivotal step in the fructose-induced hypertension cascade. Among fructose metabolites, diacylglycerol (DAG) is a potent activator of PKC (protein kinase C).[57–59] Increased PKC activity sensitizes proximal tubules to angiotensin II.[24] In addition, fructose metabolism in tubular cells increases urinary levels of uric acid, even without increasing serum uric acid.[60] Fructose-induced local uric acid production is a potent stimulator of renal full length and soluble PRR ((pro)renin receptor) expression and

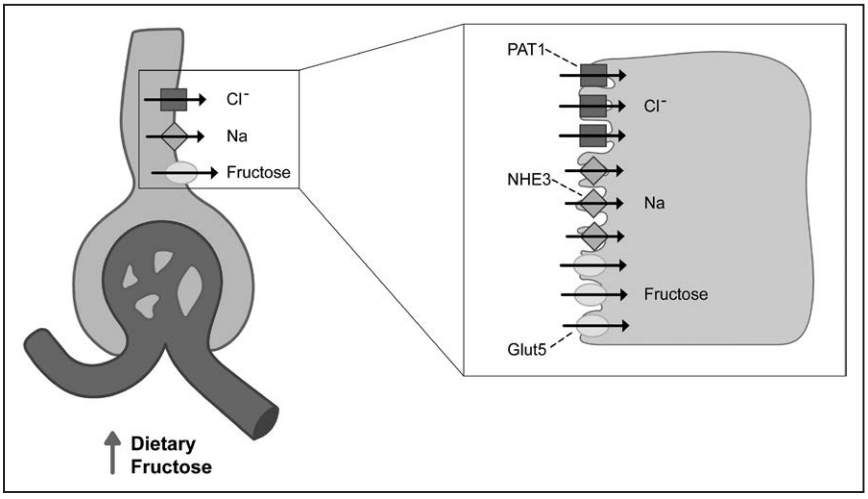

Figure 2. Excess dietary fructose and sodium retention through increased jejunal NaCl absorption and increased proximal tubular NaCl reabsorption. NHE3 indicates sodium/hydrogen exchanger 3; and PAT1, putative anion transporter 1.

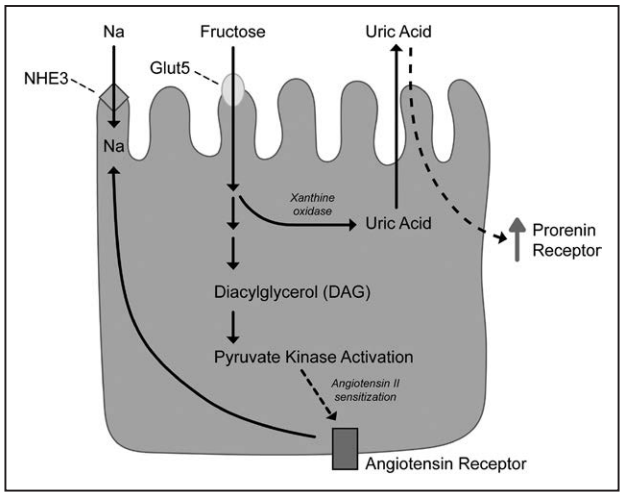

Figure 3. Excess dietary fructose leads to local renal renin-angiotensin system activation and increased proximal tubular sodium reabsorption. NHE3 indicates sodium/hydrogen exchanger 3.

local intrarenal renin-angiotensin system activation.[25,61] Both PRR blockade and prevention of uric acid formation by the xanthine-oxidase inhibitor, allopurinol, independently prevented the hypertensive cascade to the dietary combination of fructose and salt in rats.[25]

Around 65% of filtered sodium is reabsorbed in proximal tubules via the NHE3 in an angiotensin II-sensitive manner.[62–65] A high-fructose diet enhances NHE3 expression and activity, increases intracellular angiotensin II levels and sensitizes the cell to angiotensin II, thus increasing Na reabsorption and water retention by proximal tubules.[24,66,67] In this regard, fructose- and angiotensin II-induced hypertension are prevented by NHE3deficiency in mice,[68] and by the angiotensin II receptor blocker, losartan[69] (Figure 3).

Increased fructose intake may also enhance glucocorticoid action that has an antinatriuretic action. Bursać et al[70] showed that a high-fructose diet in rats led to increased 11βHSD1 (11β-hydroxysteroid dehydrogenase Type 1) and H6PDH (hexose-6-phosphate dehydrogenase) expression and elevated corticosterone level within the adipose tissue, which was paralleled with enhanced glucocorticoid receptor nuclear accumulation.

Salt Intake Increases Endogenous Fructose Production

There are strong interactions between salt and fructose intake, and it has been proposed that salt intake, by increasing thirst, might encourage the intake of sugary beverages thereby enhancing fructose intake.[71] Indeed, high-salt diets have been associated with a higher risk of developing diabetes mellitus regardless of the calorie intake.[21,72] However, the relationship of salt with fructose may be more complex (Figure 1), for while a high-salt diet may encourage intake of sugary beverages, recent studies suggest a high-salt diet may activate processes that result in fructose generation in the liver (endogenous fructose production).[21] Salt intake activates TonEBP (tonicity-responsive enhancer binding protein) NFAT5 (nuclear factor of activated T-cells 5), a transcription factor that promotes kidney inflammation and osmolyte production in response to inflammation and osmotic stress.[39] In turn, TonEBP activates the aldose reductase pathway, which results in the conversion of glucose to sorbitol, with the sorbitol being further metabolized by sorbitol dehydrogenase to generate fructose. The metabolism of endogenous fructose by fructokinase leads to intracellular energy (ATP) depletion, resulting in leptin resistance that decreases satiety.[21] Over time mice develop insulin resistance and metabolic syndrome, with increases in BP. Of note, the effects of a high-salt diet to raise BP and induce metabolic syndrome is abrogated when fructose metabolism is blocked.[21] This suggests that fructose generation might have a role in how salt raises BP.

Fructose-Induced Insulin Resistance and Subsequent Sodium Retention

Fructose-rich feeding has been linked with insulin resistance in rats, represented by high insulin levels and abnormal plasma lipid profiles.[73–75] As argued by Catena et al,[26] mechanisms proposed to explain the prohypertensive nature of insulin include activation of the sympathetic nervous system,[76] growth-promoting activity on vascular smooth muscle cells,[77] increased intracellular calcium level,[78] and increased renal sodium reabsorption[79] (Figure 4). Reinforcing the latter, the antinatriuretic effect has been proven to stem from direct effects on various segments of nephron,[26,80–82] such as stimulation of epithelial Na channel via phosphatidylinositide-3 (PI3)-kinase.[83]

Appreciating that insulin stimulates Na reabsorption in the kidney,[84–87] there was an inverse relationship between salt intake and insulin receptor mRNA levels, suggesting a protective mechanism against insulin-induced hypertension via excessive Na-retention.[88] Fructose-fed rats failed to show a significant downregulation of insulin receptor mRNA levels as dietary salt consumption increased from low to normal or to a high-salt diet. As the protective mechanism is impaired in fructose-fed rats, insulin resistance and high insulin levels could lead to high systolic BP via salt retention. Of importance, the finding was not reflected in rats fed with a high-fructose low-salt diet, further supporting the salt dependence of fructose-induced hypertension.[26]

Targeting these mechanisms, animal studies have succeeded in altering the BP response to chronic fructose and salt ingestion.[89,90] SGK1 (serum and glucocorticoid-inducible kinase) is one of the mediators of PI3-kinase-induced epithelial Na channel stimulation.[91,92] The combination of dietary salt loading and high-fructose levels increased in BP of $SGK1^{+/+}$ mice, but not in $SGK1^{-/-}$ mice.[90]

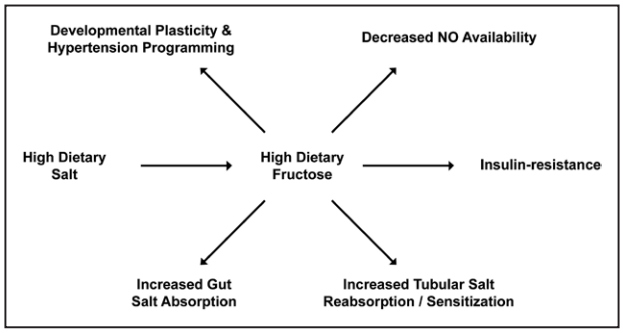

Figure 4. Fructose-induced insulin resistance contribution to hypertension. NO indicates nitric oxide.

α-Lipoic acid (LA, thioctic acid) is an antioxidant, thiol-replenisher, and redox-modulator, that improves insulin sensitivity.[89,93–96] α-Lipoic acid prevented hypertension in rats fed a high-fructose diet for 20 days and this was associated with lower Homeostasis Model Assessment index.[89]

Decreased NO Availability Contributes to Fructose-Induced Salt-Sensitive Hypertension

A substantial literature suggests that NO deficiency may cause salt-sensitive hypertension through a variety of mechanisms, including enhanced sensitivity to vasoconstrictors, increased basal renal vascular resistance, increased renal tubular sodium reabsorption, and amplified renin release.[97] A high-salt diet causes a compensatory increase in renal NO levels.[98] Thus, the urinary excretion of NO metabolites, NO_2/NO_3, is higher in rats on high-salt or high-salt/high-fructose diets than in control and high-fructose rats. However, urinary NO metabolites were lower in high salt/high fructose than in high salt alone rats. This suggests that fructose interferes with adaptive NO production in response to a high-salt diet. Supporting the view, renal medullary eNOS (endothelial NO synthase) levels were lower in fructose-fed, salt-sensitive hypertensive rats.[99] In addition, one major mechanism by which fructose may reduce NO bioavailability is by generating uric acid, which reduces NO levels by blocking L-arginine uptake, stimulating arginase, inhibiting eNOS, and by direct scavenging.[18,100–103]

Finally, decreased NO availability further impairs renal function, both because of salt or fructose supplementation.[104–107] Treatment of rats on high-salt/high-fructose diets with N-acetyl-cysteine (antioxidant) and L-arginine (NOS substrate) prevented the increase in BP after 3 weeks of diet.

Further Perspective: In Utero Programming of Hypertension

Accumulating evidence supports the view that in utero and early postnatal events define predisposition to chronic conditions such as metabolic syndrome, osteoporosis, or even cancer.[108] The process can be explained by the concept of developmental plasticity, referring to the capacity of an organism to thrive in a specific way that is shaped by environmental cues.[109] Early insults hence program the development of certain diseases, decades before their clinical onset. From this aspect, although renal programming to some extent is thought to be related to maternal fructose intake, development of programmed hypertension remains unclear as the specific genetic and epigenetic mechanisms involved have not been discovered yet.[110]

Tain et al[29] examined the synergistic effect between maternal high fructose and postnatal high salt, focusing on the concept of programmed hypertension. Some pregnant rats receive high fructose during pregnancy and lactation, while others received normal chow. Male offspring from each group were again separated in 2 groups so that 1 received high salt load while the other did not. From 4 to 12 weeks of age, the presence of either maternal high fructose or postnatal high salt was sufficient for offsprings to develop hypertension. More interestingly, systolic BP was highest when maternal high fructose and postnatal high salt were combined, as expected from the synergistic effect of fructose and sodium hypothesis. Supporting these results, a high-fructose diet in pregnancy increased mean arterial pressure and peak glucose levels in offspring.[111]

Clinical Relevance

Fructose is the primary sugar in fruits, but is also a key component in added sugars, most notably sucrose and HFCS. A common confusion is why sugary beverage intake strongly predicts metabolic syndrome, diabetes mellitus, and hypertension[112,113] while intake of natural fruits is associated with improved metabolic profiles.[114] However, natural fruits tend to contain less fructose (typically 3–6 g per fruit) and to be high in fiber, potassium, magnesium, flavonols, vitamin C, and other substances that tend to block fructose effects. In contrast, sugary beverages have high-fructose content, are often ingested rapidly, and have the glucose component that accelerates fructose absorption. Fruit juices may carry some ingredients that are protective, but they often contain higher fructose content since they often result from >1 fruit. Indeed, some studies, but not all, have associated fruit juice intake with greater risk for metabolic syndrome.[115]

Studies have also documented a benefit of lowering intake of fructose-containing added sugars on BP.[16] For example, a low-fructose diet reduced BP in chronic kidney disease subjects with a dipping pattern.[116] The DASH (Dietary Approaches to Stop Hypertension) diet that is effective at lowering BP is essentially a low-added sugar, high-fruit diet,[117] and its effect to lower BP is enhanced when salt intake is further reduced.[118] A low-fructose diet (reducing fructose from added sugars) also reduced BP even if supplemented by fruit in obese adults.[119]

Perspectives

Fructose is a common sugar present in sucrose and HFCS that is present in sugary beverages and nearly 70% of processed foods found in the marketplace. Here we review the association of fructose with hypertension and its potential mechanisms, focusing on its interaction with salt. Fructose enhances salt absorption in the gut and kidney and enhances intracellular angiotensin formation. In turn, salt-induced increases in osmolarity feedback to generate fructose generation, documenting a complex interplay in which the 2 synergize together to raise BP. Thus sugar and salt work together to drive the BP response.

Conclusions

Combining its detrimental effects with the commonality of the entity itself, hypertension is among—if not the most—serious health threat of the society. From a bottom-up perspective, understanding the codependence of fructose and salt in the development of the disease may contribute to novel therapeutic approaches to hypertension focusing on the different contributing pathways identified (Figure 5). Directly or via insulin-resistance associated cascades or other pathways, fructose consumption promotes high BP in the individual and may program hypertension in the offsprings when pregnant women are exposed. Animal studies also showed limiting dietary fructose improves the outcome. As a final word, we suggest novel therapies targeting this synergistic effect would be helpful against the disease itself and associated cardiovascular or kidney complications.

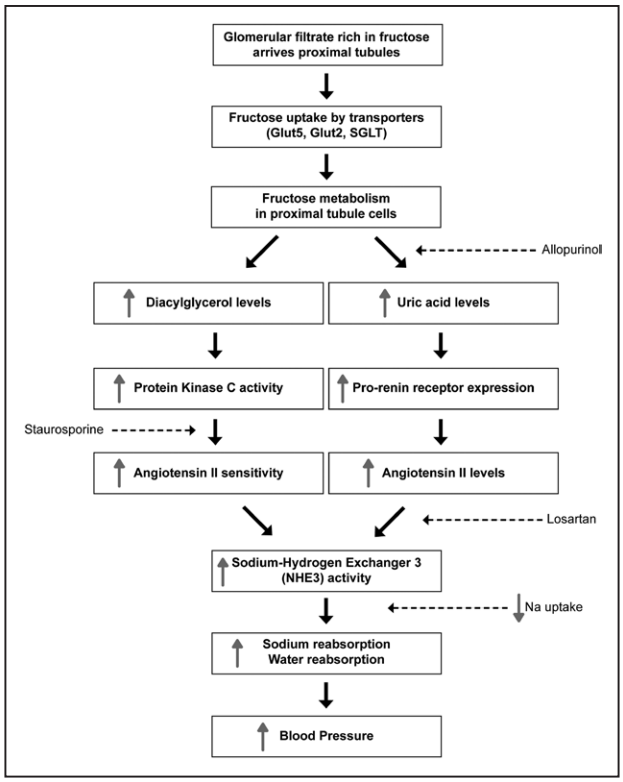

Figure 5. Pathways contributing to promotion of hypertension by high-dietary fructose. SGLT indicates sodium-glucose linked transporter.

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Disclosures

None.

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