GUT SWEET TASTE RECEPTORS

HOW SWEETENERS CONTRIBUTE TO OBESITY

The gastrointestinal tract represents a sensory organ that responds to a large array of signals originating in the lumen. Molecular sensing by specific gastrointestinal cells plays a crucial role in the control of multiple fundamental functions including digestion, regulation of caloric intake, pancreatic insulin secretion, metabolism, as well as protection from ingested harmful drugs and toxins. However, despite the fact that these fundamental properties of the gastrointestinal tract have been recognized for a considerable amount of time, the initial molecular recognition events that sense the chemical composition of the luminal contents of the GI tract have remained elusive until very recently. However, as it has now been understood, the chemosensory machinery discovered in specialized neuroepithelial taste receptor cells of the lingual epithelium appears as well operational in different clusters of intestinal cells that sense the chemical composition of the luminal content of the gut.

A novel family of mammalian taste receptors has been identified in 2000, consisting in about 40 different G protein-coupled receptors (GPCRs) expressed in taste receptor cells of the tongue and palate. The GPCR superfamily results from the expression of about 1000 genes known to code mostly for sensory receptors involved in vision (rhodopsin) and in olfaction (hundreds of odorants with specific GPCRs). Still in 2000, bitter taste receptors were discovered: they are exclusively expressed in taste receptor cells that contain the rare G protein α-subunit **gustducin**, identified and cloned in 1992 from taste buds of tongue taste papillae. The same team reported in 2001 the characterization of ***sweet taste*** receptors, which also express gustducin.

Five years before, a German team had already addressed the question of whether the epithelium of the gut might also express α-gustducin. They have shown that this specific G protein subunit is expressed in the epithelium of the gut where it is associated with a specialized cell type that was long known under the name of **tuft cell**. The function of this cell type, widespread in the digestive and respiratory tracts from simple vertebrates to humans, had always been enigmatic. However, the discovery of the presence of α-gustducin has provided a clue to the long-sought function of tuft cells, which appear to possess the cellular and molecular basis for chemoreception.

Besides, α-gustducin is expressed in different subsets of enteroendocrine cells such as intestinal L-cells that secrete **peptide YY** and **GLP-1**, two gastrointestinal peptides involved in satiety signaling. In August 2007, an article published in the *PNAS* showed that human L-cells express sweet taste receptors and taste G protein subunit α-gustducin. This protein has also been found recently (article published in November 2007) in another cluster of enteroendocrine cells, the stomach cells secreting **ghrelin**, a satiety promoting (orexigenic) peptide.

It appears that both natural sugars and artificial ***sweeteners*** are sensed by sweet taste receptors. Thus, sweeteners are nutritionally active and their intake may have an impact on the carbohydrate metabolism despite their lack of calories. The composition of the intestinal luminal content varies considerably with the diet. It is therefore important that the intestinal lumen "senses" and responds to any significant change by regulating its function accordingly. A prototype example of this process is the modulation in the capacity of the gut to absorb monosaccharides via the intestinal luminal membrane glucose transporter **SGLT1**. Located in the brush border within the apical membrane, it transports ***glucose*** and ***galactose*** from the intestinal lumen to the cytoplasm.

Sugar consumption is known to regulate the expression of genes involved in intestinal sugar absorption. Therefore, it is logical to consider that sugar-sensing receptors in membranes facing the intestinal lumen can also modulate intestinal sugar absorption. In 2003, a team from the University of Liverpool used sheep intestine as a model to show that luminal monosaccharides, both metabolisable (i.e. simple ***sugars***) and non metabolisable (i.e. ***sweeteners***), regulate the expression of SGLT1. Introduction of D-glucose and of some D-glucose analogues into ruminant sheep intestine resulted in more than 50-fold enhancement of SGLT1 expression.

The authors concluded that luminal glucose is sensed by a glucose sensor - distinct from SGLT1 - located on the luminal membrane of the gut epithelium and linked to a G protein-coupled receptor, resulting ultimately in the modulation of intestinal monosaccharide absorption. The sweet taste receptor and the taste G protein subunit α-gustducin, expressed in enteroendocrine cells, underlie intestinal sugar sensing and regulate the expression of SGLT1. Indeed, dietary ***sugars*** as well as artificial ***sweeteners*** increase SGLT1 expression together with glucose absorptive capacity in wild-type mice, but not in knockout mice lacking the sweet taste receptor or α-gustducin.

In an extensive interview realized by Health Orbit on the 21st of August 2007, the leading author declared that: "*Surprisingly we also found that the receptor was able to detect artificial sweeteners in foods and drinks resulting in increased capacity of the intestine to absorb dietary sugars, which would explain why these sweeteners are unsuccessful at helping people lose weight*". Interestingly, Professor Soraya SHIRAZI-BEECHEY belongs to the University of Liverpool Faculty of Veterinary Science and she will research how to activate the receptor through dietary supplements, before and during horse races, in order to increase intestinal absorption of glucose among horses, as they need high levels of glucose to sustain them in long races.