Direct Renal effects of a fructose-enriched diet: interaction with high salt intake

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Abstract

Consumption of fructose has increased during the last 50 years. Excessive fructose consumption has a detrimental effect on mammalian health but the mechanisms remain unclear. In humans, a direct relationship exists between dietary intake of added sugars and increased risk for cardiovascular disease mortality (52). While the causes for this are unclear, we recently showed that fructose provided in the drinking water induces a salt-dependent increase in blood pressure in Sprague-Dawley rats in a matter of days (6). However, little is known about the effects of fructose in renal salt handling and whether combined intake of high fructose and salt can lead to salt-sensitive hypertension prior to the development of metabolic abnormalities. The long-term (more than 4 weeks) adverse effects of fructose intake on renal function are not just due to fructose but are also secondary to alterations in metabolism which may have an impact on renal function. This mini-review focuses on the acute effect of fructose intake and its effect on salt regulation, as they affect blood pressure.

Introduction

In the late 1960s, refining, isomerization, and separation technologies made possible the production from corn starch of high-fructose syrup (32). Since then, consumption of fructose in the human diet increased has dramatically reaching a maximum level between 2005-2010, which has been maintained during the last 10 years (16, 49). One of the principal sources of added sugars (fructose and glucose) in our diet, is sugar-sweetened beverages. The effect of fructose on glucose and lipid metabolism is dependent on the dose and duration of consumption (9). For instance,
metabolic syndrome (defined in humans as a large waistline, high triglycerides, high blood glucose, low High Density Lipoproteins levels and high blood pressure) can be induced in rodents by feeding concentrations of fructose as low as 20% for 8 weeks or more (43), with metabolic alterations (including insulin resistance) usually starting after 6 weeks. Independently from the amount of fructose, most studies report an increase in plasma uric acid, leptin, glucose, insulin, cholesterol and triglycerides starting after 6-8 weeks on 10-60% fructose intake (14, 20, 22, 23, 34, 43). However, most studies do not directly report the percent of caloric intake consumed from fructose since varying concentrations in the drinking water result in differences in volume intake. Thus the majority of data in rodents support a detrimental effect on chronic fructose consumption, however new evidence indicates that important renal physiological parameters are affected by acute fructose consumption. Fructose intake induces signaling in the gut and liver within minutes after consumption and during its transport. However, little is known about the effects of acute (hours) and chronic (weeks-months) fructose consumption on renal NaCl reabsorption and its potential role in blood pressure (BP) regulation. To understand these mechanisms it would require an approach that includes a comparison between a time-dependent effect of fructose and glucose on renal physiological changes and blood pressure regulation while varying salt content in the diet.

**Hypertension, fructose and salt intake**

Hypertension is a complex polygenic disorder that is often influenced by dietary factors. Salt handling by the kidney is essential for long-term BP control. The
relationship between high fructose consumption and human hypertension is the subject of debate. Some clinical studies have shown no association with fructose intake and hypertension (8, 15) while others have shown a positive correlation (4, 5, 9). In addition to high fructose, most people consume excess salt, fat and protein in their diets. It is not clear how these secondary factors affect the response of elevated fructose intake. A single study in humans examined the combined effect of fructose and salt intake (5) and showed a positive correlation between fructose consumption and hypertension, which was enhanced by high salt intake. In most rat studies, high fructose intake (40-60%) for prolonged periods of time (more than 2 months), causes hypertension, insulin resistance and hyperuricemia (14, 20, 34, 43, 45). However, human consumption is generally lower than 40% of caloric intake (20, 31). In the US the upper quartile of the adult population (up to 30 million Americans), consume 20-40% of their caloric intake from added sugars, with half of those calories (10-20%) comes from fructose. However in most studies, feeding rats 10-20% of caloric intake from fructose does not increase BP prior to the development of metabolic alterations (6, 19). This suggest that high fructose intake may not cause hypertension during normal salt intake despite inducing deleterious signaling in the kidney and other organs. Yet it is unclear whether a fructose-enriched diet induces a salt-dependent increase in BP because the acute and chronic effects of fructose on nephron salt handling have been poorly studied. Recently Cabral et al. (6) showed that in rats fed fructose (20% in drinking water) plus high salt, induced salt-sensitive increase in BP, whereas fructose alone did not. These data are in agreements with a 1994 study conducted by Reed et al. showing that fructose (10-20% in drinking water) induced salt-sensitive hypertension in other strains of salt-resistant
Thus, it is possible to speculate that enhanced fructose intake prevents adequate NaCl handling by the kidney in rodents and humans.

**Effect of fructose in nephron ion transport**

There are large differences between glucose and fructose metabolism as well as their handling by the kidney. First, glucose and fructose are not metabolized equally by the liver and the transporters and enzymes involved are different (13, 17, 29, 49). Second, in humans and rodents on normal diets, baseline plasma glucose is ~5 mM whereas plasma fructose is ~0.05 to 0.25 mM (30, 39). Third, glucose filtered through the glomeruli is completely reabsorbed in the proximal tubule by SGLT1 and SGLT2, whereas fructose is not, and considerable amounts of fructose can be measured in human and rodent urine after an oral fructose load (24, 27). Part of the filtered fructose is reabsorbed by the proximal tubule via the fructose transporters SGLT5, GLUT5 and GLUT2 and metabolized, while approximately half of filtered fructose is excreted in urine (10, 31, 37, 45, 48). Since fructose is not completely reabsorbed in the proximal tubule, it moves along the nephron and gets concentrated in the forming urine (27). It is not known how concentrated fructose could be in the distal nephron segments since this has not been measured.

Few investigators have studied the effect of fructose on renal salt reabsorption. Queiroz-Leite et al. studied the acute effect of fructose in proximal tubule bicarbonate reabsorption using *in vivo* micropuncture (40). They reported that luminal fructose 2-3 mM increased bicarbonate reabsorption indicative of a stimulation of NaCl reabsorption,
whereas glucose did not affect transport. This effect seemed to be secondary to enhanced NHE3 activity because fructose 3 mM increased NHE3 activity in the proximal tubule cell line. Recently Cabral et al. (6) found that 20-30 min incubation with fructose 3 or 5 mM in the luminal solution enhanced NHE3 activity in isolated perfused rat proximal tubules. Fructose 5 mM also enhanced the stimulatory effect of Ang II on NHE3 activity. These data suggest that an acute increase in filtered fructose, as it occurs after ingestion of fructose, may increase proximal tubule NaCl reabsorption directly or by enhancing the stimulatory effect of Ang II. The chronic effect of fructose consumption in proximal tubule NaCl reabsorption has not been studied to our knowledge. Also, the acute or chronic effects of fructose on the thick ascending limb, distal tubule or collecting ducts ion transport have not been studied. We recently began studies to address the effect of fructose on thick ascending limb NaCl transport. Our unpublished data (1) suggest that acute treatment with fructose 5 mM (but not glucose 5 mM) increases NaCl transport by rat thick ascending limbs. This acute effect may be related to activation of the apical Na-K-2Cl cotransporter NKCC2, because fructose, but not glucose, enhanced apical surface NKCC2 levels (unpublished results). Collectively, these data suggest that fructose per se can rapidly enhance proximal tubule and thick ascending limb NaCl transport. This effect could be related to the salt sensitivity observed when rats are fed high fructose and high salt diets. However little is known about the effect of fructose in the kidney and whether the mechanism for its action is due to fructose activating signaling along the nephron.

In humans, plasma fructose increases from 0.2 to 1 mM after post-prandial fructose (24, 27). In the gut and liver, fructose activates signaling after it is transported
into the cell by GLUT2 transporters (11, 31). In the kidney, filtered fructose reaches not
just the proximal tubule (where it is reabsorbed) but also distal parts of the nephron via
the forming urine (27). To our knowledge, the effect of fructose in the distal nephron
segments is unclear. While these questions have not been explored, it is clear that we
cannot extrapolate concepts learned from hyperglycemic-induced signaling in the distal
nephron because glucose-induced signaling is likely to be completely different from
fructose-induced signaling. Concentrations of glucose high enough to reach the distal
nephron are only found in diabetic patients or animal models of diabetes, whereas a
relevant concentration of fructose along the nephron occur every time after ingestion of
fructose-sweetened beverages. Given that most people consume high fructose and high
salt containing diets, we think that the interaction between these dietary factors is an
important area of investigation that has been overlooked.

Fructose consumption has also been linked to obesity (12, 49) based on studies
showing that fructose increases food intake in rodents, when compared to glucose (7).
Other studies indicated that both fructose and glucose increase appetite and/or
decreases satiety (33, 36). Fructose consumption affects de novo lipogenesis (42), and
ectopic lipid disposition in human (26, 47) and rodents (25). Taken together, these
studies suggest that in rats sugar (both fructose and glucose) provide calories to the
diet without providing a negative feedback to decrease appetite thereby leading to
weight gain. However, whether fructose induces obesity and weight gain in humans is
not so clear. This is based on the nature of the studies, in which detrimental metabolic
effects have been observed after excessive isolated fructose intakes in human subjects
(21, 38). On the other hand, food disappearance data indicate that fructose
consumption from added sugars has increased over time and paralleled the increase in
obesity (23, 49). However, studies performed under isocaloric exchange conditions in
humans testing the effect of fructose on weight gain, showed there was no difference
compared to other sugars (2, 28). While it is known that fructose consumption leads to
lipid accumulation in the liver (3, 51) whether fructose induces obesity and weight gain
(when compared to glucose for instance) needs further investigation.

**Perspective**

Hypertension is now the leading cause of “loss of health” worldwide. Genetic
background and dietary factors (such as fructose intake) influence the response to salt
in humans, and may contribute to salt-sensitive hypertension. However, little is known
about the interaction and renal effects of high fructose and high salt intake in humans or
animal models. Thus, understanding the effect of fructose (without the confounding
effect of other metabolic changes) on renal function and blood pressure regulation may
help to understand the real effect of the added sugars in our diet and may help justify a
decrease in their intake in humans.
<table>
<thead>
<tr>
<th>Fructose Concentration</th>
<th>Salt</th>
<th>Species</th>
<th>Duration of Treatment</th>
<th>Effect/Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In food</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>3%</td>
<td>Rats</td>
<td>2 weeks</td>
<td>Salt-sensitive hypertension.</td>
<td>(35)</td>
</tr>
<tr>
<td>60%</td>
<td>normal</td>
<td>Rats</td>
<td>10 weeks</td>
<td>Metabolic syndrome.</td>
<td>(34)</td>
</tr>
<tr>
<td>60%</td>
<td>normal</td>
<td>Rats</td>
<td>8 weeks</td>
<td>Metabolic Syndrome/renal hypertrophy, glomerular hypertension, cortical vasoconstriction.</td>
<td>(43)</td>
</tr>
<tr>
<td>60%</td>
<td>normal</td>
<td>Rats</td>
<td>12 days</td>
<td>↑ Blood pressure &amp; induces Salt-sensitivity.</td>
<td>(41)</td>
</tr>
<tr>
<td>60%</td>
<td>normal</td>
<td>Rats</td>
<td>6 weeks</td>
<td>↓ creatinine clearance, induces chronic kidney disease.</td>
<td>(14)</td>
</tr>
<tr>
<td>60%</td>
<td>normal</td>
<td>Rats</td>
<td>12 weeks</td>
<td>Metabolic Syndrome, ↑ Blood pressure.</td>
<td>(45)</td>
</tr>
<tr>
<td>65%</td>
<td>normal</td>
<td>Mice</td>
<td>12 weeks</td>
<td>No change in BP, ↓ NKCC2 expression and ↓ aquaporin-2.</td>
<td>(44) (46)</td>
</tr>
<tr>
<td>65%</td>
<td>normal</td>
<td>Rats</td>
<td>2 weeks</td>
<td>↑ Blood pressure, Hyperinsulinemia, Hypertriglyceridemia.</td>
<td>(20)</td>
</tr>
<tr>
<td><strong>In drinking water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>normal</td>
<td>Rats</td>
<td>within 7 days</td>
<td>↑ Blood pressure.</td>
<td>(9)</td>
</tr>
<tr>
<td>10%</td>
<td>4%</td>
<td>Mice</td>
<td>3 weeks</td>
<td>Salt-sensitive hypertension, ↑ Insulin.</td>
<td>(19)</td>
</tr>
<tr>
<td>11%</td>
<td>normal</td>
<td>Humans</td>
<td>1 week</td>
<td>Salt is a major determinant of fluid &amp; sugar-sweetened drink consumption during childhood.</td>
<td>(18)</td>
</tr>
<tr>
<td>15%</td>
<td>normal</td>
<td>Humans</td>
<td>1-2 day</td>
<td>↓ Insulin, ↓ glucose; ↓ Ghrelin; ↑ triglycerides.</td>
<td>(50)</td>
</tr>
<tr>
<td>20%</td>
<td>8%</td>
<td>Rats</td>
<td>1 Week</td>
<td>Salt-sensitive hypertension.</td>
<td>(6)</td>
</tr>
</tbody>
</table>


6. **Cabral PD, Hong NJ, Hye Khan MA, Ortiz PA, Beierwaltes WH, Imig JD, Garvin JL.** Fructose Stimulates Na/H Exchange Activity and Sensitizes the Proximal Tubule to Angiotensin II. *Hypertension* 63(3): e68-e73, 2014.


