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肠道菌群对现代膳食糖和甜味剂的适应性改变

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摘　要

现代社会人均摄糖量不断增长，由高糖饮食带来的各类代谢性疾病也是对人类健康的重要威胁，各种代替糖的甜味剂的使用正在迅速增加。本文综述了食物中的膳食糖和甜味剂对人类肠道微生物产生的各种潜在影响。

关键词

糖，甜味剂，肠道微生物，适应性改变

Adaptation of Gut Microbiota to Modern Dietary Sugars and Sweeteners

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Abstract

The daily sugar consumption of modern society is growing, and the various kinds of metabolic diseases, which are brought by the high sugar diet, are also a major threat to human health, and the use of sweeteners for sugar is increasing rapidly. This paper reviews the potential effects of dietary sugar and sweeteners on human intestinal microorganisms.

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Keywords

Sugar, Sweeteners, Gut Microbes, Adaptive Changes

1. 引言

糖的起源最早可以追溯至公元前 9000 年至公元前 6500 年之间[1]。此时大洋洲的原始居民开始从甘蔗中榨取蔗糖，但这种糖非常昂贵，仅限于药用或者作为贵族们的奢侈品。17 世纪甘蔗种植园的兴起降低了糖的成本，增加了糖的可获得性，这时糖开始出现在英国工人阶级的日常食物中。从此以后，全球糖的消耗量呈现出一个不断增长的趋势，现今的美国膳食糖的消耗量为每人每天 100 克，这已经是医生建议的最大摄入量的 4 倍以上[2]。随着饮食中过量的糖被认定为许多现代慢性病的主要诱因，这些疾病包括代谢综合征及肥胖、糖尿病、心血管疾病[3] [4] [5]、肝病[6]、龋齿[7]和阿尔茨海默病等[8] [9]，西方国家饮食中开始出现越来越多的代糖甜味剂，包括低聚糖、糖醇、糖苷以及合成糖和一些天然不含糖基团的人工甜味剂。

有研究表明，人类肠道菌群在糖诱发上述疾病的过程中发挥着重要作用[10] [11] [12]。这意味着摄入大量糖可以改变人类肠道微生物组成[13]，影响这些微生物所利用的碳水化合物池[14] [15]，并改变肠道微生态[16]。通常来说，这个过程对于人类健康是有害的。

2. 研究进展

2.1. 糖和甜味剂改变肠道微生物的机制

肠道微生物群被定义为微生物及其栖息地的组合[17]。在特定宿主内，饮食因素是微生物组组成的主要调控因素[18] [19]。饮食已被证明能够在数天内重塑整个肠道微生物种群，在各种营养元素中，碳水化合物和蛋白质已被证实是最具影响力的[20] [21] [22] [23]，并以单糖的调控能力最强[13]。目前一个普通美国人饮食中大约 48%的热量来自于摄入碳水化合物[24]，另有 13%的热量来自于所添加的膳食糖[25]。各种甜味剂由于在人体中无法代谢分解(如糖醇和一些高热量甜味剂)和/或在很低的剂量下即可以提供蔗糖的有效甜度(高热量甜味剂)，都被称为低热量甜味剂。这些甜味剂改变了美国人饮食中热量的来源，最重要的是减少了葡萄糖和蔗糖等摄入量。

由于葡萄糖的分解代谢可以抑制人体对其他碳水化合物摄取和利用[14] [15]，而葡萄糖和蔗糖等膳食易于被人体所吸收，人体细胞在接触到此类能量来源时会自动关闭其他更加耗能的代谢途径以保存能量。由于每种糖/甜味剂容易被人体吸收的情况各不相同(表 1)，大多数糖和甜味剂通过糖转运体在小肠中被积极吸收，只有 5%~30%的糖和甜味剂到达大肠[26]。因此小肠环境中糖和甜味剂的浓度是大肠中浓度的 10 倍以上。但大肠中仍有相当数量糖和甜味剂，例如果糖、糖醇和一些甜味剂(如三氯蔗糖)在小肠中的吸收是被动且缓慢的，多达 30%~90%的糖和甜味剂仍会进入大肠，但这个数量在每个人的体内并不完全相同，男性和女性对糖和甜味剂的吸收能力就表现出相当大的差异[27] [28] [29] [30] [31]。研究表明，女性比男性更能抵抗大量摄入非消化性糖类引起的腹泻，即男性吸收非消化性糖类的最大无效剂量可能低于女性[32]。此外，被称为葡萄糖转运体(GLUT) 5 型(GLUT5)的果糖转运体在婴儿体内并不存在[33]，而

在成年人中，当有大量葡萄糖存在时，GLUT5 以剂量依赖的方式增强吸收[34]。因此肠道中糖和甜味剂的浓度取决于个体的吸收能力和肠道微生物的代谢活动。

Table 1. Consumption of common dietary sugar and sweeteners and their absorption in the intestine
表 1. 常见膳食糖和甜味剂的使用量和肠道中吸收情况

糖和甜味剂	第一次批准使用的日期	单份用量	每天每公斤消耗的重量	在小肠吸收或消耗的百分比%	在大肠吸收或消耗的百分比%	在粪便中百分比%
蔗糖	不适用	35 g	1~2 g	>95	<5	<1
高果糖玉米糖浆-55	1970	30 g	1~2 g	看见果糖和葡萄糖	看见果糖和葡萄糖	看见果糖和葡萄糖
葡萄糖	NA	25 g	1~2 g	>95	<5	<1
果糖	不适用	25 g	1~2 g	90	10	<1
海藻糖	2000	3 g	0.5 g	>20	-	-
山梨糖醇	1972	2~90 g	<1 g	25	75	<1
赤藓糖醇	1996	500 mg~10 g	<1 g	90	10	<7
木糖醇	1960	300 mg~1 g	<1 g	50	50	1
甘露醇	1950	40 mg	35 mg	25	75	<3
甜叶菊	2008	30 mg	2 mg	60%在小肠和大肠之间		5%斯提味醇
阿斯巴甜	1981	120 mg	8.7 mg	70%甲醇；85%苯丙氨酸；>95%天冬氨酸	30%甲醇；13%苯丙氨酸；<3%天冬氨酸	0%甲醇；2%苯丙氨酸；2%天冬氨酸
糖精	1972~1977	30 mg	<5 mg	95	-	3
三氯蔗糖	1998	40 mg	1.6 mg	10~30	-	70~90
安塞蜜钾	1988	30 mg	5 mg	95	-	-

2.2. 肠道微生物对肠道中糖和甜味剂的适应

人对糖和甜味剂吸收、肠道微生物种类和其他肠道环境的复杂性综合在一起，会显著影响肠道内微生物的种类和数量[16] [35] [36]。研究糖和甜味剂重塑肠道微生物群并影响人体生理机能的机制，需要确定肠道微生物可以利用糖和甜味剂种类，以及这些糖和甜味剂所影响微生物代谢过程，了解肠道微生物如何适应改变的碳水化合物池以及这种适应性变化对人类生理的影响。目前通常使用实验模拟和类器官等技术来研究这些问题。

实验模拟是通过各种培养系统(如生物反应器、发酵罐和化学反应器等)测试糖和甜味剂在各种培养系统中的代谢过程。肠道类器官是一种更为先进的研究方法，可以测试研究发生在肠道任何区域的上皮层中反应[37]。例如富集肠道中分泌细胞构建类肠器官可以用于研究肠道微生物代谢物引起的激素变化[38] [39]，类肠器官还可以用来研究肠道微生物的生理变化以及其对肠道黏膜屏障的影响和宿主－微生物之间相互作用等[40]。通过对个人肠道微生物结构的分析可以获知他的肠道适合于哪些糖或甜味剂。例如，有些人成年后不能产生乳糖酶导致饮用牛奶后会发生腹泻，但此类人肠道中双歧杆菌的水平较正常更高，经过一定时间适合后肠道中双歧杆菌可以利用乳糖，进而使此类人群变成可以饮用牛奶[41] [42]。

肠道内微生物适应性变化有 3 种情况。首先，当糖和甜味剂与微生物转运系统，包括磷酸转移酶系统、主要协同转运蛋白超家族、ABC 超家族、钠－葡萄糖连接转运蛋白之间相互作用，促进微生物改变

以适应肠道中糖和甜味剂的新环境[43]。肠道中的微生物可以通过改变转录和表达相关酶以及各种运输蛋白表达来适应环境[44]，同时肠道中微生物的定植和维持正常肠黏膜屏障能力也会发生改变，可能有些改变会对人体健康产物负面影响[44]。其次，微生物的代谢改变可能会导致肠道微生物的种类和组成的变化，研究表明喂食高蔗糖饮食的动物粪便中微生物多样性减少，即肠道微生物组成发生变化[45]。最后，糖和甜味剂可以诱导肠道内细菌变异，肠道内环境变化可以导致细菌某些基因表达增强或被抑制。例如采用高蔗糖饲料喂养小鼠一段时间，其粪便中含有蔗糖水解酶的突变体细菌较正常饲料喂养小鼠高出 115% [46]。

2.3. 微生物的糖和甜味剂适应性改变对宿主的影响

首先，微生物的糖和甜味剂适应性改变会显著影响宿主与肠道微生物之间的相互作用[47]。

细菌所含有的蛋白质和脂质会与环境中糖形成糖缀合物，糖缀合物与树突状细胞特异性粘附分子和 IgA 等结合后有利于细菌在肠道中定植[48]。有证据表明鞭毛糖基化降低了条件致病菌 *Burkholderia cenocepacia* 对 TLR5 的识别能力，TLR5 用来介导细菌免疫系统，增强了艰难梭菌对上皮细胞的粘附。其次，糖缀合物可以降低宿主免疫细胞 ToLL 样受体的识别[49]，抑制宿主免疫细胞 ToLL 样受体活化，减少促炎细胞因子和 IgA 分泌。例如，特异的胞外蛋白可以促进白细胞介素-10 介导的抗炎免疫反应[36]。另一方面，脂多糖通过 toll 样受体 4 (TLR4)信号传导刺激促炎免疫反应[50]。当肠道内存在大量糖缀合物时，其 ToLL2/4 活化受到抑制，有利于艰难梭菌等病原菌在肠道中定植并诱发疾病[49]。最后，糖和甜味剂可以调控细菌各种转运系统，所产生的细菌代谢物变化也可以对宿主产生影响。例如各种乳酸菌在高糖环境中发酵产生大量乳酸，乳酸可以刺激肠道黏膜上皮细胞的增殖，有利于维持肠黏膜屏障[51]。除了以上列举的影响机制，还有更多的机制有待探索。

3. 结论与展望

除了作为人体的营养物质，膳食糖和甜味剂也可能对微生物的定植和增殖产生抑制和毒性作用。例如口腔中致病菌无法适应木糖醇环境，因此可以使用木糖醇抑制细菌滋生防止龋齿发生[52] [53]。现有的研究结果表明，在高糖环境下肠黏膜细胞与细胞间紧密连接会变得疏松，并进一步抑制上皮细胞黏蛋白分泌，使得屏障完整性受损，肠道内细菌和内毒素易位造成全身炎症反应[52] [54]。目前的首要问题是进一步开展甜味剂使用安全性问题，以减少人类糖摄入量，减少高糖饮食带来的健康隐患。

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