Ex. 8A

Effect of Fructose on Caloric Intake, Appetite Hormones and Obesity

Overview of Recently Published Scientific Studies

Summary

Introduction

In this overview, the term "sugar" is restricted to sucrose. Whenever the term "sugar" is used, it means no free glucose or free fructose (glucose – fructose bond is 100-% intact) is present in the experimental (test) product. All other products tested in nutrition studies cited in this review will be described with terms other than "sugar."

The ratio of fructose to glucose will be inserted parenthetically as "F:G ratio" the first time this terminology is used. The F:G ratio will be reported on a weight:weight basis unless noted otherwise. The F:G ratio for sucrose is 1.00. Thus, sucrose is unique because of its 1) molecular bond between fructose and glucose and 2) F:G ratio of 1.00.

Any experimental product containing free fructose and free glucose will be described by its relative weight percentages of fructose and glucose. A product containing 80% fructose and 20% glucose, for example, will be designated as "F80:G20." The F:G ratio of F80:G20 is 4.00.

An F50:G50 test product is unique because, while the fructose-glucose bond is 100% cleaved, its F:G ratio is 1.00. This detail becomes meaningful when commercial sweeteners are considered. A commercial F50:G50 sweetener (F:G = 1.00) can be made only from sucrose. The F:G ratio of any fructose-containing commercial sweetener manufactured today from starch is either greater than 1.00 or less than 1.00. Since a test F50:G50 product could duplicate a commercial sugar product, the term "100% invert sugar" will be inserted parenthetically when a F50:G50 test product is first introduced.

However, it is incorrect to use the term "invert sugar" to describe any laboratory test product made exclusively from fructose and glucose. Since commercial invert sugar products typically are mixtures of sucrose, free glucose and free fructose, labeling any laboratory mixture of fructose and glucose as "invert sugar," whether or not a percentage is specified, can be challenged. Second, it might be worthwhile to examine the metabolic response of a test product that mimics 50% invert sugar (50% sucrose, 25% glucose and 25% fructose), the sucrose-based product predominantly used carbonated soft drinks until the early 1970s.

Background

During the 1980s, starch-based fructose-containing sweeteners began to replace sugar in foods and beverages. The most common starch-based, fructose-containing sweeteners contain either 55% or 42% fructose by weight (HFCS-55 and HFCS-42, respectively). Based on 2006 USDA delivery data, the split between HFCS-55 and HFCS-42 is approximately 60:40.[1] Since there are no reliable data on the amount of HFCS-90 used by the US food and beverage industries, the amount of dietary fructose contributed by starch-based fructose-containing sweeteners is essentially unknown.

On the other hand, USDA delivery data show that per capita sucrose consumption has declined from 72.5 pounds per year in 1970 to 45.0 pounds per year in 2005.[2] Per capita sucrose consumption has averaged 45 pound per year since 2000.[5]

The widespread practice of classifying individual sugars as a single entity implies that sucrose is chemically and metabolically equivalent to starch-based sweetener syrups containing varying amounts of fructose and glucose. The major difference between sucrose and starch-based glucose-fructose syrups is chemical bonding. The glucose and fructose in sucrose are linked molecularly, while the fructose and glucose in glucose-fructose syrups derived from starch are not molecularly linked, ie the fructose and glucose are chemically free.

A more subtle but equally important dissimilarity is the relative amounts of fructose and glucose in sucrose and starch-based glucose-fructose syrups. Sucrose contains equal amounts of glucose and fructose, ie the F:G ratio is 1.00. This feature is true for all dry and liquid sucrose products, including invert sugar. The amount of fructose in any commercial sugar product can never exceed its corresponding amount of glucose, ie the F:G ratio never exceeds 1.00. By comparison, the F:G ratio of HFCS-55 is 1.22 on a weight basis.

Has the direct replacement of sucrose with sweeteners containing free fructose generated unintended, negative health outcomes? When published data are analyzed critically, it becomes evident that metabolic events are governed not only by the balance between fructose and glucose but also by the molecular bond between fructose and glucose. If the biologic meaningfulness of the molecular bond or the balance between glucose and fructose is dismissed out-of-hand as insignificant, the concept of glycemic load, so central to the discussion of dietary guidance regarding carbohydrates and sugars,[3] also has to be rejected. Selective application of the recognized inherent physiologic differences between individual dietary sugars[4,5,6,7] is flawed scientifically.

The common practice of using the term “sugar” to describe foods, and beverages in particular, containing starch-based sweeteners further muddle the subject matter.[8] The same analytical precision applied to the measurement and description of dietary fatty acids must be applied to dietary carbohydrates, especially the dietary sugars.

This review will summarize the most recently published scientific literature comparing the effects of fructose-containing test beverages on caloric intake, appetite hormones and obesity. Obesity will be reviewed from the perspectives of lipogenesis and uric acid since these biomarkers are recognized as contributors to the obesity – diabetes – cardiovascular disease cluster.

Gastrointestinal malabsorption will not be part of this overview. Repeated studies have proven that, in healthy individuals, fructose is absorbed less readily than either glucose or sucrose, with the intensity of malabsorption determined by the proportional excess of fructose.[9,10] As the relative amount of fructose increases, malabsorption intensifies.[11] Not only does the ratio of fructose to glucose control gastrointestinal absorption, the absolute amount of fructose influences its rate of uptake.[12]

Caloric Intake

The majority of relevant commentaries,[13] editorials,[14,15] reviews[16] and experimental studies[7,17] published over the past three years have major shortcomings. The research community as a whole doesn't understand the chemical differences between sucrose and the variety of other dietary sugars present in today's food supply.

Short-term energy intakes are commonly measured in studies where a beverage (preload) is consumed at a prescribed time before a test meal is served. Among the more crucial variables controlling short-term energy intakes are type of participant, time interval between preload and test meal, caloric content of the preload, volume of the preload, and type of foods available at the test meal.[18] Time intervals, caloric contents, preload volumes and test meal foods are not consistent from study to study, which complicates data analysis.

A study design variable unique to sucrose is the pH of the beverage preload. If the test beverage is acidic such as the case with soft drinks, a portion of sucrose in that test beverage will have hydrolyzed to free fructose and free glucose. Only when the pH of a test beverage containing sucrose is above 5 is the comparison between sucrose and sweeteners in which some or all of the fructose is free valid. This means when studies are designed to "compare soft drinks containing sucrose and HFCS-55," the comparison is not between sucrose and HFCS-55 but between soft drinks sweetened with invert sugar (sucrose-free fructose-free glucose mixture) and HFCS-55.

Energy intakes are often measured with beverage preloads whose F:G ratio does not equal that of either sucrose or HFCS-55.[18] Reporting such energy intakes as if they had been determined with sucrose or HFCS-55 is not only irresponsible but inflammatory.

Another feature of short-term energy intake studies is the calculation of a statistical significance for the caloric differences between test meals consumed after each specific beverage preload. In most instances, there are too few participants in such studies to assign a statistical confidence level (95% minimum standard) to the observed caloric differences. The salient point is caloric intake differences are biologically meaningful even if they lack minimum statistical significance.

Four recently published studies have been analyzed and are summarized below.

- Only one study[19] has compared sucrose and HFCS-55 head-to-head. The volume and caloric content of the test beverages were 300 mL (~ 10 fl oz) and 300 calories, respectively. Each test beverage was consumed by each participant over a 3-minute period. The six test beverages were consumed in random order. The time interval between preload and test meal was 80 minutes. Study participants were young males. Participants were instructed to eat as much of the pizza test meal as desired.

    1. Energy intake at test meals following the sucrose beverage averaged 80 calories less than after the HFCS-55 beverage. While this average difference lacked statistical significance, an extra 80 calories is biologically meaningful.
    2. Energy intake at test meals following the sucrose beverage averaged 192 calories less than after a G50:F50 beverage. While this average difference lacked statistical significance, an extra 192 calories has biologic significance.
    3. After normalization of absolute energy intake values, relative caloric intakes following the HFCS-55 and F50:G50 preloads were identical.

4. The results of this study infer the reduced short-term caloric intakes observed after sucrose beverages are determined more by the presence of the molecular bond between fructose and glucose than by its F:G ratio of 1.00.

- A study[20] claiming to compare sucrose and HFCS-55 not only used acidic soft drinks but also did not utilize the preload – test meal design. The calorie content of each day-1 meal (breakfast/lunch/dinner) was controlled to meet the daily energy requirements calculated for each participant. Additionally, each participant ate the same type of food at each day-1 meal. The sucrose and HFCS-55 soft drinks were consumed as part of each day-1 meal, accounting for 30% of the meal's calories.

  On day 2, each participant was served a variety of foods for breakfast, lunch and dinner and was instructed to select the foods they liked and to eat as much of them as desired.

  Study participants were young females. Each study participant consumed both soft drinks in random order. Meals including test beverages were consumed over a 15-minute period.

  1. Total energy intake averaged 1,790 calories (calorie range = 1,518 – 2,063) on day 1.
  2. On day 2, participants ate an average of 82 more calories (60% from fat) after consuming the HFCS-55 soft drink on day 1 than after consuming the sucrose soft drink on day1. While this average difference lacked statistical significance, an extra 82 calories per day is biologically meaningful.
  3. The results of this study infer the reduced short-term caloric intakes observed after sucrose soft drinks are determined more by its F:G ratio of 1.00 than by the presence of its molecular bond.
  4. The authors dismissed the meaningful caloric and food intake differences observed on day 2 by stating that "ad libitum energy and macronutrient intakes and most appetite ratings were similar."

- A second study[21] claiming to compare sucrose and HFCS-55 also used soft drinks. However, this study had a preload – test meal design. The volume and caloric content of the test beverages were 525 mL (~ 18 fl oz) and ~ 215 calories, respectively. Each test beverage was consumed by each participant over a 15-minute period. The five test beverages were consumed in random order. The time interval between preload and test meal was 120 minutes. Study participants were young males and young females. Participants were instructed to eat as much or as little of any of the various foods served at the test meal. Participants could also request unlimited additional portions of any food item.

  1. The "sucrose soft drink" was approximately 36% sucrose at the start of the study but no more than 11% sucrose at study end. This detail is critical. Not all participants consumed the same "sucrose soft drink" over the course of the study. Since the five test beverages were served in random order, it is impossible to know which "sucrose soft drink" was consumed by which participant and to determine how that particular "sucrose soft drink" affected caloric intake during the subsequent test meal.
  2. Even with this glaring flaw, energy intake at test meals following the "sucrose soft drink" averaged 12 calories less than after the same individuals consumed the HFCS-55 soft drink.
  3. The results of this study infer the reduced short-term caloric intakes observed after sucrose soft drinks are determined more by its F:G ratio of 1.00 than by the presence of its molecular bond.

- A fourth study[17] also claiming to compare sucrose and HFCS-55 used acidic test beverages whose F:G ratios were not representative of sucrose and HFCS-55. The volume and caloric content of the test beverages were 800 mL (~ 27 fl oz) and ~375 calories, respectively. Each test beverage was consumed by each participant over a 15-minute period. The five test beverages were consumed in random order. The time interval between preload and test meal was 50 minutes. Study participants were young males and young females. Participants were instructed to eat as much the granola cereal with yogurt test meal until they "felt comfortably full."

  1. The "sucrose beverage" was 66% sucrose and 34% glucose syrup, which was defined as 91% glucose and 9% fructose. This means that the "sucrose beverage" was 64% glucose and 36% fructose on a weight basis.
  2. The "HFCS beverage" was 55% sucrose and 45% glucose syrup, also defined as 91% glucose and 9% fructose. This means that the "HFCS beverage" was 59% fructose and 41% glucose on a weight basis.

Appetite Hormones

Obesity

Lipogenesis

Lipogenic variations are observable when the relative amount of dietary fructose increases. A recent study[24] clearly confirms that calorically balanced diets high in free fructose uniquely elevate triglyceride levels, particularly in men. Further research is needed to determine whether this documented observation is due *per se* to the inflated fructose – glucose ratio, or to the fact that the majority of the fructose and glucose were provided as molecularly free fructose and glucose.

A more recent study documents that women experienced hypertriglyceridemia when consuming beverages high in fructose, but not glucose, with meals.[25] Plasma triglycerides not only peaked more rapidly but remained at significantly higher levels throughout the 24-hour measurement period when the fructose-rich beverages were consumed.

Additionally, molecularly free fructose elevates plasma triglycerides in both non-diabetic and diabetic individuals.[26] In fact, the increased lipogenic potential of free fructose is highlighted in an exhaustive literature review commissioned by the American Diabetes Association.[27] In its revised dietary recommendations, the Diabetes Association advises that usage of free fructose to reduce postprandial insulin requirements is not recommended on the basis of its documented elevation of plasma lipids.[28] The Diabetes Association further advises diabetics to not restrict sucrose intake but to include sucrose within their carbohydrate allotment.[17]

Recent animal studies confirm that diets high in molecularly free fructose exacerbate not only hypertriglyceridemia[29] but also its accompanying inflammation.[30] These results are consistent with the results of earlier animal and human studies summarized in a 2002 review.[31]

Food Intake and Energy Homeostasis

Regulation of food intake and maintenance of energy homeostasis are controlled by independent but interactive short-term and long-term physiologic signals.[32,33] Short-term signals, in general, govern satiety by

regulating the size of an individual meal and how its energy content is assimilated during and immediately after ingestion of the meal. Common short-term regulators include nutrients, like glucose, amino acids and fatty acids, and gastrointestinal peptides like glucagon-like peptide-1 and cholecystokinin.[23,24]

By contrast, satiation is governed by long-term regulators of food intake and energy homeostasis. These long-term signals are controlled by the amount of energy consumed over prolonged periods and by the dynamics of energy partitioning mediated by *in vivo* adipose stores.[23,24] Common long-term regulators include the hormones insulin and leptin.[23,24]

Insulin has been shown[34] to not only control food intake and increase energy expenditure over the long term but also to induce[35] the production and release of leptin. Insulin and leptin are now recognized as two of the fundamental modulators of long-term food intake and energy homeostasis, with the requisite production of leptin being dependent on insulin secretion. Thus, insulin and leptin work in tandem to keep long-term energy homeostasis within physiologic boundaries by concurrently dampening appetite and inhibiting food intake.

Since human physiology is encoded to maintain body weight and adiposity within innate boundaries, peripheral signals that initiate food intake are necessary.[25] One such appetite-stimulating regulator in humans is the gastric hormone ghrelin.[36]

Originally, it was hypothesized[22,23] that the weight gain observed when humans were fed diets high in fructose was due solely to reduced insulin secretion coupled with the resulting blunted leptin production. Recent data not only substantiate that diets high in molecularly free fructose diminish insulin and leptin production, but that these same diets also concurrently increase long-term ghrelin levels.[16] While more research is needed, these synchronous results indicate that diets rich in free fructose are predestined to increase long-term energy intake.

While body adiposity is now thought to be determined more by long-term than short-term physiologic signals,[23] recent data imply that the paradigm where insulin and its cascade of induced signaling agents are exclusively long-term regulators of food intake may need to be expanded.[37] The fact that short-term food intake and appetite were more suppressed as blood glucose levels increased suggests that the same results would have been observed with concurrent increasing levels of insulin secretion. Minimally, these results indicate that areas under insulin response curves should accompany areas under blood glucose response curves whenever short-term satiety experiments are designed in the future.

It is instructive to note that short-term food intakes increased between the sucrose and the 80% fructose – 20% glucose treatments.[28] Energy intake was nearly 100 kcal higher after the 80% fructose – 20% glucose treatment than after the sucrose treatment. Whether this documented difference is due to a fructose – glucose ratio exceeding 1.00, or to the lack of molecular bonding between the fructose and glucose in the 80% fructose – 20% glucose treatment, requires appropriately designed experiments to provide unequivocal answers. This fact shows that the paradigm of sugars, in general, stimulating satiety mechanisms which reduce short-term food intake[38] requires more precise definition.

Conclusion

Irrefutable data are limited. However, what data are available corroborate that the fructose molecularly bonded in sucrose generates physiologic effects distinct from those established by molecularly free fructose. The same precision applied to differentiating the health outcomes of individual dietary fatty acids must be

adopted when individual dietary sugars are considered. As outlined above, it is scientifically inappropriate to continue the practice of assigning dietary sugars into a single generic, nonspecific class.

The Association respectfully asks FDA to comprehensively review its current regulations governing the food ingredient category of caloric sweeteners, and to establish objective sweetener food label definitions and rules that communicate the distinctive physiologic effects of the individual dietary sugars.

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[2] United States Department of Agriculture. Economic Research Service, Briefing Room. ***Sugar and Sweetener Yearbook Tables: Excel (.xls) Spreadsheets***, Table 51. http://www.ers.usda.gov/briefing/sugar/Data/data.htm. Last ERS Update: March 15, 2007. Accessed December 19, 2007.

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