An isotopic method for quantifying sweeteners derived from corn and sugar cane[1–3]

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ABSTRACT

Background: Consumption of high-fructose corn syrup, as well as cane sugar, has been implicated in the rise of the obesity and diabetes epidemics. To date, however, no reliable biomarker for the consumption of these sweeteners is available.

Objective: The objective of the study was to determine the natural abundance stable-carbon-isotope signature of commonly consumed foods of plant origin.

Design: Samples from ≈100 plant-derived food products purchased from local grocery stores were analyzed for ^{13}C content by using stable-isotope mass spectroscopy.

Results: Measurement of natural abundance ratios of ^{13}C to ^{12}C in ≈100 off-the-shelf foods found a distinct range of values for corn- and sugar cane–derived foods, particularly those rich in high-fructose corn syrup.

Conclusion: A new technique, in which consumption of these foods may be estimated in humans by measuring the natural abundance stable-carbon-isotope profile of corn- and sugar cane–sweetened or sugar-containing foods as tracked in tissue or blood, could potentially provide an objective assessment of dietary intake and offer new opportunities for the study of diet-disease relations. *Am J Clin Nutr* 2006;84:1380–4.

KEY WORDS Sweetener, stable carbon isotope, obesity, chronic diseases, dietary intake, biomarker, high-fructose corn syrup

INTRODUCTION

The worldwide epidemic of diabetes (1, 2) is known to be closely tied to the concurrent epidemic of overweight and obesity. It is generally accepted that key factors associated with obesity are the increased availability of high-calorie foods and an increasingly sedentary lifestyle. In addition, it has been suggested that a high consumption of sugars [including high-fructose corn syrup (HFCS)] could contribute to excess energy intake and weight gain (3). It is important to test the hypothesis that sweets-enriched diets can lead to increased obesity; if an association can be established, it would present a common target for population-based prevention of obesity.

Current approaches to assessing dietary intake rely on self-reporting and thus have obvious limitations. A pressing need exists for objective, reliable methods of measuring food-type intake in free-living persons. To date, no reliable biomarkers for HFCS or cane sugar consumption exist. We present a proposal based on the natural abundance stable-carbon-isotope signature of foods of plant origin; this technology could be used to differentiate sugars (particularly corn-derived HFCS and cane-derived syrups) from other sources of caloric intake by using the inherent and distinct, measurable $\delta^{13}C$ signature in these foods.

During the photosynthetic fixation of atmospheric carbon dioxide, enzymes impart selectivity over 2 stable isotopes of carbon, ^{12}C (≈99% of all biosphere carbon) and ^{13}C. Most plants (called C3 plants) employ one enzyme: ribulose biphosphate carboxylase-oxygenase. A small subset of plants (called C4 plants) employ an additional enzyme: phosphoenolpyruvate carboxylase. Because of this extra enzyme, the ratio of ^{13}C to ^{12}C (^{13}C:^{12}C) within the tissues of C3 and C4 plants fall within distinct ranges. When this ratio is measured in the laboratory, it is reported as a $\delta^{13}C_{tissue}$ value; the median $\delta^{13}C_{tissue}$ value for C3 plants is −27 per mil (ie, ‰), whereas the median $\delta^{13}C_{tisse}$ value for C4 plants is −14‰ (4, 5). With respect to dietary application, both corn (*Zea* spp) and sugar cane (*Saccharum* spp) are C4 plants, and therefore they carry a conspicuously high $\delta^{13}C_{tisse}$ value.

In this report, we quantify the conspicuous $\delta^{13}C_{tisse}$ values associated with corn and cane sugars and show their dissimilarity from a wide variety of edible plants. We also show that these values propagate to processed sweetened foods, such as HFCS-rich soda and candy. We suggest that an assay of the $\delta^{13}C$ value of human substrates may be used to quantify HFCS or other sweetener consumption, and we envision applicability of this technique to a variety of population studies, specifically to testing the relation between the intake of added sweeteners and the prevalence of obesity. We wish to stress that this application involves the naturally occurring (and thus very low) ^{13}C content in plant material and thus is unlike more commonly employed "tracer studies" that involve artificial spiking of substrates with heavy isotopes. Our method relies on natural-abundance mass

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TABLE 1
The carbon isotope value of common unprocessed foods[1]

Food	$\delta^{13}C_{VPDB}$ C4 signature	$\delta^{13}C_{VPDB}$ C3 signature
	‰	
Corn products[2]	—	—
Corn starch	−10.68	—
Corn syrup	−10.22	—
Corn syrup (light)	−10.49	—
Popcorn	−11.66	—
Sugar cane products	—	—
Molasses[3]	−12.71	—
Cane sugar (plain)	−11.99	—
Cane sugar (dark brown)	−11.75	—
Cane sugar (light brown)	−11.63	—
Powdered cane sugar	−11.59	—
Other natural sweeteners	—	—
Beet sugar	—	−25.62[4]
Maple sugar[5]	—	−23.81
Fruit and vegetables	—	—
Apple	—	−24.11
Apple juice	—	−24.13
Banana	—	−24.68
Beets	—	−25.43
Butternut squash	—	−26.42
Cucumber	—	−28.67
Golden raisins[6]	—	−25.50
Lemon	—	−24.27
Mushroom	—	−22.27
Orange	—	−26.87
Raisins[6]	—	−24.92
Tomato	—	−26.49
Protein	—	—
Garbanzo beans	—	−25.88
Hazelnuts	—	−25.72
Lentils	—	−25.78
Mung beans	—	−25.45
Pine nuts	—	−25.59
Pistachios	—	−26.37
Pumpkin seeds	—	−25.59
Soy beans	—	−27.35
Tofu[7]	—	−26.31
Walnuts	—	−26.45
Wheat germ	—	−24.43
Whey	—	−21.43
Starch	—	—
Arrowroot	—	−26.00
Barley	—	−24.49
Basmati brown rice	—	−27.52
Brown rice	—	−26.17
Cracked wheat	—	−24.85
Flax	—	−27.57
Flour	—	−25.93
Gluten	—	−25.35
Matzo meal[8]	—	−26.44
Potato flour	—	−23.71
Potatoes	—	−25.77
Rye flour	—	−25.03
Tapioca	—	−25.91
Unbleached flour	—	−25.05
White rice	—	−26.88
Wild rice	—	−26.54

[1] VPDB, Vienna Pee Dee Formation limestone. Foods are listed alphabetically within type categories; values are presented graphically within Figure 1. For complete ingredient lists, *see* "Supplemental data" in the current issue at www.ajcn.org.

spectrometry, a much more sensitive form of isotope measurement, and does not require any chemical treatment of diet components before consumption.

MATERIALS AND METHODS

Approximately 100 off-the-shelf plant-derived food products were obtained from grocery stores (**Tables 1** and **2**). Aliquots of the foods were lyophilized, ground to a fine uniform powder, and analyzed for $\delta^{13}C$ value by using an automated combustion system (Euro.EA3000; EuroVector Instruments and Software, Milan, Italy) in conjunction with a stable-isotope mass spectrometer (Isoprime; Micromass UK Ltd, Manchester, United Kingdom); samples were introduced to the combustion system in high-purity tin capsules. Natural-abundance stable isotope ratios are quantified in terms of the deviation of the ^{13}C:^{12}C in a sample from that of a known standard. The per mil (‰) convention is used when reporting stable isotope values, as shown in the following equation:

$$\delta^{13}C_{sample}(‰) = [(^{13}C{:}^{12}C_{sample} - {}^{13}C{:}^{12}C_{std})/{}^{13}C{:}^{12}C_{std}] \times 1000 \quad (1)$$

The reporting standard for this experiment was Vienna Pee Dee Belemnite Formation limestone with a ^{13}C:^{12}C of 0.011237. Analytic uncertainty associated with each measurement was ± 0.1‰. The values presented represent the average of 3 replicate capsules, and the SD of replicate capsules averaged 0.2‰. All analyses were performed at the stable isotope laboratories of Department of Earth and Planetary Sciences at Johns Hopkins University.

RESULTS

The food products chosen for analysis (Tables 1 and 2) represent a range of common calorie sources supplied to the human diet by the first trophic level (ie, plant materials and their derivatives). Several grains and a wide range of fruit, vegetables, starches, and proteins (especially soy) are included. Many processed foods, such as diet and regular beverages, are also included, as are commercially prepared snacks and desserts. (For a detailed description of each food sampled, including its manufacturer and ingredient list, *see* Table 1 under "Supplemental Data" in the current issue at www.ajcn.org.)

Clear patterns of $\delta^{13}C$ values emerged from these analyses. The fruit, vegetables, proteins, and starches (including rice and wheat flour) had an obvious C3 signature (**Figure 1**; Table 1). In sharp contrast, corn- and sugar cane–derived foods (including HFCS) had a clear C4 signature. It is important to note that both

[2] Argo Corn Starch and Karo Light Corn Syrup; Bestfoods, Englewood Cliffs, NJ: Betty Crocker Corn Syrup; Signature Brand, Ocala, FL.

[3] Grandma's Robust Molasses; Mott's, Inc, Stamford, CT.

[4] As reported by the International Atomic Energy Agency, Atomic and Molecular Data Unit, 1995 (beet sugar is considered an international isotopic standard).

[5] Vermont Powdered Maple Sugar; The Vermont Country Stone, Weston, VT.

[6] California Golden Raisins and Natural California Raisins; Sunmaid Growers of California, Kingsburg, CA.

[7] Silken Tofu Extra Firm; Mori-nu, Torrance, CA.

[8] Unsalted Matzo Meal; Manischewitz, Jersey City, NJ.

TABLE 2
The carbon isotope value of selected processed foods[1]

Food	$\delta^{13}C_{VPDB}$ C4 signature	$\delta^{13}C_{VPDB}$ C3 signature
	‰	
Sweetened beverages[2]	—	—
Iced tea	−10.27	—
Soda 1	−10.59	—
Soda 2	−10.77	—
Root beer	−11.52	—
Other beverages[3]	—	—
Buttermilk	—	−17.52
Whole milk	—	−20.57
Fruit punch	—	−25.03
Coffee	—	−26.77
Sweetened processed foods[4]	—	—
Hard candy 1	−10.66	—
Hard candy 2	−10.68	—
Hard candy 3	−10.97	—
Gelatin	−12.45	—
Breakfast cereal 1	—	−15.27
Canned fruit 1	—	−15.53
Breakfast cereal 2	—	−16.39
Canned fruit 2	—	−17.17
Dark chocolate	—	−18.20
Coffee creamer	—	−21.42
Breakfast cereal 3	—	−21.72
Cookie	—	−21.95
Breakfast cereal 4	—	−22.96
Milk chocolate	—	−23.28
Breakfast cereal 5	—	−24.27
Jam	—	−24.95
Soy mix	—	−25.01
Breakfast cereal 6	—	−25.46
Mayonnaise	—	−25.52
Breakfast cereal 7	—	−25.66
Cake mix	—	−25.90
Mustard	—	−26.19
Ramen noodles	—	−26.43
Peanut butter	—	−26.48
Crackers	—	−26.78
Dijon mustard	—	−27.25
Cocoa	—	−28.09
Artificial sweeteners[5]	—	—
Sucralose	−10.56	—
Aspartame	−10.58	—
Saccharin 1	−10.97	—
Saccharin 2	−11.34	—
Artificially sweetened beverages[6]	—	—
Diet ginger ale	—	−16.77
Diet lemon-lime soda	—	−19.78
Diet soda 1	—	−20.11
Diet soda 2	—	−24.52
Diet soda 3	—	−24.65
Diet soda 4	—	−25.75

[1] VPDB, Vienna Pee Dee Belemnite Formation limestone. Foods are listed (within type categories) in descending carbon isotope value so as to emphasize the groupings of isotopic signatures. For complete ingredient lists, *see* "Supplemental data" in the current issue at www.ajcn.org.

[2] Iced tea: Snapple Iced Tea All-Natural Lemon; Snapple Beverage Corp, Rye Brook, NY; soda 1: Pepsi Cola; PepsiCo, Purchase, NY; soda 2: Coca-Cola; Coca-Cola Co, Atlanta, GA; root beer: Mug Root Beer (caffeine-free); PepsiCo.

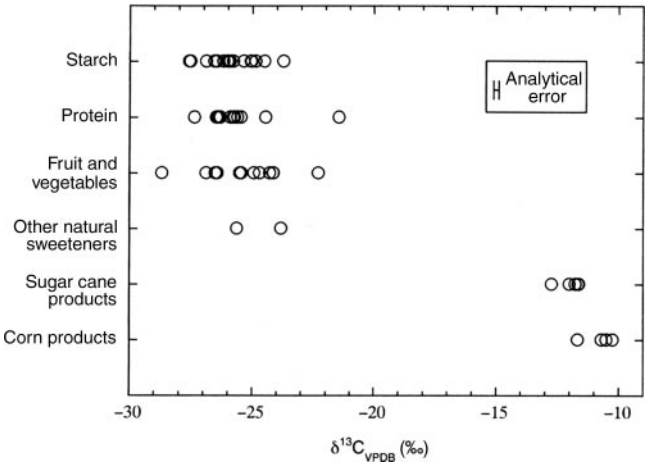

FIGURE 1. Carbon-stable-isotope composition of foods listed in Table 1 grouped by category. Corn- and sugar cane–derived foods have C4 signatures (high values), whereas all other foods have C3 signatures (low values). The experimental uncertainty associated with each measurement is very small [ie, 0.1‰ (per mil)] compared with the separation between C3 and C4 values. VPDB, Vienna Pee Dee Belemnite Formation limestone.

maple sugar and beet sugar had a C3 signature; maple sugar does not contribute significant calories to the common American diet. However, beet sugar is a significant source of calories: to illustrate, much of the sugar marketed in the United States is beet

[3] Fruit punch: Juicy Juice 100% Juice Punch; Nestlé USA, Glendale, CA; coffee: Folgers Instant Coffee Classic Roast; Folger Coffee Co, Cincinnati, OH.

[4] Hard candy 1: Runts; hard candy 2: SweeTarts; hard candy 3: Bottle caps; all, Willy Wonka's Candy; Nestlé, Vevey, Switzerland; breakfast cereal 1: Kellogg's Corn Pops; Kellogg's, Battle Creek, MI; canned fruit 1: Lychee in Syrup; Thep Padung Porn Coconut Co, Ltd, Nakhonpathon, Thailand; breakfast cereal 2. Kellogg's Frosted Flakes; Kellogg's; canned fruit 2: Del Monte Fruit Cocktail; Del Monte Foods, San Francisco, CA; dark chocolate: Sweet Chocolate Bar; Ibarra Co, Ltd, Guadalajara, Mexico; coffee creamer: Coffee-mate Coffee Creamer (Original); Nestle USA; breakfast cereal 3: Kellogg's Froot Loops; Kellogg's; cookie: Nabisco Ginger Snaps; Nabisco, East Hanover, NJ; breakfast cereal 4: Kellogg's Apple Jacks; Kellogg's; milk chocolate: Hershey's Milk Chocolate; Hershey Foods Corp, Hershey, PA; breakfast cereal 5: Kellogg's Honey Smacks; Kellogg's; jam: Bonne Maman Strawberry Preserves; American Marketing Team, Bloomfield, NJ; soy mix: Atkins Bake Mix; Atkins Nutritionals, Ronkohhoma, NJ; breakfast cereal 6: Rice Chex (Oven Toasted Rice Cereal); General Mills Cereals, LLC, Minneapolis, MN; mayonnaise: Hellmann's Light Mayonnaise; Unilever Best Foods Foodservice, Franklin Park, IL; breakfast cereal 7: Kellogg's Cocoa Krispies; Kellogg's; cake mix: Double Pudding Moist Supreme Classic Yellow Premium Cake Mix; Multifoods Inc, Minneapolis, MN; mustard: Heinz Yellow Mustard; Heinz Co, Pittsburgh, PA; ramen noodles: Maruchan Ramen Noodle Soup Oriental Flavor; Maruchan, Irvine, CA; crackers: Sunshine Cheez-it; Sunshine Biscuits, LLC, Elmhurst, IL; dijon mustard: Grey Poupon Dijon Mustard; Ridge's Finer Foods Inc, Glenview, IL; cocoa: Hershey's Cocoa; Hershey Foods.

[5] Sucralose: Splenda No Calorie Sweetener; McNeil PPC, Inc, Fort Washington, PA; Aspartame: Equal Sweetener; Merisant Co, Chicago, IL; saccharin 1: Sweet Plus Sugar Substitute; Sysco Corp, Houston, TX; saccharin 2: Sugar Twin Calorie Free Sweetener; Sysco Corp.

[6] Diet ginger ale: Seagram's Diet Ginger Ale; Coca-Cola Co; diet lemon-lime soda: Diet Mountain Dew; PepsiCo; diet soda 1: Diet Coke; Coca-Cola Co; diet soda 2: Red Bull Sugarfree; Red Bull NA, Inc, Santa Monica, CA; diet soda 3: Diet Dr. Pepper; Dr. Pepper Co, Plano, TX; diet soda 4: Diet Pepsi; PepsiCo.

sugar. It is also increasingly true that sweetened juice (prepared from concentrate) provides substantial calories to children's diets. For these reasons, we have proposed that this application is most useful in the context of HFCS studies and studies of other corn- and sugar cane–derived sweeteners.

Table 2 shows the carbon isotope value of processed foods: it is notable that sweetened beverages, including soda, clearly carry a C4 signature, which reflects their HFCS content; similarly, a C4 signature was found in hard candy. In contrast, a C3 signature was found in unsweetened caloric beverages (ie, milk products, coffee, and unsweetened juice). Highly processed foods with added sugars, such as sugared breakfast cereals, cookies, and crackers, exhibited $\delta^{13}C$ values that were dominated by the signature of the primary grain ingredient—ie, cookies, cake mixes, and condiments all plotted within the C3 zone. Artificial sweeteners, such as saccharin and aspartame, had a C4 signature; however, artificially sweetened beverages (eg, diet sodas) had C3 signatures. The very low carbon (and very low calorie) content of these foods ensures that they will not impart significant ^{13}C to diets of interest. Our results emphasize the unique and conspicuous $\delta^{13}C$ value within corn- and sugar cane–derived sweeteners and concordantly within sugared soda and hard candy.

DISCUSSION

These initial analyses show definitively that food groups of importance in the American diet can be identified by their natural-abundance carbon isotope ratio. We note that, in recent characterizations (6–9), Western diets, including the diet of American toddlers, are rich in corn-derived sweeteners—ie, those with conspicuous $\delta^{13}C$ signatures. The potential limitations to the application of this technique in epidemiologic studies are twofold. First, foods derived from corn come in many forms, including corn oil and corn flour. Second, the increasing consumption of corn-fed animals poses a possible confounding effect. Clearly, early studies meant to trace the consumption of corn- and cane- derived sweeteners would have to control for any and all dietary inclusion of corn.

The ability to distinguish dietary patterns (specifically, diets high in HFCS and cane sugars) in an objective way has important implications for studies of the relation between dietary patterns and diseases. Data obtained from mammals indicate that the $\delta^{13}C$ value of an animal's diet is reflected in the $\delta^{13}C$ value of that animal's blood, teeth, bones, and other tissues (10–17). Given a recent study reporting changes in the $\delta^{13}C$ values of bovine muscle and adipose tissue that reflected a clear change in dietary isotope profile only 160 d after a change in diet (18), we feel particularly optimistic about the likelihood that changes in diet will be reflected by changes in the $\delta^{13}C$ value of human tissues. Those results in cows bode well for the application of carbon isotope analysis to studies of human diet; however, a completed bioassay of sweetener consumption that is usable in the public health setting will require additional experiments. Such experiments include the use of the assay in human tissues; comparison of different tissues; validation that tissue concentration reflects dietary intake; assessment of the kinetics over time, potentially of different tissues; and, ultimately, optimization of assay convenience and reliability. The American diet is rich in corn and corn derivatives, such as HFCS; in addition, certain population groups may consume corn in greater proportions, and therefore further studies must take into consideration the ethnic identities of the group or groups studied. This report describes the concept that commonly ingested plants have unique signatures of interest; it also describes the testing of that concept, which cements the validity of the first step of this new approach.

The unique $\delta^{13}C$ signature of sweetened sodas may lead to several important applications. For example, $\delta^{13}C$ measurements could be used to track HFCS consumption through blood, hair, or nail samples and to explore whether that consumption adversely affects lipid profile, as suggested by one study (19). As another example, virtually absolute stability of this measurement postmortem would make it possible (eg, through the measurement of bone or hair) to compare the diets of various populations over long periods, as was done by Ebbeling et al (20).

The strength of our proposal is that it takes advantage of a clearly shown difference in stable isotope abundance in different foodstuffs and, specifically, a distinct pattern for one controversial component of the modern diet, HCFS. Tissue carbon signatures would be expected to reflect ingested carbon, although the time kinetics of such reflection may vary from tissue to tissue. Further evaluation of the methods by including the study of humans who are consuming relatively well-defined diets, particularly the isotope profile resulting from mixed diets containing plant and animal products, is needed. Nonetheless, the results presented here give reason for optimism that the method can eventually be used to objectively quantify HFCS and cane sugar dietary intake patterns in human populations.

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AHJ was responsible for generating the hypothesis, obtaining funding for and conducting the data collection and analysis, and drafting the manuscript. CS, EHY, WHLK, RAK, and BC participated in conceptualizing the study and in writing and editing the manuscript. None of the authors had a personal or financial conflict of interest.

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