Effects of Excess Maternal Fructose Intake

Subjects: Endocrinology & Metabolism

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Fructose is a 6-carbon polyhydroxy ketone monosaccharide that shares the same chemical formula and is an isomer of glucose. Fructose consumption is now recognised as a major risk factor in the development of metabolic diseases, such as hyperlipidaemia, diabetes, non-alcoholic fatty liver disease and obesity. In addition to environmental, social, and genetic factors, an unfavourable intrauterine environment is now also recognised as an important factor in the progression of, or susceptibility to, metabolic disease during adulthood. Developmental trajectory in the short term, in response to nutrient restriction or excessive nutrient availability, may promote adaptation that serves to maintain organ functionality necessary for immediate survival and foetal development. Consequently, this may lead to decreased function of organ systems when presented with an unfavourable neonatal, adolescent and/or adult nutritional environment. These early events may exacerbate susceptibility to later-life disease since sub-optimal maternal nutrition increases the risk of non-communicable diseases (NCDs) in future generations. Earlier dietary interventions, implemented in pregnant mothers or those considering pregnancy, may have added benefit.

fructose metabolic disease liver

1. Fructose Metabolism

Following consumption, fructose is absorbed by the small intestine, primarily the jejunum, passing through the brush border of the intestinal wall by glucose transporters [1]. Fructose is transported into the enterocyte by glucose transporter 5 (GLUT5), which is specific to fructose, and through the basolateral pole primarily by glucose transporter 2 (GLUT2) and into systemic circulation via the hepatic portal vein and primarily transported to the liver for metabolism [1][2][3][4]. Additionally, glucose transporter 7 (GLUT7), glucose transporter 8 (GLUT8), glucose transporter 9 (GLUT9) and glucose transporter 11 (GLUT11) have been shown to be fructose transporters, in various degrees of specificity to fructose, due to their sequence homology to glucose transporters [4][5][6][7]. Hepatic fructose uptake from portal circulation is faster than glucose uptake [8] because glucose is not only utilised in the liver but virtually all cells; therefore, glucose is transported from the portal vein to be used by other tissues in the body for energy [9]. Conversely, fructose is minimally used (30–50%) by peripheral tissues, such as kidney, fat, skeletal muscle, brain and testis [10][11]. Moreover, fructose is metabolised differently compared to glucose due to hepatic uptake (50–70%) and rapid conversion into glucose, glycogen, lactate and, more specifically, fat [10][12].

2. Hepatocyte Metabolism of Fructose

The primary pathway of fructose metabolism occurs through phosphorylation by fructokinase/ketohexokinase. In comparison to glucose, fructose immediately bypasses phosphofructokinase, a main regulator of glycolysis and glucose metabolism, by negative feedback inhibition of intracellular adenosine triphosphate (ATP) and citrate build-up. Fructose is rapidly phosphorylated by fructokinase/ketohexokinase, which is specific to fructose, to produce fructose-I-phosphate (fructose-1-P) [2][9][13][14]. Aldolase B initiates the lysis of fructose-1-P to produce dihydroxyacetone phosphate (DHAP) and glyceraldehyde [2][9][13][14]. Fructose enters glycolysis at the tri-phosphate level, without encountering rate-limiting and regulatory enzymes, providing an unregulated source of both glycerol-3-phosphate (G-3-P) and acetyl-CoA, increasing pyruvate availability to enter the mitochondrion for energy production or hepatic de novo lipogenesis [15]. Primary hepatic metabolites of excessive fructose intake can include glucose, glycogen, lactate, uric acid, free fatty acids (FFA), very low-density lipoproteins (VLDL) and triglycerides (TAG) [2][16] (**Figure 1**).

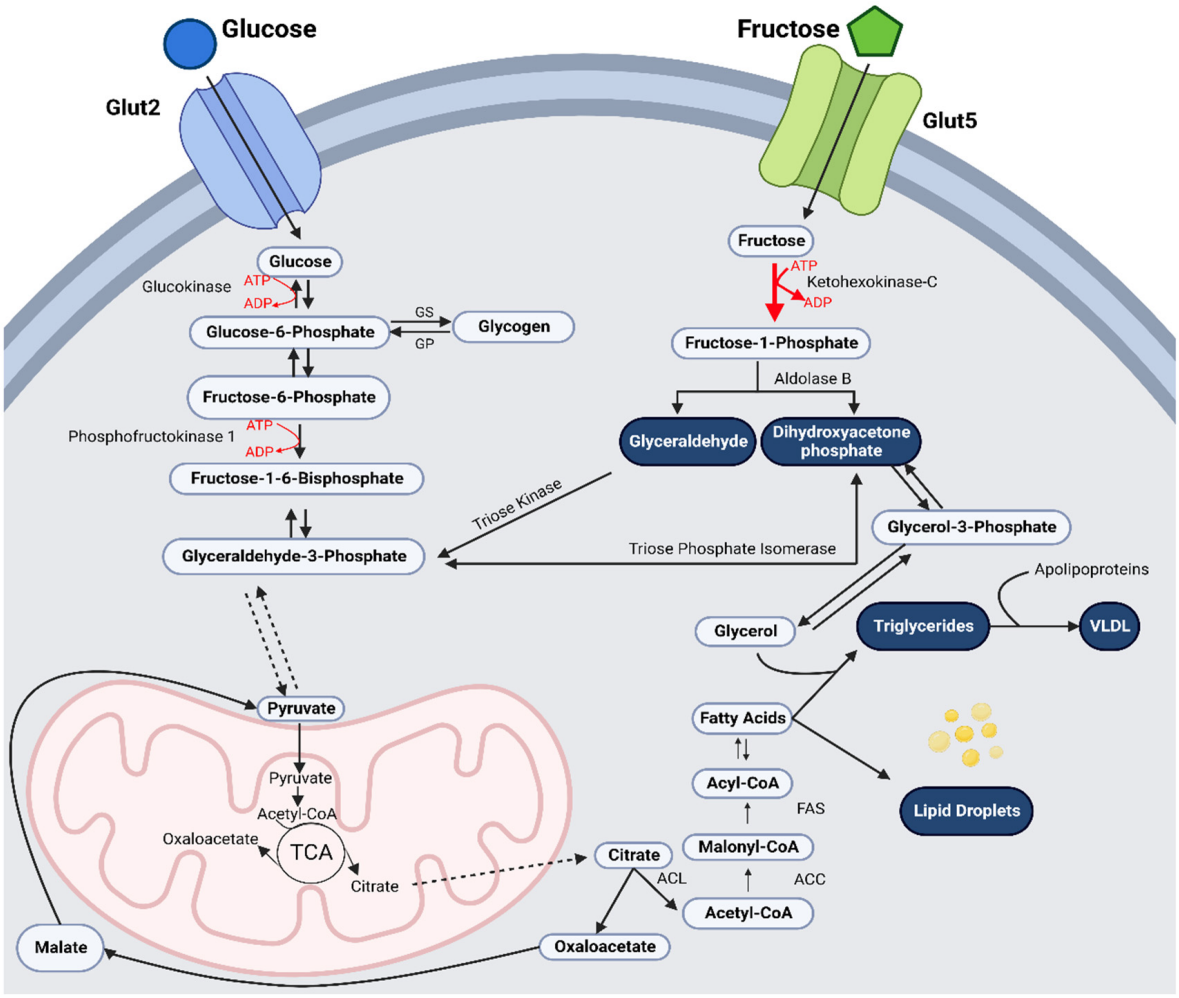

Figure 1. Fructose Hepatocyte Uptake and Metabolism. Fructose immediately bypasses phosphofructokinase, a main regulator of glycolysis, and is instantly phosphorylated by fructokinase/ketohexokinase to produce fructose-I-phosphate (fructose-1-P). Aldolase B initiates the lysis of fructose-1-P to produce dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Triose kinase converts glyceraldehyde into glyceraldehyde-3-phosphate (Glyc-3-P). Fructose enters glycolysis at the tri-phosphate level without encountering rate-limiting and regulatory enzymes,

providing an unregulated source of both glycerol-3-phosphate (G-3-P) and acetyl-CoA, increasing pyruvate availability to enter the mitochondrion for energy production or hepatic de novo lipogenesis. Primary hepatic metabolites of fructose include glucose, glycogen, lactate, uric acid, free fatty acids (FFA), very low-density lipoproteins (VLDL) and triglycerides (TAG). Diagram created with BioRender.com, accessed on 27 September 2022.

Hepatocytes' specialised ability to rapidly break down fructose is of key importance to support the body's energy requirements. When consumed with glucose, fructose catalyses glucose uptake and glycogen storage in the liver [17]. When plasma levels of glucose or hepatic glycogen stores are low, fructose can enter the glycolytic pathway at the tri-phosphate level to be used to create glucose, glycogen, or lactate for oxidation in extrahepatic tissues [17]. The rapid increase in fructose breakdown increases metabolite production. Metabolites of FFA, VLDL and TAG are essential for cellular function and provide energy reserves in adipose tissue [18]. Whereas hepatic glucose metabolism is tightly regulated by current energy status, fructose is unregulated, even in the presence of high energy availability [10]. When glucose and glycogen are accessible for energy use, hepatic fructose metabolism favors lipogenesis. Consequently, chronic consumption of excess fructose from sweetened processed foods and SSB increases fructose metabolism, increasing abnormal energy flux and hepatic de novo lipogenesis [19][20], accelerating the release of FFA, TAG, and VLDL into circulation [9][14]. Increased lipogenesis has been the cornerstone of the preceding biochemical reactions induced by excess fructose consumption; however, recent evidence suggests that activation of alternate physiological and signaling pathways may contribute to direct and indirect metabolic dysregulation [2][8][19].

3. Excess Fructose and Hepatic De Novo Lipogenesis and Triglyceride Synthesis

Hepatic de novo lipogenesis is the liver's ability to create new lipids from excess non-lipid substrates (acetyl-CoA, DHAP and G-3-P), primarily from carbohydrates [21][22][23][24]. Hepatic de novo lipogenesis is a highly regulated biosynthetic lipogenic pathway that is responsible for synthesising fatty acids, elongation and desaturation of fatty acids and TAG synthesis [8][24][25]. Within the liver, TAG-VLDL lipid droplets can be stored in the perisinusoidal space (space of Disse) as intra-hepatocellular lipids or exported from sinusoids to be released into circulation and stored as TAG in adipose tissue [3][10][24][25][26]. The lipid droplets stored within hepatocytes are energy reservoirs, which can be used when other energy sources are depleted [27]. In addition, hepatic lipid droplets provide reservoirs of structural elements for cellular membrane synthesis, such as sterols, fatty acids, and phospholipids [27][28]. The diverse functions of lipid droplets allow them to facilitate hepatic homeostasis.

While glucose is a principal substrate for hepatic de novo lipogenesis, fructose favours lipogenesis [8][23]. Through a coordinated sequence of enzymatic reactions, de novo lipogenesis following fructose intake can be initiated quickly through the following pathways: (1) via entrance into glycolysis as Glyc-3-P via the unregulated accumulation of intermediates dihydroxyacetone phosphate (DHAP) and/or glyceraldehyde, thereby increasing the production of acetyl-CoA, and (2) via the more direct entrance of lipogenesis as G-3-P via the unregulated accumulation of intermediate DHAP [21][22][24]. Additionally, fructose availability can also indirectly activate hepatic

de novo lipogenesis by increasing conversion of glucose and lactate to form TAG [22]. Following fructose intake, the availability of acetyl-CoA entering the tricarboxylic acid (TCA) cycle increases. TCA intermediates accumulate and are released as citrate into the cytoplasm, where it is converted to acetyl-CoA by ATP-citrate lyase [21][23][28].

Additionally, citrate is an allosteric activator of acetyl-Co-A carboxylase, which converts acetyl-CoA to malonyl-CoA [21][23][28]. Fatty acid synthase uses malonyl-CoA as a substrate to produce palmitate. Palmitate can be elongated to fatty acid stearate by enzyme elongation of long-chain fatty acid protein 6 [29]. The saturated fatty acids, palmitate, and stearate are desaturated by stearoyl-CoA desaturase to become monounsaturated fatty acids, palmitolate and oleate [29]. Following desaturation, monounsaturated fatty acids may be esterified to the glycerophosphate backbone of G-3-P to produce the following additional complex lipids: fatty acids, such as stearic acid, palmitoleic acid and oleic acid, membrane phospholipids, cholesterol esters and TAG [28][30]. G-3-P, fructose's more direct entrance into de novo lipogenesis, favours esterification of unbound free fatty acids to produce TAG [22][25]. Thereby, for the first step of de novo TAG synthesis, fatty acid acyl-Co-As are added to G-3-P by glycerol-3-phosphate acyltransferase to produce lysophosphatidic acid. 1-acylglcyerol-3-phosphate acyltransferase adds another acyl-CoA to produce phosphatidic acid. Phosphatidic acid is then dephosphorylated by lipin1 to produce 1,2-diacylglycerol. Finally, 1,2-diacylglycerol is esterified to a second acyl-CoA by diacylglycerol acyltransferase to form TAG [24][29]. The TAG produced are packaged with apolipoprotein B 100 by the lipidation of microsomal triglyceride transfer protein and neutral lipids within the endoplasmic reticulum to form VLDL. The TAG-VLDL can either be stored in the liver in the space of Disse, as intra-hepatocellular lipids, or exported from sinusoids and released into blood circulation. Animal and human studies have shown that continued excessive dietary fructose intake increases activity of lipogenic liver enzymes, lipid synthesis and circulating LDL, VLDL, HDL and TAG concentrations in the blood [2][16][31][32][33]. It has been established that dysregulation within de novo lipogenesis can give rise to metabolic diseases such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [23].

Excess fructose consumption has been shown to cause adaptive increased activity of the hepatic enzymes involved in fructose uptake into the hepatocyte, metabolism, and de novo lipogenesis of FFA and TAG [3]. Chronic increased activation of hepatic enzymes can, therefore, cause continued metabolic dysregulation, leading to obesity, type 2 diabetes and NAFLD. Continued metabolic dysregulation from increased fructose metabolism can lead to postprandial hypertriglyceridaemia [16], which results in the accumulation of hepatic lipids, plasma VLDL, and visceral adipose deposition [10][16]. Visceral adiposity subsequently further contributes to hepatic TAG accumulation, and the increased portal delivery of FFA to the liver can result in hepatic insulin resistance [16]. Studies in humans and rodents [33][34][35][36][37], dogs [38] and non-human primates [39] have demonstrated that excess fructose or sucrose intake induces hyperlipidaemia more than excessive glucose [40] or a high-fat diet [31] (**Figure 2**).

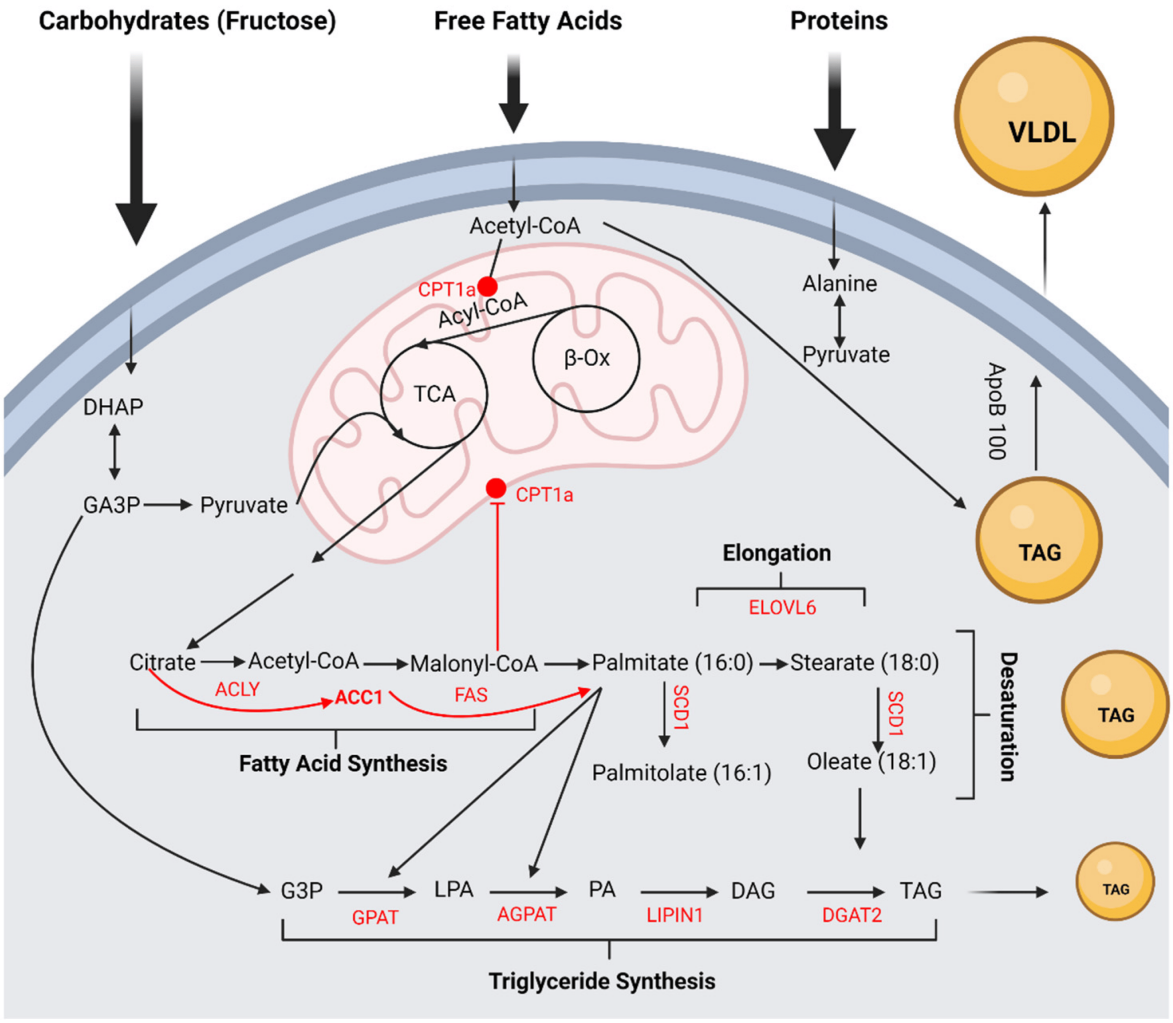

Figure 2. Fructose and Hepatic De Novo Lipogenesis. Fructose intake can initiate de novo lipogenesis quickly through the following pathways: (1) via entrance into glycolysis as glyceraldehyde-3-phosphate (Glyc-3-P or GA3P) *via* the unregulated accumulation of intermediates dihydroxyacetone phosphate (DHAP) and/or glyceraldehyde thereby, increasing the production of acetyl-CoA, and (2) via the more direct entrance of lipogeneses as glycerol-3-phosphate (G-3-P) via the unregulated accumulation of intermediate DHAP. In the presence of excess acetyl-CoA, following fructose intake, in the tricarboxylic acid (TCA) cycle, TCA intermediates accumulate and release citrate into the cytoplasm. Citrate is converted by ATP-citrate lyase (ACLY) to acetyl-CoA. Additionally, citrate is an allosteric activator of acetyl-Co-A carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA. Fatty acid synthase (FAS), a biosynthetic enzyme, uses malonyl- CoA as a substrate to produce palmitate (C16:0), the first fatty acid product. Palmitate (C16:0) can be elongated to fatty acid stearate (18:0) or longer fatty acids by enzyme elongation of very long chain fatty acid protein 6 (ELOVL6). The saturated fatty acids, palmitate (C16:0) and stearate (18:0), are desaturated by stearoyl-CoA desaturase (SCD1) to become monounsaturated fatty acids palmitolate (16:1) and oleate (18:1). Following desaturation, monounsaturated fatty acids may be esterified to the glycerophosphate backbone of G-3-P to produce the following additional complex lipids: fatty acids, such as stearic acid, palmitoleic acid and oleic acid, and TAG. Fatty acid acyl-Co-As are added to G-3-P by glycerol-3-phosphate acyltransferase (GPAT) to produce lysophosphatidic acid (LPA). 1-acylglcerol-3-phosphate acyltransferase (AGPAT) adds another acyl-CoA to produce phosphatidic acid (PA). PA is then dephosphorylated by lipin1 (LPIN1)

to produce 1,2-diacylglycerol (DAG). Finally, DAG is esterified to a second acyl-CoA by diacylglycerol acyltransferase (DGAT) to form TAG [30][41][42]. The TAGs produced are packaged with apolipoprotein B 100 (apoB100) to form VLDL. Diagram created with BioRender.com, accessed on 27 September 2022.

4. Adverse Effects of Excessive Fructose Intake

To better understand offspring predisposition to metabolic disease following excess maternal fructose exposure *in utero*, it is imperative to understand the direct and indirect dysregulation associated with modern fructose intake. In the modern Westernised diet, fructose intake from natural whole foods has declined, while intake from sweetened processed foods and SSB supersedes levels beneficial for survival and health maintenance [43][44]. The typical daily intake of fructose in Westernised diets has become a major public health concern due to the paralleled increase in metabolic diseases, such as dyslipidaemia, hyperlipidaemia, insulin resistance, visceral adiposity, obesity, diabetes, high blood pressure, cardiovascular disease, and NAFLD [8][10][25][31][32][45][46].

The contribution of fructose in the rise of metabolic diseases has remained controversial, despite the increasing evidence in humans and experimental animal models [8][12]. Results from some animal studies may be conflicting because some models utilise supraphysiological levels of dietary fructose—as high as 30–70% [10][32][47][48]. Some human short-term mechanistic studies have also used levels that exceeded the typical level of dietary fructose, ranging from 25% to 35% and 50% of total caloric intake [40][49][50]. While supraphysiological levels of dietary fructose used in animal and human studies are not comparable to the current amounts consumed, they reinforce the adverse metabolic effects of excess fructose intake. However, the use of animal and human studies that utilise comparable ranges to the average dietary fructose intake still show features of hyperlipidaemia, increased plasma lipid concentrations, increased TAG and VLDL, increased uric acid and dose-dependent weight gain [10][32][41][51][52][53]. Some studies have argued that the rise in metabolic diseases may be associated with excess caloric intake rather than the form or quality of the calories consumed [54][55]. It is critical to keep in mind that the chemical form or ‘quality’ of the calorie may be more metabolically influential than the caloric content itself. For example, even though glucose and fructose are calorically equal (4 kcal/g [9]), there are fundamental differences in their metabolic regulation. The difference in metabolic regulation between glucose and fructose, not caloric content, is the primary implicating factor of fructose’s ability to initiate metabolic dysregulation [10]. Therefore, when considering the impact of fructose on the prevalence of metabolic disease in Westernised countries, several factors appear clear. The pathways that direct fructose’s metabolism are unregulated. In the presence of readily available hepatic glucose and glycogen stores, fructose metabolism favours lipogenesis. Consequently, chronic consumption of excess fructose initiates an adaptive series of synchronised responses with interrelated signalling pathways. These adaptive responses to an abnormal energy flux and hepatic de novo lipogenesis may contribute to direct and indirect metabolic dysregulation [2][8][19].

5. Excess Maternal Fructose Intake and Offspring Predisposition to Metabolic Dysfunction

Animal models have shown that unbalanced maternal nutrition, in particular, overnutrition, can have permanent effects on the offspring's organ structure and function, predisposing them to adult-onset of non-communicable diseases, such as obesity, diabetes, NAFLD and cardiovascular risk factors [10][43][56][57]. Contemporary Western women's consumption of high levels of fructose before and/or during pregnancy and lactation may alter critical phases of pregnancy, such as embryogenesis, foetal-placental development, and milk production and quality [10].

Previous research in rodents has demonstrated maternal consumption of 10% fructose in water during pregnancy and lactation resulted in maternal hyperglycaemia, hyperinsulinaemia, and hypertriglyceridaemia; which were subsequently associated with significantly elevated plasma insulin in the offspring at weaning, suggesting offspring susceptibility to diabetes during adulthood [58]. In animal models where 20% of caloric intake was from fructose during gestation, this resulted in maternal hyperinsulinaemia and sex-specific effects in the offspring, with female offspring having higher plasma leptin and glucose levels and displaying greater vulnerability to metabolic disturbances in neonatal life than male offspring [59]. The research has shown sex-specific cardio-metabolic differences in the offspring of maternal 10% *w*/*v* fructose-fed rat dams [60]. In addition, a 10% *w*/*v* fructose intake in guinea pigs produced changes in dams' milk quality, and offspring liver function, lipid metabolism, and programmed hepatic mitochondrial dysfunction [32][61][62].

In guinea pig model, dams' dietary intervention of 10% *w*/*v* fructose intake finished immediately following spontaneous delivery of offspring, and consequently, fructose concentrations in dams' milk were not assessed [32]. However, two studies have shown that during breastfeeding, fructose is transferred from the mother to the infant and that a positive association between breast milk fructose concentration and infant adiposity at 6 months of age can be observed [63][64].

Researchers were interested in excess maternal fructose intake and dams' milk FFA composition, and the effects of altered milk composition on the vertical transmission of FFA from dam to offspring [32][61][62]. Research from lab has shown significantly increased FFA in dams' maternal milk, including myristic acid, total trans FFA, vaccenic acid, linolelaidic acid, cis-vaccenic acid, total omega-7 and gamma-linolenic acid, the majority of which are trans-fats [32][62]. Other studies have also shown that trans FFA content in lactating mothers is both directly associated with short and long-term maternal diet and independent of diet via maternal adipose tissue [65][66]. Research has also shown significantly increased FFAs and, specifically, palmitoleic acid and total omega-7 in both mother and offspring from age day 0 to 4 months [25][60][62]. Studies have demonstrated that increases in serum palmitoleic acid indicate a shift of carbon from carbohydrates to FFA and visceral lipid cell lipolysis [61][62][67][68][69]. These results suggest a programming effect on *in utero* exposure to excess fructose on FFA synthesis, fatty acid oxidation and subsequent excess palmitoleic acid.

Similar to researchers' previous studies, others have also reported that a high fructose intake alters β-oxidation, increases FFAs and TAG, causing dyslipidaemia, hepatic lipid accumulation and insulin resistance [19][52][70], and increases in foetal hepatic enzyme activity are associated with fructose uptake, metabolism, lipogenesis and inflammatory response. These early physiological adaptations may potentially predispose offspring to metabolic diseases in later life [10][33][51][71].

In relation to energy availability, insulin signals the hypothalamus to regulate food intake and energy homeostasis. It has been shown that fructose does not stimulate insulin secretion from pancreatic B-cells, most likely due to the low expression of GLUT5 fructose transporters in B-cells, and its effects are, therefore, independent of insulin secretion [72][73][74]. Furthermore, there is strong evidence in animal and human studies that shows that decreases in hepatic and muscle insulin sensitivity are associated with ectopic lipid deposition and tissue-specific lipotoxicity, following long-term excess fructose consumption [12][49]. It is suggested that the increase in hepatic lipids following fructose intake increases the concentrations of diacylglycerol (DAG), which activates protein kinase C epsilon (PKCε), leading to increased serine phosphorylation of the insulin receptor and insulin receptor substrate 1 (IRS-1), resulting in impaired insulin activation [75][76]. Typically, when excess lipids are stored within adipose tissue, adipocytes release the leptin peptide in proportion to the amount of adipose in the body. Leptin signals the hypothalamus when there is enough stored energy by decreasing appetite stimulation and food intake, increasing the sympathetic nervous system to activate the metabolic rate, and decreasing insulin secretion from pancreatic beta cells to decrease energy storage [77]. However, when fructose is consumed in excess, leptin's feedback signals are perturbed, and as a result, the unregulated over-abundant source of lipid synthesis increases energy availability within adipose tissue. Chronic high concentration of leptin results in leptin resistance, which inhibits satiety signals to the hypothalamus, causing appetite dysregulation by overeating [78].

Ghrelin is an orexigenic peptide hormone produced by endocrine cells in the stomach. It is involved in regulating food intake by stimulating neuropeptide Y and agouti-related protein neurons in the hypothalamus. It acts by decreasing fat oxidation and regulates energy homeostasis [79][80]. Dietary glucose has been shown to suppress ghrelin secretion, in contrast to fructose, which increases ghrelin secretion [81][82]. There is significant evidence that suggests that the consumption of fructose increases circulating ghrelin but has little effect on the secretion of insulin and leptin. This dysregulation may result in impaired intracellular communication of energy availability, contributing to metabolic and appetite dysregulation [78][81][82]. A recent study in rats demonstrated that the maternal fructose-induced dysregulation of satiety signals via ghrelin pathways in the mother was vertically transmitted to the offspring, with both dams and pups having significantly increased ghrelin following maternal fructose intake [83].

Leptin, ghrelin, and insulin-like growth factors are known to represent mediators of appetite and metabolism. Additionally, they play an important role in the brain somatic crosstalk and the complex axis, which controls the gastrointestinal tract and hypothalamic regulation of hunger and satiety. When excess fructose is consumed, circulating leptin decreases, causing increased appetite signals to the hypothalamus [78][81][82]. Recent studies have demonstrated that maternal fructose intake of 10%*w*/*v* increased leptin signalling in the offspring [83][84]. Kisioglu et al. also found that maternal fructose increased offspring leptin levels, despite obesity-related leptin resistance, indicating that fructose intake can affect appetite regulation in offspring from mothers that consumed increased fructose consumption during pregnancy, without the offspring consuming fructose themselves [83].

In context, dysregulation of the insulin–leptin–ghrelin axis may have important consequences for the development of energy homeostasis and appetite regulation in offspring. The long-term effects of excess maternal fructose consumption on offspring appetite regulation are largely unknown. However, it has been shown that fructose in highly processed foods and SSBs can alter hypothalamic response to appetite regulation via the imbalance of

leptin and ghrelin secretion in offspring [83][84]. The dysregulated signals of leptin and ghrelin in the hypothalamus stimulate appetite, causing increased consumption and increased lipogenesis. There is an increasing body of literature that highlights a life-long susceptibility to adverse metabolic effects of dietary consumption of fructose in these offspring exposed to high fructose *in utero*. Further studies are needed to better understand the mechanisms underlying the effects of excess maternal fructose through pathways of insulin, leptin, ghrelin, and altered hypothalamic function, which may be important in acutely fed individuals and maternally fructose-exposed offspring.

There is a paucity of data that examine the mechanistic impact of increased fructose intake before and during pregnancy and subsequent adverse effects on lactation, foetal development, and offspring metabolic function. It is essential to determine how the vertical transmission of such deleterious metabolic effects might increase de novo lipogenesis, fatty acid acylation and subsequent metabolic programming in offspring. During foetal development, the liver will undergo many changes in structure and function, which can influence the rate of absorption and metabolism of nutrients received and supply of metabolites in circulation. It has been shown that the combination of increased plasma levels of VLDL and TAG and inhibition of fat oxidation following fructose consumption may lead to increased intracellular lipid accumulation. Animal studies indicate that the foetal liver is highly influenced by the activation of these pathways when exposed to excess maternal fructose intake, making the offspring vulnerable to insulin resistance later in life. In a rat model, HFCS increased insulin resistance in dams; however, free fructose had a greater effect on insulin resistance in pups [85]. It was proposed that the effects of HFCS may stem from the fructose content rather than sucrose, indicating that excess maternal fructose alters the regulation pathways of glucose and insulin and cell function during development.

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