Neuroendocrine Control of Carbohydrate Metabolism

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Abstract

The neuroendocrine control of metabolism is of paramount importance for life. The control over appetite and satiety are very important for the brain to sustain homeostasis of the body, its weight, and the metabolic processes within. In the past, not so much attention was payed towards separate control systems in the brain that selectively control uptake and metabolism of the main constituents of food, namely, proteins, carbohydrates, and fat.

This chapter tries to address the complex systems that control metabolism of especially carbohydrates, including the effects of carbohydrate intake on the brain.

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Introduction

In the Western world, consumption of soft drinks has increased the last three decades and is partly responsible for the epidemic-like increase in obesity. Soft drinks, originally sweetened by sucrose, are now sweetened by other caloric sweeteners, such as fructose. In a study by Lindqvist et al., they investigated the short-term effect of sucrose, glucose, or fructose solutions on food intake and body weight in rats, and on peripheral and central appetite signals (Lindqvist et al. 2008). All rats offered the sugar solutions increased their total caloric intake. The increased caloric intake occurred even though the rats offered either of the sugar solutions consumed less chow. Because of the increased caloric intake, the sugar-drinking rats had elevated serum levels of free fatty acids, triglycerides, and cholesterol (Lindqvist et al. 2008).

Stanhope and coworkers also addressed these effects of high sugar intake (Stanhope et al. 2008). High-fructose corn syrup (HFCS) has replaced sucrose as the predominant sweetener in beverages. They compared the metabolic/endocrine effects of HFCS with sucrose and, in a subset of subjects, with pure fructose and glucose by studying 34 men and women who consumed three isocaloric meals with either sucrose- or HFCS-sweetened beverages (Stanhope et al. 2008). Eight of the male subjects were also studied when fructose- or glucose-sweetened beverages were consumed. Unexpectedly, postprandial triglycerides (TG) profiles after HFCS or sucrose were not intermediate but comparably high as after pure fructose (Stanhope et al. 2008). Apparently, short-term consumption of sucrose and HFCS results in postprandial TG responses comparable to those induced by fructose (Stanhope et al. 2008).

Nonalcoholic fatty liver disease (NAFLD) is the most frequent liver disease worldwide and is commonly associated with the metabolic syndrome. Secular trends in the prevalence of these diseases may be associated with the increased fructose consumption observed in the Western diet. NAFLD is characterized by two steps of liver injury: intrahepatic lipid accumulation (hepatic steatosis) and inflammatory progression to nonalcoholic steatohepatitis (NASH) (the "two-hit" theory) (Lim et al. 2010). Diet is an important contributor to the pathogenesis of NAFLD. In a recent review by de Wit et al., they focused on recent publications reporting on the effect of macro- and micronutrients on development and progression of NAFLD (de Wit et al. 2012). In general, saturated fat and fructose seem to stimulate hepatic lipid accumulation and progression into NASH, whereas unsaturated fat, choline, antioxidants, and high-protein diets rich in isoflavones seem to have a more preventive effect. In two recent and very informative reviews, the link between simple sugar intake and fatty liver disease has been further addressed. In the first "hit," hepatic metabolism of fructose promotes de novo lipogenesis and intrahepatic lipid, inhibition of mitochondrial beta-oxidation of long-chain fatty acids, triglyceride formation and steatosis, hepatic and skeletal muscle insulin resistance, and hyperglycemia (Lim et al. 2010). In the second "hit," owing to the molecular instability of its

five-membered furanose ring, fructose promotes protein fructosylation and formation of reactive oxygen species (ROS), which require quenching by hepatic antioxidants (Lim et al. 2010). Many patients with NASH also have micronutrient deficiencies and do not have enough antioxidant capacity to prevent synthesis of ROS, resulting in necroinflammation (Lim et al. 2010). Lim et al. postulated that excessive dietary fructose consumption may underlie the development of NAFLD and the metabolic syndrome (Lim et al. 2010). Furthermore, they also stated that NAFLD and alcoholic fatty liver disease share the same pathogenesis (Lim et al. 2010).

Yki-Jarvinen also concluded in her review that cross-sectional increased intake of fructose and simple sugars characterizes patients with NAFLD compared with weight-matched controls (Yki-Jarvinen 2010). Increased fructose intake is also associated with hepatic insulin resistance and fibrosis severity in non-alcoholic steatosis hepatis (NASH) (Tappy et al. 1986). Intake of saturated fat may also be increased in NAFLD (Yki-Jarvinen 2010). Dietary intervention studies have shown that liver volume and fat content changes significantly within a few days in response to caloric restriction or excess despite no or small changes in body weight (Tappy et al. 1986). Therefore, maintenance of normal body weight and avoidance of intake of excess lipogenic simple sugars would seem beneficial for prevention of NAFLD and its metabolic consequences (Tappy et al. 1986).

How Objective Are the Studies that Report on the Link Between Carbohydrate Intake and Diabetes and Obesity?

The outcomes of recent regulatory initiatives, tax measures, and federal nutritional guidance designed to curb consumption of sugar-sweetened beverages (SSBs) have hinged on whether these beverages are a proven cause of obesity and diabetes (Schillinger et al. 2016). The SSB industry has opposed such initiatives, claiming that causation is scientifically controversial. Schillinger et al. comprehensively surveyed the literature to determine whether experimental studies that found no association between SSBs and obesity- and diabetes-related outcomes (negative studies) are more likely than positive studies to have received financial support from this industry (Schillinger et al. 2016). They searched PubMed from January 2001 to July 2016 for English-language experimental studies on the effects of SSB consumption on obesity- and diabetes-related outcomes, augmented by hand-searching recent reviews (Schillinger et al. 2016). They classified articles as having positive or negative associations versus no associations. They also identified whether articles were independently funded or were funded by, or had authors with financial conflicts with, the SSB industry (Schillinger et al. 2016). They identified 60 studies (28 trials and 32 systematic reviews/meta-analyses of trials) that examined the effects of SSB consumption on obesity- and diabetes-related outcomes. Twenty-six articles (8 trials and 18 systematic reviews/meta-analyses) described no associations, and 34 articles (20 trials and 14 systematic reviews/meta-analyses) described positive associations (Schillinger et al. 2016). Studies funded by the SSB industry were significantly more likely to find no associations than independently funded ones; 26 of 26 negative

studies (100%) had funding ties to this industry, whereas only 1 of 34 positive studies (2.9%) had such ties (Schillinger et al. 2016). Apparently, experimental studies that have financial conflicts with the SSB industry are much more likely than independently funded ones to find no relationship between SSB consumption and metabolic outcomes (Schillinger et al. 2016). The SSB industry seems to be manipulating contemporary scientific processes to create controversy and advance their business interests at the expense of the public's health (Schillinger et al. 2016).

Food Addiction

"Food addiction" has become a focus of interest for researchers attempting to explain certain processes and/or behaviors that may contribute to the development of obesity (Hebebrand et al. 2014). Although the scientific discussion on "food addiction" is in its nascent stage, it has potentially important implications for treatment and prevention strategies (Hebebrand et al. 2014). As such, it is important to critically reflect on the appropriateness of the term "food addiction," which combines the concepts of "substance-based" and behavioral addiction. The currently available evidence for a substance-based food addiction is poor, partly because systematic clinical and translational studies are still at an early stage (Hebebrand et al. 2014). Hebebrand et al. do, however, view both animal and existing human data as consistent with the existence of addictive eating behavior (Hebebrand et al. 2014). Accordingly, they stress that like other behaviors, eating can become an addiction in thus predisposed individuals under specific environmental circumstances (Hebebrand et al. 2014). In a review, they introduced diagnostic and neurobiological concepts of substance-related and non-substance-related addictive disorders and highlight the similarities and dissimilarities between addiction and overeating (Hebebrand et al. 2014). Via that review process, they concluded that "food addiction" is a misnomer because of the ambiguous connotation of a substance-related phenomenon (Hebebrand et al. 2014). They instead proposed the term "eating addiction" to underscore the behavioral addiction to eating (Hebebrand et al. 2014).

The Hedonic Rewards System

The learning function is mediated by neuronal reward prediction error signals which implement basic constructs of reinforcement learning theory (Schultz 2015). These signals are found in dopamine neurons, which emit a global reward signal to striatum and frontal cortex, and in specific neurons in striatum, amygdala, and frontal cortex projecting to select neuronal populations. The approach and choice functions involve subjective value, which is objectively assessed by behavioral choices eliciting internal, subjective reward preferences (Schultz 2015). Although all reward, reinforcement, and decision variables are theoretical constructs, their neuronal signals constitute measurable physical implementations and as such confirm the validity of these concepts. The neuronal reward signals provide guidance for

behavior while constraining the free will to act (Schultz 2015). The brain responds to macronutrients via intricate mechanisms. Tulloch et al. reviewed how the brain's neural systems implicated in homeostatic control of feeding and hedonic responses are influenced by the ingestion of specific types of food (Tulloch et al. 2015).

Obesity and substance abuse during adolescence have reached epidemic proportions, and both are among the leading major public health problems in the United States. There is a significant amount of weight and BMI gain in adolescent ex-addicts during supervised and confirmed abstinence from drugs and alcohol (Hodgkins et al. 2007).

Xue et al. focused on recent findings elucidating nutrient-related epigenetic changes linked to obesity (Xue and Ideraabdullah 2016). They highlighted studies demonstrating that obesity is a complex disease linked to disruption of epigenetically regulated metabolic pathways in the brain, adipose tissue, and liver. According to Xue, these pathways regulate (1) homeostatic and hedonic eating behaviors, (2) adipocyte differentiation and fat accumulation, and (3) energy expenditure (Xue and Ideraabdullah 2016). By compiling these data, they illustrated that obesity-related phenotypes are repeatedly linked to disruption of critical epigenetic mechanisms that regulate key metabolic genes.

The sensory experience of eating is an important determinant of food intake control, often attributed to the positive hedonic response associated with certain sensory cues (McCrickerd and Forde 2016). However, palatability is just one aspect of the sensory experience. Sensory cues based on a food's sight, smell, taste, and texture are operational before, during, and after an eating event (McCrickerd and Forde 2016). McCrickerd and coworkers considered the role of visual and odor cues in identifying food in the near environment, guiding food choice and memory for eating, and highlight the ways in which tastes and textures influence meal size and the development of satiety after consumption (McCrickerd and Forde 2016).

Carbohydrate intake is regulated by metabolic, neuronal, and hedonic factors, and gene polymorphisms are involved in determining sugar preference (Leturque et al. 2012). Genetic diseases linked to mutations in the disaccharidase genes (sucrase-isomaltase, lactase) and in sugar transporter genes (sodium/glucose cotransporter 1, glucose transporters 1 and 2) severely impact carbohydrate intake (Leturque et al. 2012). These diseases are revealed upon exposure to food containing the offending sugar, and withdrawal of this sugar from the diet prevents disease symptoms, failure to thrive, and premature death (Leturque et al. 2012).

Ventura et al. conducted a review of the neurobiologic basis for carbohydrate craving (Ventura et al. 2014). They reported that research on the basis of carbohydrate craving is varied but may be grouped into five main areas: the serotonergic system, palatability and hedonic response, the motivational system, stress response systems, and gene-environment interaction (Ventura et al. 2014).

A primary behavioral pathology in addiction is the overpowering motivational strength and decreased ability to control the desire to obtain, e.g., carbohydrates (Kalivas and Volkow 2005). While dopamine is critical for acute reward and initiation of addiction, end-stage addiction results primarily from cellular adaptations in anterior cingulate and orbitofrontal glutamatergic projections to the nucleus

accumbens (Kalivas and Volkow 2005). Mainly cellular adaptations in prefrontal glutamatergic innervation of the accumbens promote the compulsive character of seeking in addicts by decreasing the value of natural rewards, diminishing cognitive control (choice), and enhancing glutamatergic drive in response to drug-associated stimuli (Kalivas and Volkow 2005).

There is increasing evidence that the pathological overeating underlying some forms of obesity is compulsive in nature and therefore contains elements of an addictive disorder (Brown et al. 2015). Brown et al. sought to establish whether the propensity to diet-induced obesity (DIO) is associated with addictive-like behavior, as well as synaptic impairments in the nucleus accumbens core considered hallmarks of addiction in rats (Brown et al. 2015). They found that propensity to develop DIO is linked to deficits in the ability to induce long-term depression in the nucleus accumbens, as well as increased potentiation at these synapses as measured by AMPA/*N*-methyl-D-aspartate currents (Brown et al. 2015). Their results show overlap between the propensity for DIO and the synaptic changes associated with facets of addictive behavior, supporting partial coincident neurological underpinnings for compulsive overeating and drug addiction (Brown et al. 2015).

High-Carbohydrate Diets and the Hedonic System

In Fig. 1, the three most important regulators of food intake are depicted, the homeostatic system with its main physiological messengers, the psychological factor, and hedonic factors that all together determine what somebody eats, or wants to eat. High-carbohydrate meal or a glucose injection increases NPY mRNA in the ARC of rats, as

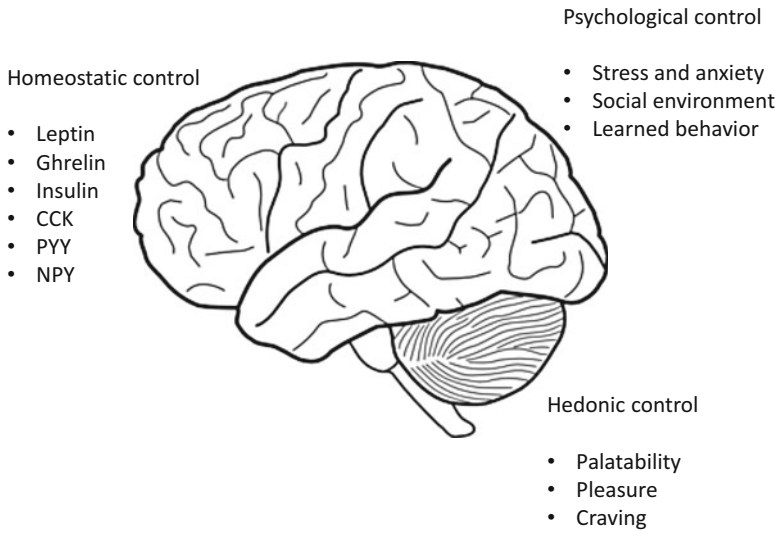

Fig. 1 The multiple factors that regulate food intake

well as levels of NPY protein in the ARC and PVN, compared with either a diet high in fat or a moderate-carbohydrate diet (Tulloch et al. 2015; Wang et al. 1999). Prior studies have demonstrated that chronic consumption over several weeks of a high-carbohydrate (65%) diet, compared to a moderate-carbohydrate (45%) or low-carbohydrate (15%) diet, potentiates the expression, synthesis, and release of hypothalamic NPY. This effect occurs specifically in neurons of the arcuate nucleus (ARC) which project to the paraventricular nucleus (PVN). After a high-carbohydrate meal compared to a moderate-carbohydrate or high-fat meal, NPY gene expression examined via in situ hybridization is found to be significantly enhanced in the ARC (Wang et al. 1999). After a high-carbohydrate meal, levels of glucose, together with corticosterone and insulin, are significantly elevated, while nonesterified fatty acids are reduced (Wang et al. 1999). A possible effect of circulating glucose on hypothalamic NPY is further suggested by the finding that the consumption or a single injection of a glucose solution at the onset of the feeding cycle similarly elevates NPY mRNA and peptide immunoreactivity in the ARC and PVN (Wang et al. 1999). The results of Wang et al. demonstrate that hypothalamic NPY can change rapidly in response to dietary carbohydrate (Wang et al. 1999).

Hajnal showed that the effects of sucrose on brain reward circuitry indicate that sweet taste has a role in hedonic-based eating. Sucrose licking increases release of dopamine in the nucleus accumbens (Hajnal and Norgren 2001).

Tulloch et al. in their review mentioned several studies that investigated the effects of carbohydrate intake on brain responses in humans (Tulloch et al. 2015). Carbohydrate intake appears to decrease the activation and cerebral blood flow of hypothalamic regions in healthy adults, while increasing the activation of regions associated with reward and motivation (Stice et al. 2013). Fat caused greater activation of the caudate and oral somatosensory regions than did sugar, while sugar caused greater activation in the putamen and gustatory regions than did fat (Stice et al. 2013). Increasing sugar intake caused greater activity in gustatory regions, while increasing fat did not affect the activation (Stice et al. 2013). The results of Stice et al. imply that sugar more effectively recruits reward and gustatory regions, suggesting that policy, prevention, and treatment interventions should prioritize reductions in sugar intake (Stice et al. 2013).

So carbohydrates appear to excite reward-associated regions and can have an acute inhibitory effect in hypothalamic regions associated with appetite. However, studies did produce mixed findings, perhaps due to differences in procedural and outcomes measures (Tulloch et al. 2015).

Differences Between Fructose and Glucose Metabolism

In a recent study by Lustig et al., they observed that isocaloric fructose restriction improved surrogate metabolic parameters in children with obesity and metabolic syndrome irrespective of weight change (Lustig et al. 2016). Changes in dietary composition associated with the Western diet are responsible for biochemical alterations known collectively as metabolic syndrome (Lin et al. 2016; Tappy and Le 2015).

Others could not confirm this relation, however (Angelopoulos et al. 2016; Rippe and Angelopoulos 2015).

Fructose has attracted particular attention, due to several unique metabolic and neuroendocrine properties (Lustig et al. 2016): it is metabolized almost exclusively in the liver and it serves as a substrate for de novo lipogenesis and drives hepatic triglyceride synthesis and accumulation (Lim et al. 2010). Fructose also engages in non-enzymatic fructation and ROS formation which causes cellular dysfunction (Schalkwijk et al. 2004). On top of that, it does not suppress ghrelin, resulting in excessive consumption (Van Name et al. 2015).

Basaranoglu et al. investigated whether increased consumption of fructose is linked to the increased prevalence of fatty liver (Basaranoglu et al. 2013). As high-fat diet alone produces obesity, insulin resistance, and some degree of fatty liver with minimal inflammation and no fibrosis, the fast food diet which includes fructose and fats produces a gene expression signature of increased hepatic fibrosis, inflammation, endoplasmic reticulum stress, and lipoapoptosis (Basaranoglu et al. 2013). Several other reviews addressed this relationship (Bantle 2009; Elliott et al. 2002; Kelishadi et al. 2014; Segal et al. 2007). Elliott et al. explored whether fructose consumption might be a contributing factor to the development of obesity and the accompanying metabolic abnormalities observed in the insulin resistance syndrome (Elliott et al. 2002). The per capita disappearance data for fructose from the combined consumption of sucrose and high-fructose corn syrup have increased by 26%, from 64 g/d in 1970 to 81 g/d in 1997 (Elliott et al. 2002). Both plasma insulin and leptin act in the central nervous system in the long-term regulation of energy homeostasis. Because fructose does not stimulate insulin secretion from pancreatic beta cells, the consumption of foods and beverages containing fructose produces smaller postprandial insulin excursions than does consumption of glucose-containing carbohydrate (Elliott et al. 2002). The combined effects of lowered circulating leptin and insulin increase the likelihood of weight gain and its associated metabolic sequelae (Elliott et al. 2002). In addition, fructose, compared with glucose, is preferentially metabolized to lipid in the liver. Fructose consumption induces insulin resistance, impaired glucose tolerance, hyperinsulinemia, hypertriacylglycerolemia, and hypertension in animal models (Rebollo et al. 2012). The data in humans are less clear, however (Elliott et al. 2002). Although there are existing data on the metabolic and endocrine effects of dietary fructose that suggest that increased consumption of fructose may be detrimental in terms of body weight and adiposity and the metabolic indexes associated with the insulin resistance syndrome, much more research is needed to fully understand the metabolic effect of dietary fructose in humans (Elliott et al. 2002).

The Role of Uric Acid

Fructose is distinct from other sugars in its ability to cause intracellular ATP depletion, nucleotide turnover, and the generation of uric acid (Johnson et al. 2013). Fructose is metabolized primarily in the liver. When it is taken up by the liver, ATP decreases rapidly as the phosphate is transferred to fructose in a form that

makes it easy to convert to lipid precursors. Fructose intake enhances lipogenesis and the production of uric acid. By worsening blood lipids, contributing to obesity, diabetes, fatty liver, and gout, fructose in the amounts currently consumed is hazardous to the health of some people (Bray 2013).

Several reviews address the potential role of uric acid in the metabolic syndrome and NAFLD (Johnson 2015; Kanbay et al. 2016; Lima et al. 2015; Lombardi et al. 2016; Sun et al. 2016). Petrie et al. reports on the cellular mechanisms by which uric acid interferes with hepatocyte function (Petrie et al. 2013). Plasma levels of uric acid, the final product of purine degradation in humans, are elevated in metabolic syndrome and are strongly associated with insulin resistance and nonalcoholic fatty liver disease (NAFLD) (Petrie et al. 2013). Hepatic and blood levels of purine metabolites (inosine, hypoxanthine, and xanthine) are also altered in pathophysiological states. Petrie and coworkers optimized a rat hepatocyte model to test the hypothesis that the production of uric acid by hepatocytes is a potential marker of compromised homeostasis of hepatocellular inorganic phosphate (Pi) and/or ATP (Petrie et al. 2013). The basal rate of uric acid production from endogenous substrates in rat hepatocytes was comparable to that in human liver and was $<10\%$ of the maximum rate with saturating concentrations of purine substrates (Petrie et al. 2013). It was marginally (~20%) decreased by insulin and increased by glucagon but was stimulated more than twofold by substrates (fructose and glycerol) that lower both cell ATP and Pi, and by inhibitors of mitochondrial respiration (complexes I, III, and V) that lower ATP but raise cell Pi. Clearance of inosine and its degradation to uric acid were also inhibited by cell Pi depletion. Apparently, uric acid production by hepatocytes is a very sensitive index of ATP depletion irrespective of whether cell Pi is lowered or raised. This suggests that raised plasma uric acid may be a marker of compromised hepatic ATP homeostasis (Petrie et al. 2013).

The discovery that fructose-mediated generation of uric acid may have a causal role in diabetes and obesity provides new insights into pathogenesis and therapies for this important disease (Johnson et al. 2013).

Aspects of Human Evolution on Obesity and Sugar Intake

Uricase is an enzyme involved in purine catabolism and is found in all three domains of life (Kratzer et al. 2014). Curiously, uricase is not functional in some organisms despite its role in converting highly insoluble uric acid into 5-hydroxyisourate (Kratzer et al. 2014). Of interest is the observation that apes, including humans, cannot oxidize uric acid, and it appears that multiple, independent evolutionary events led to the silencing or pseudogenization of the uricase gene in ancestral apes (Kratzer et al. 2014).

Uric acid is the highly insoluble end-product of purine metabolism in humans. Serum levels exceeding the solubility threshold can trigger formation of urate crystals resulting in gouty arthritis (Tan et al. 2016). Uric acid is primarily excreted through the kidneys with 90% reabsorbed back into the bloodstream through the uric

acid transporter URAT1 (Tan et al. 2016). This reabsorption process is essential for the high serum uric acid levels found in humans. Tan et al. discovered that URAT1 proteins from humans and baboons have higher affinity for uric acid compared with transporters from rats and mice (Tan et al. 2016). This difference in transport kinetics of URAT1 orthologs, along with inability of modern apes to oxidize uric acid due to loss of the uricase enzyme, raised the question whether these events occurred concomitantly during primate evolution (Tan et al. 2016). Ancestral URAT1 sequences were computationally inferred and ancient transporters were resurrected and assayed, revealing that affinity for uric acid was increased during the evolution of primates. This molecular fine-tuning occurred between the origins of simians and their diversification into New- and Old-World monkey and ape lineages. Remarkably, it was driven in large-part by only a few amino acid replacements within the transporter (Tan et al. 2016). This alteration in primate URAT1 coincided with changes in uricase that greatly diminished the enzymatic activity (Tan et al. 2016). These results suggest that the modifications to URAT1 transporters were potentially adaptive and that maintaining more constant, high levels of serum uric acid may have provided an advantage to our primate ancestors.

Kratzer et al. applied evolutionary models to understand the history of primate uricases by resurrecting ancestral mammalian intermediates before the pseudogenization events of this gene family (Kratzer et al. 2014). Resurrected proteins reveal that ancestral uricases have steadily decreased in activity since the last common ancestor of mammals gave rise to descendent primate lineages. They were also able to determine the 3D distribution of amino acid replacements as they accumulated during evolutionary history by crystallizing a mammalian uricase protein (Kratzer et al. 2014).

Various arguments have been made to suggest why natural selection would allow the accumulation of uric acid despite the physiological consequences of crystallized monosodium urate acutely causing liver/kidney damage or chronically causing gout. In fact, all humans are double knockouts. Humans lack the ability to synthesize vitamin C due to a mutation in L-gulono-lactone oxidase that occurred during the late Eocene, and humans have higher serum uric acid levels due to a mutation in uricase that occurred in the mid Miocene (Johnson et al. 2010). In the review by Johnson et al. they investigated the hypothesis that these mutations have in common the induction of oxidative stress that may have had prosurvival effects to enhance the effects of fructose to increase fat stores (Johnson et al. 2010). Fructose was the primary nutrient in fruit which was the main staple of early primates, but this food likely became less available during the global cooling that occurred at the time of these mutations (Johnson et al. 2010). However, today the intake of fructose, primarily in the form of added sugars, has skyrocketed, while the intake of natural fruits high in vitamin C has fallen (Johnson et al. 2010). They suggest that it is the interaction of these genetic changes with diet that is responsible for the obesity epidemic today (Johnson et al. 2010). Hence, Johnson also proposes that Neel's thrifty gene hypothesis is supported by these new insights into the mechanisms regulating fructose metabolism (Johnson et al. 2010).

Is There Specific Role for Ghrelin?

It is now more than 17 years since ghrelin was identified as the ligand of the growth hormone secretagogue receptor type 1a (GHSR-1a). The story of unacylayed ghrelin (UAG) also began in 1999, when Kojima and co-workers described this peptide in the same report that introduced ghrelin to the scientific world (Kojima et al. 1999). The preproghrelin gene-derived peptides include acyl ghrelin (AG), UAG, and obestatin. AG is produced mainly by the stomach and exerts its central and peripheral effects through the GHSR-1a (Kojima et al. 1999).

Ghrelin is a 28-amino-acid peptide that was identified in 1999 as the ligand of the growth hormone secretagogue receptor (GHSR) (Kojima et al. 1999). Produced mainly by the stomach, AG is acylated by the enzyme ghrelin O-acyl transferase (GOAT) (Gutierrez et al. 2008; Yang et al. 2008). UAG does not bind with high-affinity to the GHSR (Kojima et al. 1999) and was initially considered to be a degradation product of AG without intrinsic biological activities (Kojima et al. 1999). However, UAG overexpression increases circulating UAG and reduces epididymal and perirenal fat in transgenic animals with improved glucose tolerance attributable to increased insulin sensitivity (Zhang et al. 2008). In animal models of diabetes and obesity, administration of UAG improves glucose and lipid metabolism (Delhanty et al. 2013). In healthy volunteers, UAG administration improves glucose metabolism and inhibits lipolysis (Benso et al. 2012). In overweight patients with type 2 diabetes (T2D), continuous overnight infusion of UAG decreases postprandial blood glucose following a standard breakfast meal while insulin sensitivity is increased (Ozcan et al. 2014).

The most striking example of neuroendocrine control of appetite is Prader-Willi syndrome (PWS). PWS is a rare genetic neurodevelopmental disorder arising from the lack of expression of paternally imprinted genes in the 15q1–q12 chromosomal region (Kalsner and Chamberlain 2015). This syndrome is characterized by various nutritional phases, from suckling deficit with failure to thrive in infancy to early onset of obesity with hyperphagia (Miller et al. 2011). The mechanisms driven those different phases are not yet unraveled. In addition to enhance growth hormone secretion, ghrelin stimulates appetite and increase adiposity (Tschop et al. 2000). PWS patients have very high AG with normal UAG levels, resulting in an elevated AG/UAG ratio, suggesting an intrinsic defect in the ghrelin regulation (Kuppens et al. 2015). Compared to adiposity-matched control subjects, hyperphagia in PWS is not related to a lower postprandial GLP-1 or PYY response. Elevated ghrelin levels in PWS are consistent with increased hunger and are unrelated to insulin levels (Bizzarri et al. 2010; Haqq et al. 2008; Purtell et al. 2011).

Recently, Beauloye and coworkers demonstrated normal circulating AG and increased UAG levels in PWS infants compared to age-matched controls thus driving a low AG/UAG ratio, independently from their body mass index. This finding supports the concept of an UAG dependent anorexia in the early phases of the disease and may drive the switch from failure to thrive to obesity.

Parker et al. examined in humans the relative contributions of small intestinal and gastric nutrient exposure to postprandial suppression of ghrelin. They observed that

although the primary source of ghrelin is the gastric mucosa, that small intestinal nutrient exposure is sufficient for food-induced plasma ghrelin suppression in humans, and that gastric nutrient exposure is not necessary for suppression (Parker et al. 2005).

Maffeis et al. explored the changes in ghrelin levels induced by a mixed meal and their relationship with postprandial substrate oxidation rates in overweight and obese children with different levels of insulin sensitivity (Maffeis et al. 2006). The test meal induced a rapid decrease in ghrelin levels (Maffeis et al. 2006). Apparently, a relevant association between postprandial insulin-mediated glucose metabolism and ghrelin secretion in children with different levels of overweight exists (Maffeis et al. 2006).

Ghrelin, through the GHS-R1a, exerts a variety of metabolic functions including stimulation of appetite and weight gain and suppression of insulin secretion. Esler et al. examined the effects of novel small-molecule GHS-R1a antagonists on insulin secretion, glucose tolerance, and weight loss. They demonstrate that GHS-R1a antagonists have the potential to improve the diabetic condition by promoting glucose-dependent insulin secretion and promoting weight loss (Esler et al. 2007).

Ozcan et al. studied the effects of continuous overnight infusion of UAG on ghrelin levels and glucose and insulin responses to a standard breakfast meal (SBM) in 8 overweight patients with type 2 diabetes (Ozcan et al. 2013). Further, in the same patients plus two additional subjects, the effects of UAG infusion on AG concentrations and insulin sensitivity during a hyperinsulinemic-euglycemic clamp (HEC) were assessed (Ozcan et al. 2013). They reported that UAG administration improves glycemic control in obese subjects with type 2 diabetes (Ozcan et al. 2013). UAG might therefore be a good candidate for the development of compounds in the treatment of metabolic disorders or other conditions with a disturbed AG/DAG ratio, such as type 2 diabetes mellitus or Prader-Willi syndrome.

Summary

So, fructose-containing sugars are a focus of attention as a public health target for their putative role in obesity and cardiometabolic disease including diabetes. However, the fructose moiety is singled out to be the primary driver for the harms of sugars due to its unique endocrine signal and pathophysiological role. The point is that this is only supported by ecological studies, animal models of overfeeding and select human intervention studies with supraphysiological doses or lack of control for energy. Fructose-containing sugars can only lead to weight gain and other unintended harms on cardiometabolic risk factors insofar as the excess calories they provide. Prospective cohort studies, which provide the strongest observational evidence, have shown an association between fructose-containing sugars and cardiometabolic risk including weight gain, cardiovascular disease outcomes, and diabetes only when restricted to sugar-sweetened beverages and not for sugars from other sources, e.g., fruits. So, sugar content should not be the sole determinant of a healthy diet. There are many other factors in the diet – some providing excess

calories while others provide beneficial nutrients. Rather than just focusing on one energy source, we should consider the whole diet for health benefits.

What remains interesting is the specific metabolism of humans regarding their inability to synthesize vitamin-C and their lack of clearing uric acid. As today the intake of fructose, primarily in the form of added sugars, has skyrocketed, while the intake of natural fruits high in vitamin C has fallen, it is the interaction of these genetic changes with diet that might also be responsible for the obesity epidemic today. Finally, food addiction might be a misnomer because of the ambiguous connotation of a substance-related phenomenon. The recently proposed term eating addiction probably better underscores the behavioral addiction to eating.

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