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Review

Low calorie sweeteners: Evidence remains lacking for effects on human gut function

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ABSTRACT

The importance of nutrient induced gut-brain signalling in the regulation of human food intake has become an increasing focus of research. Much of the caloric excess consumed comes from dietary sugars, but our knowledge about the mechanisms mediating the physiological and appetitive effects of sweet tastants in the human gut and gut-brain axis is far from complete. The comparative effects of natural sugars *vs* low calorie sweeteners are also poorly understood. Research in animal and cellular models has suggested a key functional role in gut endocrine cells for the sweet taste receptors previously well described in oral taste. However human studies to date have very consistently failed to show that activation of the sweet taste receptor by low calorie sweeteners placed in the human gut fails to replicate any of the effects on gastric motility, gut hormones or appetitive responses evoked by caloric sugars.

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1. Introduction

Obesity is a global health problem and its prevalence continues to rise. The factors behind this are complex, but there is no doubt that ready access to cheap and highly caloric foods is a key factor. Recognised as one of the most significant contributors to ill health, obesity, and its associated chronic diseases carry a large economic burden, and highlight the need for cost-effective strategies and therapies, both for prevention and to enable safe and sustainable weight loss. Clearly more tractable solutions must be found, and dietary approaches will be fundamental.

The ability to modulate energy intake and match energy requirements from meal to meal is under strict control. In most people, weight remains relatively constant despite constant variations in food intake, meal frequency, meal volume, energy density and expenditure. The gut is highly efficient in health and will digest and absorb whatever is consumed. The brain is the key controller in appetite control and food intake but there are important homeostatic signals transmitted from gut-to-brain that modulate food intake, at least in animal models and experimental conditions.

2. Signals arising from the gastrointestinal tract

The gut–brain axis and its regulation of food intake is a complex system that enables cross-talk between peripheral and central mechanisms that influence hunger and food intake in response to ingested nutrients [6]. One key area warranting further investigation is the mechanism by which sugars influence gastrointestinal signalling to the brain and therefore affect appetite and food intake. Episodic postprandial signals are synchronised with eating episodes so that during the course of

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eating the gastrointestinal tract can efficiently digest and absorb nutrients from ingested foods. The gastrointestinal tract is optimised to carry out these functions regulated by peptide hormones secreted by enteroendocrine cells (EEC). However post-absorptive metabolic effects of caloric sugars also play a role. Ingestion of carbohydrate increases the blood glucose concentration *via* intestinal digestion and absorption and stimulates the release of a number of gut hormones that have a fundamental role in food intake [18]. Ingestion of carbohydrate classically stimulates the release of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and to a lesser extent peptide YY (PYY). In addition, the release of GLP-1 and GIP stimulates glucose dependent insulin secretion from beta-cells of the pancreas. Circulating insulin promotes glucose uptake into cells for utilisation and has been implicated in the long term regulation of energy balance [25].

3. Sugars, low calorie sweeteners and sweet taste receptors

Sweetness perception involves two G protein receptors (GPCR), T1R2 and T1R3, which dimerize to form the sweet taste receptor [22]. Its biology is best understood in oral sweet tasting where receptor stimulation by natural sugars or low calorie sweeteners activates intracellular signalling elements *via* the receptor–coupled G protein α-gustducin. This in turn leads to activation of gustatory nerves transmitting sensory information to the brain.

4. Sweet taste receptors in the intestine: cell and animal models

The potential functional role of "taste receptors" in the gastrointestinal tract has recently been established, but with positive data largely derived from cell lines and animal models. The expression of sweet taste receptors (T1R2 + T1R3), as well as the G protein α-gustducin involved in taste-specific signalling, have been found in enteroendocrine cells (EEC) in rats [14], mice [3,7], pigs [16] horses [2] and cows [17]. This raises the possibility that they may mediate the well-established effects of carbohydrates on gut hormone release described above. Published studies are summarised in Table 1. T1Rs and α-gustducin were found to be expressed in a human enteroendocrine L cell line and stimulate the release of GLP-1 [7]. In addition, α-gustducin was also shown to be co-localised with GIP expressing enteroendocrine K cells and GIP and GLP-1 co-expressing enteroendocrine K/L cells [7]. Rozengurt and colleagues also demonstrated that α-gustducin was expressed in human colonic enteroendocrine L cells expressing PYY and GLP-1 and co-expression with CCK in enteroendocrine I cells [19,20]. Although molecular evidence for expression may not always translate to physiological function, the significance of these taste signalling elements in EEC has been investigated in these models with compelling data to support functional roles. However it is also important to note that cellular localisation of sweet taste receptors in human gut has not been achieved.

Evidence for a possible functional role of sweet taste receptors was established by Margolskee et al. who demonstrated that T1R2 + T1R3 sweet receptor regulated sodium-glucose linked transporter 1 (SGLT1) expression and increased glucose absorptive capacity in response to luminal sugars and low calorie sweeteners in mice [14]. Prior studies found SGLT1 expression was enhanced by glucose sensing, occurring independently of its capacity for metabolism (Dyer et al., 2003). This was confirmed by Margolskee et al. to be a function of the T1R3 subunit [14]. Furthermore, apical enterocyte membrane Glucose transporter 2 (GLUT2) transporter insertion is inhibited if SGLT1 activity is blocked, and stimulation of the T1R3 also increases GLUT2 insertion [13]. Comparable to the taste receptors found in the mouth, gut expressed "taste receptors" respond to nutrients but signal and communicate *via* mediators such as GLP-1. These signals are detected by the enterocytes to cause an increase in SGLT1 expression and mediate glucose metabolism, gastric emptying and augment satiety.

The sensing mechanisms involved were shown to be reliant upon direct contact with EEC as intravenous administration of nutrients has shown no effect on gut hormone release [24]. Using rodent EEC lines it was demonstrated that GLP-1 and GIP secretion were enhanced when the concentration of sucralose, a low calorie sweeteners, was

Table 1
Comparative summary of known effects on common low calorie sweeteners in reported animal and human studies.

		Model					
		In vitro		*In vivo*-animals		*In vivo*-humans	
		Method	Effect	Method	Effect	Method	Effect
Sweetener	Ace-K	Rat intestinal and human cell line	↑ Glucose absorption ↑ insulin secretion	Gastric gavage in rats	No effect on GIP or GLP-1 [5]	Intragastric infusion	No effect on GLP-1 or PYY [23]
		mouse pancreatic cell line		*ad libitum* drinking water × 14 days in mice	↑ SGLT-1 expression [14]	oral (ace-K + sucralose)	↑ glucose stimulated GLP-1 secretion [1]
				perfused into small intestine of rats	↑ glucose absorption [13]		
	Sucralose	Human intestinal cell line	↑ GLP-1 secretion [7] ↑ GIP and GLP-1 secretion [14]	Gastric gavage in rates	No effect on GIP or GLP-1 [5]	Intragastric infusion	No effect on GLP-1 or PYY [23]
		mouse intestinal cell line		*ad libitum* drinking water × 14 days in mice	↑ SGLT-1 expression [14]	intragastric infusion	no effect on GIP or GLP-1
				perfused into small intestine of rats	↑ glucose absorption [13]	intraduodenal infusion	no effect of glucose stimulated GLP-1 secretion [12]
	Aspartame	No evidence		*Ad libitum* drinking water × 14 days in mice	No effect on SGLT-1 expression [14]	Intragastric infusion	No effect on GLP-1 or PYY [23]
	Saccharin	Mouse pancreatic cell line	↑ Insulin secretion	*Ad libitum* drinking water × 14 days in mice	↑ SGLT-1 expression [14]	No evidence	
				perfused in small intestine of rats	↑ glucose absorption [13]		