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Dietary fructose, salt absorption and hypertension in metabolic syndrome: Toward a new paradigm

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Abstract

The worldwide increase in the incidence of metabolic syndrome correlates with marked increase in total fructose intake in the form of high-fructose corn syrup, beverage and table sugar. Increased dietary fructose intake in rodents has been shown to recapitulate many aspects of metabolic syndrome by causing hypertension, insulin resistance, and hyperlipidemia. Recent studies demonstrated that increased dietary fructose intake stimulates salt absorption in the small intestine and kidney tubules, resulting in a state of salt overload and thus causing hypertension. The absorption of salt (sodium and chloride) in the small intestine is predominantly mediated via the chloride/base exchangers DRA (SLC26A3) and PAT1 (SLC26A6), and the Na^+/H^+ exchanger NHE3 (SLC9A3). PAT1 and NHE3 also co-localize on the apical membrane of kidney proximal tubule. Luminal fructose stimulated salt absorption in the jejunum and kidney tubules, responses that were significantly diminished in PAT1 null mice. These studies further demonstrated that Glut5 (SLC2A5) is the major fructose-absorbing transporter in the small intestine (and kidney proximal tubule) and plays an essential role in the systemic homeostasis of fructose. Increased dietary fructose intake for several weeks upregulated the expression of NHE3, PAT1 and Glut5 in the intestine and resulted in hypertension in wild type mice, a response that was almost abolished in PAT1 null mice and abrogated in Glut5 null mice. This article will discuss the interaction of Glut5 with salt absorbing transporters and review the role of dietary fructose in enhanced salt absorption in intestine and kidney as it relates to the pathogenesis of hypertension in metabolic syndrome.

Keywords

Glut5; DRA; PAT1; NHE3; fructose-stimulated salt absorption; Glut2

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CONFLICTS OF INTEREST

There is no conflicts of interst.

Overview and Discussion

Metabolic Syndrome and Hypertension

Metabolic syndrome is manifested by visceral obesity, glucose intolerance, hypertension, hyperinsulinism and atherogenic dyslipidemia (1–6). The prevalence of obesity and metabolic syndrome is reaching epidemic proportions in adults and school age adolescents and children, specifically in United States, and portends ominously for the future health of people in both developed and developing countries (7). There is no universal agreement as to the underlying pathophysiology of metabolic syndrome.

At its core, the metabolic syndrome is the result of energy excess; therefore treating obesity is a good strategy to reverse the clinical features of the metabolic syndrome. While the increase in the incidence of obesity has been attributed to increased calorie intake and decreased physical activity, the pathogenesis of hypertension in metabolic syndrome remains less well understood. Possibilities such as activation of renin angiotensin system, enhanced insulin secretion, obesity, elevated serum uric acid and decreased nitric oxide generation by vascular endothelial cells have been implicated, and evidence in support of their role in the generation of hypertension has been presented (8–10). For example, insulin resistance and compensatory hyperinsulinemia have been shown to play a role in blood pressure elevation. Separate studies have implicated sodium retention, sympathetic activation and impairment of endothelial nitric oxide production as pathogenic factors in the generation of hypertension (11, 12). In addition, increased expression of angiotensin II type 1 receptor in mesangial cells has been suggested to play an important role in the pathogenesis of hypertension in metabolic syndrome (13). Recent studies have also implicated stress response, with an underlying abnormality in the enzyme 11beta-hydroxysteroid dehydrogenase (HSD1), as a contributing factor (14). At the cellular level, HSD1 locally regenerates active cortisol from inactive cortisone, amplifying glucocorticoid receptor activation and promoting preadipocyte differentiation and adipocyte hypertrophy (14, 15).

Metabolic Syndrome and increased dietary fructose intake

Americans are consuming around 22 teaspoons of sugar each day, the American Heart Association reports (7). A national health survey has shown that teens between ages 14 to 18 consume an astonishing 34 teaspoons of added sugar a day (7). Most of the added sugar comes from soft drinks and candy - a staggering 355 calories, and is predominantly in the form of fructose. The steep increase in fructose consumption directly correlates with the increased incidence of Metabolic Syndrome and prevalence of hypertension in developed countries (7).

In rats, mice and dogs, increased dietary fructose intake for several weeks has been shown to recapitulate many parameters of metabolic syndrome including hypertension, insulin resistance, and hyperlipidemia (16–25). Indeed, increased dietary fructose intake has been shown to cause hypertension in rats, as early as 2 to 4 weeks after the start of the experiment (16–22). While dogs develop hypertension as early as 2 weeks after the start of high fructose diet, it takes more than 10 weeks for mice to develop hypertension when fed increased dietary fructose (23–25).

Increased dietary fructose, high salt diet and hypertension

In addition to fructose, Americans consume two to three times the recommended amount of salt, according to the Center for Disease Control (CDC), which warns that increased salt intake is significantly raising the risk of hypertension, cardiovascular disease, and kidney failure (2009).

Hypertension is a complex, multi-factorial disorder and attributing its etiology to a single factor is probably simplistic. One major factor, however, which is essential to the understanding of blood pressure regulation and hypertension, is altered salt absorption in the kidney (26–29). Several studies have implicated enhanced salt intake and absorption in the kidney, in the context of high insulin levels, as important factors in the pathophysiology of hypertension in metabolic syndrome (30–32).

Given the role of increased dietary fructose or salt intake in causing hypertension independent of each other, and given the increased consumption of both fructose and salt in our daily diet, the question should be asked as to whether increased dietary fructose and salt have any additive effect on blood pressure elevation. The answer to this important question remains speculative. Recent studies have shed new light on the role of dietary fructose on salt absorption in the intestine or kidney, which will be discussed below.

Fructose absorption in the small intestine and kidney proximal tubule

The absorption of fructose occurs in the small intestine and kidney proximal tubule, predominantly via members of facilitative carbohydrate transporters (Gluts). Both Glut2 and Glut5 are expressed in the small intestine and are able to transport fructose (33–39). The Schematic diagram 1 (left and right) depicts the localization and role of Glut2 and Glut5 in fructose absorption in jejunum at basal state and in response to increased dietary fructose intake. As indicated, Glut5 is expressed on the apical membrane of enterocytes whereas Glut2 is located intracellularly and on the basolateral membrane at basal state (left) and is recruited to the apical membrane in the presence of luminal fructose or glucose (right). Glut5 is detected in the apical membrane at both the basal state and in response to increased dietary fructose intake (Schematic diagram 1). It has been proposed that Glut2 is a major glucose and fructose-absorbing transporter, at least in the presence of increased dietary fructose or glucose intake. In addition to the small intestine, Glut5 is abundantly expressed in the proximal tubule, specifically in the S3 segment (40). Few studies have speculated that the absorption of fructose in the small intestine and kidney proximal tubule is mediated in part via Glut5 (Slc2a5).

Salt absorption in the small intestine and kidney proximal tubule

The absorption of salt in the small intestine is mediated via two apical Cl^-/HCO_3^- exchangers DRA (Slc26a3) and PAT1 (Slc26a6) working in coordination with the Na^+/H^+ exchanger NHE3 (Slc9a3) (41–56). The Schematic diagram 2 (left and right) depicts the localization of salt absorbing transporters in the small intestine (left) and kidney proximal tubule (right). As shown, SLC26A6 (human)/Slc26a6 (mouse), also known as PAT1 (Putative Anion Transporter 1) or CFEX (chloride/formate exchanger), is expressed on the apical membrane of upper villous epithelium in small intestine and kidney proximal

tubule (44–52). PAT1, which can function in Cl^-/HCO_3^- and Cl^-/oxalate exchange modes *in vivo*, plays an important role in the absorption of salt and secretion of bicarbonate in the small intestine (44–52). PAT1 also plays an important role in chloride absorption in the kidney proximal tubule (45).

DRA (Slc26a3) is expressed on the apical membrane of mid to lower villous epithelium in small intestine and upper villous epithelium of large intestine (53–55). DRA plays an essential role in chloride absorption in the small and large intestines and its mutation inactivation in human results in chloride-losing diarrhea (53). Genetic deletion of DRA recapitulates the phenotype of chloride losing diarrhea in mice (54).

The sodium absorption in the small intestine as well as the kidney proximal tubule is mediated predominantly via NHE3 (left and right panels) (41, 56, 57). In addition to NHE3, the Na+/H+ exchanger NHE2 is also expressed on the apical membrane domain of enterocytes in the small intestine, but it does not seem to play a major role in sodium absorption in mammalians. As shown in the right panel (Schematic diagram 2), PAT1 and NHE3 also co-localize on the apical membrane of kidney proximal tubule (41, 51, 52, 56, 57).

Glut5 and PAT1 in the small intestine: interaction and localization

DNA microarray experiments revealed that a total of 27 genes were upregulated by at least twofold in the small intestine of PAT1−/− mice (personal observation). The most notable was that of Glut5 (Slc2a5), a fructose transporter which showed a ~fivefold upregulation (Fig. 1). As shown, mRNA expression of Glut5 increased significantly in jejunum of PAT1 ko mice (Figure 1). Glut5 shows similar pattern of expression in jejuna of PAT1 wt and ko mice (25). Immunofluorescence labeling indicated apical co-localization of Glut5 and PAT1 on jejunal villi in wt mice (25).

Fructose stimulates salt absorption in the jejunum predominantly via PAT1 activation

Given the co-localization of Glut5 and PAT-1 (25) and the upregulation of Glut5 mRNA in the small intestine of $PAT1^{-/-}$ mice (Fig. 1), we entertained the possibility that fructose may stimulate salt absorption by activating PAT1. To test this possibility, proximal jejunum was perfused *in vivo* with isotonic perfusate and net fluid absorption was examined, before and after the addition of fructose (25). The results demonstrated that fructose at 40 mM elicited a significant increase in fluid absorption in $PAT1^{+/+}$ mice ($p<0.01$, n=5), a response which was blunted in $PAT1^{-/-}$ mice (25). The removal of chloride from the perfusate inhibited the basal fluid absorption by 75%, and completely abrogated the fructose-stimulated fluid absorption in $PAT1^{+/+}$ mice (25).

Contrary to the blunted response in jejunum of PAT1 ko mice, luminal fructose elicited a very robust stimulatory effect on salt absorption in jejunum of DRA ko mice (Seidler, Soleimani communication), indicating that DRA is not the target of fructose action in jejunum. The fructose-stimulated salt absorption in jejunum was completely abrogated in NHE3 ko mice (Seidler, Soleimani communication). Taken together, these studies strongly suggest that fructose-stimulated salt absorption is mediated via PAT1 and NHE3 working in parallel.

Increased fructose intake enhances the expression of Glut5, PAT1, and NHE3 in the small intestine

The above studies in perfused jejunum were acute and the onset of the effect of fructose was observed in a matter of minutes. To examine the role of long term consumption of fructose on ion transporters, animals were fed 60% fructose diet and compared to 60% starch as control. Increased dietary fructose intake (60% fructose) for two weeks enhanced the mRNA expression and protein abundance of Glut5, PAT1, and NHE3 in jejunum Vs. control diet (60% starch) (25). The two-week time point was chosen because animals had not yet developed hypertension (personal observation).

Increased dietary fructose intake decreases urinary salt excretion in rats and mice

To examine the role of dietary fructose on renal salt excretion balanced studies were performed in rats and mice before and after switching to high fructose diet. The results demonstrated that high fructose diet significantly decreased the daily excretion of chloride and sodium in rat kidney (25). The kidney function, including BUN and serum creatinine and urine osmolarity remained unchanged (25). The stimulatory effect of high fructose diet on salt absorption in the kidney was also evident in wild-type ($PAT1^{+/+}$) mice. However, PAT1 ko mice displayed enhanced kidney salt excretion when subjected to increased dietary fructose intake. The sodium and chloride excretion rates in PAT1 wt and null mice on control diet were comparable and significantly lower than PAT1 null mice on high fructose diet. Kidney function and serum uric acid remained normal and comparable in $PAT^{+/+}$ and $PAT^{-/-}$ mice on high fructose diet, indicating the absence of dehydration or any correlation between increased dietary fructose intake and serum uric acid levels.

Fructose-induced hypertension: Role of salt absorbing transporters in intestine and kidney

To determine the impact of fructose-stimulated salt absorption on blood pressure, systolic blood pressure was measured in conscious mice by tail cuff method. The results indicated that $PAT1^{+/+}$ mice on a high fructose diet for 12 weeks developed significant increase in their blood pressure Vs. control diet (25). The systolic blood pressure in $PAT1^{+/+}$ mice increased from 102 ± 2 mm Hg on a normal diet to 111 ± 2.2 on a high fructose diet ($p<0.02$) (25). However, $PAT1^{-/-}$ mice failed to develop hypertension on a high fructose diet (25). $PAT1^{-/-}$ mice displayed normal food intake and weight gain on either diet Vs. $PAT1^{+/+}$ mice. Blood sugar increased in both $PAT1^{+/+}$ and $PAT1^{-/-}$ mice on increased dietary fructose intake (25). The increase in plasma fructose, measured by HPLC, was comparable in both $PAT1^{+/+}$ and $PAT1^{-/-}$ mice on increased dietary fructose (25).

Fructose absorption in the small intestine and fructose-induced hypertension are absolutely dependent on Glut5

Glut5 transports fructose; whereas, Glut2 transports both glucose and fructose (schematic diagram 1). To ascertain the role of Glut5 in fructose absorption, animals with genetic deletion of Glut5 were placed on high fructose diet and compared to control diet (58). Our results indicated that increased dietary fructose intake (60% fructose) in Glut5 ko mice causes severe small intestinal malabsorption, as evident by massive dilation of bowel

loops and specifically caecum as early as 72 hours after the start of fructose-containing diet (58). Glut5$^{+/+}$ mice showed a six-fold increase in their blood fructose levels (58). However, Glut5$^{-/-}$ mice did not show any noticeable increase in their blood fructose level after five days of high fructose diet (58). Glut5$^{-/-}$ mice develop hypotension after 5 days of increased dietary fructose intake, due to volume depletion (58). Interestingly, Glut5$^{-/-}$ mice did not demonstrate any fructose-stimulated salt absorption in their jejuna (58), indicating that presence of Glut5 is essential for the fructose-stimulated salt absorption in the intestine. Schematic diagram 3 depicts the role of fructose and Glut5 in fructose absorption and fructose-stimulated salt absorption in the small intestine..

The absence of hyperuricema in early stages of fructose-induced hypertension

Our studies in rats on high fructose diet for five weeks or in mice on high fructose diet for 12 weeks did not demonstrate any elevation in serum uric acid; however, they showed enhanced excretion of uric acid in the urine (25). These results clearly demonstrate that serum uric acid is not causally linked to the generation of hypertension in fructose-induced hypertension.

Role of increased dietary salt intake and gender in fructose-induced hypertension

Recent studies in our laboratories have indicated that increased dietary fructose intake accelerated the onset of hypertension relative to normal salt intake, an effect that was more pronounced in male mice (personal observation). Our results further demonstrate that increased dietary fructose intake decreased the concentration of urinary cGMP in animals on either normal or high salt diet, suggesting the impairment of the natriuretic crosstalk between intestine and kidney.

It is widely believed that enhanced salt absorption in the intestine per se should not in and out of itself lead to a state of salt overload, if the kidney retains its ability to excrete the excess salt. However, it should be noted that the same salt absorbing transporters in the small intestine (namely PAT1 and NHE3) are also expressed in the proximal tubule (Schematic diagram 2). As such, increased dietary fructose intake will likely enhance salt absorption in both organs by activating PAT1 (and NHE3), therefore preventing the kidney from excreting the excess salt load. In support of the role of salt excess in the pathogenesis of fructose-mediated hypertension, studies in rats demonstrated that low salt diet completely abrogated fructose-stimulated hypertension (59).

Summary and Conclusions

Increased dietary fructose intake stimulates salt and fructose absorption in the small intestine and kidney proximal tubule through coordinated activation of PAT1, NHE3, and Glut5. PAT1, NHE3 or Glut5 deletion blunts fructose-stimulated salt absorption in the small intestine. Deletion of PAT1 also blocks the stimulatory effect of fructose on salt absorption in the kidney proximal tubule. Further, fructose-induced hypertension was almost abolished in PAT1 ko mice on high fructose diet.

The exact mechanism(s) linking fructose and Glut5 to PAT1 (and NHE3) stimulation in the small intestine remains speculative. The absence of any stimulatory effect of fructose

on salt absorption in Glut5 KO mice intestine strongly suggests that fructose exerts its stimulatory effect after it is being absorbed via Glut5. Whether, the absorbed fructose changes the electrochemical gradients for salt absorption across the luminal membrane or directly activates PAT1 (and NHE3) through signaling pathways remains speculative.

Taken together, these results strongly suggest that fructose-induced hypertension is generated in large part by an state of salt overload resulting from enhanced salt absorption in intestine and kidney. We propose that reducing dietary intake of fructose and salt as well as maneuvers aimed at inhibiting salt absorption in the intestine and kidney tubules could have profound beneficial effect on controlling blood pressure in patients with metabolic syndrome.

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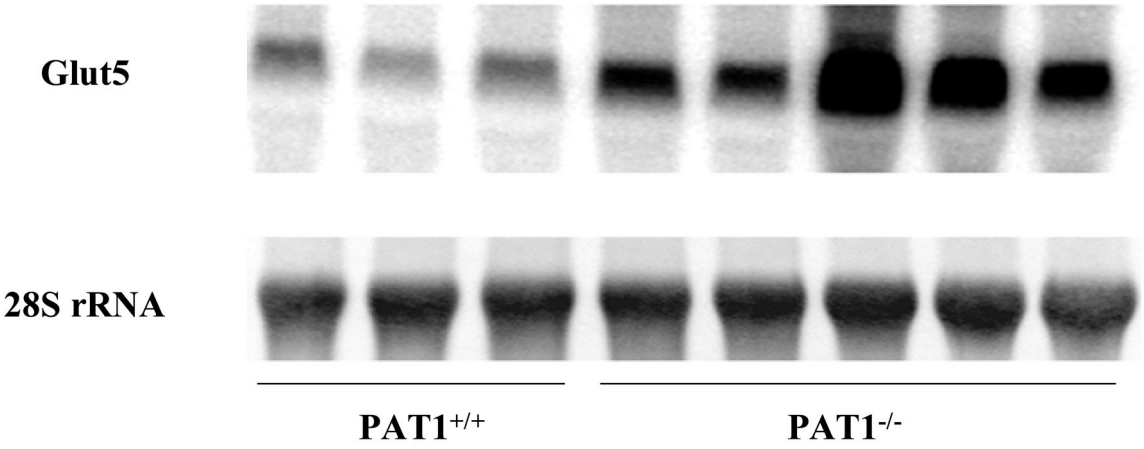
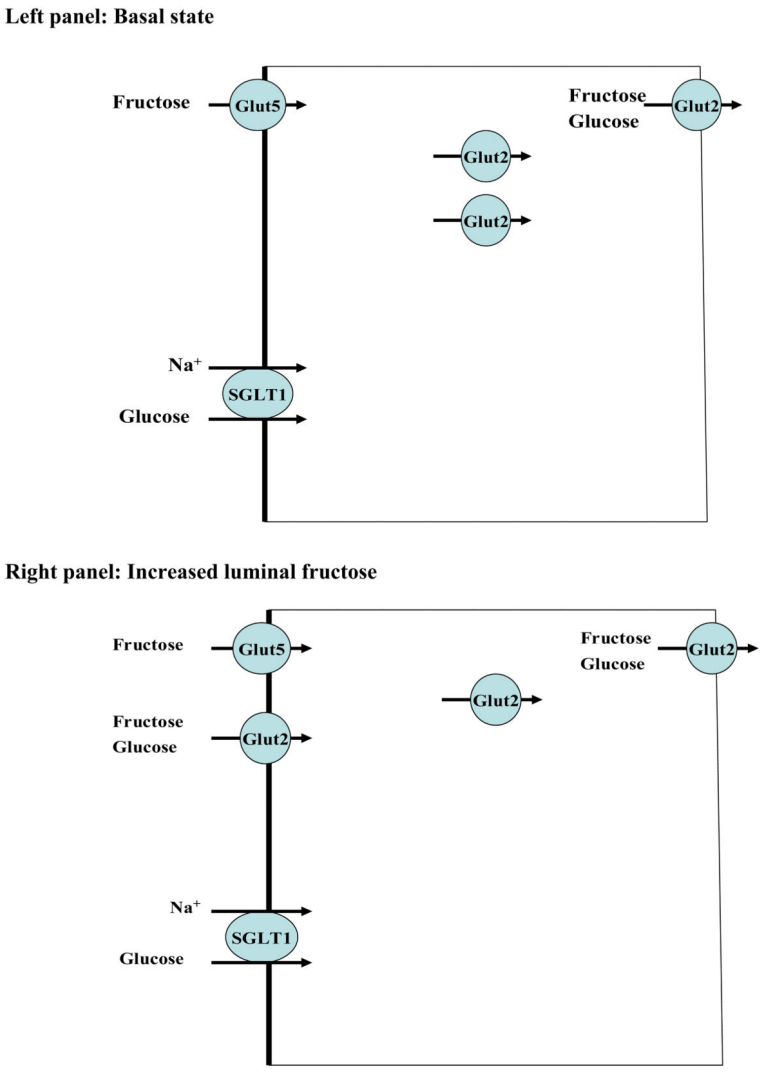


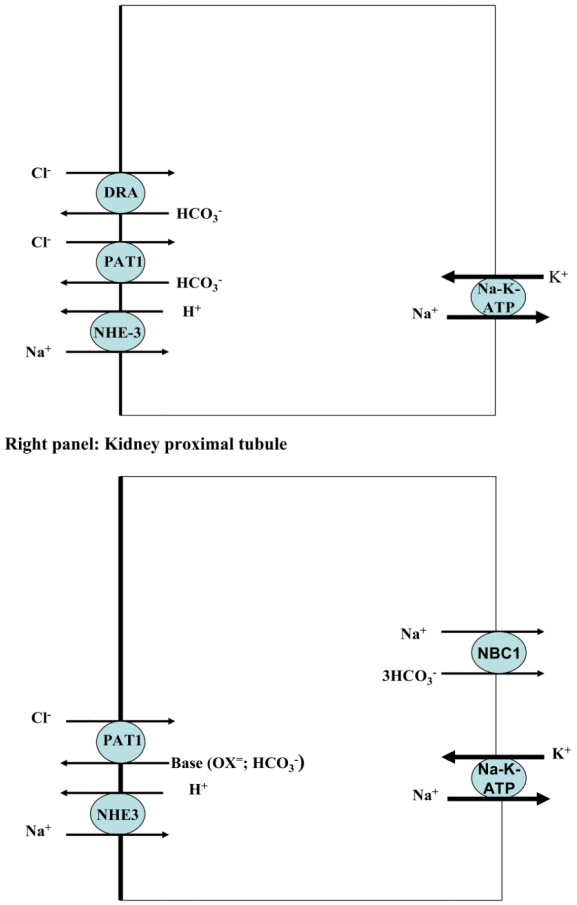
Figure 1. Expression of Glut5 increased significantly in jejunum of PAT1 ko mice

Northern hybridizations verified the results of DNA microarray and demonstrated that the expression of Glut5 increased by ~5 folds in jejunum of PAT1 null mice.



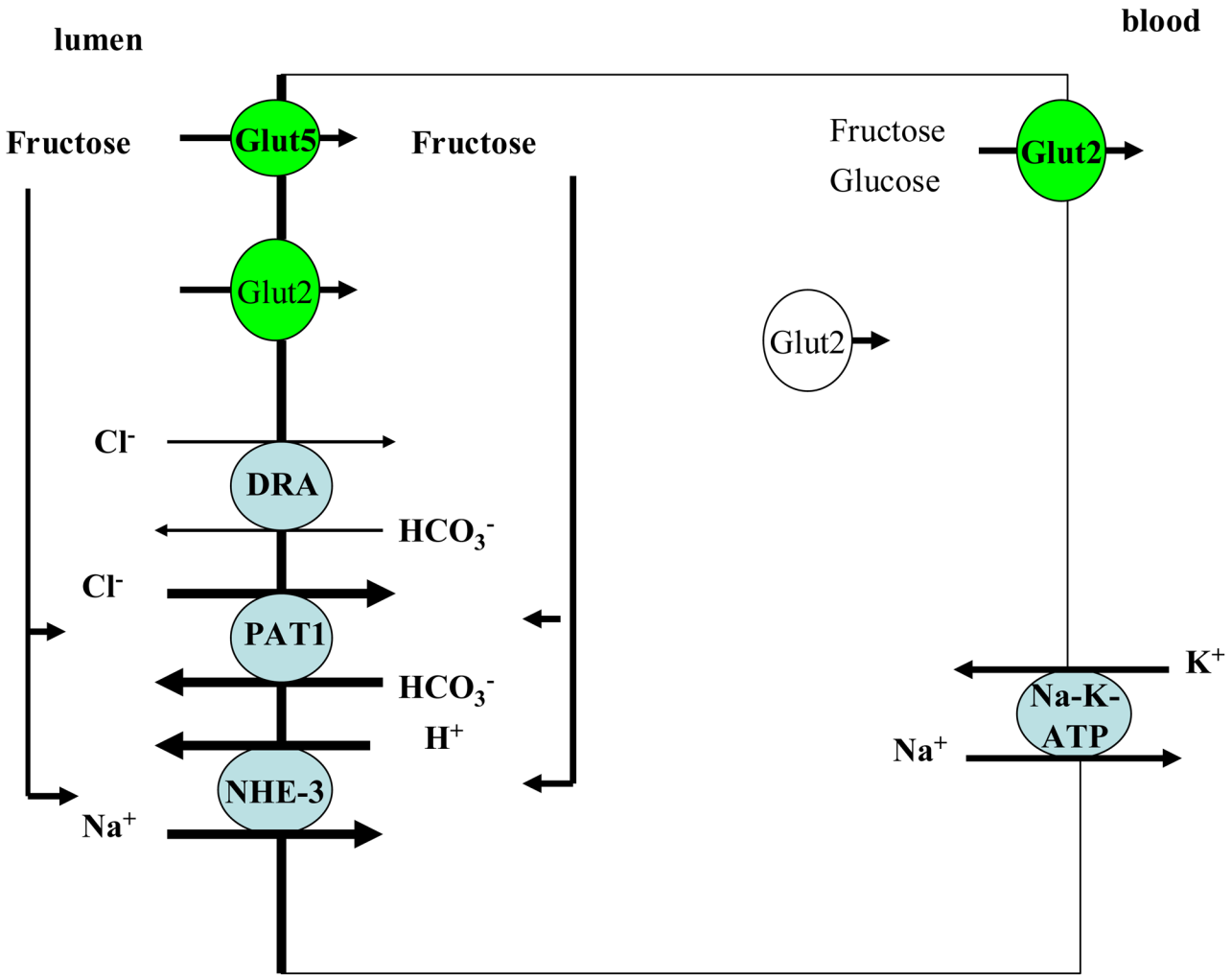
Schematic diagram 1. Localization and role of Glut2 and Glut5 in fructose absorption in jejunum at basal state (left panel) and in response to increased dietary fructose intake (right panel)

SGLT1 (sodium glucose cotransporter 1) facilitates glucose and sodium absorption. Glut2 can transport both glucose and fructose and is recruited to the apical membrane in the presence of increased dietary fructose or glucose intake. Glut5 only transports fructose and resides in the apical membrane at basal state and in response to increased dietary fructose intake.



Schematic diagram 2. Localization of salt absorbing transporters in the small intestine (left panel) and kidney proximal tubule (right panel)

NHE3 = Sodium Hydrogen Exchanger3= SLC9A3; PAT1 = Putative Anion Transporter 1= SLC26A6; DRA = Down Regulated in Adenoma =SLC26A3; NBC1: Sodium:bicarbonate cotransporter1 =SLC4A4



Schematic diagram 3. The role of fructose and Glut5 in fructose absorption and fructose-stimulated salt absorption in the small intestine

Luminal fructose, via Glut5 action, stimulates PAT1 and NHE3, therefore enhancing salt absorption in the jejunum. The stimulatory effect of luminal fructose on salt absorption in jejunum was completely abrogated in Glut5 null mice (ref. 58).