Sugar, Stress and Metabolism: Relevance to Food Addiction

Candice A. Price, PhD , UC Davis
Elissa S. Epel, PhD, UCSF, Department of Psychiatry & Behavioral Sciences

Abstract

Excess sugar alters homeostatic mechanisms regulating glucose and lipid metabolism, as well as hunger and appetite. These pathways are also affected by the metabolic 'stress' hormone, cortisol. Thus, acute and chronic stress may interact with sugar consumption to further dysregulate metabolic homoeostasis. This chapter reviews how added sugar intake, including sugar-sweetened beverages (SSBs)--the single largest and most well-studied source of added sugars--, increases risk factors associated with cardiometabolic disease, while also increasing appetite and failing to suppress hunger. Chronic psychological stress alters neuro satiety and appetitive pathways in a similar way as sugar, promoting hedonic eating behaviors (the desire to consume highly palatable foods). The combination of stress and sugar is of high relevance to addiction. Rodent models show that psychological stress with sugar intake induces what looks like food addiction behavior. In humans, chronic stress is associated with dampened reward signaling, suggesting that when chronically-stressed individuals consume sugar, hedonic feeding behavior is reinforced in order to restore the dopaminergic reward response. Together, these findings suggest that while excessive sugar alone can increase reward drive, chronic stress may synergize this relationship, and lead to habitual overeating, and consequently reduced sensitivity to sweet taste. Therefore, synergistic effects of chronic stress and high sugar intake contribute to the phenotype of compulsive sugar consumption. Although there remain significant gaps in understanding the synergistic effects of sugar and stress, disparities linked to psychological stress and sugar consumption appear to play significant roles in driving preventable social and race-based health disparities in the U.S.

Keywords: Sugar, psychological stress, dopamine, melanocortin, cortisol, visceral adiposity, obesity, health disparities

Excessive sugar consumption and disease.
In the U.S., added sugar makes up an average of 13.6% of an individual's daily calories.[1] This exceeds the Dietary Guidelines for Americans recommendation that no more 10% of calories be consumed as added sugars,[2], and far exceeds the more stringent guidelines set by the World Health Organization of consuming no more than 5% of calories as added sugar.[3] The term 'added sugar' refers to sugar that is not naturally present in the respective food or beverage. This does not include items that contain only naturally occurring sugar such as whole fruit or 100% fruit juice. Sucrose and high fructose corn syrup (HFCS) are the two most commonly consumed types of added sugars in the U.S. The top source of added sugars in the U.S. diet are sugar-sweetened beverages (SSBs) (e.g., sodas, sports drinks, fruit drinks containing added sugar), contributing 23% of added sugar consumed. Unlike other sources of added sugar, SSBs are also the single largest source of added sugars as it does not contain any other macro- or micronutrients [4]. Baked goods (e.g. cakes, cookies) are the second most popular source of added sugar, making up about 19% of added sugar consumed in the U.S. diet.[4]

High consumption of added sugars is associated with increased risk for cardiometabolic disease development, including obesity, type 2 diabetes and cardiovascular disease.[5-8] Interestingly, this association appears to be strongest when examining the impact of SSBs versus added sugar from all food and beverage sources.[9-12] Clinical trials have largely focused on SSBs with very few trials testing the effects of added sugar provided in solid form.[13,14] Thus, the majority of evidence presented here will stem from trials manipulating sugar intake through SSBs. Further, it has been argued that added sugar provided in liquid form may have lower satiation effects than added sugar provided in solid form,[15,16] which further supports our emphasis on SSBs.

Controlled experimental studies in humans demonstrate that regular consumption of added sugar provided in addition to or as part of an individual's usual calorie intake over two to 36 weeks increases body weight, *de novo* lipogenesis, plasma triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), total cholesterol, uric acid,[13,17-20] liver fat storage,[21-23] visceral fat [24] and reduces insulin sensitivity.[18,25] Some studies suggest there may be a lack of caloric compensation [26], resulting in excess calorie intake and weight gain.[17,24,27] However, not all added sugar interventions in humans resulted in weight-gain.[18,22] Plus, the detrimental effects of high SSB consumption remain significant after adjusting for change in body weight[17] and even in the absence of weight gain.[22,28] Thus, habitual consumption of added sugar is not simply a matter of consuming excess calories, but moreso a matter of disrupting metabolic processes and energy homeostasis.

Excess sugar consumption alters energy homeostasis.
Maintaining energy homeostasis is a coordinated control of food intake (calories in) and energy expenditure (calories out) and is influenced by dietary intake, particularly sugar, and level of

insulin resistance. The direct effects of sugar on metabolism (e.g. enhanced hepatic lipid production) are further exacerbated by the indirect effects of sugar on dysregulating energy intake (e.g. increasing food intake in the absence of hunger). In this next section, we review basic regulation of hunger and appetite, both peripheral and neural pathways, and how sugar impacts these systems. As shown in **Figure 1**, hunger and satiety are regulated by the melanocortin system, while appetite and reward are regulated by the mesolimbic dopaminergic system. Activation of these pathways is triggered by external cues like food, but these systems also interact with other. Excessive sugar consumption leads to dysregulated energy intake via alterations in these hunger and appetite-regulating systems.

Regulation of hunger. Homeostatic control of energy intake is largely regulated by endocrine and neuroendocrine signaling by key hormones insulin, leptin, and ghrelin on the hypothalamus. These hormones have both endocrine and neuroendocrine functions, meaning they elicit action on both peripheral target tissues and serve as neurotransmitters in the brain. Insulin, an anabolic hormone most known for its primary role in regulating glucose homeostasis, is produced and secreted by pancreatic beta-cells. It acts on various tissues including the liver, muscle and adipose tissue to regulate glucose metabolism and production, lipogenesis (the synthesis of lipids), lipid storage and protein synthesis. Insulin also acts on various regions in the brain, including the hypothalamus, to regulate food intake. In concert with leptin, insulin binds to its receptor on the proopiomelanocortin (POMC) neuron to promote satiety while simultaneously acting on the agouti-peptide (AgRP) and neuropeptide Y (NPY) neurons to further inhibit hunger.[29,30] Ghrelin, on the other hand, stimulates hunger by binding to its receptor on AgRP and NPY. These hormonal actions, all part of the melanocortin system, are all key in the central nervous system's role in regulating hunger. Importantly, high added sugar intake has the ability to disrupt energy homeostasis through dysfunction in this system.

Regulation of hedonic drive. Hedonic drive is the *desire* to consume food or beverage, rather than consumption based on a physiological response to the body's energy needs. This is an important distinction from hunger. As previously mentioned, hunger is a hypothalamic response driven by a feedback mechanism by peripheral signals in response to the body's energy needs. Appetite is driven by *desire* and mediated through the dopaminergic pathway, or mesolimbic system, a reward and motivation-regulating system. The mesolimbic pathway, mediated by dopamine (DA), drives hedonic eating behaviors, or the habitual intake of highly palatable foods such as those containing added sugar.[31-34] The high palatability of sweet foods and beverages appears to drive hedonic eating behaviors,[35,36] via the release of DA in the ventral tegmental area (VTA).[34,37] Repeated stimulation of the mesolimbic system creates a persistent motivation to acquire the same stimuli,[38] for example craving sugar in the presence of a sweet visual cue.[39]

Dopamine (DA) is most commonly known as the 'pleasure hormone' and is triggered by behaviors such as the consumption of sugar to elicit feelings of reward and motivation. Interestingly, the same peripheral hormones (insulin, leptin and ghrelin) that regulate hunger also affect appetite via ability to regulate dopaminergic responses. Ghrelin promotes appetite by activating the dopaminergic pathway to enhance motivation .[40,41] Insulin and leptin oppose the actions of DA by inhibiting DA signaling,[42,43] thereby suppressing the reward response.[44,45]

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Excess sugar intake on hunger and reward signaling.

Insulin's ability to suppress the dopaminergic reward response likely occurs through dopamine receptor 2 (DR2), which is responsible for repressing DA activity after stimulation. Lower insulin sensitivity is associated with lower DR2 expression in humans, indicating reduced inhibition of reward seeking.[46] Therefore, insulin resistant individuals may have a greater reward response to sugar. Animal models have shown that DR2 expression is also lower with glucose- or sucrose-sweetened beverage, while the reward-stimulating dopamine receptor 1 (DR1) as well as opioid receptor activation are increased.[32,47] This suggest that habitual sugar intake is in part mediated by a lack of reward inhibition, which can lead to binge eating of sugar. Due to the effect of insulin on DRs, this behavior may be worse in insulin resistant individuals. This is of particular concern for chronically-stressed individuals who may use sugar intake as a stress coping mechanism.

Type of sugar may matter. Trials in humans have shown dietary sucrose as being less effective at stimulating feelings of fullness as compared with starch or non-caloric sweeteners, [48,49] while others found no significant effect.[50-52] Consuming sucrose in the form of a sweetened beverage for two weeks increases energy intake.[53] Surprisingly though, circulating leptin also increased in study participants. In rats, acute sucrose-sweetened beverage intake just before a meal temporarily reduced NPY/AgRP expression and led to hyperphagia, which the researchers found were independent of differences in total caloric intake and palatability.[54] Additional evidence in free-living humans consuming sucrose- or HFCS-sweetened foods/beverages are needed to better determine the effects of added sugar on inhibiting satiety. Studies comparing pure glucose versus pure fructose (the two monosaccharides that make up sucrose and HFCS) provide a clearer understanding of the mechanisms through which a diet high in added sugar promote the overconsumption of calories.

Pure glucose consumption stimulates satiety hormones like leptin, insulin and peptide YY (PYY) and does so to a greater extent as compared with fructose.[55-57] Glucose also suppresses hunger-stimulating hormones like, ghrelin,[55] and activates satiety hormones like insulin and leptin. Fructose on the other hand is less effective at suppressing hunger hormones and activating satiety hormones.[56-59] As a result, the ability of fructose to trigger satiety even when caloric needs are met, is much lower than that of glucose. Fructose also prohibits satiety by failure to suppress hypothalamic malonyl co-enzyme A (malonyl Co-A), through a depletion in ATP and deactivation of AMPK, the energy sensing enzyme.[60] This in turn effects downstream neurotransmitter signaling of POMC/CART and AgRP/NPY neurons.

Synergistic effects of sugar and stress on cardiometabolic disease risk

As shown in **Figure 1**, chronic, moderate stress has similar effects as sugar, but also synergistic effects, on dysregulating hunger and reward systems. Together, sugar and stress further lead to excessive consumption of high sugar foods and its associated metabolic health consequences. Human studies investigating the effects of consuming sugar under stressful conditions on the

regulation of hunger and appetite control are lacking, and studies in animals are inconclusive. A prior review summarized the potential effects of sugar and stress[61] but since its publication, few advancements have been made. Some have demonstrated synergistic effects of stress and glucose on increasing plasma ghrelin[62] and decreasing leptin.[62] However, the glucose used in this study was 2-[^{18}F]-fluoro-d-deoxy-d-glucose, which although it can cross the blood brain barrier, it cannot be metabolized. Another study in which chronically-stressed rats were fed a high-fat, high-sucrose diet observed increased visceral fat accumulation via peripheral NPY.[63] Others found reductions in insulin but no effects on other hunger-regulating hormones in chronically-stress rats fed a high-fructose diet.[64]

Psychological stress can be acute or when repeated can manifest into chronic stress over time. The body's response to stress is mediated in part by the hypothalamic pituitary adrenal (HPA) axis, which releases the 'stress hormone' cortisol. Psychological stress also mediates the mesolimbic response and can drive a low-quality diet and hedonic eating.[65,66] Old and new studies in animal models suggest that acute, moderate stress activates the release of DA and promotes reward activity.[67,68] In contrast, chronic stress may dampen DA release, explaining why chronic stress is linked to depression.[69,70] Habitual sugar consumption may ameliorate this effect of stress on DA by repeatedly releasing DA.[33] As seen in models of chronic stress, absence of sugar in habitual consumers can lead to behaviors reflecting anxiety and depression due to a dampened DA response.[71] This suggests that habitual sugar intake results from the loss of usual reward sensations in the absence of sugar and is an effort to restore DA activity and reward sensations.[65,66] Chronic stress, which dampens DA may therefore promote hedonic eating behavior.

The effects of sugar on stress may depend on sex, gender, whether stress is acute or chronic, and the presence of excess adipose tissue. In some individuals, acute stress reduces hunger and appetite but increases appetite in the majority of individuals.[72,73] Under stress, the HPA axis turns on to release cortisol for the mobilization of fat and glucose stores to fuel the stress response. However, repeated stress exposure means repeated cortisol release and subsequently elevated cortisol exposure and its downstream consequences (e.g. visceral fat accumulation, inflammation).[74] Cortisol opposes the actions of insulin, and excess cortisol promotes insulin resistance.[75] Therefore, when food is consumed as a coping mechanism against stress the metabolic response is conflated with the simultaneous elevated cortisol and insulin secretion, which will be exacerbated in insulin resistant individuals. However, the cortisol response to sugar appears to depend on whether sugar and stress exposures are acute versus repeated. When sugar is consumed prior to an acute stress test, stress-induced cortisol reactivity is greater compared to individuals who did not receive a sugary beverage.[76] Whether or not participants were high-sugar consumers was not reported, nor was their perceived level of stress at recruitment. The same stress test has been used in a prior study in which women who had been consuming sucrose-sweetened beverages for two weeks. After the acute stress test, cortisol release was dampened compared to women who had been consuming non-caloric sweetened beverages.[77] Thus, the calming effect of sugar on stress-induced HPA activation may encourage sugar intake with continuous stress exposure. Recent research demonstrates that overweight

individuals experiencing chronic stress exhibit amplified cortisol reactivity to an acute stress exposure as compared to their chronically-stressed lean counterparts.[78] However, other features of diurnal cortisol patterns like the cortisol awakening response (CAR) or the slope of decline after an acute stressor are dampened in chronically-stressed individuals.[79-82] Chronically-stressed individuals also consume more calories of a high fat-high sugar snack item following an acute stress test.[78,83] This may be due to 1) potentially dampened DA release and 2) the calming effect of regular sugar intake on the HPA response to an acute stressor [77]; similar findings were observed in rats.[84] Although in a lean cohort the effect of stress on hedonic eating is not always observed, [85] potentially suggesting greater impairment of the mesolimbic and the melanocortin system in overweight individuals. Thus, chronically-stressed individuals who are also overweight may be more vulnerable to the effects of sugar.
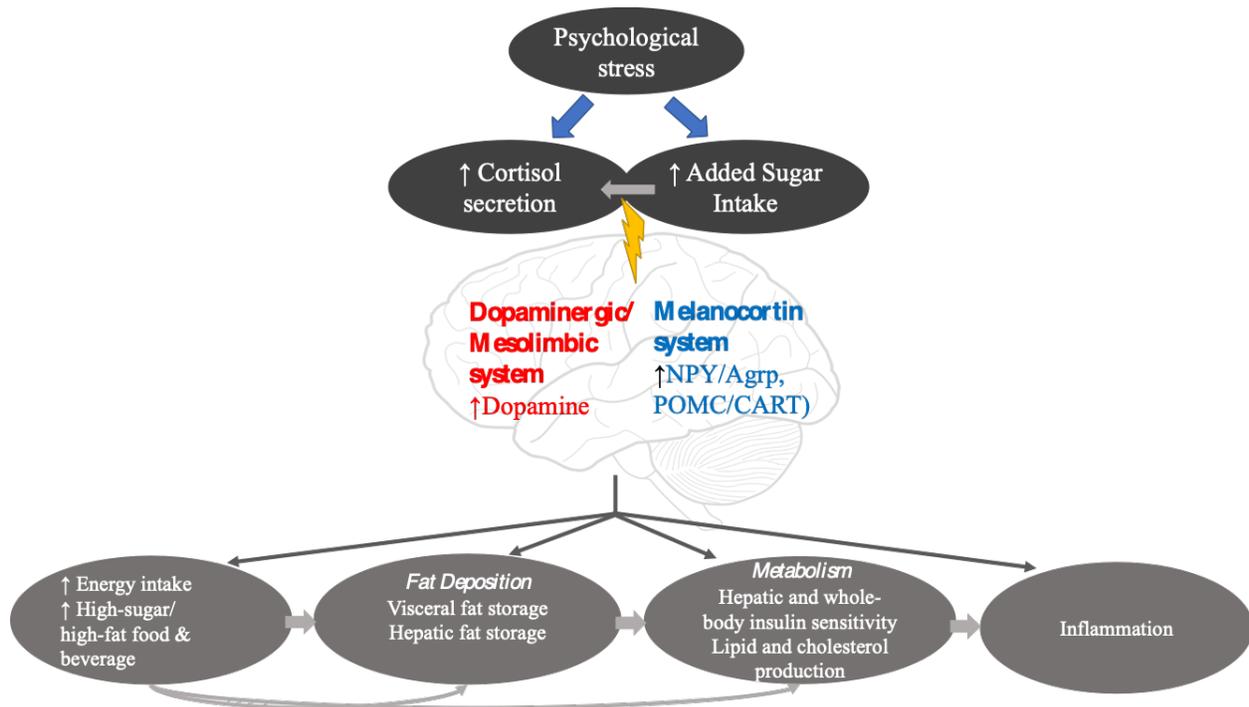

Figure 1: Proposed model of the synergistic effects of sugar and stress. Both stress and sugar have the ability to excite or inhibit the dopamine (DA) mesolimbic pathway, depending on whether the stressor is moderate versus high intensity, and acute versus chronic. Moderate and chronic stress leads to long term changes in neural circuitry toward habitual consumption of high sugar. High sugar intake also disrupts the melanocortin neurons responsible for regulating food intake. Together, sugar and stress disrupt hepatic lipid production and adipose tissue deposition, reduces insulin sensitivity and increases inflammation, with and without weight gain.

Implications for racial and sociodemographic related cardiometabolic health disparities

The potential for sugar and stress to more significantly impact individuals who are overweight or have obesity could have important implications in understanding mechanisms of cardiometabolic disease health disparities in racially/ethnically diverse women. Studies have shown that women

may be more amenable to the effects of chronic stress on hedonic eating behaviors [83,86,87]. As researchers have pointed out, sex and gender differences in metabolic responses to stress require more investigation [88]. Low resource environments, particularly common for women and children, and minoritized populations, particularly Blacks, lead to food deserts and forced choices for excessively high sugar diets. Furthermore, racial differences in sugar intake and experiences of psychological stress coincide with race and ethnic differences in cardiometabolic disease prevalence [89,90]. For example, Black women are disproportionately affected by psychological stress[91,92], have the highest prevalence of obesity [93] and cardiovascular disease mortality [94], and compared to women of other race and ethnicities, are the highest consumers of SSB [7]. Psychological stress has the potential to be the single most important social determinant of health in Black women. Psychological stress stemming from racial discrimination, structural racism and gender-specific stress are sources of chronic stress in Black women and is associated with a dysregulated hypothalamic pituitary adrenal axis (HPA) stress) [95] and greater consumption of high-sugar/high-fat feeding behaviors (hedonic eating) [90]. The link between sugar intake and risk for cardiometabolic disease in Blacks serves as a prime example of framing race as a social construct when investigating the mechanisms and prevention of cardiometabolic health disparities. Blacks are not inherently consuming more sugar because of a genetic predisposition to enhance dopaminergic response to sweet taste. The same should be reiterated for Hispanics who are the second-largest consumers of SSBs and also experience disproportionately greater health risks than white populations in the U.S. Blacks and Hispanics are also disproportionately affected by targeted marketing with significantly more marketing of highly palatable foods and beverages but low marketing of healthy, low-calorie foods and beverages being advertised to this population [96,97]. This repeated visual cue paired with greater access to highly palatable foods makes this population particularly susceptible to the potential effects of chronic stress and sugar intake. The intersection of environmental factors, stress, and high sugar intake [89] may be key in understanding the mechanisms by which women and those from historically marginalized communities are disproportionately affected by obesity [98], hypertension [99], T2D [100] and T2D-related CVD mortality [101-105].

Conclusion

In summary, both sugar and stress alter energy intake and metabolic homeostasis, and when occurring simultaneously, appear to have synergistic effects on HPA regulation, hunger, appetite and metabolism. Our early model of stress-induced, food-reward addiction from 15 years ago was a simplified model depicting how elevated stress-hormones, mainly cortisol, leads to elevations in NPY and activates the reward system [101]. Since then, a body of research elucidating the potential impact of stress and sugar on the brain and metabolism has led us to this updated model that demonstrates potential interactions between high stress exposure and high sugar consumption (**Figure 1**). Gaps remain in understanding differences in the type of sugar (liquid or solid) on altering the melanocortin and mesolimbic systems, and the long-term impact of sugar consumption as a stress-coping mechanism. Future studies should also focus on understanding the roles of these pathways on disparate cardiometabolic disease risk in

communities experiencing excessive social stress in addition to the marketing and pervasive availability of high-sugar foods and beverages.

References

1.	Bowman SA, John C Clemens, James E Friday, Natalia Schroeder, Miyuki Shimizu, Randy P LaComb, and Alanna J Moshfegh. Food Patterns Equivalents Intakes by Americans: What We Eat in America, NHANES 2003-2004 and 2015-2016. US Department of Agriculture 2018;20.

2.	United States Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans 2020-2025. 2020.

3.	World Health Organization. Guideline: Sugars intake for adults and children. 2015;Available at: http://apps.who.int/iris/bitstream/ 10665/149782/1/9789241549028_eng.pdf.

4.	Ricciuto L, Fulgoni VL, Gaine PC, Scott MO, DiFrancesco L. Sources of Added Sugars Intake Among the U.S. Population: Analysis by Selected Sociodemographic Factors Using the National Health and Nutrition Examination Survey 2011–18. Frontiers in Nutrition 2021;8.

5.	Allister Price C, Stanhope KL. Understanding the Impact of Added Sugar Consumption on Risk for Type 2 Diabetes. J Calif Dent Assoc 2016;44:619-26.

6.	Welsh JA, Sharma A, Cunningham SA, Vos MB. Consumption of added sugars and indicators of cardiovascular disease risk among US adolescents. Circulation 2011;123:249-57.

7.	Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med 2014;174:516-24.

8.   Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation;121:1356-64.

9.   Sundborn G, Thornley S, Merriman TR, et al. Are Liquid Sugars Different from Solid Sugar in Their Ability to Cause Metabolic Syndrome? Obesity (Silver Spring) 2019;27:879-87.

10.   Tasevska N, Park Y, Jiao L, Hollenbeck A, Subar AF, Potischman N. Sugars and risk of mortality in the NIH-AARP Diet and Health Study. Am J Clin Nutr 2014;99:1077-88.

11.   Wang J, Light K, Henderson M, et al. Consumption of added sugars from liquid but not solid sources predicts impaired glucose homeostasis and insulin resistance among youth at risk of obesity. J Nutr 2014;144:81-6.

12.   Zheng M, Allman-Farinelli M, Heitmann BL, et al. Liquid versus solid energy intake in relation to body composition among Australian children. J Hum Nutr Diet 2015;28 Suppl 2:70-9.

13.   Reiser S, Hallfrisch J, Michaelis OEt, Lazar FL, Martin RE, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. I. Effects on levels of fasting blood lipids. Am J Clin Nutr 1979;32:1659-69.

14.   Mann JI, Truswell AS. Effects of isocaloric exchange of dietary sucrose and starch on fasting serum lipids, postprandial insulin secretion and alimentary lipaemia in human subjects. Br J Nutr 1972;27:395-405.

15.   Cassady BA, Considine RV, Mattes RD. Beverage consumption, appetite, and energy intake: what did you expect? Am J Clin Nutr 2012;95:587-93.

16.   DiMeglio DP, Mattes RD. Liquid versus solid carbohydrate: effects on food intake and body weight. Int J Obes Relat Metab Disord 2000;24:794-800.

17.   Stanhope KL, Medici V, Bremer AA, et al. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. Am J Clin Nutr 2015;101:1144-54.

18.   Aeberli I, Hochuli M, Gerber PA, et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes Care 2013;36:150-6.

19.   Cox CL, Stanhope KL, Schwarz JM, et al. Consumption of fructose- but not glucose-sweetened beverages for 10 weeks increases circulating concentrations of uric acid, retinol binding protein-4, and gamma-glutamyl transferase activity in overweight/obese humans. Nutr Metab (Lond) 2012;9:68.

20.   Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OEt, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. Am J Clin Nutr 1979;32:2206-16.

21.   Sigala DM, Hieronimus B, Medici V, et al. Consuming Sucrose- or HFCS-Sweetened Beverages Increases Hepatic Lipid and Decreases Insulin Sensitivity in Adults. J Clin Endocrinol Metab 2021.

22.   Schwarz JM, Noworolski SM, Wen MJ, et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. J Clin Endocrinol Metab 2015;100:2434-42.

23.   Maersk M, Belza A, Stodkilde-Jorgensen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 2012;95:283-9.

24.   Stanhope KL, Griffen SC, Hellerstein MK, et al. Consumption of Fructose-, but not Glucose-Sweetened Beverages for 10 Weeks Induces Glucose Intolerance, Insulin Resistance, Increased Visceral Adipose Mass in Overweight/Obese Men and Women. . Diabetes 2008 57:A101.

25.   Price CA, Medici V, Nunez MV, et al. A Pilot Study Comparing the Effects of Consuming 100% Orange Juice or Sucrose-Sweetened Beverage on Risk Factors for Cardiometabolic Disease in Women. Nutrients 2021;13.

26.   Pan A, Hu FB. Effects of carbohydrates on satiety: differences between liquid and solid food. Curr Opin Clin Nutr Metab Care 2011;14:385-90.

27.   de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med 2012;367:1397-406.

28.   Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. Am J Clin Nutr 2000;72:1128-34.

29.   Konner AC, Janoschek R, Plum L, et al. Insulin action in AgRP-expressing neurons is required for suppression of hepatic glucose production. Cell Metab 2007;5:438-49.

30.   Varela L, Horvath TL. Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis. EMBO Rep 2012;13:1079-86.

31.   Olszewski PK, Wood EL, Klockars A, Levine AS. Excessive Consumption of Sugar: an Insatiable Drive for Reward. Curr Nutr Rep 2019;8:120-8.

32.   Colantuoni C, Schwenker J, McCarthy J, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport 2001;12:3549-52.

33.   Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 2005;134:737-44.

34.   Frank GK, Oberndorfer TA, Simmons AN, et al. Sucrose activates human taste pathways differently from artificial sweetener. Neuroimage 2008;39:1559-69.

35.   Raben A, Macdonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14 d ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. Int J Obes Relat Metab Disord 1997;21:846-59.

36.   Tellez LA, Han W, Zhang X, et al. Separate circuitries encode the hedonic and nutritional values of sugar. Nat Neurosci 2016;19:465-70.

37.   van Opstal AM, Kaal I, van den Berg-Huysmans AA, et al. Dietary sugars and non-caloric sweeteners elicit different homeostatic and hedonic responses in the brain. Nutrition 2019;60:80-6.

38.   Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry 2004;12:305-20.

39.   Monteleone P, Piscitelli F, Scognamiglio P, et al. Hedonic eating is associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoyl-glycerol in healthy humans: a pilot study. J Clin Endocrinol Metab 2012;97:E917-24.

40.   Overduin J, Figlewicz DP, Bennett-Jay J, Kittleson S, Cummings DE. Ghrelin increases the motivation to eat, but does not alter food palatability. Am J Physiol Regul Integr Comp Physiol 2012;303:R259-69.

41.   Perello M, Zigman JM. The role of ghrelin in reward-based eating. Biol Psychiatry 2012;72:347-53.

42.   Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? Trends Neurosci 2007;30:375-81.

43.   Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science 2007;317:1355.

44.   Figlewicz DP, Benoit SC. Insulin, leptin, and food reward: update 2008. Am J Physiol Regul Integr Comp Physiol 2009;296:R9-R19.

45.   Mebel DM, Wong JC, Dong YJ, Borgland SL. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased reuptake. Eur J Neurosci 2012;36:2336-46.

46.   Caravaggio F, Borlido C, Hahn M, et al. Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy nonobese humans. Int J Neuropsychopharmacol 2015;18:pyv014.

47.   Naneix F, Darlot F, De Smedt-Peyrusse V, Pape JR, Coutureau E, Cador M. Protracted motivational dopamine-related deficits following adolescence sugar overconsumption. Neuropharmacology 2018;129:16-25.

48.   Sorensen LB, Vasilaras TH, Astrup A, Raben A. Sucrose compared with artificial sweeteners: a clinical intervention study of effects on energy intake, appetite, and energy expenditure after 10 wk of supplementation in overweight subjects. Am J Clin Nutr 2014;100:36-45.

49.   Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr 2002;76:721-9.

50.   Anton SD, Martin CK, Han H, et al. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite 2010;55:37-43.

51.   Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a 4-week period. Br J Nutr 2007;97:193-203.

52.   Canty DJ, Chan MM. Effects of consumption of caloric vs noncaloric sweet drinks on indices of hunger and food consumption in normal adults. Am J Clin Nutr 1991;53:1159-64.

53.   Sigala DM, Widaman AM, Hieronimus B, et al. Effects of Consuming Sugar-Sweetened Beverages for 2 Weeks on 24-h Circulating Leptin Profiles, Ad Libitum Food Intake and Body Weight in Young Adults. Nutrients 2020;12.

54.   Gaysinskaya VA, Karatayev O, Shuluk J, Leibowitz SF. Hyperphagia induced by sucrose: relation to circulating and CSF glucose and corticosterone and orexigenic peptides in the arcuate nucleus. Pharmacol Biochem Behav 2011;97:521-30.

55.   Teff KL, Elliott SS, Tschop M, et al. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. J Clin Endocrinol Metab 2004;89:2963-72.

56.   Teff KL, Grudziak J, Townsend RR, et al. Endocrine and metabolic effects of consuming fructose- and glucose-sweetened beverages with meals in obese men and women: influence of insulin resistance on plasma triglyceride responses. J Clin Endocrinol Metab 2009;94:1562-9.

57.   Aeberli I, Gerber PA, Hochuli M, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. Am J Clin Nutr 2011.

58.   Bowen J, Noakes M, Clifton PM. Appetite hormones and energy intake in obese men after consumption of fructose, glucose and whey protein beverages. Int J Obes (Lond) 2007;31:1696-703.

59.   Kyriazis GA, Soundarapandian MM, Tyrberg B. Sweet taste receptor signaling in beta cells mediates fructose-induced potentiation of glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A 2012;109:E524-32.

60.   Cha SH, Wolfgang M, Tokutake Y, Chohnan S, Lane MD. Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake. Proc Natl Acad Sci U S A 2008;105:16871-5.

61.   Brownell KDaW, B. Timothy. Eating Disorders and Obesity: A Comprehensive Handbook. Third Edition. 2018.

62.   Carneiro-Nascimento S, Opacka-Juffry J, Costabile A, et al. Chronic social stress in mice alters energy status including higher glucose need but lower brain utilization. Psychoneuroendocrinology 2020;119:104747.

63.   Kuo LE, Czarnecka M, Kitlinska JB, Tilan JU, Kvetnansky R, Zukowska Z. Chronic stress, combined with a high-fat/high-sugar diet, shifts sympathetic signaling toward neuropeptide Y and leads to obesity and the metabolic syndrome. Ann N Y Acad Sci 2008;1148:232-7.

64.   Kovacevic S, Nestorov J, Matic G, Elakovic I. Chronic Stress Combined with a Fructose Diet Reduces Hypothalamic Insulin Signaling and Antioxidative Defense in Female Rats. Neuroendocrinology 2019;108:278-90.

65.   Avena NM. The study of food addiction using animal models of binge eating. Appetite 2010;55:734-7.

66.   Volkow ND, Wang GJ, Maynard L, et al. Brain dopamine is associated with eating behaviors in humans. Int J Eat Disord 2003;33:136-42.

67.   Dunn AJ, File SE. Cold restraint alters dopamine metabolism in frontal cortex, nucleus accumbens and neostriatum. Physiol Behav 1983;31:511-3.

68.   Stelly CE, Tritley SC, Rafati Y, Wanat MJ. Acute Stress Enhances Associative Learning via Dopamine Signaling in the Ventral Lateral Striatum. J Neurosci 2020;40:4391-400.

69.   Calabrese F, Molteni R, Racagni G, Riva MA. Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology 2009;34 Suppl 1:S208-16.

70.   Mangiavacchi S, Masi F, Scheggi S, Leggio B, De Montis MG, Gambarana C. Long-term behavioral and neurochemical effects of chronic stress exposure in rats. J Neurochem 2001;79:1113-21.

71.   Colantuoni C, Rada P, McCarthy J, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes Res 2002;10:478-88.

72.   Grunberg NE, Straub RO. The role of gender and taste class in the effects of stress on eating. Health Psychol 1992;11:97-100.

73.   Oliver G, Wardle J. Perceived effects of stress on food choice. Physiol Behav 1999;66:511-5.

74.   Marin P, Darin N, Amemiya T, Andersson B, Jern S, Bjorntorp P. Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism 1992;41:882-6.

75.   Adam TC, Hasson RE, Ventura EE, et al. Cortisol is negatively associated with insulin sensitivity in overweight Latino youth. J Clin Endocrinol Metab 2010;95:4729-35.

76.   Zankert S, Kudielka BM, Wust S. Effect of sugar administration on cortisol responses to acute psychosocial stress. Psychoneuroendocrinology 2020;115:104607.

77.   Tryon MS, Stanhope KL, Epel ES, et al. Excessive Sugar Consumption May Be a Difficult Habit to Break: A View From the Brain and Body. J Clin Endocrinol Metab 2015;100:2239-47.

78.   Wijnant K, Klosowska J, Braet C, et al. Stress Responsiveness and Emotional Eating Depend on Youngsters' Chronic Stress Level and Overweight. Nutrients 2021;13.

79.   Seaton EK, Zeiders KH. Daily racial discrimination experiences, ethnic-racial identity, and diurnal cortisol patterns among Black adults. Cultur Divers Ethnic Minor Psychol 2021;27:145-55.

80.   Zeiders KH, Hoyt LT, Adam EK. Associations between self-reported discrimination and diurnal cortisol rhythms among young adults: The moderating role of racial-ethnic minority status. Psychoneuroendocrinology 2014;50:280-8.

81.   Fuller-Rowell TE, Doan SN, Eccles JS. Differential effects of perceived discrimination on the diurnal cortisol rhythm of African Americans and Whites. Psychoneuroendocrinology 2012;37:107-18.

82.   Fuller-Rowell TE, Homandberg LK, Curtis DS, Tsenkova VK, Williams DR, Ryff CD. Disparities in insulin resistance between black and white adults in the United States: The role of lifespan stress exposure. Psychoneuroendocrinology 2019;107:1-8.

83.   Tryon MS, DeCant R, Laugero KD. Having your cake and eating it too: a habit of comfort food may link chronic social stress exposure and acute stress-induced cortisol hyporesponsiveness. Physiol Behav 2013;114-115:32-7.

84.   Ulrich-Lai YM, Ostrander MM, Herman JP. HPA axis dampening by limited sucrose intake: reward frequency vs. caloric consumption. Physiol Behav 2011;103:104-10.

85.   Klatzkin RR, Baldassaro A, Hayden E. The impact of chronic stress on the predictors of acute stress-induced eating in women. Appetite 2018;123:343-51.

86.   Buczek L, Migliaccio J, Petrovich GD. Hedonic Eating: Sex Differences and Characterization of Orexin Activation and Signaling. Neuroscience 2020;436:34-45.

87.   Trainor BC. Stress responses and the mesolimbic dopamine system: social contexts and sex differences. Horm Behav 2011;60:457-69.

88.   Ruiz D, Padmanabhan V, Sargis RM. Stress, Sex, and Sugar: Glucocorticoids and Sex-Steroid Crosstalk in the Sex-Specific Misprogramming of Metabolism. J Endocr Soc 2020;4:bvaa087.

89.   Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. Arch Intern Med 2008;168:1487-92.

90.   Longmire-Avital B, McQueen C. Exploring a relationship between race-related stress and emotional eating for collegiate Black American women. Women Health 2019;59:240-51.

91.   Richman LS, Bennett GG, Pek J, Siegler I, Williams RB. Discrimination, dispositions, and cardiovascular responses to stress. Health Psychol 2007;26:675-83.

92.   Suglia SF, Staudenmayer J, Cohen S, Enlow MB, Rich-Edwards JW, Wright RJ. Cumulative Stress and Cortisol Disruption among Black and Hispanic Pregnant Women in an Urban Cohort. Psychol Trauma 2010;2:326-34.

93.   Centers for Disease Control aP. Prevalence of Obesity Among Adults and Youth. US Department of Health and Human Services 2017.

94.   Carnethon MR, Pu J, Howard G, et al. Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association. Circulation 2017;136:e393-e423.

95.   Busse D, Yim IS, Campos B, Marshburn CK. Discrimination and the HPA axis: current evidence and future directions. J Behav Med 2017;40:539-52.

96.   Wilson L, James Wood, Molly McKaughan. The Marketing of Unhealthy Food and Beverages in African-American Communities. Robert Woods Jr Foundation Program Results Report 2015.

97.   Grier SA, Kumanyika SK. The context for choice: health implications of targeted food and beverage marketing to African Americans. Am J Public Health 2008;98:1616-29.

98.   Centers for Disease Control and Prevention USDoHaHS. Table 26. Normal weight, overweight, and obesity among adults aged 20 and over, by selected characteristics: United States, selected years 1988–1994 through 2013–2016. Health, United States 2018:1-9.

99.   Gaillard T, Schuster D, Osei K. Independent role of blood pressure on cardiovascular risk factors in nondiabetic, obese African-American women with family history of type 2 diabetes: Implications for metabolic syndrome components. J Am Soc Hypertens 2009;3:25-34.

100.   Statistics NCfH. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Library of Congrress 2016;76.

101.   Adam TC, Epel ES. Stress, eating and the reward system. Physiol Behav 2007;91:449-58.

102.   Braun LT, Wilbur J, Buchholz SW, et al. Cardiovascular Risk in Midlife African American Women Participating in a Lifestyle Physical Activity Program. J Cardiovasc Nurs 2016;31:304-12.

103.   Link CL, McKinlay JB. Disparities in the prevalence of diabetes: is it race/ethnicity or socioeconomic status? Results from the Boston Area Community Health (BACH) survey. Ethn Dis 2009;19:288-92.

104.   Katz SF, Rodriguez F, Knowles JW. Health disparities in cardiometabolic risk among Black and Hispanic youth in the United States. Am J Prev Cardiol 2021;6:100175.

105.   Mau MK, Sinclair K, Saito EP, Baumhofer KN, Kaholokula JK. Cardiometabolic health disparities in native Hawaiians and other Pacific Islanders. Epidemiol Rev 2009;31:113-29.