OPINION

The obesogenic effect of high fructose exposure during early development

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Abstract | Obesogens are compounds that disrupt the function and development of adipose tissue or the normal metabolism of lipids, leading to an increased risk of obesity and associated diseases. Evidence for the adverse effects of industrial and agricultural obesogens, such as tributyltin, bisphenol A and other organic pollutants is well-established. Current evidence suggests that high maternal consumption of fat promotes obesity and increased metabolic risk in offspring, but less is known about the effects of other potential nutrient obesogens. Widespread increase in dietary fructose consumption over the past 30 years is associated with chronic metabolic and endocrine disorders and alterations in feeding behaviour that promote obesity. In this Perspectives, we examine the evidence linking high intakes of fructose with altered metabolism and early obesity. We review the evidence suggesting that high fructose exposure during critical periods of development of the fetus, neonate and infant can act as an obesogen by affecting lifelong neuroendocrine function, appetite control, feeding behaviour, adipogenesis, fat distribution and metabolic systems. These changes ultimately favour the long-term development of obesity and associated metabolic risk.

Goran, M. I. *et al. Nat. Rev. Endocrinol.* advance online publication 4 June 2013; doi:10.1038/nrendo.2013.108

Introduction

Although genome-wide association studies have identified numerous loci associated with obesity, their total contribution to variation in BMI and body weight is estimated to be <2%, suggesting that environmental influences such as exposure to obesogens during critical periods of development are more important than genetic factors.[1] Obesogens are chemicals that promote obesity by increasing the number of fat cells or promoting the storage of fat into existing cells. Obesogens can act indirectly by changing the basal metabolic rate, shifting the energy balance to favour increased calorie storage, or altering hormonal control of appetite and satiety.[2–7] Several obesogenic chemicals have been identified. Estrogenic compounds such as diethylstilbestrol[8] and bisphenol A,[9,10] organotins such as tributyltin (Box 1),[11] and perfluorooctanoates[12] are obesogenic in animals. Exposure to phthalates is correlated with increased waist diameter,[13,14] and high levels of several persistent organic pollutants (for example, polybrominated diphenylethers) have been linked with obesity in humans.[15]

In this Perspectives, we examine the growing evidence linking an increased intake of fructose, especially during fetal development, the neonatal period and infancy, with altered metabolism and early obesity. Furthermore, we discuss the evidence to suggest that dietary fructose exposure has increased in the past two generations and that high fructose exposure during critical developmental periods might have a key role in the development of adult obesity.

Dietary sugars and obesity

Strong and consistent evidence supports a link between high intakes of dietary sugars and obesity in children.[16–19] However, most of these studies have not differentiated between the effects of different sugars. The limited number of studies that have been conducted in infants and young children suggest that this strong association is present even in early life. In a retrospective cohort study, analysis of data from 10,904 children aged 2–3 years showed that those who consumed sugar-sweetened beverages (SSB; defined as any drink sweetened with glucose, sucrose, fructose or high-fructose corn syrup [HFCS]) had a twofold increased probability of becoming overweight compared with children who did not consume such beverages.[20] Our research group examined 1,483 Hispanic children from low-income families and showed that any consumption of SSB at 2–4 years was strongly associated with obesity.[21] Consumption of SSB was defined as high (≥2 servings daily), medium (1 serving daily) or none. We found striking differences in the prevalence of obesity (defined as a BMI >95th percentile for age). In children who were not breastfed at all or were breastfed for <1 year, SSB consumption had a strong effect: the prevalence of obesity was ~23% among toddlers with high consumption of SSB, versus ~14% in children who did not consume any SSB. When breastfeeding was sustained for >12 months, SSB consumption had no effect on obesity.

Considerably more data are available for children aged >4 years. A meta-analysis of 12 studies in children and adolescents, published in 2008, found a near-zero effect of SSB consumption on obesity,[22] although this conclusion was later challenged by another group that reanalysed the same data and found a clear association between SSB consumption and obesity.[23] In a longitudinal study, 196 prepubertal girls, aged 8–12 years, were followed up until 4 years after menarche.[16] Among all the categories of energy-dense food and drink considered (baked goods, ice cream, chips, sugar-sweetened soda and candy), consumption of SSB was the only factor that was linked to BMI z-score over the 10-year study period. The percentage of body fat, however, was not associated with consumption of any type (or with overall consumption) of energy-dense foods or drinks.[16]

Increased fructose consumption

In determining the potential link between dietary sugar intake and obesity, it is

Competing interests
B. Blumberg declares that he is a named inventor on the following US patents: 5,861,274; 6,200,802; 6,815,168; and 7,250,273. See the article online for full details of the relationship. The other authors declare no competing interests.

Box 1 | Obesogenic effects of organotins

The organotins tributyltin and triphenyltin are the only obesogens with a known pathway of action. Both compounds are nanomolar-affinity ligands for two nuclear receptors that are critical for adipocyte development: 9-*cis* retinoic acid receptor α (RXR-α) and peroxisome proliferator activated receptor γ (PPAR-γ).[11,93] Current evidence suggests that these compounds act as obesogens through altering the regulation of adipose tissue development, and that the effects of these changes are inheritable.

Effects of tributyltin in mice

Promotion of adipocytogenesis in mouse 3T3-L1 preadipocytes[11,93] and human and mouse multipotent MSCs, via a PPAR-γ-dependent pathway[94,95]

Prenatal exposure (a single maternal oral dose) resulted in increased fat deposition in offspring at birth, increased adipose depot size in adults and increased expression of adipogenic markers[94]

Prenatal exposure also influenced the differentiation of MSCs toward the development of new fat cells at the expense of bone[11,94]

The effects of prenatal exposure on fat mass, adipocyte size and multipotent MSC gene expression profiles were heritable through at least three generations, suggesting that the effects are permanent[96]

Sources of human organotin exposure[97,98]

Dietary (seafood and shellfish)

Fungicides and miticides (on food crops, in wood treatments, industrial water systems and textiles)

Leaching from organotin-stabilized plastics (including water pipes and food wrapping*)

*Tributyltin is a contaminant in plastics rather than an intentionally added component. Abbreviation: MSCs, mesenchymal stem cells.

important to appreciate the shifts in dietary sugar consumption. A study conducted in 2–18-year-old individuals, using National Health and Nutrition Examination Survey data, showed that nearly 40% of their total energy consumption consisted of calories from solid fats and added sugars. About half of this 40% came from six sources: soda, fruit drinks, dairy desserts, grain desserts, pizza and whole milk.[24] These epidemiological observations are of particular concern given the increasing use of HFCS in commercial food and beverage production. HFCS is a highly processed sweetener derived from maize, in which the glucose from cornstarch is chemically converted to fructose.[25] HFCS was introduced into the US food supply in the 1970s, and its consumption increased dramatically over the ensuing years, plateauing around the year 2000. This shift probably accounts for the reported increase of 10–20% in the amount of fructose consumed by children between 1977 and 2004.[26] In an ecological analysis that looked at changes in diet and in the prevalence of type 2 diabetes mellitus (T2DM) in the USA between 1900 and 1997, increased consumption of HFCS from the 1970s onwards was identified as the primary nutritional factor associated with the increase in prevalence of T2DM.[27] Our research group published an updated global ecological analysis in 2013, which showed that countries including HFCS in their food supply had a 20% higher national prevalence of T2DM than countries that did not include HFCS in the food supply.[28]

A major difference between HFCS and sucrose is that HFCS is composed of free fructose and free glucose monosaccharides, whereas in sucrose, a glycosidic bond joins the fructose and glucose molecules. An important remaining question is whether the presence or absence of this glycosidic bond influences the subsequent digestion and metabolism of these sugars; for example, free fructose might be more rapidly metabolized than the fructose contained in sucrose. In fact, one study showed that the consumption of free fructose had more detrimental effects (on fasting glucose levels, weight gain and fat mass) than the consumption of sucrose.[29] Perhaps even more importantly, the actual levels of fructose in foods and beverages made with HFCS are not entirely clear. A common assumption is that sucrose and HFCS contain similar amounts of free fructose because they have a similar fructose:glucose ratio (50:50 in sucrose versus 55:40 in HFCS-55, the most commonly used form of HFCS).[30] However, 55% of HFCS-55 consists of fructose, another 40% is glucose and the remaining 5% is other sugars, predominantly maltose and maltotriose. Thus, HFCS-55 contains 10% more fructose than sucrose does, and foods and beverages made with HFCS-55 contain 10% more fructose than they would if they were made with sucrose.

Moreover, HFCS can be blended to increase the fructose content. In a study from 2011, our group measured the sugar composition of popular SSBs and found that in most beverages fructose accounted for >55% of the sugar content, and reached 65% in the three most popular carbonated beverages.[31] A HFCS fructose:glucose ratio of 65:35 (approaching 2:1) is equivalent to these drinks containing 30% more fructose than if they were made with sucrose alone. Our initial analysis was limited to popular beverages and we have not yet investigated the possibility that higher than expected levels of fructose also occur in other processed foods made with HFCS, including breads, yogurts, cookies, breakfast cereals and other beverages (such as fruit juices) that contain naturally high levels of fructose. Thus, with the ubiquitous presence of HFCS in our food supply and the increased consumption of fruit juices by infants and children, along with the unknown fructose content of commercially prepared foods and beverages, the actual level of fructose consumption in the population might be higher than predicted on the basis of common assumptions regarding HFCS composition. However, even given these limitations, the most recent data available (1977–2004) on population levels of fructose consumption indicate that infants and children have the highest levels of fructose consumption when normalized to body weight.[26]

Obesogenic effects of fructose

Feeding studies in humans

A growing body of evidence supports the hypothesis that the adverse effects of sugar intake on obesity and metabolic risk are largely driven by fructose rather than glucose.[32–36] For example, several studies show that fructose (owing to its high lipogenic potential) is a major contributor to excess liver fat deposition. In one study, 47 overweight persons were randomly assigned to drink 1 litre daily of cola, milk (containing the same amount of calories as the cola), sugar-free cola or water.[37] The total fat mass was not altered across the groups after 6 months, but the cola group had a significant increase in liver fat (~35%) as well as increased visceral adipose tissue (~25%) and triglycerides (32%). In a crossover study, 16 boys who had at least one parent with T2DM and eight boys matched for age, BMI and total body fat received 7 days of two different diets: an isocaloric diet containing 55% carbohydrate, 30% fat, and 15% protein, or a hypercaloric diet (the same diet supplemented with fructose to achieve a 35% increase in daily energy intake).[38] Compared with the isocaloric diet, the high-fructose diet increased liver fat by 76%

in controls and by 79% in the boys whose parents had T2DM.[38] The increase in liver fat was similar in T2DM offspring and controls, hence independent of T2DM status. Persons with overweight or obesity who consumed beverages sweetened with either glucose or fructose for 10 weeks, in amounts supplying 25% of their daily energy requirements, have been examined under closely controlled conditions.[39] Despite similar weight gain in the two groups, the fructose group had significant increases in visceral adipose tissue mass (14% versus 3%) and in hepatic *de novo* lipogenesis (75% versus 27%). The adverse effects of fructose have also been suggested to relate to the metabolic effects of uric acid, a by-product of fructose metabolism in the liver.[40] A study in 2,727 teenagers showed that individuals who consumed high amounts of HFCS-rich beverages had significantly elevated levels of circulating uric acid compared with those who did not drink such beverages.[41]

Despite numerous findings supporting an obesogenic role for HFCS, other researchers have disputed the view that consumption of fructose is more metabolically damaging than glucose, and have suggested that the published studies involved supraphysiological levels of fructose ingestion.[42–44] In 2012, however, a study in healthy men showed that consumption of moderate amounts of fructose over 3 weeks had worse adverse effects on insulin sensitivity than consumption of equivalent amounts of glucose.[45]

Feeding studies in rodents

Rigorous pair-feeding studies in rodent models have also demonstrated that excess fructose consumption induces metabolic changes independent of increased adiposity. Compared to rats fed a high-starch diet, rats fed a diet containing 68% of total calories as sucrose develop hepatic insulin resistance after as little as 1 week, and muscle insulin resistance by 2 weeks, as assessed by the hyperinsulinaemic-euglycaemic clamp.[46] These impairments in insulin sensitivity were accompanied by hypertriglyceridaemia and increased hepatic triglyceride content.[46] Other studies showed that the fructose moiety, rather than the glucose, confers this sucrose-induced insulin resistance.[47] Diets containing 68% of calories as sucrose far exceed the levels that occur human consumption, but rodent chow containing only 18% of calories as sucrose also induces insulin resistance, primarily in the liver.[48]

However, not all studies in rodents have demonstrated deleterious effects of excess fructose consumption. For example, in one study, neither high sucrose[49] nor high fructose[50] consumption led to increases in body weight, total body fat or regional adiposity, nor did high sucrose consumption cause insulin resistance in weaned male[51] or in adult female rats.[52] *Ad libitum* access to fructose-containing diets does not necessarily increase body weight in rodents, but it consistently increases fat mass. Mature male rats gained more weight when given solutions composed of 32% fructose or 32% sucrose than when given a solution of 32% glucose, although all three solutions increased retroperitoneal fat pad weights compared to controls fed the same chow and given plain water.[53] Weanling rats, on the other hand, failed to gain more weight when given a 32% sucrose solution, despite an energy intake greater than age-matched controls given water.[54] However, sucrose feeding did increase fat mass in young rats by postnatal day 46 and, by postnatal day 70, had resulted in approximately 50% greater wet-carcass fat mass compared to control rats on a standard diet.[55]

The effects of HFCS or HFCS-like solutions (that is, solutions with a high fructose content or high levels of free monosaccharides, respectively) have also been compared to the effects of sucrose. When mice were given solutions containing 15% of fructose, sucrose-sweetened soda or artificially sweetened diet soda, the fructose solution was the only one that resulted in increased bodyweight and hepatic steatosis.[56] In another study, dark-cycle *ad libitum* access to HFCS-sweetened water for 8 weeks increased body weight of male rats, whereas identical access to a sucrose solution did not increase body weight above that of control animals fed the same chow and plain water.[57] Unfortunately, differences in body composition were not assessed in this study.

Effects of fructose in the brain

Evidence from both human studies and animal models also support the notion that fructose and glucose have different effects in the brain, such that consumption of fructose promotes food intake and obesity. In a well-controlled human study, changes in appetite-related hormone levels over 24 h were examined in response to meals containing either glucose or fructose.[58] Levels of insulin and leptin were significantly lower after the fructose meal than after the glucose meal, and fructose failed to suppress post-meal ghrelin levels as effectively as glucose, which suggests that consumption of fructose could disrupt energy balance signalling to the brain and result in excess energy consumption and obesity.[58]

One study compared the effects of fructose and glucose in the human brain using functional MRI.[59] This study showed that in nine healthy, lean adults, fructose and glucose had similar effects on hypothalamic activity, whereas the cortical response was increased in response to glucose and decreased in response to fructose.[59] In this study, however, the doses of glucose and fructose were relatively small (~20–25 g, depending on body weight), and the sugar solution was infused intravenously. In another imaging study, regional cerebral blood flow (a marker of neuronal activation) was assessed in response to oral consumption of either fructose or glucose.[60] In a randomized, blinded, crossover imaging study, 20 healthy, nonobese, primarily white volunteers underwent MRI and blood sampling 60 min after ingestion of a drink containing 75 g of either fructose or glucose. Neuronal activation was significantly increased in the hypothalamus, orbitofrontal cortex and ventral striatum after ingestion of fructose, compared to activation levels after glucose ingestion. This study provides further evidence that fructose and glucose have differential effects on brain regions involved in feeding behaviour.[60]

In animal studies, direct administration of either fructose or glucose into the brain has opposing effects on obesity and food intake regulation.[61] Essentially, these studies show that fructose metabolism in the brain is poorly controlled and rapidly depletes hypothalamic ATP, whereas glucose metabolism is closely regulated and increases ATP levels in the hypothalamus. Consequently, ingestion of fructose leads to a reduction in malonyl coenzyme A in the brain, a factor known to contribute to increased food intake.[61] In another study, rats fed a very high fructose diet for 6 months demonstrated leptin resistance and reduced hypothalamic phosphorylation of STAT3 (a downstream component of the leptin receptor signalling cascade). The leptin-resistant animals gained more weight and had greater fat pad weights than control animals when they were switched to a high-fat diet for 2 weeks.[50]

Fructose-mediated induction of leptin resistance would be particularly relevant during both the fetal and neonatal period; our group has shown that leptin is a key

neurotrophic factor for the developing hypothalamus.[62] Leptin resistance during this critical period could impair energy balance throughout life.[63,64]

The role of maternal nutrition

Growing evidence supports a link between maternal nutrition and obesity in offspring. Studies in pregnant female primates indicate that maternal nutrition during critical developmental periods in gestation might alter the development of fetal metabolic systems.[65] Fetuses from lean and obese mothers (both fed a high-fat diet) had a threefold increase in liver triglyceride levels, increased hepatic oxidative stress, increased serum triglycerides and a twofold increase in body fat, consistent with the development of nonalcoholic fatty liver disease.[65] These adverse effects of excess maternal fat consumption during pregnancy might be due to the fact that fetuses of most species lack white adipose tissue until late in pregnancy (in humans, typically until the third trimester). White adipose tissue is critical for the storage of excess lipids, and the results of studies of maternal obesity and hyperglycaemia in humans suggest that this fetal lack of structurally or functionally sufficient adipose tissue depots leads to ectopic lipid storage under conditions of high maternal fat consumption.[66,67] In turn, this excess lipid storage induces whole-body insulin resistance and susceptibility to fatty liver disease in adulthood.[66,67] Other studies in humans suggest that altered maternal nutrition during critical developmental periods, including pregnancy and lactation, might predispose offspring to long-term metabolic, neuroendocrine and behavioural dysfunction.[66–69]

Fructose exposure during development

The deleterious effects of excess fructose consumption in adults are well researched, but limited data are available on the long-term effects of high fructose exposure during gestation, lactation and infancy. These periods are, however, critically important in determining an individual's lifelong health. Emerging research suggests that fructose consumption by both mothers and their offspring during these stages of early life can lead to persistent neuroendocrine and metabolic dysfunction.

Appetite, energy balance and metabolism are regulated by the central nervous system and the important components include neurons located in the arcuate nucleus of the hypothalamus. The hypothalamus primarily regulates the homeostatic drive to eat, whereas other regions (such as the ventral striatum, insula, amygdala and hippocampus) include a behavioural pathway that controls the hedonic drive to eat.[70] The regions that control homeostatic and hedonic feeding are tightly interconnected and form an integrated network that dictates overall feeding behaviour. This network is activated during hunger, and its activity normally decreases in response to food intake.[70] The hypothalamus undergoes tremendous growth from early gestation, which continues during the postnatal period. These developmental windows represent periods of vulnerability during which alterations in the environment can perturb hypothalamic development and subsequent function.

Fructose exposure during critical development periods has been examined by feeding lactating rats either tap water or a 10% fructose solution in addition to their chow, starting on postnatal day 1.[71] The offspring of fructose-fed rats showed increased body weight, decreased hypothalamic sensitivity to exogenous leptin, increased food intake, insulin resistance and increased retroperitoneal adipose tissue (with an increase in both fat mass and adipocyte size).[71] Additional studies have further elucidated the effects of the fructose moiety during these critical development periods by comparative analyses of experiments using different sugar concentrations. In one study, female rats were fed *ad libitum* diets containing either 40% fructose or 50% sucrose during gestation and lactation.[72] Control animals received the same *ad libitum* diet without additional sugars. During gestation, the fructose-fed rats developed elevated levels of circulating glucose and triglycerides, and their offspring were hyperglycaemic at birth.[72] Further investigation revealed that only the fructose-fed rats and their offspring had hyperglycaemia during pregnancy and after birth, respectively,[72] suggesting that a possible mechanism underlying the development of hyperglycaemia in these two groups might be the increased concentration of the fructose moiety in the 40% fructose diet. In another study, female rats were randomly assigned to 8 weeks of deionized distilled water or deionized distilled water sweetened with 13% of glucose, sucrose, fructose or HFCS-55.[73] The 13% value was selected to reflect the concentrations of these sugars typically found in the human diet. No difference was found in energy intake between the rats given plain water and those given sweetened water. However, the type of sugar influenced body fat mass, as only HFCS-55 promoted adiposity.[73]

Additional studies in rats fed a diet containing either 10% fructose or 10% glucose showed that fructose-fed dams ate more food and drank less water than dams fed glucose.[74] Moreover, the offspring of fructose-fed dams had almost double the fasting insulin levels at weaning compared with the offspring of glucose-fed dams.[74] However, in another study, the offspring of fructose-fed dams showed increased plasma leptin and plasma glucose levels but had no change in insulin levels.[75] Furthermore, one study has examined the effect of a diet containing fructose on successive generations. Female rats were weaned onto a diet containing either starch (no fructose) or sucrose (50% fructose and 50% glucose), and the same diet was maintained through successive generations bred from these dams. The first-generation offspring born to sucrose-fed dams were heavier, had more body fat and higher circulating glucose and triglyceride levels than rats born to starch-fed dams.[76]

Other studies have focused on understanding the effect of maternal nutrition on the development of taste preferences (termed nutrient conditioning) in their offspring. Human studies showed that maternal intakes of protein, fat and carbohydrates during pregnancy were associated with their children's intakes of these nutrients at 10 years of age.[77] Rodent studies show that a preference for sweet flavours can develop before weaning, suggesting that nutrient conditioning is transmitted through breast milk.[78] Furthermore, 10-week old rat pups whose dams were fed a diet containing high levels of fat, sugar and salt (as found in 'junk food') during gestation and lactation showed a greater preference for fatty, sugary and salty foods than pups whose mothers were fed a balanced chow diet.[79] Further experiments revealed that offspring of dams fed the junk-food diet during gestation and lactation developed more obesity, greater elevations in glucose and insulin levels and had an increased risk of fatty liver disease, as well as signs of steatosis and liver damage, when given free access to the same junk-food diet, compared with rats whose mothers had a normal chow diet.[80]

Potential obesogenic mechanisms

In this Perspectives, we propose a novel hypothesis that high levels of fructose in beverages, fruit juices, infant food and processed foods can act as an obesogen when

ingested during critical perinatal periods of adipose tissue and brain development. Several potential mechanisms could explain the adverse effects of high fructose exposure during these periods. From an evolutionary perspective, infants would not typically be exposed to high levels of fructose, given that the main sugar in breast-milk is lactose (a disaccharide consisting of glucose bound to galactose). Although 30 or more oligosaccharides are also present in breast-milk, fructose is not a natural component of human breast-milk.[81] However, no study has yet investigated whether fructose is present in human breast-milk from mothers who eat high levels of this sugar. Under normal conditions, the abundance of mRNAs encoding the sugar transporters SLC5A1, GLUT-2 and GLUT-5 is developmentally modulated, with higher levels in adult than in fetal intestines. Moreover, immunohistochemical analysis showed that the fructose transporter GLUT-5 was expressed on the luminal surface of mature enterocytes in adult intestine, whereas in fetal intestine, expression of GLUT-5 occurred only along the intercellular junctions in developing villi.[82] These observations suggest that the mechanism of fructose absorption may not be fully or even partially functioning during gestation and early life. Lack of functional fructose transport could be protective, because an infant might not have the ability to absorb dietary fructose. However, in rat models, a high-fructose diet,[83] as well as hyperglycaemia and T2DM, upregulate expression of *Slc2a5* (which encodes GLUT-5) in the intestine.[84,85] Whether this upregulation of GLUT-5 occurs during fetal development or infancy is unknown, but fructose does cross the placenta, and infants can be exposed to fructose either by direct consumption or through breast-milk. Studies in humans revealed a higher fructose concentration in fetal blood than in maternal blood, showing that the human placenta actively transfers fructose to the fetal circulation.[86,87] Thus, fetal and infantile exposure to fructose, through placental transmission, breastfeeding or direct consumption, is possible and would have detrimental metabolic effects on the fetal and infant metabolism.

We hypothesize that fructose directly promotes adipogenesis during critical periods of adipose tissue development. A study from 2012 showed that fructose induced adipocyte differentiation in 3T3–L1 preadipocytes, and that *Slc2a5*$^{-/-}$ mice (which lack uptake of fructose) had a dramatic reduction in epididymal fat mass compared with wild-type controls.[88] In our opinion, a high fructose intake during development could also promote obesity by disrupting neuroendocrine signalling between adipose tissue and the hypothalamus. The arcuate nucleus of the hypothalamus contains neurons that respond to various circulating factors, including glucose, insulin and leptin.[89] By acting on the arcuate nucleus, leptin conveys the level of adiposity to the brain, thereby regulating both energy expenditure and food intake.[90] Our research group has shown that leptin acts as a critical growth factor connecting the arcuate nucleus to other hypothalamic nuclei during brain development in mice.[62] However, as fructose does not stimulate leptin release, an imbalance in fetal exposure to fructose and glucose could potentially limit the effects of leptin on these important brain development pathways. Indeed, other studies have shown that prenatal or early-life overnutrition leads to hypothalamic leptin insensitivity, impaired signalling via phosphorylated STAT3 and obesity in adulthood.[91,92] Collectively, the evidence supports the concept that exposure to high levels of fructose during critical periods of development could promote obesity by several mechanisms: direct effects of fructose on adipose tissue; direct or indirect actions of fructose on the developing hypothalamus; and by disrupting neuroendocrine signalling between adipose tissue and the hypothalamus (Figure 1).

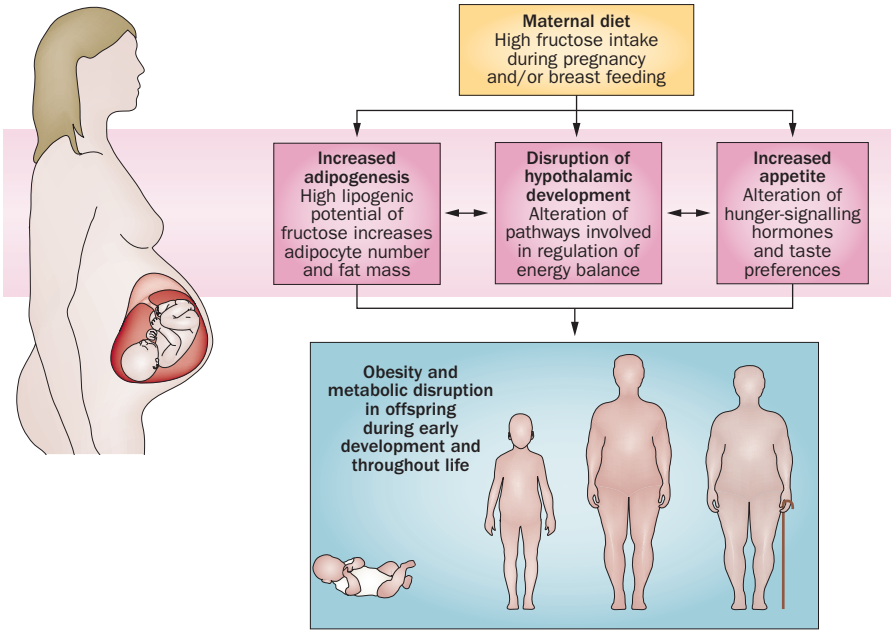

Figure 1 | Links between obesity and fructose exposure during critical developmental periods. High levels of exposure to fructose during gestation and infancy influence the development of adipose tissue, hypothalamic signalling and appetite regulation. In turn, these changes promote long-term obesity, metabolic dysfunction and disease.

Conclusions

Evidence from human and animal studies suggests that the link between dietary sugars and obesity is probably driven by the metabolic effects of fructose. Fructose has a unique metabolic fate that favours the development of obesity and, so far, no data suggest that the developing fetus, neonate or infant would be protected from these well-known adverse effects. Thus, exposure to fructose, which is not a natural component of an infant's diet, in conjunction with the active transport of fructose across the placental barrier, probably increases the propensity of fructose to cause metabolic and developmental dysfunction. Further investigations are required to determine the effects of high levels of fructose consumption during critical periods of gestation, lactation and infancy.

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Author contributions

M. I. Goran, S. G. Bouret, B. Kayser, R. W. Walker and B. Blumberg researched the data for the article. All authors contributed to writing the manuscript, provided substantial contributions to discussions of its content, and reviewed and/or edited the manuscript before submission.