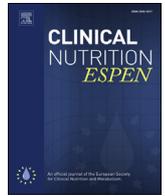




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Opinion Paper

Evolutionary physiology shows the need for an unprecedented study on sugar



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SUMMARY

Many experimental studies on sugar (sucrose) omitted its form of ingestion. Often their findings were mutually incompatible. A comparison of the results of the few studies that administered sugar in a single specified form suggests that the metabolic effects of sugar depend on its form of ingestion, because even 80% of calories as diluted sugar proved harmless, but only 30% of calories as undiluted sugar proved harmful. These opposite effects of sugar can be explained by the published hypothesis that evolution adapted genetically our ancestors to cope with sugar only in diluted forms, because prehistorically diluted sugar was available abundantly in fresh fruits, but undiluted sugar was inexistent. The purpose of this review, based mainly on the evolutionary interpretation of published data of physiology, is to encourage researchers to perform an unprecedented experimental study to compare the metabolic effects of diluted sugar with the effects of undiluted sugar. The data of physiology analyzed in this review suggest that the absorption of diluted sugar within the caloric range of total sugars diluted in fresh fruits is slow and calorie-constant, thus preserving blood glucose homeostasis, whereas the absorption of concentrated sugar exceeding that caloric range is rapid, which can disrupt blood glucose homeostasis. Dietary salt, which was unknown to prehistoric humans, unnaturally accelerates the absorption of sugars. This can explain the harmful effects attributed to sugar-sweetened beverages per se, because these drinks are generally co-ingested with foods containing salt, which partly yet unavoidably passes into those beverages, thereby unhealthily accelerating their absorption.

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1. Introduction

Many experimental studies on sugar omitted its form of ingestion [1]. These omissions can explain why several results of those studies are mutually incompatible [1]. Their discrepant findings can be explained by comparing the results of the few studies that administered sugar in a single form and specified it [1]. For example, after giving sugar only in diluted form, some authors wrote: “the feeding of 80% of calories as sucrose did not lead to an impairment of the GTT [Glucose Tolerance Test] in any subject” [2] (p. 600); antithetically, after giving only 30% of calories as undiluted sugar, others wrote: “sucrose feeding produces undesirable changes in several of the parameters associated with glucose tolerance” [3] (p. 2206). These contradictory findings and the omissions mentioned above can explain why “studies that have examined the addition of sucrose to the diet of noninsulin-

dependent diabetes mellitus (NIDDM) subjects for periods of 2–6 wk have produced conflicting results” [4] (p. 474).

Conflicting results between studies on sugar also regard its effects on cholesterol and triglycerides. Indeed, “Several authors have reported no change in plasma cholesterol in response to sucrose, even when sucrose was given as a very high proportion of the diet (11–65% of energy) ... In contrast, in other studies, plasma cholesterol concentrations were observed to rise in response to sucrose consumption within a broad range (18–52% of energy)” [5] (p. 251S). Additionally, as some authors wrote, “there is evidence from several well-controlled prospective studies demonstrating that the consumption of moderate amounts of sucrose may result in hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, and reduced high-density lipoprotein cholesterol concentrations. The fact that not all studies demonstrate these deleterious effects does not negate the positive data” [6] (p. 62). Those “discrepancies between studies” [5] (p. 251S), besides causing “considerable debate concerning the effects of sucrose on

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plasma lipids and in particular triglyceride levels” [7] (p. 498), also understandably resulted in medical guidelines that could hardly be more discrepant [1]. Indeed, most conflictingly, some guidelines recommend that the ingestion of sugar should not exceed 5% of energy requirement [8], whereas other guidelines imply that even 25% of total energy can safely derive from sugar [8].

As “the issue of dietary sucrose must assume a prominent role in the discussion of the dietary treatment of diabetes” [6] (p. 62), which “is becoming the plague of the 21st century” [9], it has been proposed to perform an unprecedented experimental study aimed at clarifying the real effects of sugar intake on human health by directly comparing the metabolic effects of diluted sugar with the metabolic effects of undiluted sugar [1]. The following rationale based on evolutionary physiology highlights the scientific advisability to conduct that unprecedented research.

2. Rationale for the unprecedented study on sugar

As the thoughtful article “Evolutionary physiology” [10] correctly underlined, “Physiologists are interested in how organisms work. A subset of physiologists also wants to know why organisms are designed to work in particular ways. Unless one assumes special creation of all organisms, an understanding of such why questions requires an evolutionary perspective” [10] (p. 581). This perspective reveals that “Bodies are not designed; they are shaped by natural selection” [11] (p. 42). By implication, “One of the most important influences affecting genetic selection and adaptation is the interaction between a species and its food supply” [12] (p. 814). In line with the view that “Medicine needs evolution” [13], because “Nothing in medicine makes sense, except in the light of evolution” [14], two correlated hypotheses have been advanced [1,15]. These hypotheses inspired by evolutionary theorizing, which “points to hypotheses that we otherwise might not even think of” [16] (p. 642), are based on the idea that evolution adapted genetically the metabolic physiology of our ancestors to cope with sugar only in diluted forms, because prehistorically diluted sugar was available abundantly in fresh fruits but undiluted sugar was inexistent [1,15].

Those hypotheses [1,15] posit that evolutionarily conserved physiological traits make diluted sugar harmless and undiluted sugar harmful. The evolutionary conservation of ancestrally selected physiological traits is likely, because “Humans are not self-made creations dietarily, but rather have an evolutionary history as anthropoid primates stretching back more than 25 million years, a history that shaped their nutrient requirements and digestive physiology well before they were humans or even protohumans. In hominoids, features such as nutrient requirements and digestive physiology appear to be genetically conservative” [17] (p. 665). Given that “modern humans and chimpanzees diverged from a common ancestor who was chimp-like, — forest-dwelling, and predominantly arboreal and fruit-eating — between 5 and 8 Myr ago” [18] (p. 219), evolutionary reasoning forces us to realize that “Available food shapes all species, and we were shaped by the fruit of the tree” [19] (p. 737), because “We are what we ate” [18].

Considering that “During the Miocene era (from about 24 to about 5 million years ago) fruits appear to have been the main dietary constituent for hominids” [20] (p. 284), the most compelling explanation for the otherwise puzzlingly conflicting results of many studies on sugar [1–6] emerges from the following data of physiology interpreted in the light of evolution:

I. Importantly, “gastric emptying is a major factor in blood glucose homeostasis, in normal subjects and in patients with diabetes” [21] (p. 857). Diluted glucose and diluted sucrose, which is a mixture of glucose and fructose [22], empty

identically from the stomach [22], because “The effects of sucrose and a glucose and fructose mixture ... are indistinguishable ... in slowing gastric emptying” [22] (p. 323–4).

- II. The gastric emptying of diluted glucose is “a linear function” [23] (p. 78), i.e., it is “a slow and calorie-constant emptying pattern” [23] (p. 76), which proceeds “progressively more slowly with increasing concentrations” [24] (p. R254). For this reason, “Glucose empties so as to maintain a constant rate of delivery of calories to the small intestine over a range of energy densities of 0.2–1.0 kcal/ml” [24] (p. R256). As this range virtually overlaps the caloric range of total sugars diluted in fresh fruits [1], which were the main food of humankind's ancestors for millions of years [1,18–20], intuition tells us that human gastrointestinal physiology is evolutionarily adapted to the wide caloric range of fresh fruits, to preserve blood glucose homeostasis [1]. One might object that intuition is unreliably subjective and thus scientifically valueless. However, as Albert Einstein famously pointed out, “The only real valuable thing is intuition”.
- III. Thanks to evolutionarily conserved physiological traits adapted to fresh fruits, “Although gastric emptying slowed as glucose concentration increased, when gastric emptying was expressed as the rate of calories delivered to the intestine, all three glucose solutions emptied at indistinguishable rates” [23] (p. 78). Within the range 0.2–1.0 kcal/ml, “Doubling the volume of a glucose meal does not significantly alter the rate of emptying” [24] (p. R256). This suggests that even the ingestion of large quantities of fresh fruits did not affect the glucose homeostasis of humankind's ancestors [1]. Notably, “The number of glucose calories passed per unit time (2.13 kcal/min) remained the same over a fivefold concentration range” [23] (p. 78). Within this range (0.2–1.0 kcal/ml), “Such constancy suggests in humans, as in the monkey, that glucose emptying differs from the emptying of physiological saline in being subject to tight regulation” [23] (p. 80).
- IV. In sharp contrast with the slow and calorie-constant emptying pattern of diluted glucose [23,24], the gastric emptying of concentrated glucose is rapid, because “when glucose concentration exceeds 1.0 kcal/ml, gastric emptying does not slow further. As a result with each increment in concentration above 1.0 kcal/ml, there is more rapid delivery of calories to the small bowel, i.e., a loss of regulation to caloric concentration” [24] (p. R256). This loss of regulation occurring exactly above the highest caloric concentration of fresh fruits [1] suggests that undiluted sugars are “genetically unknown foods” [15]. Indeed, although humankind's ancestors occasionally ate honey, which was rare before apiculture, its sporadic and scanty ingestion could not modify the genetic physiological molding produced by the daily and plentiful ingestion of fresh fruits [1]. With respect to dried fruits, which by far exceed the caloric range of fresh fruits, presumably they were rarer than honey in the “relatively heavily wooded habitats” [25] (p. 368) of humankind's ancestors, because of the frequent tropical-equatorial rains and the shade of those tick forests [1].

The data of physiology recalled above suggest that even 80% of calories as diluted sugar did not impair glucose tolerance in any subject [2] because the intestinal absorption of sugar was slow and calorie-constant, which preserved blood glucose homeostasis, whereas only 30% of calories as undiluted sugar affected undesirably glucose tolerance [3] because the absorption of sugar was rapid, which disrupted blood glucose homeostasis.

Although some millennia ago an incipient agriculture and apiculture enabled humankind to consume undiluted sugars rather

frequently, these concentrated carbohydrates still remain “genetically unknown foods” [15], because “the introduction of agriculture and animal husbandry ~10,000 y ago occurred too recently on an evolutionary time scale for the human genome to adjust” [26] (p. 341). Therefore, “Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected” [27] (p. S10). Consequently, “From a genetic standpoint, humans living today are Stone Age hunter-gatherers” [28] (p. 739), which can explain why a recent systematic review and meta-analysis concluded that “The Paleolithic diet resulted in greater short-term improvements in metabolic syndrome components than did guideline-based control diets” [29] (p. 922).

3. Dietary salt accelerates the absorption of sugars

Prehistorically, dietary salt (sodium chloride, NaCl) was unknown. Indeed, “The diet of early humans was unsalted, and the Na content of breast milk (6 mmol/kg) shows how little NaCl is needed even during the most rapid period of growth” [30] (p. S35). As was rightly observed, “salt appetite is not to be equated with salt requirement” [31] (p. 151), because some Indians whose diet is unsalted [31] “are physically a highly active people” [31] (p. 150). Of note, “Humans began to use large amounts of salt for the main purpose of food preservation approximately 5000 years ago” [32] (p. 83). This period is “brief, by evolutionary standards ... and thus, there has been little time for the physiologic systems ... to adapt” [33] (p. 45E). As a consequence, dietary salt causes many harmful effects in addition to hypertension [34]. Another harmful effect of dietary salt is its capacity to turn the slow and calorie-constant absorption of diluted sugars into a rapid absorption, because “At low concentrations the addition of sodium chloride ... to test meals increased the rate of gastric emptying” [35] (p. 268). This occurs because “Sodium ion greatly facilitates glucose uptake” [36] (p. 1228). Consequently, “Sodium ion ... increases the rate of absorption of glucose” [22] (p. 318). Hence, even “a small amount of NaCl in the solutions can potentiate intestinal absorption of sugars” [37] (p. 558). Unsurprisingly, therefore, “the addition of sodium chloride enhances the glycemic response to glucose ingestion through facilitation of intestinal absorption” [38] (p. 458).

That enhanced glycemic response resulting from the addition of dietary salt can explain the association between sugar-sweetened beverages (SSBs) intake and type 2 diabetes [39,40], because “The consumption of sugar sweetened soft drink is associated with reduced vegetable and milk consumption (typically low-salt foods) and higher consumption of fast food and fried meats and fried snacks (eg, hamburgers and French fries; typically high-salt foods)” [41] (p. 19). Intuitively, in the stomach at least a small amount of the dietary salt contained in those high-salt foods unavoidably passes into SSBs, thereby unhealthily accelerating their absorption. This unnaturally accelerated absorption, besides probably accounting for other harmful effects attributed to SSBs intake per se [42–44], can also explain why the consumption of SSBs is associated with obesity, too [41]. Some studies did report that this association is mediated by dietary salt, but they omitted to mention the harmful accelerating effect of salt on the absorption of sugars [41,45,46].

4. Conclusions

As *The Lancet* has recently emphasized in a timely editorial [47] written to introduce three articles on the medical implications of an evolutionary perspective [48–50], “Evolution is perhaps the most basic scientific theory. Some would say it is the most powerful. And yet its application to health and medicine is vastly underutilised” [47]. Indeed, “the value of evolutionary analyses of human

physiology ... is only beginning to be recognized in the field of public health” [48] (p. 500). Therefore, it is to be hoped that those recent evolution-promoting articles published in *The Lancet* [48–50] and the evolutionary analysis of human physiology expounded in the present article will encourage some researchers to perform the unprecedented dietary trial aimed at comparing the metabolic effects of diluted sugar with the metabolic effects of undiluted sugar. The present article and two hypotheses based on evolutionary reasoning [1,15] theoretically predict that a given quantity of sugar will prove harmless if it is ingested in diluted forms within 1.0 kcal/ml (i.e., 250 g of sugar per liter), but the same quantity of sugar will prove harmful if it is ingested in forms exceeding 1.0 kcal/ml.

Conflicts of interest

None declared.

Appendix

This appendix may be useful to researchers who could be willing to perform the unprecedented study discussed above. Precisely because of its unprecedentedness, this study should have a simple design and should be relatively inexpensive, thereby encouraging researchers and funders to plan other studies aimed at replicating its findings, because “Replicating studies is important”, as an editorial of *The Lancet* rightly pointed out [51]. Indeed, in the present case, should other studies confirm that diluted sugar is harmless and undiluted sugar is harmful, then humankind will soon be healthier, by adhering to new and better medical guidelines regarding sugar. One of the simplest designs of that unprecedented research on diluted sugar vs undiluted sugar could assess whether these different forms of ingesting sugar produce different effects on triglycerides and cholesterol. These lipids are notoriously the main culprits of the “significant relationship between added sugar consumption and increased risk for CVD [cardiovascular disease] mortality” [52] (p. 516). This exhaustively commented [53–58] relationship might be inaccurate, however, because the study that reported it [52] failed to distinguish diluted sugar from undiluted sugar.

The volunteers who participated in some studies on sugar were twelve [59], nine [60], or only eight [61]. Therefore, ten healthy adult normal-weight volunteers may well suffice as participants in the unprecedented study on sugar. As its findings will theoretically depend on gastric emptying, the volunteers should be male, because there are “Gender differences in gastric emptying” [62,63]. Useful suggestions for the experimental protocol of that unprecedented study can be drawn from a research of Reiser et al. [64], who found that “Total serum lipids, triglycerides, and total cholesterol levels were significantly higher when the subjects consumed the sucrose diet than when they consumed the starch diet” [64] (p. 1659). Although the sucrose diet of Reiser et al. included 210 g of sucrose [64], such a copious quantity of sucrose is unnecessary in the unprecedented study discussed here. In this novel research, therefore, a diet including 100 g of sucrose should suffice to determine whether this quantity of sucrose is harmless in diluted form and harmful in undiluted form.

The participants in the study of Reiser et al. [64] “consumed the sucrose diet during the first 6-week period. After a 4-week rest period, the starch diet was consumed during the second 6-week period” [64] (p. 1661). Similarly, the participants in the unprecedented study under discussion should consume a diet including 100 g of diluted sucrose during the first 6-week period; after a 4-week rest period, 100 g of undiluted sucrose should be included in the diet during the second 6-week period. Importantly, during

the experimental periods, the volunteers should keep their usual eating habits unchanged except for breakfast. Indeed, in the fasting state, as a sole breakfast, the participants should consume only 100 g of diluted sucrose during the first 6-week period, whereas they should consume 100 g of undiluted sucrose during the second 6-week period. This undiluted sucrose, to be ingested more easily, can be in the form of lumps, which practically would have the same facilitating role of the “sucrose patty” [64] (p. 1661) used by Reiser et al. [64] to make the ingestion of undiluted sucrose easier.

Although diluted sugar, as argued in the main text, is theoretically harmless even if its concentration is 1000 kcal per liter, this high and somewhat unrealistic caloric density is unworthy to be used in the unprecedented study under discussion. It is more realistic to use a caloric concentration of 500 kcal per liter, because this caloric density is approximately comparable to the highest caloric concentration of various industrial beverages containing added sucrose. In fact, “The sugar content of colas, soft drinks, fruit punches, 100% fruit juices, and liquid shakes is ~10–12 g/100 g” [65] (p. 658). Therefore, during the first experimental period, the volunteers should ingest as a breakfast only 100 g of sucrose diluted homogeneously in a quantity of water abundant enough to result in 800 ml of sweetened beverage. Should the participants find it difficult to drink such a large sugared solution in one swallow, they can sip it gradually in tens of minutes, because the metabolic equivalence of gorging and sipping, in the context of the gastric emptying of diluted sugars, can be clearly inferred from the abovementioned physiological fact that “Doubling the volume of a glucose meal does not significantly alter the rate of emptying” [24] (p. R256).

As discussed in the main text, the postulated metabolic difference between ingesting diluted sucrose and ingesting undiluted sucrose would reflect their different rates of gastric emptying. Therefore, it is experimentally essential to prevent intragastric and metabolic interferences that could result in misleading findings by altering the normal process of gastric emptying. Bearing in mind that 100 g of diluted sucrose provide 400 kcal and considering that the rate of gastric emptying of diluted sugars is presumably a function of the oxidation of the exogenous glucose [62,63], the volunteers should not ingest any other substance, excluding plain water if thirst occurs, for at least 4 h after the ingestion of diluted sucrose. Indeed, it can reasonably be estimated that an adult normal-weight male volunteer at rest oxidizes about 100 kcal per hour. Of note, as was suggested on theoretical grounds, it is probably the oxidation of the exogenous glucose that regulates the intestinal absorption [62,63], which, in turn, determines the rate of gastric emptying. In fact, “it is the rate of absorption of nutrients by the small intestine that is the most important factor in controlling gastric emptying” [66].

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2019.03.012>.

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