Neuroscience and Biobehavioral Reviews 128 (2021) 346–357

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Neural mechanisms underlying the role of fructose in overfeeding

Mikayla A. Payant, Melissa J. Chee *

Department of Neuroscience, Carleton University, Ottawa, ON, K1S 5B6, Canada

ARTICLE INFO

Keywords:
Brain
Diet
Reward
Sugar
Systems neuroscience

ABSTRACT

Fructose consumption has been linked with metabolic syndrome and obesity. Fructose-based sweeteners like high fructose corn syrup taste sweeter, improve food palatability, and are increasingly prevalent in our diet. The increase in fructose consumption precedes the rise in obesity and is a contributing driver to the obesity epidemic worldwide. The role of dietary fructose in obesity can be multifactorial by promoting visceral adiposity, hypertension, and insulin resistance. Interestingly, one emergent finding from human and animal studies is that dietary fructose promotes overfeeding. As the brain is a critical regulator of food intake, we reviewed the evidence that fructose can act in the brain and elucidated the major brain systems underlying fructose-induced overfeeding. We found that fructose acts on multiple interdependent brain systems to increase orexigenic drive and the incentive salience of food while decreasing the latency between food bouts and reducing cognitive control to disinhibit feeding. We concluded that the collective actions of fructose may promote feeding behavior by producing a hunger-like state in the brain.

1. Introduction

Fructose is a sugar naturally-occurring in fruits and vegetables, so it may not be judged to be as harmful as other types of sugars. The other common dietary sugars are glucose and sucrose, but fructose has the sweetest taste and is hence used to enhance food palatability, especially that of processed and/or packaged goods. Fructose is found in table sugar (sucrose), a disaccharide made of one fructose and one glucose molecule, but it appears in its free form as high fructose corn syrup (HFCS), which has progressively replaced sugar and became increasingly prevalent in the diet since the early 1970s (Smith, 1988). HFCS is used in sweetened beverages and processed foods and now comprises 40 % of all caloric sweeteners (Bray et al., 2004; Fields, 2004; Goran et al., 2013a; Stanhope, 2015) largely because it is cheaper to produce, tastes sweeter, and increases the palatability of drinks, baked goods, or processed foods. The use of HFCS has led to an increase in daily fructose intake, where fructose may comprise approximately 10 % of daily calories (Sun et al., 2011). However, in addition to HFCS, fructose is also disguised in the diet via added sugars or sweeteners, including table sugar, honey, molasses, and various nectars. The World Health Organization recommends that added sugars should be limited to just 10 % of our diet (World Health Organization, 2015) and yet fructose intake in young people may exceed 15 % of total caloric intake (Vos et al., 2008).

Excessive fructose intake can be problematic because unlike glucose, which is used by all cells as an energy source, fructose is broken down primarily by the intestine and liver to stimulate lipogenesis (Jang et al., 2018). At small amounts, fructose can be broken down entirely by the small intestine, and fructose absorption leads to increases in plasma triglycerides (Steenson et al., 2020; Theytaz et al., 2014). However, large amounts of fructose can overload the intestine and spillover into the liver where it is a substrate for fatty acid synthesis and contributes to the accumulation of fatty liver and adiposity (Faeh et al., 2005; Schwarz et al., 2015; Stanhope et al., 2009; Taskinen et al., 2019). Furthermore, while both glucose and fructose are broken down to generate substrates for energy production via glycolysis, the entry of fructose-derived intermediates into the glycolytic pathway is not regulated by negative feedback, so there is an increased availability of substrates for metabolic pathways like lipogenesis (Samuel, 2011). In fact, participants consuming fructose-sweetened beverages for seven weeks showed two-fold higher liver fat compared to those consuming a glucose-sweetened beverage (Geidl-Flueck et al., 2021). Meanwhile, short term reduction of fructose intake can decrease fatty liver (Schwarz et al., 2017). Excessive fructose intake may also underlie the development of non-alcoholic fatty liver disease, which is a manifestation of metabolic syndrome and known to be a fructose-linked disease affecting 25 % of individuals (Younossi et al., 2016). Non-alcoholic fatty liver disease is also the most common liver abnormality in

* Corresponding author at: HS 5309, 1125 Colonel By Drive, Ottawa, ON, K1S 5B6, Canada.
E-mail address: melissa.chee@carleton.ca (M.J. Chee).

https://doi.org/10.1016/j.neubiorev.2021.06.034
Received 6 August 2020; Received in revised form 16 June 2021; Accepted 23 June 2021
Available online 25 June 2021

children, and the incidence of fatty liver disease in children is becoming more prevalent (Sahota et al., 2020). Furthermore, excessive fructose intake also aggravates key elements of metabolic syndrome, including high circulating triglycerides, "bad" LDL cholesterol, visceral adiposity, insulin resistance, as well as cardiometabolic risk (Bantle et al., 2000; Pollock et al., 2012; Teff et al., 2004); this is linked with diabetes (Goran et al., 2013b) and obesity (Goran et al., 2013a; Stanhope, 2015). In fact, an observational population study showed that the increase in fructose intake starting in the early 1970s (Smith, 1988) preceded and paralleled the rise in obesity and suggested that fructose may be a contributing driver to the obesity epidemic (Bray et al., 2004).

Metabolic syndrome has been reproduced in animal models using fructose, and most models utilize a 55–60 % high fructose diet (Ackerman et al., 2005) or 10–15 % fructose solution (Dai and McNeill, 1995). Effectively, animals drinking or eating fructose also develop impaired glucose homeostasis, insulin resistance, elevated triglycerides, higher systolic blood pressure, and increased adiposity (Dai and McNeill, 1995; Faeh et al., 2005; Huang et al., 2004; Jürgens et al., 2005; Lanaspa et al., 2018; Suga et al., 2000). One critical observation from animal studies is that dietary fructose induces hyperphagia. Fructose stimulates feeding (Cha et al., 2008; Tordoff et al., 1988), so animals given access to fructose in their diet (Kasim-Karakas et al., 1996; Oh et al., 2018) or drinking water (Bursac et al., 2014; Dai and McNeill, 1995; Sanguesa et al., 2018) will consume more total calories. Intermittent fructose access can also induce bingeing behavior as animals consume excessive calories in a short period (Rorabaugh et al., 2015). Furthermore, human participants, also report having a larger appetite (Luo et al., 2015) and higher feelings of hunger after consuming a fructose drink (Jastreboff et al., 2016).

While animal studies typically provide a fructose diet or drink at concentrations higher than what is normally consumed in humans, the animals are feeding voluntarily. Regardless, the animals still exhibit hyperphagia and consume more calories than when given standard chow or plain water. In experiments where animals are given the choice between standard chow and a fructose solution, animals commonly reduce chow intake to compensate for fructose consumption, but the total caloric intake is still higher than when animals do not have access to fructose (Bursac et al., 2014; Dai and McNeill, 1995; Sanguesa et al., 2018). Although many papers in the field suggest that fructose increases food intake, there are also others that suggest otherwise, and in order to provide a balanced review, we included a sample of such recent papers here (Khan and Sievenpiper, 2016; Noble et al., 2017, 2019). It is notable however that even despite no differences in caloric intake in these experiments, animals given access to fructose do gain adiposity and exhibit metabolic syndrome (Jürgens et al., 2005; Ramos et al., 2017; Zubiria et al., 2013).

Therefore, in addition to peripheral metabolic processes, the hyperphagic effects of fructose implicate the brain as an effector target in the control of feeding behavior. Moreover, it is noteworthy that the brain is associated with the effects of fructose-induced metabolic syndrome on hypertension, and this is largely attributed to the actions of fructose on the baroreflex located in the brainstem (He et al., 2016). Here we present evidence that dietary fructose may act within the brain, and we summarize the literature from human and animal students showing that dietary fructose may influence hunger, the salience of food, impulsivity towards food, and impair cellular function underlying memory processes during food intake. These feeding systems form an interdependent network to orchestrate a response to dietary fructose. The sections that follow describe the different ways in which fructose may engage the brain to promote feeding and weight gain.

2. Aims and approach

We first present the evidence that fructose can enter the brain and that cells within the brain have the capacity to metabolize fructose. In order to determine which brain systems fructose acts on to mediate feeding behavior, we performed a keyword search for "*fructose*" (in the title/abstract or medical subject headings (MeSH)) and "AND *brain*" (in the title/abstract and MeSH), ranging from 2010 to 2020. We excluded analysis involving fructose as an antiepileptic agent by including "NOT *topiramate*" (in the title/abstract or MeSH) in the search entry. This yielded 156 articles, of which we excluded review articles or articles focusing on fructose derivatives or mixed diets. These articles presented human and animal studies with or without obesity to study the effect of dietary fructose on the brain. We analyzed these articles to determine the major brain systems recently investigated to elucidate the role of fructose on food intake.

3. Fructose can enter the brain to regulate feeding neural circuitry

Historically, it was believed that fructose cannot penetrate the blood brain barrier, but this was based on examining the uptake of fructose within 15 s of systemic administration (Oldendorf, 1971). Unlike glucose, whose brain penetrance increases within seconds following systemic administration, fructose requires several minutes to reach the brain and fructose levels increase over a prolonged time course even as glucose levels begin returning to baseline (Thurston et al., 1972). Indeed, fructose has been detected in the brain (Xu et al., 2016) and cerebrospinal fluid (Hubbard and Russell, 1937; Hwang et al., 2015; Wray and Winegrad, 1966). Moreover, systemic administration of fructose accumulates in the brain (Page et al., 2013; Thurston et al., 1972), and fructose consumption can increase the permeability of the blood brain barrier to facilitate fructose entry into the brain (Mamo et al., 2019; Takechi et al., 2017). Fructose levels within the brain can also increase during pregnancy (Hwang et al., 2015), ischemia (Park et al., 2017), and hypoglycemia (Thurston et al., 1972), which may reflect the utility of fructose under conditions of high energy demand or as a substitute energy source when glucose is not available. Even as fructose is not the preferred energy substrate of the brain, and it alone is insufficient for neuronal survival (Rastedt et al., 2017), its presence in the brain suggests that brain cells can utilize fructose or that fructose may influence cellular processes. Cells may use fructose to restore normal functions when glucose is depleted, thus fructose may serve as an alternative energy source during glucopenia (He et al., 1999; Thurston et al., 1972).

Interestingly, the brain can also produce fructose from glucose via the polyol pathway under conditions of hyperglycemia (Hwang et al., 2017) and water restriction (Song et al., 2017). These findings suggest that fructose is utilized in the brain, and while the function of fructose produced in the brain has not been determined, it has been suggested that brain-derived fructose may regulate glial function (Hwang et al., 2017). Furthermore, as the polyol pathway is linked to hyperglycemia and oxidative stress (Chung et al., 2003), fructose production in cells could have significant implications for cellular stress and dysfunction, especially in patients with diabetes (Asnaghi et al., 2003; Hwang et al., 2017). Peripheral fructose production is hypothesized to have evolved as a survival mechanism against the lack of food, water, or oxygen (Johnson et al., 2020b). These mechanisms that may have once supported survival may now contribute to the development of metabolic syndrome (Johnson et al., 2020b) and other brain disorders such as Alzheimer's disease (Johnson et al., 2020a). Interestingly, endogenous fructose levels are increased in response to other common components of a Western diet, such as salt and glucose. Diets high in salt or glucose have been shown to upregulate fructose in the liver and serum, and lead to metabolic dysfunction. The effects of these diets are, in part, dependent on fructose metabolism as ketohexokinase (KHK) deletion is protective against metabolic changes (Lanaspa et al., 2013, 2018). Thus, both fructose consumed via the diet and endogenously produced fructose may contribute to the development of metabolic syndrome when on a Western diet (Fig. 1).

Fructose is first absorbed by the intestine in order to reach the circulation (Ferraris et al., 2018). It can then be transported into the brain from the periphery through fructose-specific (GLUT5) and

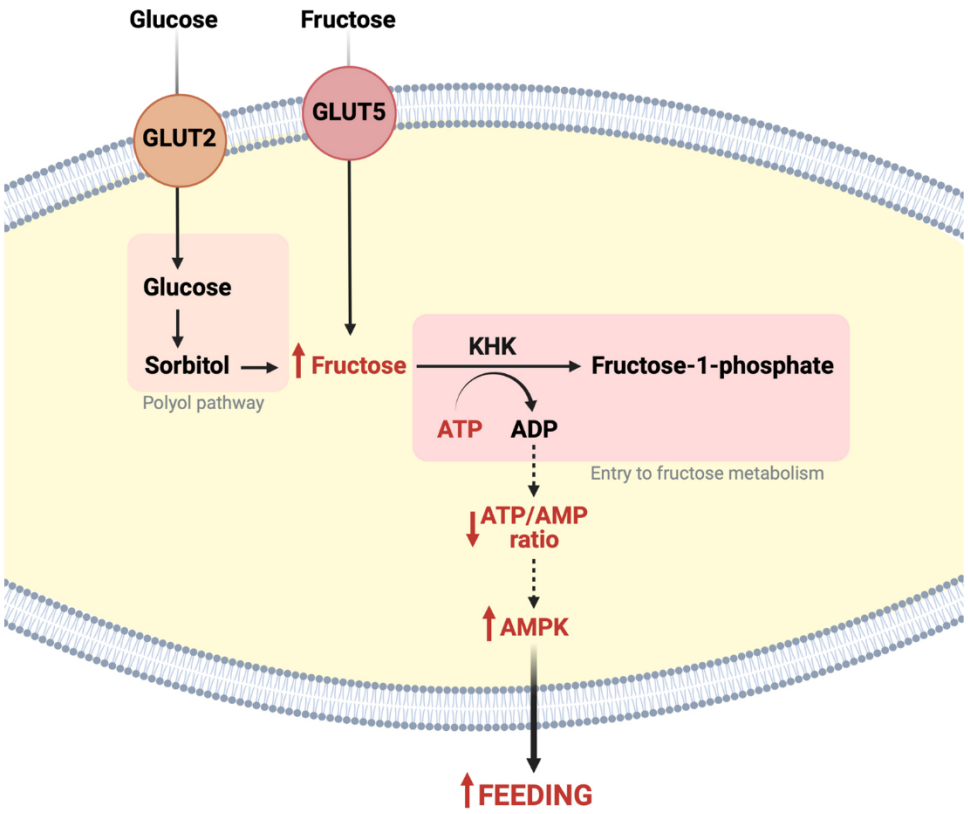

Fig. 1. Intracellular mechanisms leading to underlying fructose-mediated feeding.
Fructose can be transported into the cell via GLUT5, and fructose can also be synthesized inside the cell, especially during hyperglycemia when excess glucose builds up inside cells, through the polyol pathway. Within the cell, fructose metabolism is phosphorylated by ketohexokinase (KHK) into fructose-1-phosphate, and this phosphorylation depletes ATP levels. In effect, this reduces the ratio of ATP to AMP levels inside the cell and promotes the activation of AMP kinase (AMPK), which is associated with food intake in hunger-like states.

non-selective glucose and fructose transporters (GLUT2, GLUT8, GLUT9). GLUT5 is found in the choroid plexus, ependymal cells, and tanycytes that form the blood-cerebrospinal fluid barrier (Kojo et al., 2016; Ueno et al., 2014) and thus may be important for fructose transport into the brain (Mantych et al., 1993; Shepherd et al., 1992). GLUT5 is also found on neurons (Kojo et al., 2016) and glia (Horikoshi et al., 2003; Kojo et al., 2016; Payne et al., 1997) within several brain regions, including the hippocampus (Kojo et al., 2016), cortex (Kojo et al., 2016; Oppelt et al., 2017), and hypothalamus (Kojo et al., 2016). This means that many different types of cells in the brain can take up and use fructose (Fig. 1). GLUT5 expression in the brain is upregulated following ischemia (Vannucci et al., 1997) and may increase fructose entry into the brain to provide additional energy. Furthermore, fructose consumption upregulates GLUT5 so that the brain may take up more fructose when fructose levels are high (Jiménez-Maldonado et al., 2018; Meng et al., 2016; Shu et al., 2006).

GLUT2 is a major transporter for glucose in the liver, intestines, pancreatic β-cells, and brain (Thorens, 2015). However, it can also transport fructose and is known to play an important role in fructose uptake in the intestine. In the brain, GLUT2 expression, especially at the nucleus tractus solitarius of the brainstem (Lamy et al., 2014; Wan et al., 1998) is important for glucose-sensing and glucose homeostasis. However, as the loss of GLUT2 suppresses food intake and body weight, it suggests that GLUT2 can also control feeding (Bady et al., 2006; Wan et al., 1998). The feeding effects can be supported by hypothalamic GLUT2 expression at tanycytes (García et al., 2003), as the knockdown of GLUT2 expression in tanycytes results in increased food intake (Barahona et al., 2018). Furthermore, the feeding effects of GLUT2 is related to its ability to detect extracellular glucose. Blocking GLUT2-mediated glucose detection can increase food intake (Stolarczyk et al., 2010), and it has been hypothesized that fructose may compete with glucose for transport via GLUT2 (Miller et al., 2002). Intracerebroventricular administration of fructose blocks the hyperglycemic effects of the glucose analog 2-deoxy-D-glucose (Fiorentini and Müller, 1975). Therefore, it is possible that high fructose can saturate GLUT2 and block glucose detection, which may lead to increased feeding.

Fructose can also be metabolized by cells within the brain. It is preferentially phosphorylated by KHK and then cleaved by aldolase B or aldolase C (Oppelt et al., 2017). Therefore, cells expressing KHK and aldolase can metabolize fructose, and this includes cells located within the hypothalamus, cerebellum, hippocampus, cortex, and olfactory bulb (Andres-Hernando et al., 2021; Oppelt et al., 2017; Song et al., 2017). KHK activity has been shown in brain slices, and fructose intake upregulates its activity (Oppelt et al., 2017). Moreover, fructose administered centrally can be metabolized and used for protein synthesis in the brain (Hassel et al., 2015). Overall, the presence of fructose and fructose-specific transporters or enzymes is consistent with the position that fructose can have direct functions within the brain. The metabolism of fructose by KHK rapidly depletes cellular adenosine triphosphate (ATP) (van den Berghe et al., 1977) and increases adenosine monophosphate (AMP). This change in the ATP/AMP ratio in turn activates AMP kinase (AMPK) (Fig. 1), reduces acetyl-CoA carboxylase activity, and decreases malonyl-CoA levels. This cascade of events is thought to underlie the cellular actions of fructose that drive hyperphagia (Cha et al., 2008). Moreover, fructose uptake may also influence cellular processes and neuronal function indirectly. For example, glia-neuron interactions in hippocampal slices show that fructose uptake in glia releases alternative fuel sources to neighboring neurons (Izumi and Zorumski, 2009). Fructose transport in relevant regions may thus act directly or indirectly to influence neuronal function in the regulation of feeding.

4. Dietary fructose regulates appetite and hunger via interdependent brain systems

Dietary fructose may exert direct or indirect actions on multiple brain systems to influence feeding behavior. Additionally, as dietary fructose is absorbed by the gut, the enteric nervous system may also aid

the brain in coordinating a response to fructose. The enteric nervous system communicates with the brain, and fructose may activate neurons in the vagal afferent system within the hindbrain (Horn et al., 1998), which activates forebrain neurons implicated in the control of feeding (Horn and Friedman, 1998). As well, like high glucose intake, excessive fructose consumption can influence gut microbiota and metabolic syndrome, without necessarily altering body weight (Do et al., 2018; Noble et al., 2021). Moreover, gut dysbiosis provoked by fructose can affect hippocampal inflammation (Li et al., 2019), which may be linked to neurodegenerative disorders. In fact, as gut microbial changes may affect brain functioning underlying stress or mood disorders that can produce anhedonia and food intake (Cryan et al., 2019), the role of the gut and gut microbiota may also play a role in fructose-mediated actions in the brain.

With regards to food intake, it is important to consider that behavior toward food is not only impacted by feelings of hunger (Section 4.1), but also by food cravings (Section 4.2), impulses and decisions to act on cravings (Section 4.3), or even the memories related to food (Section 4.4). The ensuing sections will describe the brain systems involved and then identify potential mechanisms, where applicable, to expand on how dietary fructose may exacerbate food-related behaviors in the promotion of metabolic syndrome.

4.1. *Fructose effects on homeostatic feeding systems*

Glucose is well-established to be a satiety signal that would suppress feeding (Page et al., 2013). Since fructose is a sugar, it might be thought that fructose would produce satiety to curb additional feeding, but in fact, unlike glucose, fructose does not induce satiety. Whereas consuming a glucose drink increases ratings of fullness and satiety, consuming a fructose drink does not (Page et al., 2013). In humans, a glucose drink inhibits hypothalamic activity to induce satiety, an effect not seen with fructose (Page et al., 2013; van Opstal et al., 2019b). This is to be expected given that fructose does not stimulate satiety hormones such as leptin and insulin to the same degree as glucose (Luo et al., 2015; Page et al., 2013; Teff et al., 2004). Furthermore, the postprandial decrease in ghrelin is attenuated after fructose intake (Teff et al., 2004). These findings suggest that there is a deficit in peripheral satiety signals to convey energy status to the brain and may reflect an indirect mechanism underlying how fructose can promote feeding.

The hypothalamus is the primary regulator of satiety or hunger-driven feeding, which is maintained by balancing orexigenic and anorexigenic signals that stimulate and inhibit feeding, respectively. Tipping the scale in favour of orexigenic signaling, such as during fasting, puts the brain in a hunger-like state, and hence factors that recreate this state may increase feeding. The arcuate nucleus is a key component of energy balance regulation at the hypothalamus. Cells coexpressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) are first-order arcuate neurons activated by fasting (Yang et al., 2011). As the arcuate nucleus is located adjacent to the median eminence, a circumventricular organ that lacks a fully functional blood brain barrier, this hypothalamic region may be exposed to higher levels of blood-borne molecules. Indeed, NPY/AgRP neurons are activated by the hunger hormone ghrelin to promote feeding (Cowley et al., 2003) and are inhibited by satiety signals like leptin (Elias et al., 1999), insulin (Davidowa and Plagemann, 2007), and glucose (Fioramonti et al., 2007). By contrast, proopiomelanocortin (POMC) neurons in the arcuate inhibit feeding (Andermann and Lowell, 2017) and are activated by glucose (Ibrahim et al., 2003), fatty acids (Jo et al., 2009), and leptin (Elias et al., 1999). Furthermore, in addition to endogenous signals, arcuate neurons can also respond to dietary nutrients. For instance, dietary fat can activate NPY/AgRP neurons (Wei et al., 2015), therefore consumption of a high fructose diet may similarly impact the activity of NPY/AgRP cells to regulate hypothalamic feeding circuitry and promote feeding.

To date, no study has assessed whether fructose directly influences arcuate neurons. However, the arcuate is the hypothalamic headquarter for metabolic regulation, and fructose can induce hypothalamic gene expression changes related to central or peripheral metabolic disturbance (Meng et al., 2016). Hence, it would be important to consider that fructose-mediated regulation at any hypothalamic region may alter orexigenic or anorexigenic output, such as via the arcuate.

4.1.1. *Fructose increases orexigenic drive via common hypothalamic neurocircuitry*

The central response to fructose can promote feeding by rendering the homeostatic hypothalamic network in a hunger-like state and increasing orexigenic drive from various hypothalamic neuronal populations (Table 1). The actions of fructose on feeding are mediated by central processes, as intracerebroventricular administration of fructose increases feeding (Cha et al., 2008; Miller et al., 2002) by stimulating intracellular pathways that signal energy depletion (Cha et al., 2008). Upon entry into a cell, fructose is rapidly phosphorylated. As a result, a transient drop in ATP levels and reduced ATP/AMP ratio can activate AMP kinase (AMPK), which is associated with a hunger-like state. Stimulating this pathway upregulates excitatory drive to NPY/AgRP neurons (Yang et al., 2011) and promotes food intake to boost energy levels (Cha et al., 2008). In effect, fructose-mediated increase in AMPK activity can activate orexigenic neurons to promote hyperphagia.

Table 1
Central and peripheral changes to orexigenic and anorexigenic signals following fructose intake.

Net effect	Signal origin	Outcome of fructose intake	Reference(s)
Orexigenic	**Periphery**	Increased post-prandial ghrelin	Teff et al., 2004
		Increased phospho-AMPK	Cha et al., 2008
	Hypothalamus	Short-term fructose intake decreased *Npy* expression	Lindqvist et al., 2008
		Chronic fructose intake increased *Npy* expression	Bursac et al., 2014; Nabil et al., 2020
		Increased c-Fos in orexin neurons	Rorabaugh et al., 2014
		Increased orexin levels	Franco-Perez et al., 2018
		Increased anandamide and 2-AG synthesis	Erlanson-Albertsson and Lindqvist, 2010
		Increased *Cb1* receptor expression	Lindqvist et al., 2008
		Increased CB1 receptor function in ventromedial hypothalamus	Rojo et al., 2014
		Vasopressin signaling at V1b receptors (i.e., *V1b* deletion suppressed food intake)	Andres-Hernando et al., 2021
Anorexigenic	**Periphery**	Decreased circulating leptin	Luo et al., 2015; Page et al., 2013; Teff et al., 2004
		Decreased circulating insulin	Luo et al., 2015; Page et al., 2013; Teff et al., 2004
	Hypothalamus	Decreased *Pomc* expression	Lindqvist et al., 2008; Nabil et al., 2020; Levy et al., 2018; Cha et al., 2008
		Vasopressin signaling at V1a receptors (i.e., *V1a* deletion increased food intake)	Andres-Hernando et al., 2021

The upregulation and downregulation of *Npy* and *Pomc* gene expression, respectively, may underlie the orexigenic actions of dietary fructose. Rats became hyperphagic after drinking a fructose solution, but *Npy* expression was downregulated (Lindqvist et al., 2008). The brain may initially downregulate *Npy* as a compensatory mechanism and upregulate *Npy* following chronic fructose intake. Consistent with this, prolonged fructose exposure elevated *Npy* expression (Bursac et al., 2014; Nabil et al., 2020), so that these rats consumed more calories (Bursac et al., 2014). This is similar to the actions of sucrose solutions that immediately downregulate *Agrp* and *Npy* expression but that are subsequently upregulated (Gaysinskaya et al., 2011). There is also a decrease in *Pomc* expression when fructose is consumed (Lindqvist et al., 2008; Nabil et al., 2020), administered systemically (Levy et al., 2018), or administered directly into the brain (Cha et al., 2008) thus supporting a net increase in orexigenic drive.

Orexin is another orexigenic signal that contributes to fructose-induced hyperphagia. Orexin neurons in the lateral hypothalamus promote feeding and project to the arcuate to excite NPY/AgRP cells and inhibit POMC cells (Arrigoni et al., 2019). Chronic, but not acute, access to fructose increased the activation of orexin neurons (Rorabaugh et al., 2014) and increased orexin levels in the hypothalamus (Franco-Perez et al., 2018). Consistently, blocking orexin signaling decreased food intake and fructose drinking (Rorabaugh et al., 2014). The overall upregulated orexin signaling with fructose intake thus supports fructose-mediated feeding.

In addition to neuropeptides, synaptic messengers like the endocannabinoids anandamide and 2-arachinodoyl glycerol (2-AG) can also impact feeding. Hunger increases the hypothalamic level of endocannabinoids (Kirkham et al., 2002), which promotes feeding by activating CB1 receptors (Di Marzo and Matias, 2005) typically located on presynaptic nerve terminals. CB1 receptor antagonism prevents hyperphagia (Kirkham et al., 2002) and has also been shown to decrease sucrose intake (Arnone et al., 1997). In order to sustain endocannabinoid levels in the brain, fructose intake may increase 2-AG levels and suppress the synthesis or facilitate the breakdown of anandamide in the brain (Erlanson-Albertsson and Lindqvist, 2010). Furthermore, fructose consumption elevated hypothalamic *Cb1* receptor mRNA levels (Lindqvist et al., 2008) and may specifically involve the functional activation of CB1 receptors at the ventromedial hypothalamus (Rojo et al., 2014). Taken together, these studies show that hypothalamic CB1 receptor signaling is critical to supporting the endocannabinoid system underlying fructose-induced hyperphagia.

Recently, vasopressin has emerged as a critical hypothalamic signal linked to fructose-induced hyperphagia and metabolic syndrome (Andres-Hernando et al., 2021). Fructose can directly stimulate vasopressin release from the hypothalamus (Song et al., 2017), and dietary fructose can stimulate vasopressin secretion in humans (Wolf et al., 1992) and animals in a dose-dependent manner (Andres-Hernando et al., 2021). Activating vasopressin neurons can have anorexigenic effects (Pei et al., 2014), but vasopressin can, in part, mediate the feeding effects of fructose (Andres-Hernando et al., 2021). Different vasopressin receptors can have opposing effects in fructose-mediated feeding. For instance, the vasopressin receptor V1a mediates anorexigenic actions, thus V1a receptor deletion increases calorie intake. Meanwhile, V1b receptors mediate orexigenic actions, and V1b receptor deletion leads to reduced calorie intake. Furthermore, vasopressin released into circulation activates V1b receptors in the liver to stimulate hepatic fructose metabolism and metabolic syndrome (Andres-Hernando et al., 2021). Thus, vasopressin represents an important signal in both the hyperphagic and metabolic effects of dietary fructose.

In summary, fructose may stimulate feeding by recreating a hunger-like state at hypothalamic neurons to increase the drive to feed. This may occur by increasing orexigenic drive via elevating hunger hormones, activating gene expression of NPY or orexin, increasing endocannabinoid-mediated synaptic transmission, stimulating vasopressin release to act on V1b receptors, as well as reducing anorexigenic drive by suppressing satiety and melanocortin signaling (Table 1). Moreover, hypothalamic signals that enter circulation may mediate metabolic syndrome peripherally. These effects may stimulate feeding and dampen internal cues that curb feeding in the expression of fructose-induced hyperphagia, however the resulting changes to neural activity and the neural circuitry underlying the hyperphagic effects of fructose have not been determined.

4.2. Fructose actions on the reward system

The response to foods involves much more than just satiety processes and is in part attributed to reward processes leading to cravings (Section 4.2) as well as decision-making processes that enable or curb these cravings (Section 4.3).The primary reward circuit involves output from dopaminergic neurons in the ventral tegmental area (VTA) to the striatum (accumbens (NAc) and caudate nucleus), amygdala, and cortical areas such as the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) (Fig. 2) (Swanson, 1982). Sucrose, which is broken down into fructose and glucose molecules, activates the reward system in humans and animals (Eiler et al., 2018; Mitra et al., 2011) by increasing dopamine levels in the NAc (Avena et al., 2006; Hajnal and Norgren, 2002; Hajnal et al., 2004). Animals will also develop a preference or develop bingeing behavior when given fructose (Rorabaugh et al., 2015; Sclafani and Ackroff, 1994). As such, fructose may possess reinforcing properties that activate the reward system in the same way as sucrose.

The reward system motivates us to seek food, but when food is abundant, engaging the reward system may lead us to overeat. Food reward may be mediated by nutritional value, taste, or both, thus palatable foods are particularly effective at stimulating the reward system because they taste good and are high in calories (Leigh and Morris, 2018; Sclafani and Ackroff, 1994). Evolutionarily, when food was scarce, sweet tastes prompted the consumption of that calorie-rich food (Leigh and Morris, 2018). In fact, a sweet taste can overcome the rewarding properties of cocaine so rats will choose saccharin or sucrose over cocaine (Lenoir et al., 2007). All sugars, including fructose, are also known to recruit neural circuits similar to that associated with opiates (Levy et al., 2018) and alcohol (Ayoub et al., 2020; Daniels et al., 2016; Levy et al., 2015). Accordingly, activation of these neural circuits may produce addiction-like behaviors (Levy et al., 2015) leading to the excessive consumption of sweetened foods. It is possible then that the reinforcing properties of fructose contribute to the rise in fructose intake seen in recent years (Sun et al., 2011).

4.2.1. Fructose increases the salience of food through the accumbens

In humans, activation of the reward system can be measured as changes in blood-oxygen-level-dependent (BOLD) signal to show an increase or decrease in cerebral blood flow and neural activation. In lean participants, the consumption of a fructose solution does not change the BOLD signal in the NAc (Jastreboff et al., 2016), while one study showed that fructose consumption via a high fat, high protein milkshake decreased the striatum BOLD signal (Jastreboff et al., 2016; Page et al., 2013; van Opstal et al., 2019a). This is consistent with animal studies where fructose intake did not stimulate neuronal activation (c-Fos expression), which actually decreased with chronic fructose intake (Rorabaugh et al., 2014). In fact, there is a reduction in dopamine output in the striatum following fructose consumption (Meyers et al., 2017). Consistent with the long-term effects of fructose, dampened activity in the striatum in response to palatable food is a factor preceding weight gain (Stice et al., 2010).

That said, fructose ingestion can increase the salience of food. Participants shown images of a palatable food after drinking a fructose beverage will show a greater BOLD response in the NAc (Luo et al., 2015). The increase in striatal BOLD response was also associated with increased appetite and suggested that fructose enhances the response of humans to food cues (Luo et al., 2015). In fact, in participants with obesity, fructose intake alone increased hunger ratings and NAc BOLD

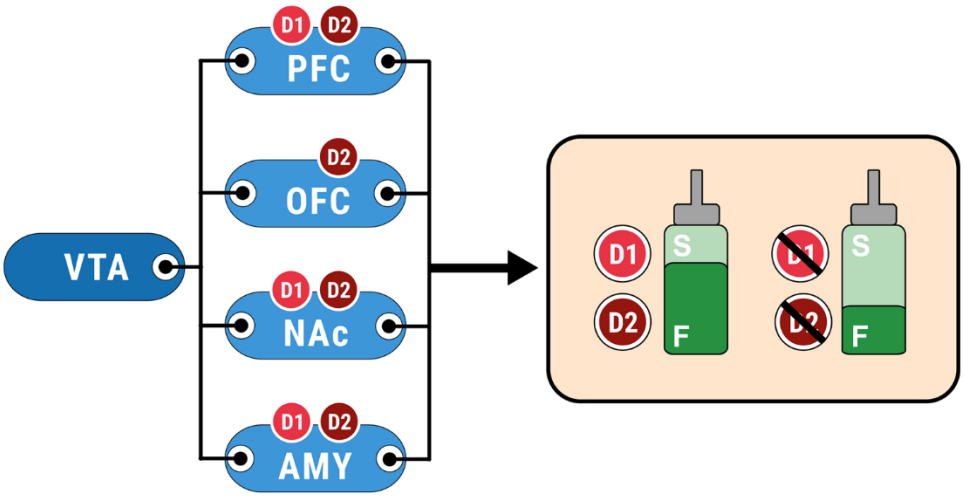

Fig. 2. Mesocorticolimbic reward circuitry promotes fructose preference.
Fructose consumption elicits and reinforces reward signals at the ventral tegmental area (VTA) and downstream VTA targets, including dopaminergic transmission within the prefrontal cortex (PFC), orbitofrontal cortex (OFC), nucleus accumbens (NAc), and amygdala (AMY). In two-bottle choice tests, activation of D1 and/or D2 receptor signaling at VTA target sites elicits fructose-conditioned flavor preference and increases the preference for fructose (F) over a drink comprising a non-caloric sweetener like saccharin (S). By contrast, D1 or D2 receptor antagonism (⦸) reduces fructose preference.

signal, even without food presentation (Jastreboff et al., 2016). These findings suggest that fructose may prime the reward system to food cues via the NAc, and this effect is more prominent in obesity. The NAc is well-established to mediate incentive food salience (i.e., the wanting of food rewards) upon the presentation of cues associated with the reward (Berridge, 2009). Interestingly, it has been shown that fructose can produce incentive salience. Indeed, when a stimulus (cherry or grape flavor) was paired with a fructose drink, rats would overconsume the drink with the conditioned flavor on test day even when the drink no longer contained fructose. This flavor association was not as robust if the flavor was initially paired with a glucose drink. In essence, the conditioned flavor was a reminder and predictive cue for fructose and shows the incentive salience of fructose (Sclafani and Ackroff, 1994). This action was, in part, mediated by dopaminergic transmission in the NAc, as blocking dopamine transmission in the NAc diminished the preference for the flavor associated with fructose (Bernal et al., 2008).

4.2.2. *Fructose activates the mesocorticolimbic dopamine system to promote fructose preference*

In addition to NAc activation in obesity, fructose also activates additional reward-related regions within the mesocorticolimbic dopamine system. This includes activation seen by c-Fos induction in the dorsal striatum, PFC, and amygdala of rats (Dela Cruz et al., 2015); increased BOLD signal in the dorsal striatum, PFC, and OFC of pigs (Ochoa et al., 2016); and increased dopamine levels in the VTA (Franco-Perez et al., 2018).

Dopamine release from the VTA is critical for fructose consumption and preference. Systemic D1 and/or D2 receptor antagonism decreases acute fructose intake (Kraft et al., 2015) and can prevent or eliminate the preference for flavors associated with fructose. In such studies, when given the choice between a fructose or a saccharin drink the animal chose to consume a drink whose flavor was associated with fructose. However, blocking dopaminergic transmission decreased both the acquisition and expression of fructose-conditioned flavor preference (Baker et al., 2003) (Fig. 2). The specific brain regions involved include the forebrain regions, as D1 and D2 antagonism in the medial PFC or D2 antagonism in the amygdala blocked the acquisition of fructose-conditioned flavor preference (Malkusz et al., 2012). Meanwhile, the expression of fructose-conditioned flavor preference can be attenuated by D1 and D2 antagonism in the NAc and amygdala (Bernal et al., 2009, 2008) or by D2 antagonism alone in the medial OFC (Malkusz et al., 2015). These findings indicate that multiple VTA projection sites are important for dopamine-mediated fructose preference (Fig. 2).

Fructose-induced reward effects are similarly related to orexin neurons in the hypothalamus. Intermittent access to fructose induces a bingeing phenotype associated with the activation of orexin neurons (Rorabaugh et al., 2014), which directly stimulate VTA neurons (Korotkova et al., 2003). Orexin neurons are activated by the availability of energy substrates like lactate to promote wakefulness and feeding (Parsons and Hirasawa, 2010). Paradoxically, orexin neurons are acutely inhibited by glucose (Burdakov et al., 2005), especially when energy levels are low (Venner et al., 2011). This inhibition is short-lived, but glucose can inhibit the firing of orexin neurons (Williams et al., 2008). Hence, when energy levels are low and glucose becomes available upon feeding, glucose may supress the activation of orexin neurons to prevent excessive feeding. Meanwhile, fructose does not inhibit orexin neurons (Gonzalez et al., 2008), and fructose consumption increases hypothalamic orexin production, leading to increased orexin and dopamine levels in the VTA (Franco-Perez et al., 2018). In effect, fructose consumption would not disable the activation of the reward pathway by orexin neurons.

In summary, fructose may alter reward circuitry through dopamine signaling to reinforce the consumption of fructose or other palatable foods, and this effect may be mediated in part through the hypothalamus. It has yet to be determined if it would be important to distinguish the impact of acute versus chronic fructose intake on the reward circuit in the development of obesity.

4.3. *Fructose diminishes cognitive control over feeding*

For humans, when food is freely available, cognitive control and executive function play important roles in determining food intake. Cognitive function is necessary for choosing sugary foods, and more importantly, for choosing to stop eating. This regulation serves to overcome the rewarding properties of sugary foods. Cognitive control and executive function are involved in the regulation of goal-directed behavior, decision making, inhibitory control, and assigning value to rewarding stimuli (Seabrook and Borgland, 2020). Accordingly, it is possible that cognitive control becomes diminished or hijacked by dietary fructose to promote further sugar intake.

There is a link between sucrose intake and worsened performance on tests of executive function (Levitan et al., 2015). Since sucrose is 50 % fructose, it is important to determine if fructose can alter the activity of such cortical regions. Whereas glucose activates cortical activity, fructose can increase oxidative damage (Lopes et al., 2014) and decrease BOLD activity in the cortex (Purnell et al., 2011). This finding may reflect an overall decrease in cortical activity in response to a fructose load.

The frontal cortex is the main brain region implicated in cognition. Specifically, the PFC and OFC, previously discussed as target sites of the dopaminergic reward system (see section 4.2.2) are two regions involved in executive function. They are also important for encoding

and predicting the reward associated with feeding and responding appropriately to food-related sensory or environmental cues (Lowe et al., 2019; Seabrook and Borgland, 2020). Their anatomical connection to the reward system highlights the contribution of executive function to the rewarding properties of food. Interestingly, activation of these regions have opposing functions, as the PFC is activated by satiety while the OFC is activated during hunger (Tataranni et al., 1999).

4.3.1. *Fructose reduces cortical inhibition to promote feeding*

The PFC utilizes contextual cues to make decisions and provide conscious control over feeding. As such, disrupting the control of the PFC over feeding may lessen cognitive inhibition, and this is associated with the susceptibility to overeat, especially calorie dense foods (Lowe et al., 2019). High sucrose diets can also enhance pathological changes within the PFC (Reichelt et al., 2015) to advance the breakdown of cognitive functioning associated with increasing sugar consumption. Acute consumption of fructose solution in rats increased c-Fos immunoreactivity in the infralimbic medial PFC (Dela Cruz et al., 2015). In pigs, chronic fructose intake, in the absence of obesity, increased BOLD signal overall in the PFC (Ochoa et al., 2016). By contrast, in adolescents with obesity, ingesting a fructose drink decreased PFC BOLD signal (Jastreboff et al., 2016), thus while fructose normally activates the PFC to inhibit further intake, this inhibition was lost in obesity. As obesity is also associated with reduced executive function, decreased activity in the PFC may result in an inability to have control over the rewarding and hyperphagic effects of fructose (Yang et al., 2018).

4.3.2. *Fructose drives feeding through activation of the orbitofrontal cortex*

The OFC neurons are activated by olfactory or visual cues during hunger and inhibited by satiety (Critchley and Rolls, 1996). Consistent with this, a recent study showed that optogenetic activation of OFC neurons increased feeding behavior (Jennings et al., 2019). Furthermore, changes in synaptic plasticity can be induced with chronic consumption of a high fat, high sugar diet, which depolarized OFC neurons due to the loss of inhibitory transmission. Consequently, the rats were less responsive to a foot shock stressor, which would normally supress food intake, and continued eating (Thompson et al., 2017). In essence, the drive to eat outweighed the fear caused by the foot shock. Fructose as a component of these diets may thus result in similar changes within the OFC with consequential increases in feeding.

Chronic fructose intake, in the absence of obesity, increased activation of the OFC in Yucatan pigs (Ochoa et al., 2016). This activation is in line with a state of hunger as opposed to a state of satiety. Additionally, human participants that consumed fructose were more likely to accept an immediate food reward versus a delayed monetary reward when compared to participants who consumed glucose. This behavioral change corresponded to a greater OFC activation in response to food cues (Luo et al., 2015), which may promote impulsivity towards palatable foods.

Together, these findings show that fructose can alter executive function by disrupting normal function of the PFC and OFC. Dietary fructose increases OFC activation, which promotes feeding (Fig. 3A). By contrast, while PFC activation inhibits feeding, fructose reduces PFC activation, which may lead to processes resulting in the disinhibition of feeding (Fig. 3B). Fructose may thus act by removing inhibitory control to promote the consumption of palatable foods. Without such cortical inhibition, the rewarding properties of high calorie foods increase so that they are more likely to be overconsumed.

4.4. *Impact of fructose on hippocampal-mediated feeding*

The processes of memory formation and recall, for example, to remember when and where food is available, allow past experiences to guide future feeding episodes. Simply asking human participants to recall their recent meal decreased subsequent food intake (Higgs, 2002). Furthermore, without remembering the appetizing taste of sugar, we may not seek out sweet-tasting foods or drinks. The hippocampus is fundamental to memory processes, including food-related memory processes (Kanoski and Grill, 2017), and plays an important role in feeding and sugar consumption (Stevenson and Francis, 2017).

Hippocampal activation inhibits food intake reflected by decreased meal initiation (Stevenson and Francis, 2017), while hippocampal lesion (Davidson et al., 2009; Davidson and Jarrard, 1993) or inhibition (Henderson et al., 2013) increases feeding frequency and sucrose intake, respectively. Specifically, while chemogenetic activation of glutamatergic neurons in the ventral hippocampus decreased food intake, inhibition of these neurons had the opposite effect (Sweeney and Yang, 2015). Such glutamatergic projections from the ventral hippocampus have also implicated their efferent targets like the PFC (Hsu et al., 2018) or lateral septum (Sweeney and Yang, 2015) in the suppression of feeding. Interestingly, consuming a fructose drink can decrease the BOLD signal in the parahippocampal gyrus (Jastreboff et al., 2016). Given the overall inhibitory role of the hippocampus and associated areas, this decrease in activity may disinhibit feeding, which may alter food bouts or meal size. For example, optogenetic inhibition of hippocampal neurons shortly after a meal to disrupt memory consolidation decreased the latency to the next meal and increased the second meal size (Hannapel et al., 2019). These results indicate that both meal-related memory consolidation and recall are critical to hippocampal-dependent feeding

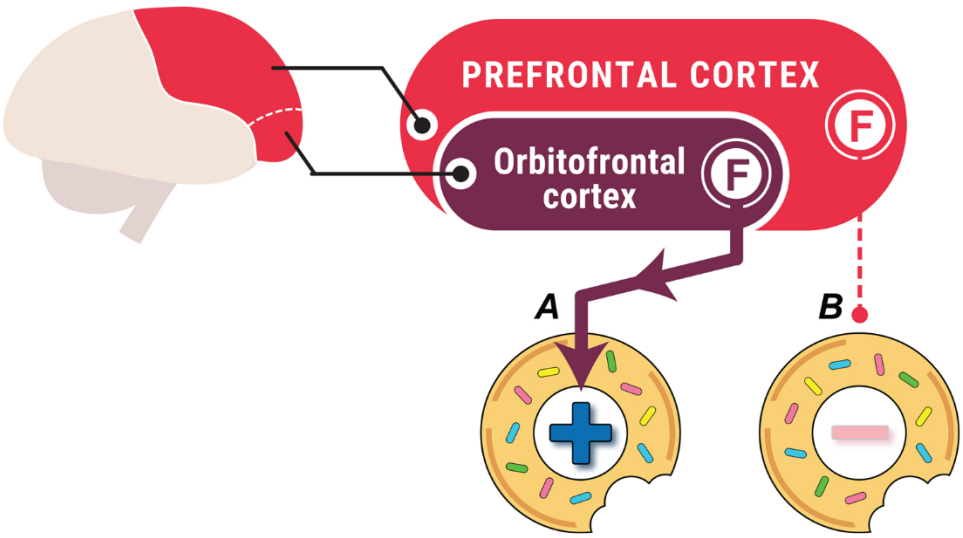

Fig. 3. Fructose intake in obesity disinhibits the cortical control of feeding.
Fructose (F) consumption can activate the orbitofrontal cortex (OFC; ***A***), which responds to food cues or hunger, to promote feeding (+). By contrast, prefrontal cortex (PFC) activity exerts inhibitory control to suppress feeding (–), but as fructose intake reduces PFC activity, this inhibition is lost (dashed line) and the resulting disinhibition would promote feeding (***B***).

inhibition. As fructose consumption can suppress hippocampal activation and shorten the interval between food bouts.

As hippocampal activation limits food intake, it follows that dietary factors that damage or inhibit the hippocampus could lead to overeating. In rats, a diet high in saturated fat and refined sugar reduced markers of synaptic plasticity and decreased spatial memory (Molteni et al., 2002). Humans who eat a western diet, also high in sugar and fat, performed worse on tests of hippocampal function, consumed more of the food provided during testing, and had worse recall of what they had eaten (Francis and Stevenson, 2011). In fact, fructose consumption can produce hippocampal gene expression changes related to attention or neurological dysfunction (Meng et al., 2016). Here we summarize the effect of short- and long-term dietary fructose on hippocampal cellular damage and memory impairment that may contribute to fructose-mediated hyperphagia.

4.4.1. *Fructose consumption impairs cellular processes underlying memory formation*

Short-term fructose intake in animals can lead to impaired cellular processes and hippocampal degeneration within one week. Rats given a fructose drink (Jiménez-Maldonado et al., 2018) or high fructose diet (Cigliano et al., 2018) had decreased markers of mitochondrial function (Jiménez-Maldonado et al., 2018), which ultimately leads to decreased neuron myelination and growth, cell loss, and reduced hippocampal volume (Jiménez-Maldonado et al., 2018). Additionally, the hippocampus of fructose-fed rats had increased inflammation, lipid peroxidation, cell death, and markers of insulin resistance (Cigliano et al., 2018). However, despite evidence of reduced hippocampal health and function, short-term fructose intake did not impair the performance of a memory task (Jiménez-Maldonado et al., 2018). Chronic fructose consumption led to significant memory impairment reflected by worsened performance on spatial memory tasks (Agrawal, 2012; Agrawal et al., 2016; Cisternas et al., 2015; Meng et al., 2016; Rivera et al., 2018; Yin et al., 2014) and social interaction (Rivera et al., 2018) or object-recognition tasks (Rivera et al., 2018; Sanguesa et al., 2018).

The mechanisms underlying fructose-mediated memory impairment are related to deficits in hippocampal synaptic transmission. Chronic consumption of fructose led to reduced axonal excitability and impaired synaptic strength at hippocampal synapses. These deficits are related to a decrease in the expression of postsynaptic glutamate receptor subunits at hippocampal synapses (Cisternas et al., 2015). Furthermore, it has been shown that chronic fructose intake produces oxidative stress (Sanguesa et al., 2018; Yin et al., 2014), lipid peroxidation (Agrawal et al., 2016; Rivera et al., 2018), and mitochondrial dysfunction (Agrawal et al., 2016). In addition, chronic fructose intake also induces inflammatory cytokines (Yin et al., 2014), owing to astrocytes (Liu et al., 2018) or microglia (Liu et al., 2018) in the hippocampus. Damage caused by oxidative stress may likewise contribute to fructose-induced hippocampal insulin resistance (Maciejczyk et al., 2019) by suppressing intracellular insulin receptor signaling (Agrawal, 2012; Agrawal et al., 2016; Liu et al., 2018; Rivera et al., 2018; Yin et al., 2014), which is important for regulating synaptic transmission and memory processes (Grillo et al., 2015; McNay et al., 2010; Soto et al., 2019). As hippocampal synaptic plasticity is critical to the expression of learning and memory, fructose-induced impairments at the synapse can negatively impact memory processes. Chronic fructose intake led to decreased neuron proliferation, growth, and maturation, including a reduction in brain derived neurotrophic factor (BDNF) and its receptor (Agrawal et al., 2016; Liu et al., 2018; Sanguesa et al., 2018). BDNF-deficiency alters synaptic structure and function by reducing the levels of presynaptic (Agrawal and Gomez-Pinilla, 2012; Agrawal et al., 2016; Rivera et al., 2018) and postsynaptic proteins (Liu et al., 2018; Rivera et al., 2018) that impaired synaptic efficacy (Rivera et al., 2018). As such, alterations in synaptic proteins may bear important functional implications by impairing synaptic transmission and neuronal plasticity underlying memory processes (Lynch, 2004).

Together, these findings show that short term fructose intake prior to obesity onset can produce hippocampal disturbances that worsen with chronic fructose intake. However, it is noteworthy that the effects of fructose, including on metabolic syndrome, spatial memory deficits, and impaired synaptic transmission, can be reversed by abstaining from fructose (Cisternas et al., 2015). The underlying cellular damage or synaptic dysfunction could impair hippocampal function known to suppress feeding.

4.4.2. *Maternal fructose intake leads to memory deficits in offspring*

Fructose-mediated cognitive impairments (Erbas et al., 2018; Wu et al., 2016; Yamazaki et al., 2018) and metabolic dysfunction (Erbas et al., 2018; Lee et al., 2016) have also been reported in offspring of dams given access to fructose during pregnancy and lactation. Offspring from fructose-fed dams show impairments in several tests of cognition and memory performance, including the Morris water maze (Wu et al., 2016), passive avoidance learning (Erbas et al., 2018), novel object recognition, and fear conditioning (Yamazaki et al., 2018), and these deficits are linked to decreased growth factors (Erbas et al., 2018; Wu et al., 2016; Yamazaki et al., 2018), inflammation (Erbas et al., 2018), and altered synaptic markers in the hippocampus (Erbas et al., 2018). Such intergenerational effects may reflect epigenetic changes (Wu et al., 2016; Yamada et al., 2019; Yamazaki et al., 2018) or metabolic processes affecting prenatal hippocampal development. In addition, it would also be important to consider early life exposure to fructose, which may also lead to impairments in hippocampal-dependent memory task performance in adulthood (Noble et al., 2021). Fructose exposure during this postnatal development period can alter the gut microbiome to enrich microbiota linked with cognitive impairment (Noble et al., 2021).

5. Conclusion

The current literature on *fructose* and the *brain* show that the effects of dietary fructose are multifaceted and engage wide-ranging central processes that underlie energy homeostasis, reward processing, cortical inhibition, and memory formation that come to influence feeding behavior. It reflects the complexity involved in understanding food intake, as eating is not only driven by hunger, but also by cravings and hedonic memories linked with palatable foods, or whether we are able to inhibit impulses to eat. By increasing the salience of food, fructose can also increase the desire to eat. However, unlike other dietary sugars, such as glucose and sucrose, fructose does not produce a satiety response so feeding would continue. Furthermore, fructose can also shorten the interval between food bouts and hijack cortical control to disinhibit feeding. The collective actions of fructose promote a brain state also seen during hunger and food-seeking and implicate the susceptibility of the brain to dietary sugars.

We ascertain that dietary fructose can impose maladaptations within the brain to promote overfeeding, which may be exacerbated in obesity. Future research, including at critical brain regions identified in this review, would be needed to elucidate the mechanisms through which fructose can promote dysfunction at the circuit or synapse level. Hippocampal studies have shown that fructose feeding can impact synaptic plasticity, and similar studies applied to metabolic centers within the hypothalamus may reveal neuronal mechanisms that underlie fructose-mediated overfeeding. For example, by targeting and suppressing maladaptations at specific circuits or synapses, it may be possible to develop interventions to curb the orexigenic actions of fructose. In addition, the availability of gene sequencing tools would be able to identify gene expression changes following fructose feeding and derive novel gene targets that can be manipulated to curb the effects of fructose in obesity. Moreover, given the overlap between neural circuits, especially that involving the mesocortical and mesolimbic circuits that underlie opioid addiction and obesity, then perhaps behavioral interventions for treating drug addiction would also be helpful for treating obesity (Volkow and Wise, 2005).

Declaration of Competing Interest

M.A.P has nothing to disclose. M.J.C reports grants from Natural Sciences and Engineering Research Council of Canada (NSERC) and Canadian Institutes of Health Research (CIHR) during the conduct of the study.

Acknowledgements

The authors thank Heather MacDonald for input using systematic literature keyword search. The authors thank A. Abizaid, H. Anisman, and J. Bruin for input during the revision of this manuscript. Fig. 1 was created using BioRender.com. M.A.P. is supported by the NSERC Post-graduate Scholarship Doctoral program and the Ontario Graduate Scholarship. M.J.C. is supported by the NSERC Discovery Grant RGPIN-2017-06272 and CIHR Project Grant PJT-175156.

References

Ackerman, Z., Oron-Herman, M., Grozovski, M., Rosenthal, T., Pappo, O., Link, G., Sela, B.A., 2005. Fructose-induced fatty liver disease: hepatic effects of blood pressure and plasma triglyceride reduction. Hypertension 45, 1012–1018.
Agrawal, R., Gomez-Pinilla, F., 2012. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. J. Physiol. 590, 2485–2499.
Agrawal, R., Noble, E., Vergnes, L., Ying, Z., Reue, K., Gomez-Pinilla, F., 2016. Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity. J. Cereb. Blood Flow Metab. 36, 941–953.
Andermann, M.L., Lowell, B.B., 2017. Toward a wiring diagram understanding of appetite control. Neuron 95, 757–778.
Andres-Hernando, A., Jensen, T.J., Kuwabara, M., Orlicky, D.J., Cicerchi, C., Li, N., Roncal-Jimenez, C.A., Garcia, G.E., Ishimoto, T., Maclean, P.S., Bjornstad, P., Sanchez-Lozada, L.G., Kanbay, M., Nakagawa, T., Johnson, R.J., Lanaspa, M.A., 2021. Vasopressin mediates fructose-induced metabolic syndrome by activating the V1b receptor. JCI Insight 6, e140848.
Arnone, M., Maruani, J., Chaperon, F., Thiebot, M.H., Poncelet, M., Soubrie, P., Le Fur, G., 1997. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. Psychopharmacology 132, 104–106.
Arrigoni, E., Chee, M.J.S., Fuller, P.M., 2019. To eat or to sleep: that is a lateral hypothalamic question. Neuropharmacology 154, 34–49.
Asnaghi, V., Gerhardinger, C., Hoehn, T., Adeboje, A., Lorenzi, M., 2003. A role for the polyol pathway in the early neuroretinal apoptosis and glial changes induced by diabetes in the rat. Diabetes 52, 506–511.
Avena, N.M., Rada, P., Moise, N., Hoebel, B.G., 2006. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. Neuroscience 139, 813–820.
Ayoub, S.M., Minhas, M., Lapointe, T., Limebeer, C.L., Parker, L.A., Leri, F., 2020. Effects of high fructose corn syrup on ethanol self-administration in rats. Alcohol 87, 79–88.
Bady, I., Marty, N., Dallaporta, M., Emery, M., Gyger, J., Tarussio, D., Foretz, M., Thorens, B., 2006. Evidence from glut2-null mice that glucose is a critical physiological regulator of feeding. Diabetes 55, 988–995.
Baker, R.M., Shah, M.J., Sclafani, A., Bodnar, R.J., 2003. Dopamine D1 and D2 antagonists reduce the acquisition and expression of flavor-preferences conditioned by fructose in rats. Pharmacol. Biochem. Behav. 75, 55–65.
Bantle, J.P., Raatz, S.K., Thomas, W., Georgopoulos, A., 2000. Effects of dietary fructose on plasma lipids in healthy subjects. Am. J. Clin. Nutr. 72, 1128–1134.
Barahona, M.J., Llanos, P., Recabal, A., Escobar-Acuña, K., Elizondo-Vega, R., Salgado, M., Ordenes, P., Uribe, E., Sepúlveda, F.J., Araneda, R.C., García-Robles, M. A., 2018. Glial hypothalamic inhibition of GLUT2 expression alters satiety, impacting eating behavior. Glia 66, 592–605.
Bernal, S.Y., Dostova, I., Kest, A., Abayev, Y., Kandova, E., Touzani, K., Sclafani, A., Bodnar, R.J., 2008. Role of dopamine D1 and D2 receptors in the nucleus accumbens shell on the acquisition and expression of fructose-conditioned flavor-flavor preferences in rats. Behav. Brain Res. 190, 59–66.
Bernal, S., Miner, P., Abayev, Y., Kandova, E., Gerges, M., Touzani, K., Sclafani, A., Bodnar, R.J., 2009. Role of amygdala dopamine D1 and D2 receptors in the acquisition and expression of fructose-conditioned flavor preferences in rats. Behav. Brain Res. 205, 183–190.
Berridge, K.C., 2009. 'Liking' and' wanting' food rewards: brain substrates and roles in eating disorders. Physiol. Behav. 97, 537–550.
Bray, G.A., Nielsen, S.J., Popkin, B.M., 2004. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am. J. Clin. Nutr. 79, 537–543.
Burdakov, D., Gerasimenko, O., Verkhratsky, A., 2005. Physiological changes in glucose differentially modulate the excitability of hypothalamic melanin-concentrating hormone and orexin neurons in situ. J. Neurosci. 25, 2429–2433.
Bursac, B.N., Vasiljevic, A.D., Nestorovic, N.M., Velickovic, N.A., Vojnovic Milutinovic, D.D., Matic, G.M., Djordjevic, A.D., 2014. High-fructose diet leads to visceral adiposity and hypothalamic leptin resistance in male rats–do glucocorticoids play a role? J. Nutr. Biochem. 25, 446–455.
Cha, S.H., Wolfgang, M., Tokutake, Y., Chohnan, S., Lane, M.D., 2008. Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake. Proc. Natl. Acad. Sci. U. S. A. 105, 16871–16875.
Chung, S.S., Ho, E.C., Lam, K.S., Chung, S.K., 2003. Contribution of polyol pathway to diabetes-induced oxidative stress. J. Am. Soc. Nephrol. 14, S233–S236.
Cigliano, L., Spagnuolo, M.S., Crescenzo, R., Cancelliere, R., Iannotta, L., Mazzoli, A., Liverini, G., Iossa, S., 2018. Short-term fructose feeding induces inflammation and oxidative stress in the Hippocampus of young and adult rats. Mol. Neurobiol. 55, 2869–2883.
Cisternas, P., Salazar, P., Serrano, F.G., Montecinos-Oliva, C., Arredondo, S.B., Varela-Nallar, L., Barja, S., Vio, C.P., Gomez-Pinilla, F., Inestrosa, N.C., 2015. Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. Biochim. Biophys. Acta 1852, 2379–2390.
Cowley, M.A., Smith, R.G., Diano, S., Tschop, M., Pronchuk, N., Grove, K.L., Strasburger, C.J., Bidlingmaier, M., Esterman, M., Heiman, M.L., Garcia-Segura, L. M., Nillni, E.A., Mendez, P., Low, M.J., Sotonyi, P., Friedman, J.M., Liu, H., Pinto, S., Colmers, W.F., Cone, R.D., Horvath, T.L., 2003. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37, 649–661.
Critchley, H.D., Rolls, E.T., 1996. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. J. Neurophysiol. 75, 1673–1686.
Cryan, J.F., O'Riordan, K.J., Cowan, C.S.M., Sandhu, K.V., Bastiaanssen, T.F.S., Boehme, M., Codagnone, M.G., Cussotto, S., Fulling, C., Golubeva, A.V., Guzzetta, K. E., Jaggar, M., Long-Smith, C.M., Lyte, J.M., Martin, J.A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., O'Connor, R., Cruz-Pereira, J.S., Peterson, V.L., Rea, K., Ritz, N.L., Sherwin, E., Spichak, S., Teichman, E.M., van de Wouw, M., Ventura-Silva, A.P., Wallace-Fitzsimons, S.E., Hyland, N., Clarke, G., Dinan, T.G., 2019. The microbiota-gut-brain axis. Physiol. Rev. 99, 1877–2013.
Dai, S., McNeill, J.H., 1995. Fructose-induced hypertension in rats is concentration- and duration-dependent. J. Pharmacol. Toxicol. Methods 33, 101–107.
Daniels, S., Marshall, P., Leri, F., 2016. Alterations of naltrexone-induced conditioned place avoidance by pre-exposure to high fructose corn syrup or heroin in Sprague-Dawley rats. Psychopharmacology 233, 425–433.
Davidowa, H., Plagemann, A., 2007. Insulin resistance of hypothalamic arcuate neurons in neonatally overfed rats. Neuroreport 18, 521–524.
Davidson, T.L., Jarrard, L.E., 1993. A role for hippocampus in the utilization of hunger signals. Behav. Neural Biol. 59, 167–171.
Davidson, T.L., Chan, K., Jarrard, L.E., Kanoski, S.E., Clegg, D.J., Benoit, S.C., 2009. Contributions of the hippocampus and medial prefrontal cortex to energy and body weight regulation. Hippocampus 19, 235–252.
Dela Cruz, J.A., Coke, T., Karagiorgis, T., Sampson, C., Icaza-Cukali, D., Kest, K., Ranaldi, R., Bodnar, R.J., 2015. c-Fos induction in mesotelencephalic dopamine pathway projection targets and dorsal striatum following oral intake of sugars and fats in rats. Brain Res. Bull. 111, 9–19.
Di Marzo, V., Matias, I., 2005. Endocannabinoid control of food intake and energy balance. Nat. Neurosci. 8, 585–589.
Do, M.H., Lee, E., Oh, M.J., Kim, Y., Park, H.Y., 2018. High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients 10, 761.
Eiler 2nd, W.J.A., Dzemidzic, M., Soeurt, C.M., Carron, C.R., Oberlin, B.G., Considine, R. V., Harezlak, J., Kareken, D.A., 2018. Family history of alcoholism and the human brain response to oral sucrose. Neuroimage Clin. 17, 1036–1046.
Elias, C.F., Aschkenasi, C., Lee, C., Kelly, J., Ahima, R.S., Bjorbaek, C., Flier, J.S., Saper, C.B., Elmquist, J.K., 1999. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. Neuron 23, 775–786.
Erbas, O., Erdogan, M.A., Khalilnezhad, A., Gürkan, F.T., Yiğittürk, G., Meral, A., Taskiran, D., 2018. Neurobehavioral effects of long-term maternal fructose intake in rat offspring. Int. J. Dev. Neurosci. 69, 68–79.
Erlanson-Albertsson, C., Lindqvist, A., 2010. Fructose affects enzymes involved in the synthesis and degradation of hypothalamic endocannabinoids. Regul. Pept. 161, 87–91.
Faeh, D., Minehira, K., Schwarz, J.M., Periasamy, R., Park, S., Tappy, L., 2005. Effect of fructose overfeeding and fish oil administration on hepatic de novo lipogenesis and insulin sensitivity in healthy men. Diabetes 54, 1907–1913.
Ferraris, R.P., Choe, J.Y., Patel, C.R., 2018. Intestinal absorption of fructose. Annu. Rev. Nutr. 38, 41–67.
Fields, S., 2004. The fat of the land: do agricultural subsidies foster poor health? Environ. Health Perspect. 112, A820–A823.
Fioramonti, X., Contié, S., Song, Z., Routh, V.H., Lorsignol, A., Pénicaud, L., 2007. Characterization of glucosensing neuron subpopulations in the arcuate nucleus: integration in neuropeptide Y and pro-opio melanocortin networks? Diabetes 56, 1219–1227.
Fiorentini, A., Müller, E.E., 1975. Sensitivity of central chemoreceptors controlling blood glucose and body temperature during glucose deprivation. J. Physiol. 248, 247–271.
Francis, H.M., Stevenson, R.J., 2011. Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. Behav. Neurosci. 125, 943–955.
Franco-Perez, J., Manjarrez-Marmolejo, J., Ballesteros-Zebadua, P., Neri-Santos, A., Montes, S., Suarez-Rivera, N., Hernandez-Ceron, M., Perez-Koldenkova, V., 2018. Chronic consumption of fructose induces behavioral alterations by increasing orexin and dopamine levels in the rat brain. Nutrients 10, 1722.
García, M., Millán, C., Balmaceda-Aguilera, C., Castro, T., Pastor, P., Montecinos, H., Reinicke, K., Zúñiga, F., Vera, J.C., Oñate, S.A., Nualart, F., 2003. Hypothalamic ependymal-glial cells express the glucose transporter GLUT2, a protein involved in glucose sensing. J. Neurochem. 86, 709–724.

Gaysinskaya, V.A., Karatayev, O., Shuluk, J., Leibowitz, S.F., 2011. Hyperphagia induced by sucrose: relation to circulating and CSF glucose and corticosterone and orexigenic peptides in the arcuate nucleus. Pharmacol. Biochem. Behav. 97, 521–530.
Geidl-Flueck, B., Hochuli, M., Németh, Á., Eberl, A., Derron, N., Köfeler, H.C., Tappy, L., Berneis, K., Spinas, G.A., Gerber, P.A., 2021. Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: a randomized controlled trial. J. Hepatol. 57, 46–54.
Gonzalez, J.A., Jensen, L.T., Fugger, L., Burdakov, D., 2008. Metabolism-independent sugar sensing in central orexin neurons. Diabetes 57, 2569–2576.
Goran, M.I., Dumke, K., Bouret, S.G., Kayser, B., Walker, R.W., Blumberg, B., 2013a. The obesogenic effect of high fructose exposure during early development. Nat. Rev. Endocrinol. 9, 494–500.
Goran, M.I., Ulijaszek, S.J., Ventura, E.E., 2013b. High fructose corn syrup and diabetes prevalence: a global perspective. Glob. Public Health 8, 55–64.
Grillo, C.A., Piroli, G.G., Lawrence, R.C., Wrighten, S.A., Green, A.J., Wilson, S.P., Sakai, R.R., Kelly, S.J., Wilson, M.A., Mott, D.D., Reagan, L.P., 2015. Hippocampal insulin resistance impairs spatial learning and synaptic plasticity. Diabetes 64, 3927–3936.
Hajnal, A., Norgren, R., 2002. Repeated access to sucrose augments dopamine turnover in the nucleus accumbens. Neuroreport 13, 2213–2216.
Hajnal, A., Smith, G.P., Norgren, R., 2004. Oral sucrose stimulation increases accumbens dopamine in the rat. Am. J. Physiol. Regul. Integr. Compar. Physiol. 286, 31–37.
Hannapel, R., Ramesh, J., Ross, A., LaLumiere, R.T., Roseberry, A.G., Parent, M.B., 2019. Postmeal optogenetic inhibition of dorsal or ventral hippocampal pyramidal neurons increases future intake. eNeuro 6, 1–16.
Hassel, B., Elsais, A., Frøland, A.S., Taubøll, E., Gjerstad, L., Quan, Y., Dingledine, R., Rise, F., 2015. Uptake and metabolism of fructose by rat neocortical cells in vivo and by isolated nerve terminals in vitro. J. Neurochem. 133, 572–581.
He, D., Funabashi, T., Sano, A., Uemura, T., Minaguchi, H., Kimura, F., 1999. Effects of glucose and related substrates on the recovery of the electrical activity of gonadotropin-releasing hormone pulse generator which is decreased by insulin-induced hypoglycemia in the estrogen-primed ovariectomized rat. Brain Res. 820, 71–76.
He, J.L., Zhao, M., Xia, J.J., Guan, J., Liu, Y., Wang, L.Q., Song, D.X., Qu, M.Y., Zuo, M., Wen, X., Yu, X., Huo, R., Pan, Z.W., Ban, T., Zhang, Y., Zhu, J.X., Shou, W., Qiao, G. F., Li, B.Y., 2016. FGF21 ameliorates the neurocontrol of blood pressure in the high fructose-drinking rats. Sci. Rep. 6, 29582.
Henderson, Y.O., Smith, G.P., Parent, M.B., 2013. Hippocampal neurons inhibit meal onset. Hippocampus 23, 100–107.
Higgs, S., 2002. Memory for recent eating and its influence on subsequent food intake. Appetite 39, 159–166.
Horikoshi, Y., Sasaki, A., Taguchi, N., Maeda, M., Tsukagoshi, H., Sato, K., Yamaguchi, H., 2003. Human GLUT5 immunolabeling is useful for evaluating microglial status in neuropathological study using paraffin sections. Acta Neuropathol. 105, 157–162.
Horn, C.C., Friedman, M.I., 1998. 2,5-Anhydro-D-mannitol induces Fos-like immunoreactivity in hindbrain and forebrain: relationship to eating behavior. Brain Res. 779, 17–25.
Horn, C.C., Kaplan, J.M., Grill, H.J., Friedman, M.I., 1998. Brain fos-like immunoreactivity in chronic decerebrate and neurologically intact rats given 2,5-anhydro-D-mannitol. Brain Res. 801, 107–115.
Hsu, T.M., Noble, E.E., Liu, C.M., Cortella, A.M., Konanur, V.R., Suarez, A.N., Reiner, D. J., Hahn, J.D., Hayes, M.R., Kanoski, S.E., 2018. A hippocampus to prefrontal cortex neural pathway inhibits food motivation through glucagon-like peptide-1 signaling. Mol. Psychiatry 23, 1555–1565.
Huang, B.W., Chiang, M.T., Yao, H.T., Chiang, W., 2004. The effect of high-fat and high-fructose diets on glucose tolerance and plasma lipid and leptin levels in rats. Diabetes Obes. Metab. 6, 120–126.
Hubbard, R.S., Russell, N.M., 1937. The fructose content of spinal fluid. J. Biol. Chem. 119, 647–661.
Hwang, J.J., Johnson, A., Cline, G., Belfort-DeAguiar, R., Snegovskikh, D., Khokhar, B., Han, C.S., Sherwin, R.S., 2015. Fructose levels are markedly elevated in cerebrospinal fluid compared to plasma in pregnant women. PLoS One 10, e0128582.
Hwang, J.J., Jiang, L., Hamza, M., Dai, F., Belfort-DeAguiar, R., Cline, G., Rothman, D.L., Mason, G., Sherwin, R.S., 2017. The human brain produces fructose from glucose. JCI Insight 2, e90508.
Ibrahim, N., Bosch, M.A., Smart, J.L., Qiu, J., Rubinstein, M., Ronnekleiv, O.K., Low, M. J., Kelly, M.J., 2003. Hypothalamic proopiomelanocortin neurons are glucose responsive and express K(ATP) channels. Endocrinology 144, 1331–1340.
Izumi, Y., Zorumski, C.F., 2009. Glial-neuronal interactions underlying fructose utilization in rat hippocampal slices. Neuroscience 161, 847–854.
Jang, C., Hui, S., Lu, W., Cowan, A.J., Morscher, R.J., Lee, G., Liu, W., Tesz, G.J., Birnbaum, M.J., Rabinowitz, J.D., 2018. The small intestine converts dietary fructose into glucose and organic acids. Cell Metab. 27, 351–361.
Jastreboff, A.M., Sinha, R., Arora, J., Giannini, C., Kubat, J., Malik, S., Van Name, M.A., Santoro, N., Savoye, M., Duran, E.J., Pierpont, B., Cline, G., Constable, R.T., Sherwin, R.S., Caprio, S., 2016. Altered brain response to drinking glucose and fructose in obese adolescents. Diabetes 65, 1929–1939.
Jennings, J.H., Kim, C.K., Marshel, J.H., Raffiee, M., Ye, L., Quirin, S., Pak, S., Ramakrishnan, C., Deisseroth, K., 2019. Interacting neural ensembles in orbitofrontal cortex for social and feeding behaviour. Nature 565, 645–649.
Jiménez-Maldonado, A., Ying, Z., Byun, H.R., Gomez-Pinilla, F., 2018. Short-term fructose ingestion affects the brain independently from establishment of metabolic syndrome. Biochim. Biophys. Acta 1864, 24–33.
Jo, Y.H., Su, Y., Gutierrez-Juarez, R., Chua Jr., S., 2009. Oleic acid directly regulates POMC neuron excitability in the hypothalamus. J. Neurophysiol. 101, 2305–2316.
Johnson, R.J., Gomez-Pinilla, F., Nagel, M., Nakagawa, T., Rodriguez-Iturbe, B., Sanchez-Lozada, L.G., Tolan, D.R., Lanaspa, M.A., 2020a. Cerebral fructose metabolism as a potential mechanism driving Alzheimer's disease. Front. Aging Neurosci. 12, 560865.
Johnson, R.J., Stenvinkel, P., Andrews, P., Sánchez-Lozada, L.G., Nakagawa, T., Gaucher, E., Andres-Hernando, A., Rodriguez-Iturbe, B., Jimenez, C.R., Garcia, G., Kang, D.H., Tolan, D.R., Lanaspa, M.A., 2020b. Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. J. Intern. Med. 287, 252–262.
Jürgens, H., Haass, W., Castañeda, T.R., Schürmann, A., Koebnick, C., Dombrowski, F., Otto, B., Nawrocki, A.R., Scherer, P.E., Spranger, J., Ristow, M., Joost, H.G., Havel, P.J., Tschöp, M.H., 2005. Consuming fructose-sweetened beverages increases body adiposity in mice. Obes. Res. 13, 1146–1156.
Kanoski, S.E., Grill, H.J., 2017. Hippocampus contributions to food intake control: mnemonic, neuroanatomical, and endocrine mechanisms. Biol. Psychiatry 81, 748–756.
Kasim-Karakas, S.E., Vriend, H., Almario, R., Chow, L.C., Goodman, M.N., 1996. Effects of dietary carbohydrates on glucose and lipid metabolism in golden Syrian hamsters. J. Lab. Clin. Med. 128, 208–213.
Khan, T.A., Sievenpiper, J.L., 2016. Controversies about sugars: results from systematic reviews and meta-analyses on obesity, cardiometabolic disease and diabetes. Eur. J. Nutr. 55, 25–43.
Kirkham, T.C., Williams, C.M., Fezza, F., Di Marzo, V., 2002. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. Br. J. Pharmacol. 136, 550–557.
Kojo, A., Yamada, K., Yamamoto, T., 2016. Glucose transporter 5 (GLUT5)-like immunoreactivity is localized in subsets of neurons and glia in the rat brain. J. Chem. Neuroanat. 74, 55–70.
Korotkova, T.M., Sergeeva, O.A., Eriksson, K.S., Haas, H.L., Brown, R.E., 2003. Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. J. Neurosci. 23, 7–11.
Kraft, T.T., Huang, D., Natanova, E., Lolier, M., Yakubov, Y., La Magna, S., Warshaw, D., Sclafani, A., Bodnar, R.J., 2015. Dopamine D1 and opioid receptor antagonist-induced reductions of fructose and saccharin intake in BALB/c and SWR inbred mice. Pharmacol. Biochem. Behav. 131, 13–18.
Lamy, C.M., Sanno, H., Labouèbe, G., Picard, A., Magnan, C., Chatton, J.Y., Thorens, B., 2014. Hypoglycemia-activated GLUT2 neurons of the nucleus tractus solitarius stimulate vagal activity and glucagon secretion. Cell Metab. 19, 527–538.
Lanaspa, M.A., Ishimoto, T., Li, N., Cicerchi, C., Orlicky, D.J., Ruzycki, P., Ruzicky, P., Rivard, C., Inaba, S., Roncal-Jimenez, C.A., Bales, E.S., Diggle, C.P., Asipu, A., Petrash, J.M., Kosugi, T., Maruyama, S., Sanchez-Lozada, L.G., McManaman, J.L., Bonthron, D.T., Sautin, Y.Y., Johnson, R.J., 2013. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. Nat. Commun. 4, 2434.
Lanaspa, M.A., Kuwabara, M., Andres-Hernando, A., Li, N., Cicerchi, C., Jensen, T., Orlicky, D.J., Roncal-Jimenez, C.A., Ishimoto, T., Nakagawa, T., Rodriguez-Iturbe, B., MacLean, P.S., Johnson, R.J., 2018. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. Proc. Natl. Acad. Sci. U. S. A. 115, 3138–3143.
Lee, W.C., Tain, Y.L., Wu, K.L., Leu, S., Chan, J.Y., 2016. Maternal fructose exposure programs metabolic syndrome-associated bladder overactivity in young adult offspring. Sci. Rep. 6, 34669.
Leigh, S.J., Morris, M.J., 2018. The role of reward circuitry and food addiction in the obesity epidemic: an update. Biol. Psychol. 131, 31–42.
Lenoir, M., Serre, F., Cantin, L., Ahmed, S.H., 2007. Intense sweetness surpasses cocaine reward. PLoS One 2, e698.
Levitan, R.D., Rivera, J., Silveira, P.P., Steiner, M., Gaudreau, H., Hamilton, J., Kennedy, J.L., Davis, C., Dube, L., Fellows, L., Wazana, A., Matthews, S., Meaney, M. J., Team, M.S., 2015. Gender differences in the association between stop-signal reaction times, body mass indices and/or spontaneous food intake in pre-school children: an early model of compromised inhibitory control and obesity. Int. J. Obes. 39, 614–619.
Levy, A., Marshall, P., Zhou, Y., Kreek, M.J., Kent, K., Daniels, S., Shore, A., Downs, T., Fernandes, M.F., Mutch, D.M., Leri, F., 2015. Fructose:glucose ratios—a study of sugar self-administration and associated neural and physiological responses in the rat. Nutrients 7, 3869–3890.
Levy, A., Daniels, S., Hudson, R., Horman, T., Flynn, A., Zhou, Y., Leri, F., 2018. Bupropion and naltrexone combination alters high fructose corn syrup self-administration and gene expression in rats. Neuropharmacology 135, 547–554.
Li, J.M., Yu, R., Zhang, L.P., Wen, S.Y., Wang, S.J., Zhang, X.Y., Xu, Q., Kong, L.D., 2019. Dietary fructose-induced gut dysbiosis promotes mouse hippocampal neuroinflammation: a benefit of short-chain fatty acids. Microbiome 7, 98.
Lindqvist, A., Baelemans, A., Erlanson-Albertsson, C., 2008. Effects of sucrose, glucose and fructose on peripheral and central appetite signals. Regul. Pept. 150, 26–32.
Liu, W.C., Wu, C.W., Tain, Y.L., Fu, M.H., Hung, C.Y., Chen, I.C., Chen, L.W., Wu, K.L.H., 2018. Oral pioglitazone ameliorates fructose-induced peripheral insulin resistance and hippocampal gliosis but not restores inhibited hippocampal adult neurogenesis. Biochim. Biophys. Acta Mol. Basis Dis. 1864, 274–285.
Lopes, A., Vilela, T.C., Taschetto, L., Vuolo, F., Petronilho, F., Dal-Pizzol, F., Streck, E.L., Ferreira, G.C., Schuck, P.F., 2014. Evaluation of the effects of fructose on oxidative stress and inflammatory parameters in rat brain. Mol. Neurobiol. 50, 1124–1130.
Lowe, C.J., Reichelt, A.C., Hall, P.A., 2019. The prefrontal cortex and obesity: a health neuroscience perspective. Trends Cogn. Sci. 23, 349–361.

Luo, S., Monterosso, J.R., Sarpelleh, K., Page, K.A., 2015. Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards. Proc. Natl. Acad. Sci. U. S. A. 112, 6509–6514.
Lynch, M.A., 2004. Long-term potentiation and memory. Physiol. Rev. 84, 87–136.
Maciejczyk, M., Zebrowska, E., Chabowski, A., 2019. Insulin resistance and oxidative stress in the brain: what's new? Int. J. Mol. Sci. 20, 874.
Malkusz, D.C., Banakos, T., Mohamed, A., Vongwattanakit, T., Malkusz, G., Saeed, S., Martinez, S., Bohn, T., Mahmud, F., Liss, C., Rozvi, A., Touzani, K., Sclafani, A., Bodnar, R.J., 2012. Dopamine signaling in the medial prefrontal cortex and amygdala is required for the acquisition of fructose-conditioned flavor preferences in rats. Behav. Brain Res. 233, 500–507.
Malkusz, D.C., Yenko, I., Rotella, F.M., Banakos, T., Olsson, K., Dindyal, T., Vig, V., Bodnar, R.J., 2015. Dopamine receptor signaling in the medial orbital frontal cortex and the acquisition and expression of fructose-conditioned flavor preferences in rats. Brain Res. 1596, 116–125.
Mamo, J.C., Lam, V., Brook, E., Mooranian, A., Al-Salami, H., Fimognari, N., Nesbit, M., Takechi, R., 2019. Probucol prevents blood-brain barrier dysfunction and cognitive decline in mice maintained on pro-diabetic diet. Diab. Vasc. Dis. Res. 16, 87–97.
Mantych, G.J., James, D.E., Devaskar, S.U., 1993. Jejunal/kidney glucose transporter isoform (Glut-5) is expressed in the human blood-brain barrier. Endocrinology 132, 35–40.
McNay, E.C., Ong, C.T., McCrimmon, R.J., Cresswell, J., Bogan, J.S., Sherwin, R.S., 2010. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiol. Learn. Mem. 93, 546–553.
Meng, Q., Ying, Z., Noble, E., Zhao, Y., Agrawal, R., Mikhail, A., Zhuang, Y., Tyagi, E., Zhang, Q., Lee, J.H., Morselli, M., Orozco, L., Guo, W., Kilts, T.M., Zhu, J., Zhang, B., Pellegrini, M., Xiao, X., Young, M.F., Gomez-Pinilla, F., Yang, X., 2016. Systems nutrigenomics reveals brain gene networks linking metabolic and brain disorders. EBioMedicine 7, 157–166.
Meyers, A.M., Mourra, D., Beeler, J.A., 2017. High fructose corn syrup induces metabolic dysregulation and altered dopamine signaling in the absence of obesity. PLoS One 12, e0190206.
Miller, C.C., Martin, R.J., Whitney, M.L., Edwards, G.L., 2002. Intracerebroventricular injection of fructose stimulates feeding in rats. Nutr. Neurosci. 5, 359–362.
Mitra, A., Lenglos, C., Martin, J., Mbende, N., Gagné, A., Timofeeva, E., 2011. Sucrose modifies c-fos mRNA expression in the brain of rats maintained on feeding schedules. Neuroscience 192, 459–474.
Molteni, R., Barnard, R.J., Ying, Z., Roberts, C.K., Gomez-Pinilla, F., 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience 112, 803–814.
Nabil, M., El Demellawy, M.A., Mahmoud, M.F., Mahmoud, A.A.A., 2020. Prolonged overnutrition with fructose or fat induces metabolic derangements in rats by disrupting the crosstalk between the hypothalamus and periphery: possible amelioration with fenofibrate. Eur. J. Pharmacol. 879, 173136.
Noble, E.E., Hsu, T.M., Jones, R.B., Fodor, A.A., Goran, M.I., Kanoski, S.E., 2017. Early-life sugar consumption affects the rat microbiome independently of obesity. J. Nutr. 147, 20–28.
Noble, E.E., Hsu, T.M., Liang, J., Kanoski, S.E., 2019. Early-life sugar consumption has long-term negative effects on memory function in male rats. Nutr. Neurosci. 22, 273–283.
Noble, E.E., Olson, C.A., Davis, E., Tsan, L., Chen, Y.W., Schade, R., Liu, C., Suarez, A., Jones, R.B., de La Serre, C., Yang, X., Hsiao, E.Y., Kanoski, S.E., 2021. Gut microbial taxa elevated by dietary sugar disrupt memory function. Transl. Psychiatry 11, 194.
Ochoa, M., Malbert, C.H., Meurice, P., Val-Laillet, D., 2016. Effects of chronic consumption of sugar-enriched diets on brain metabolism and insulin sensitivity in adult yucatan minipigs. PLoS One 11 e0161228.
Oh, A.R., Sohn, S., Lee, J., Park, J.M., Nam, K.T., Hahm, K.B., Kim, Y.B., Lee, H.J., Cha, J. Y., 2018. ChREBP deficiency leads to diarrhea-predominant irritable bowel syndrome. Metabolism 85, 286–297.
Oldendorf, W.H., 1971. Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection. Am. J. Physiol. 221, 1629–1639.
Oppelt, S.A., Zhang, W., Tolan, D.R., 2017. Specific regions of the brain are capable of fructose metabolism. Brain Res. 1657, 312–322.
Page, K.A., Chan, O., Arora, J., Belfort-Deaguiar, R., Dzuira, J., Roehmholdt, B., Cline, G. W., Naik, S., Sinha, R., Constable, R.T., Sherwin, R.S., 2013. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 309, 63–70.
Park, T.J., Reznick, J., Peterson, B.L., Blass, G., Omerbasic, D., Bennett, N.C., Kuich, P., Zasada, C., Browe, B.M., Hamann, W., Applegate, D.T., Radke, M.H., Kosten, T., Lutermann, H., Gavaghan, V., Eigenbrod, O., Begay, V., Amoroso, V.G., Govind, V., Minshall, R.D., Smith, E.S.J., Larson, J., Gotthardt, M., Kempa, S., Lewin, G.R., 2017. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science 356, 307–311.
Parsons, M.P., Hirasawa, M., 2010. ATP-sensitive potassium channel-mediated lactate effect on orexin neurons: implications for brain energetics during arousal. J. Neurosci. 30, 8061–8070.
Payne, J., Maher, F., Simpson, I., Mattice, L., Davies, P., 1997. Glucose transporter Glut 5 expression in microglial cells. Glia 21, 327–331.
Pei, H., Sutton, A.K., Burnett, K.H., Fuller, P.M., Olson, D.P., 2014. AVP neurons in the paraventricular nucleus of the hypothalamus regulate feeding. Mol. Metab. 3, 209–215.
Pollock, N.K., Bundy, V., Kanto, W., Davis, C.L., Bernard, P.J., Zhu, H., Gutin, B., Dong, Y., 2012. Greater fructose consumption is associated with cardiometabolic risk markers and visceral adiposity in adolescents. J. Nutr. 142, 251–257.
Purnell, J.Q., Klopfenstein, B.A., Stevens, A.A., Havel, P.J., Adams, S.H., Dunn, T.N., Krisky, C., Rooney, W.D., 2011. Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. Diabetes Obes. Metab. 13, 229–234.
Ramos, V.W., Batista, L.O., Albuquerque, K.T., 2017. Effects of fructose consumption on food intake and biochemical and body parameters in Wistar rats. Rev. Port. Cardiol. 36, 937–941.
Rastedt, W., Blumrich, E.M., Dringen, R., 2017. Metabolism of mannose in cultured primary rat neurons. Neurochem. Res. 42, 2282–2293.
Reichelt, A.C., Killcross, S., Hambly, L.D., Morris, M.J., Westbrook, R.F., 2015. Impact of adolescent sucrose access on cognitive control, recognition memory, and parvalbumin immunoreactivity. Learn. Mem. 22, 215–224.
Rivera, D.S., Lindsay, C.B., Codocedo, J.F., Carreño, L.E., Cabrera, D., Arrese, M.A., Vio, C.P., Bozinovic, F., Inestrosa, N.C., 2018. Long-term, fructose-induced metabolic syndrome-like condition is associated with higher metabolism, reduced synaptic plasticity and cognitive impairment in octodon degus. Mol. Neurobiol. 55, 9169–9187.
Rojo, M.L., Cipriano, M., Soderstrom, I., Simonyte, K., Olsson, T., Fowler, C.J., 2014. Effects of dietary glucose and fructose upon cannabinoid CB1 receptor functionality in the rat brain: a pilot study. Life Sci. 108, 116–121.
Rorabaugh, J.M., Stratford, J.M., Zahniser, N.R., 2014. A relationship between reduced nucleus accumbens shell and enhanced lateral hypothalamic orexin neuronal activation in long-term fructose bingeing behavior. PLoS One 9 e95019.
Rorabaugh, J.M., Stratford, J.M., Zahniser, N.R., 2015. Differences in bingeing behavior and cocaine reward following intermittent access to sucrose, glucose or fructose solutions. Neuroscience 301, 213–220.
Sahota, A.K., Shapiro, W.L., Newton, K.P., Kim, S.T., Chung, J., Schwimmer, J.B., 2020. Incidence of nonalcoholic fatty liver disease in children: 2009-2018. Pediatrics 146, e20200771.
Samuel, V.T., 2011. Fructose induced lipogenesis: from sugar to fat to insulin resistance. Trends Endocrinol. Metab. 22, 60–65.
Sanguesa, G., Cascales, M., Grinan, C., Sanchez, R.M., Roglans, N., Pallas, M., Laguna, J. C., Alegret, M., 2018. Impairment of novel object recognition memory and brain insulin signaling in fructose- but not glucose-drinking female rats. Mol. Neurobiol. 55, 6984–6999.
Schwarz, J.M., Noworolski, S.M., Wen, M.J., Dyachenko, A., Prior, J.L., Weinberg, M.E., Herraiz, L.A., Tai, V.W., Bergeron, N., Bersot, T.P., Rao, M.N., Schambelan, M., Mulligan, K., 2015. Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. J. Clin. Endocrinol. Metab. 100, 2434–2442.
Schwarz, J.M., Noworolski, S.M., Erkin-Cakmak, A., Korn, N.J., Wen, M.J., Tai, V.W., Jones, G.M., Palii, S.P., Velasco-Alin, M., Pan, K., Patterson, B.W., Gugliucci, A., Lustig, R.H., Mulligan, K., 2017. Effects of dietary fructose restriction on liver fat, de novo lipogenesis, and insulin kinetics in children with obesity. Gastroenterology 153, 743–752.
Sclafani, A., Ackroff, K., 1994. Glucose- and fructose-conditioned flavor preferences in rats: taste versus postingestive conditioning. Physiol. Behav. 56, 399–405.
Seabrook, L.T., Borgland, S.L., 2020. The orbitofrontal cortex, food intake and obesity. J. Psychiatry Neurosci. 45, 304–312.
Shepherd, P.R., Gibbs, E.M., Wesslau, C., Gould, G.W., Kahn, B.B., 1992. Human small intestine facilitative fructose/glucose transporter (GLUT5) is also present in insulin-responsive tissues and brain. Investigation of biochemical characteristics and translocation. Diabetes 41, 1360–1365.
Shu, H.J., Isenberg, K., Cormier, R.J., Benz, A., Zorumski, C.F., 2006. Expression of fructose sensitive glucose transporter in the brains of fructose-fed rats. Neuroscience 140, 889–895.
Smith, S.M., 1988. High-fructose corn syrup replaces sugar in processed foods. Environ. Nutr. 11, 7–8.
Song, Z., Roncal-Jimenez, C.A., Lanaspa-Garcia, M.A., Oppelt, S.A., Kuwabara, M., Jensen, T., Milagres, T., Andres-Hernando, A., Ishimoto, T., Garcia, G.E., Johnson, G., MacLean, P.S., Sanchez-Lozada, L.G., Tolan, D.R., Johnson, R.J., 2017. Role of fructose and fructokinase in acute dehydration-induced vasopressin gene expression and secretion in mice. J. Neurophysiol. 117, 646–654.
Soto, M., Cai, W., Konishi, M., Kahn, C.R., 2019. Insulin signaling in the hippocampus and amygdala regulates metabolism and neurobehavior. Proc. Natl. Acad. Sci. U. S. A. 116, 6379–6384.
Stanhope, K.L., 2015. Sugar consumption, metabolic disease and obesity: the state of the controversy. Crit. Rev. Clin. Lab. Sci. 53, 1–16.
Stanhope, K.L., Schwarz, J.M., Keim, N.L., Griffen, S.C., Bremer, A.A., Graham, J.L., Hatcher, B., Cox, C.L., Dyachenko, A., Zhang, W., McGahan, J.P., Seibert, A., Krauss, R.M., Chiu, S., Schaefer, E.J., Ai, M., Otokozawa, S., Nakajima, K., Nakano, T., Beysen, C., Hellerstein, M.K., Berglund, L., Havel, P.J., 2009. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J. Clin. Invest. 119, 1322–1334.
Steenson, S., Shojaee-Moradie, F., B Whyte, M., G Jackson, K., Lovegrove, J.A., A Fielding, B., Umpleby, A.M., 2020. The effect of fructose feeding on intestinal triacylglycerol production and de novo fatty acid synthesis in humans. Nutrients 12, 1781.
Stevenson, R.J., Francis, H.M., 2017. The hippocampus and the regulation of human food intake. Psychol. Bull. 143, 1011–1032.
Stice, E., Yokum, S., Blum, K., Bohon, C., 2010. Weight gain is associated with reduced striatal response to palatable food. J. Neurosci. 30, 13105–13109.
Stolarczyk, E., Guissard, C., Michau, A., Even, P.C., Grosfeld, A., Serradas, P., Lorsignol, A., Pénicaud, L., Brot-Laroche, E., Leturque, A., Le Gall, M., 2010. Detection of extracellular glucose by GLUT2 contributes to hypothalamic control of food intake. Am. J. Physiol. Endocrinol. Metab. 298, 1078–1087.
Suga, A., Hirano, T., Kageyama, H., Osaka, T., Namba, Y., Tsuji, M., Miura, M., Adachi, M., Inoue, S., 2000. Effects of fructose and glucose on plasma leptin, insulin,

and insulin resistance in lean and VMH-lesioned obese rats. Am. J. Physiol. Endocrinol. Metab. 278, E677–683.
Sun, S.Z., Anderson, G.H., Flickinger, B.D., Williamson-Hughes, P.S., Empie, M.W., 2011. Fructose and non-fructose sugar intakes in the US population and their associations with indicators of metabolic syndrome. Food Chem. Toxicol. 49, 2875–2882.
Swanson, L.W., 1982. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull. 9, 321–353.
Sweeney, P., Yang, Y., 2015. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. Nat. Commun. 6, 10188.
Takechi, R., Lam, V., Brook, E., Giles, C., Fimognari, N., Mooranian, A., Al-Salami, H., Coulson, S.H., Nesbit, M., Mamo, J.C.L., 2017. Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: an implication for causal link. Front. Aging Neurosci. 9, 399.
Taskinen, M.R., Packard, C.J., Boren, J., 2019. Dietary fructose and the metabolic syndrome. Nutrients 11, 1987.
Tataranni, P.A., Gautier, J.F., Chen, K., Uecker, A., Bandy, D., Salbe, A.D., Pratley, R.E., Lawson, M., Reiman, E.M., Ravussin, E., 1999. Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. Proc. Natl. Acad. Sci. U. S. A. 96, 4569–4574.
Teff, K.L., Elliott, S.S., Tschöp, M., Kieffer, T.J., Rader, D., Heiman, M., Townsend, R.R., Keim, N.L., D'Alessio, D., Havel, P.J., 2004. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. J. Clin. Endocrinol. Metab. 89, 2963–2972.
Theytaz, F., de Giorgi, S., Hodson, L., Stefanoni, N., Rey, V., Schneiter, P., Giusti, V., Tappy, L., 2014. Metabolic fate of fructose ingested with and without glucose in a mixed meal. Nutrients 6, 2632–2649.
Thompson, J.L., Drysdale, M., Baimel, C., Kaur, M., MacGowan, T., Pitman, K.A., Borgland, S.L., 2017. Obesity-induced structural and neuronal plasticity in the lateral orbitofrontal cortex. Neuropsychopharmacology 42, 1480–1490.
Thorens, B., 2015. GLUT2, glucose sensing and glucose homeostasis. Diabetologia 58, 221–232.
Thurston, J.H., Levy, C.A., Warren, S.K., Jones, E.M., 1972. Permeability of the blood-brain barrier to fructose and the anaerobic use of fructose in the brains of young mice. J. Neurochem. 19, 1685–1696.
Tordoff, M.G., Rafka, R., DiNovi, M.J., Friedman, M.I., 1988. 2,5-anhydro-D-mannitol: a fructose analogue that increases food intake in rats. Am. J. Physiol. 254, 150–153.
Ueno, M., Nishi, N., Nakagawa, T., Chiba, Y., Tsukamoto, I., Kusaka, T., Miki, T., Sakamoto, H., Yamaguchi, F., Tokuda, M., 2014. Immunoreactivity of glucose transporter 5 is located in epithelial cells of the choroid plexus and ependymal cells. Neuroscience 260, 149–157.
van den Berghe, G., Bronfman, M., Vanneste, R., Hers, H.G., 1977. The mechanism of adenosine triphosphate depletion in the liver after a load of fructose. A kinetic study of liver adenylate deaminase. Biochem. J. 162, 601–609.
van Opstal, A.M., Hafkemeijer, A., van den Berg-Huysmans, A.A., Hoeksma, M., Mulder, T.P.J., Pijl, H., Rombouts, S., van der Grond, J., 2019a. Brain activity and connectivity changes in response to nutritive natural sugars, non-nutritive natural sugar replacements and artificial sweeteners. Nutr. Neurosci. 1–11.
van Opstal, A.M., Kaal, I., van den Berg-Huysmans, A.A., Hoeksma, M., Blonk, C., Pijl, H., Rombouts, S., van der Grond, J., 2019b. Dietary sugars and non-caloric sweeteners elicit different homeostatic and hedonic responses in the brain. Nutrition 60, 80–86.
Vannucci, S.J., Maher, F., Simpson, I.A., 1997. Glucose transporter proteins in brain: delivery of glucose to neurons and glia. Glia 21, 2–21.
Venner, A., Karnani, M.M., Gonzalez, J.A., Jensen, L.T., Fugger, L., Burdakov, D., 2011. Orexin neurons as conditional glucosensors: paradoxical regulation of sugar sensing by intracellular fuels. J. Physiol. 589, 5701–5708.
Volkow, N.D., Wise, R.A., 2005. How can drug addiction help us understand obesity? Nat. Neurosci. 8, 555–560.
Vos, M.B., Kimmons, J.E., Gillespie, C., Welsh, J., Blanck, H.M., 2008. Dietary fructose consumption among US children and adults: the third national health and nutrition examination survey. Medscape J. Med. 10, 160.
Wan, H.Z., Hulsey, M.G., Martin, R.J., 1998. Intracerebroventricular administration of antisense oligodeoxynucleotide against GLUT2 glucose transporter mRNA reduces food intake, body weight change and glucoprivic feeding response in rats. J. Nutr. 128, 287–291.
Wei, W., Pham, K., Gammons, J.W., Sutherland, D., Liu, Y., Smith, A., Kaczorowski, C.C., O'Connell, K.M., 2015. Diet composition, not calorie intake, rapidly alters intrinsic excitability of hypothalamic AgRP/NPY neurons in mice. Sci. Rep. 5, 16810.
Williams, R.H., Alexopoulos, H., Jensen, L.T., Fugger, L., Burdakov, D., 2008. Adaptive sugar sensors in hypothalamic feeding circuits. Proc. Natl. Acad. Sci. U. S. A. 105, 11975–11980.
Wolf, J.P., Nguyen, N.U., Dumoulin, G., Berthelay, S., 1992. Influence of hypertonic monosaccharide infusions on the release of plasma arginine vasopressin in normal humans. Horm. Metab. Res. 24, 379–383.
World Health Organization, 2015. Information Note About Intake of Sugars Recommended in the WHO Guideline for Adults and Children. WHO Press, Geneva, Switzerland.
Wray, H.L., Winegrad, A.I., 1966. Free fructose in human cerebrospinal fluid. Diabetologia 2, 82–85.
Wu, K.L., Wu, C.W., Tain, Y.L., Huang, L.T., Chao, Y.M., Hung, C.Y., Wu, J.C., Chen, S.R., Tsai, P.C., Chan, J.Y., 2016. Environmental stimulation rescues maternal high fructose intake-impaired learning and memory in female offspring: its correlation with redistribution of histone deacetylase 4. Neurobiol. Learn. Mem. 130, 105–117.
Xu, J., Begley, P., Church, S.J., Patassini, S., McHarg, S., Kureishy, N., Hollywood, K.A., Waldvogel, H.J., Liu, H., Zhang, S., 2016. Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia. Sci. Rep. 6, 1–12.
Yamada, H., Munetsuna, E., Yamazaki, M., Mizuno, G., Sadamoto, N., Ando, Y., Fujii, R., Shiogama, K., Ishikawa, H., Suzuki, K., Shimono, Y., Ohashi, K., Hashimoto, S., 2019. Maternal fructose-induced oxidative stress occurs. FASEB J. 33, 11431–11442.
Yamazaki, M., Yamada, H., Munetsuna, E., Ishikawa, H., Mizuno, G., Mukuda, T., Mouri, A., Nabeshima, T., Saito, K., Suzuki, K., Hashimoto, S., Ohashi, K., 2018. Excess maternal fructose consumption impairs hippocampal function in offspring via epigenetic modification of BDNF promoter. FASEB J. 32, 2549–2562.
Yang, Y., Atasoy, D., Su, H.H., Sternson, S.M., 2011. Hunger states switch a flip-flop memory circuit via a synaptic AMPK-dependent positive feedback loop. Cell 146, 992–1003.
Yang, Y., Shields, G.S., Guo, C., Liu, Y., 2018. Executive function performance in obesity and overweight individuals: a meta-analysis and review. Neurosci. Biobehav. Rev. 84, 225–244.
Yin, Q., Ma, Y., Hong, Y., Hou, X., Chen, J., Shen, C., Sun, M., Shang, Y., Dong, S., Zeng, Z., Pei, J.J., Liu, X., 2014. Lycopene attenuates insulin signaling deficits, oxidative stress, neuroinflammation, and cognitive impairment in fructose-drinking insulin resistant rats. Neuropharmacology 86, 389–396.
Younossi, Z.M., Koenig, A.B., Abdelatif, D., Fazel, Y., Henry, L., Wymer, M., 2016. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64, 73–84.
Zubiria, M.G., Farina, J.P., Moreno, G., Gagliardino, J.J., Spinedi, E., Giovambattista, A., 2013. Excess fructose intake-induced hypertrophic visceral adipose tissue results from unbalanced precursor cell adipogenic signals. FEBS J. 280, 5864–5874.