Brain, hormone and appetite responses to glucose versus fructose
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Emerging data suggest that the monosaccharides, glucose and fructose, have disparate effects on the neuroendocrine circuits involved in appetite and reward processing. Compared to glucose, fructose ingestion results in smaller increases in circulating levels of insulin, leptin, and glucagon-like polypeptide-1, hormones that increase satiety. The central administration of fructose was shown to decrease hypothalamic satiety signaling and increase feeding in animals, whereas glucose increased satiety signaling and reduced food intake. Likewise, studies show that the hypothalamus responds differently to fructose versus glucose ingestion in humans. Moreover, fructose compared to glucose results in greater food-cue reactivity within brain reward regions and increases the motivation for food rewards. These findings provide insights into how neuroendocrine responses to specific carbohydrates may influence eating behavior.

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Fructose versus glucose: what’s the difference?
Fructose and glucose are both monosaccharides with the same number of calories and the same chemical formula (C₆H₁₂O₆), but they are absorbed and metabolized differently by the body. Fructose possesses a keto group in position 2 of its carbon chain, while glucose has an aldehyde group at position 1 of its carbon chain [5]. Fructose has a sweet taste intensity profile that reaches a larger peak and diminishes more quickly than glucose [13]. While glucose is the main circulating sugar in the bloodstream and the main fuel source for the brain, the majority of fructose is extracted from the bloodstream into the liver [5,14]. Glucose is absorbed by a sodium-coupled co-transporter and arrives at the liver via portal circulation. In contrast, fructose absorption occurs via a non-sodium-dependent process, and fructose transport through enterocytes to the portal circulation occurs through a specific fructose transporter, GLUT5 [14].

In the glycolytic pathway, glucose metabolism is tightly regulated through feedback inhibition by the end products, ATP and citrate. In contrast, fructose metabolism is unregulated because fructose bypasses the main regulatory step in glycolysis, catalyzed by phosphofructokinase [5,14]. Fructose and glucose have different effects on hormones involved in the regulation of feeding behavior. Unlike glucose, fructose does not stimulate the secretion of insulin, a hormone that increases central satiety signaling and reduces hedonic feeding behavior [15–18]. The inability of fructose to directly stimulate insulin secretion is most likely due to the low level of expression of GLUT5 fructose transporter on pancreatic beta cells [19]. Fructose compared to glucose consumption also results in decreased circulating levels of leptin, a hormone produced by adipocytes that serves as a key signal to the brain to decrease appetite and to increase energy expenditure.
Some studies indicate that fructose relative to glucose ingestion results in differential effects on gut hormones involved in satiety signaling, including a smaller reduction in the hunger-stimulating hormone, ghrelin [20], and smaller increases in the appetite suppressing hormone, glucagon-like polypeptide-1 [10**,22,23]. These unique properties of fructose compared to glucose may help explain their differential effects on brain pathways involved in the regulation of appetite (Figure 1). Studies in animal models have shown that glucose and fructose have opposing effects on satiety signaling within the hypothalamus. Glucose metabolism in the hypothalamus results in an increase in levels of ATP and malonyl coenzyme A (CoA), an important signal of satiety, whereas centrally administered fructose results in a reduction of ATP and malonyl CoA levels and an increase in food intake [7]. Advancements in neuroimaging technology have facilitated the translation of these important findings in animals into studies in humans.

**Use of functional magnetic resonance imaging (fMRI) to examine brain responses to glucose and fructose**

**fMRI studies on effects of glucose on the hypothalamus**

In studies of CNS appetite regulation, a common paradigm is to investigate brain activation before and after the ingestion of a standardized glucose solution. Neural activation can be indirectly measured through the use of fMRI, which is based on the blood oxygen level-dependent (BOLD) signal [24]. BOLD fMRI uses hemoglobin

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**Figure 1**

Differential central and peripheral responses to administration of glucose and fructose. Fructose is sweeter than glucose [13] (a). In liver cells, hepatic extraction of glucose is limited by the liver’s ability to store glycogen and by allosteric inhibition of phosphofructokinase by citrate and ATP, in contrast, fructose has a near complete hepatic extraction in the liver [5,14] (b). Glucose is easily absorbed into the blood following acute administration and is the main sugar circulating in the bloodstream, whereas only small amounts of fructose are found in the bloodstream [5] (c). Glucose enters pancreatic β-cells through GLUT2 transporters stimulating insulin secretion, whereas β-cells lack fructose specific transporters so fructose is unable to directly stimulate insulin secretion [19] (d). Consumption of fructose leads to reduced post-prandial leptin secretion from adipose tissues when compared to glucose [20] (e). When compared to ingestion of glucose, fructose ingestion results in less of a rise in the anorexigenic hormone, glucagon-like-1 polypeptide (GLP-1) in the small intestine [10**,22,23] (f). Acute ingestion of glucose leads to reductions in resting cerebral blood flow in the hypothalamus that are not seen following fructose ingestion [10**] (g). Glucose metabolism in the hypothalamus reduces appetite and food intake in animals, whereas fructose metabolism may stimulate appetite and intake [6,7,9] (h). Fructose relative to glucose consumption increases brain response in the orbital frontal cortex (OFC) and ventral striatum in response to food cues [11**] (i).
as an endogenous contrast agent because the magnetization of hemoglobin differs between oxy-hemoglobin and deoxyhemoglobin [25]. In response to neuronal firing, there is an increase in oxygen consumption by the tissue, which is accompanied by a local increase in cerebral blood flow (CBF). The increase in CBF exceeds the increase in oxygen consumption, which leads to a reduction in deoxyhemoglobin and, in turn, an increase in BOLD signal.

Typically, a 75-gram oral glucose load has been used to study brain responses to glucose because this dose reliably increases circulating levels of glucose, insulin and glucagon-like polypeptide-1, and the response to it provides a well-validated estimate of insulin sensitivity [26]. Moreover, it is the dose commonly used in oral glucose tolerance testing for the diagnosis of diabetes. Determining the brain’s response to the ingestion of a standardized glucose load provides important information about brain pathways that regulate energy homeostasis and can offer new insights into how these pathways are affected by metabolic disorders, such as obesity, insulin resistance and diabetes.

The hypothalamus is the dominant brain region responsible for sensing and integrating responses to changes in circulating glucose levels [27,28]. Thus, early fMRI studies were directed at understanding how the hypothalamus responds to an oral glucose load [29–31]. Functional scans were performed using BOLD imaging on a midsagittal section of the hypothalamus before and after the ingestion of a drink containing 75 g of glucose. Studies have consistently reported a reduction in hypothalamic BOLD signal following acute glucose ingestion in normal-weight volunteers. The hypothalamic response was found to be dose dependent, such that a 75 g glucose load resulted in a larger signal decrease than a 25 g glucose load [31]. Earlier studies [29,30] suggested that the hypothalamic response to glucose ingestion was transient, with BOLD signal changes occurring within 4 minutes and returning to baseline within 15 minutes. However, subsequent studies have shown that glucose ingestion results in a more prolonged reduction in BOLD signal lasting at least 30 minutes post-ingestion [31–33].

In addition to characterizing the hypothalamic response to oral glucose administration in lean individuals, studies have also examined potential abnormalities in individuals with obesity and type 2 diabetes [29,30,34]. Prior work indicates that the reduction in hypothalamic MRI signal in response to glucose ingestion is attenuated and delayed in obese individuals [29,30] and absent in patients with type 2 diabetes [34] suggesting that obesity and type 2 diabetes are associated with aberrant hypothalamic processing of nutrient signals. Notably, subsequent studies suggest that the abnormal hypothalamic response to glucose ingestion in these populations may be reversible [35,36]. Obese individuals who achieved significant weight loss approximately 8 months after roux-in-Y gastric bypass surgery were found to re-establish the hypothalamic response to glucose ingestion, similar to the hypothalamic response observed in lean individuals [35]. Likewise, Teeuwisse and colleagues showed that in men with well-controlled type 2 diabetes, a four-day very low-calorie diet restored the ‘normal’ hypothalamic inhibitory response to glucose ingestion. The investigators interpreted this finding to suggest that caloric restriction may recover the sensitivity of glucose-sensitive neurons in type 2 diabetes [36].

The mechanisms by which glucose administration modulates hypothalamic activity could include a direct effect of glucose on hypothalamic glucose sensing neurons and/or indirect effects via glucose sensitive neural or endocrine signaling pathways. Studies have shown that the time taken to reach the maximum hypothalamic inhibitory response to glucose ingestion correlated with fasting plasma glucose and insulin concentrations suggesting that circulating glucose and insulin levels play an important role in mediating the hypothalamic response to glucose [29,30]. The non-nutritive sweetener, aspartame, was found to have no effect on hypothalamic activity in healthy, lean men suggesting that sweet taste in the absence of nutrient content is insufficient to modulate hypothalamic activity [32].

The hypothalamic inhibitory response appears to be more robust to oral glucose in its monomeric form based on the findings that both intravenous glucose [33,37], and the glucose polymer, maltodextrin, elicited an attenuated hypothalamic response compared to ingestion of glucose in its monomeric form [32,33,37]. Intravenous glucose is different from oral glucose in that it fails to stimulate taste receptors, and it does not stimulate the release of gut peptides. The importance of gastrointestinal signals in mediating the hypothalamic response to glucose is suggested by a recent study showing that intragastric glucose administration, which resulted in an increase in the release of the gastrointestinal hormone, GLP-1, led to significant decreases in BOLD signal in the hypothalamus [38]. Moreover, fMRI studies have consistently shown that gut hormones play an important role in modulating activity in brain reward and appetite centers [39–41].

Studies have also shown that a reduction in circulating glucose levels, accomplished by infusing a constant dose of insulin along with variable amounts of glucose, results in activation of the hypothalamus [28,42,43]. It is notable that hypothalamic activation occurs even with small reductions in circulating glucose, to levels commonly observed several hours after glucose ingestion [28,43], emphasizing the exquisite sensitivity of the hypothalamus to small changes in glucose levels. These findings
provide support for the important role of the hypothalamus in glucose regulation.

Looking beyond the hypothalamus: fMRI studies on effects of glucose on hedonic and cortical regions

Recent fMRI studies have probed the effects of glucose on hedonic and prefrontal cognitive control regions by using fMRI paradigms in which comparisons are made between brain responses to pictures of highly palatable foods compared to non-food items after glucose administration [11**,**43,**44,**45**,**46]. One study used a stepped hyperinsulinemic, euglycemic–hypoglycemic clamp technique to isolate the effect of circulating glucose levels on brain and appetitive responses to food cues [43]. Under euglycemic conditions (plasma glucose ~90 mg/dl) compared to mild hypoglycemic conditions (plasma glucose ~65 mg/dl), normal-weight individuals demonstrated increased food-cue reactivity in the prefrontal cortex and reported a decreased wanting of food. In contrast, when glucose levels dropped below normal, the participants demonstrated widespread activation of striatal and limbic regions, and they reported a greater wanting of food. Interestingly, obese individuals lacked the prefrontal cortical activation to food cues observed in normal-weight individuals under euglycemic conditions. These findings suggest that circulating glucose levels modulate neural stimulatory and inhibitory control over appetitive responses and suggest that obesity may be associated with a loss of the glucose-linked prefrontal inhibitory response to food cues [43].

Several studies have used a standardized 75-gram oral glucose load to evaluate effects of glucose ingestion on brain and appetite responses to food cues. Kroemer and colleagues compared food cue reactivity before and after glucose ingestion [44]. They found that glucose ingestion resulted in decreased food cue reactivity in the basal ganglia and paralimbic regions and increased food cue reactivity in parietal and occipital regions in normal-weight volunteers. While this study did not include a water control session, they found that increases in plasma insulin levels following glucose ingestion were correlated with reduced food-cue reactivity in cortical-limbic regions and decreased ratings of appetite. Another recent study investigated the effects of glucose versus water ingestion on brain responses to food cues [45**]. This study did not find a main effect of condition (i.e. glucose vs. water) on food cue reactivity among 12 lean and 12 overweight participants, but they did observe significant relationships between brain responses to food cues and circulating levels of insulin and glucose following glucose administration. The hypothalamic response to high-calorie food cues was negatively correlated with plasma glucose levels 30 minutes after glucose ingestion, and prefrontal activation was negatively correlated with plasma insulin levels 120 minutes after glucose ingestion, after adjusting for BMI [45**]. A study in women with polycystic ovary syndrome (PCOS) found that glucose vs. water ingestion resulted in significant reductions in brain activation to food cues within cortical and limbic regions among insulin sensitive but not insulin resistant women with PCOS [46]. Thus, existing fMRI data support an important role of circulating glucose and insulin levels in modulating brain responses to food cues after glucose administration, and emerging evidence suggests that insulin sensitivity significantly affects neural food reward processing [11**,**43,**44,**45**,**46–**50].

Neuroimaging studies comparing effects of fructose and glucose on brain appetite and reward pathways

Recent studies have used neuroimaging techniques to compare brain responses to the ingestion of glucose and fructose. Arterial spin labeling (ASL) is a MRI technique for measuring cerebral blood flow (CBF), and it uses magnetically labeled arterial blood water protons as an endogenous tracer [51]. ASL offers some advantages over the more traditional fMRI-BOLD method in studies aimed at examining brain responses to slow processes such as appetite and reward signaling that occur over minutes or across test sessions. Stimulus dependent BOLD signal changes are expressed as a percent signal change and are not directly quantifiable in physiological units, whereas ASL provides a way to quantitatively measure CBF in tissue specific units of ml/g per minute [51]. Moreover, the use of ASL to measure resting state CBF may help in the interpretation of the BOLD signal change. Another newer imaging method, resting state fMRI (RS-fMRI), provides a way to identify resting state brain networks or spatially distinct regions of the brain that demonstrate synchronous BOLD fluctuations in the absence of a task or stimulus [52].

The first study to examine differential brain responses to the ingestion of fructose versus glucose used a combination of ASL and rs-fMRI methods to investigate the effects of ingestion of 300 ml drinks containing 75 g of fructose compared to 75 g of glucose on brain appetite and reward pathways in 20 normal-weight adults. Glucose but not fructose ingestion reduced CBF in the hypothalamus, insula and striatum. Glucose but not fructose also increased functional connections between the hypothalamic-striatal network and increased satiety [10**]. Higher plasma insulin levels correlated with reduced striatal CBF following glucose but not fructose ingestion, supporting the important role of circulating insulin levels on the regulation of brain activity. Another group used RS-fMRI to explore functional connectivity strengths within the basal ganglia/limbic network in 12 healthy lean males after intragastric administration of 300 ml of water containing 75 g of glucose versus 25 g of fructose [12**]. Glucose administration resulted in increased resting state functional connectivity of the caudate, putamen, precuneus and lingual gyrus relative to fructose. In contrast,
fructose relative to glucose increased functional connectivity of the amygdala, hippocampus, OFC and precentral gyrus to the basal ganglia/limbic network. Increases in resting state functional connectivity after glucose correlated with the glucose-induced increase in insulin levels, consistent with a role of circulating levels of insulin on brain networks involved in the regulation of food intake [12**]. Together these studies suggest that fructose and glucose have differential effects on resting-state activity within brain appetite and reward pathways. In contrast to these results, one prior fMRI study performed in nine normal-weight participants using fMRI-BOLD did not detect significant changes in hypothalamic activity during intravenous administration of either glucose or fructose [37], potentially due to the small sample size or the mode of delivery since oral glucose intake has been shown to inhibit hypothalamic activity more effectively than intravenous glucose administration [33].

More recently, task-based fMRI-BOLD was coupled with a behavioral decision making task to determine the effects of fructose versus glucose ingestion on food-cue reactivity within reward-related brain regions and food approach behavior [11**]. Twenty-four healthy volunteers underwent two fMRI sessions with ingestion of 300 ml of water and either 75 g of fructose or 75 g of glucose in a randomized crossover design. fMRI was performed while participants viewed blocks of pictures of high-caloric foods and non-food items and rated their hunger and desire for foods. Participants also performed a decision task in which they chose between immediate food rewards versus delayed monetary bonuses. Ingestion of fructose relative to glucose resulted in greater brain reactivity to food cues in the visual cortex, OFC and ventral striatum. Fructose relative to glucose ingestion also led to greater hunger and desire for food and a greater willingness to give up long-term monetary rewards to obtain immediate high calorie food rewards [11**]. This work suggests that the acute ingestion of fructose compared to glucose leads to greater food-cue reactivity within brain regions involved in reward processing and a greater motivation to obtain highly palatable foods. How resting state CBF responses to fructose versus glucose influence food-cue task based changes in BOLD signal is not yet known. Future studies that utilize multimodal imaging, including ASL, RS-fMRI and food-cue task based BOLD methodologies could help to address this question.

Collectively, these recent studies provide potential insights into epidemiological evidence linking fructose consumption to overeating behavior. However, future work is necessary to determine the long-term effects of chronic high fructose intake on neuroendocrine pathways involved in the regulation of eating behavior, and the effects of obesity and other metabolic conditions on these responses. In addition, future studies are needed to determine neuroendocrine and appetitive responses to different doses of fructose and glucose and to combinations of fructose and glucose, as they are commonly consumed in the real world.

Conflict of interest
Nothing declared.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as: • of outstanding interest
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11. Luo S, Monterosso JR, Sarpelli K, Page KA: Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards. Proc Natl Acad Sci 2015, 112:6509-6514. This fMRI study showed that the ingestion of fructose relative to glucose resulted in greater brain reward and appetitive responses to food cues and a greater willingness to forgo delayed monetary rewards to obtain immediate food rewards.
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Using resting state fMRI this study showed that resting state connectivity is differentially regulated by fructose compared to glucose within basal ganglia and limbic networks.


Findings from this study support the role of increases in plasma insulin levels in response to glucose ingestion in modulating prefatorial activation to food cues, and suggest a contribution of circulating hormones in the regulation of appetite.


