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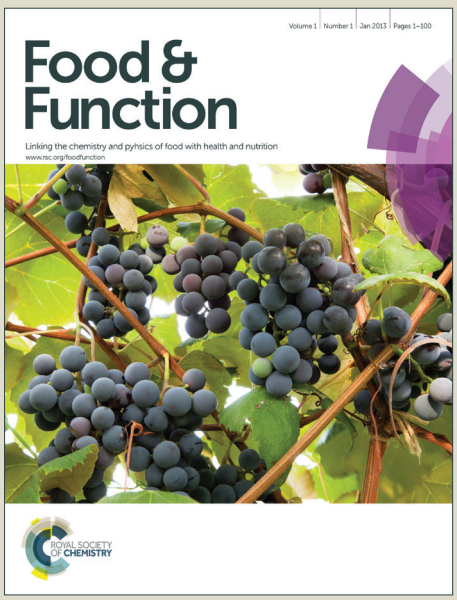

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Gut Feedback Mechanisms and Food Intake:

A Physiological Approach to Slow Carbohydrate Bioavailability

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Abstract

Glycemic carbohydrates in foods are one important macronutrient providing the biological fuel of glucose for a variety of physiological processes. A classification of glycemic carbohydrates into rapidly digestible carbohydrate (RDC) and slowly digestible carbohydrate (SDC) has been used to specify their nutritional quality related to glucose homeostasis that is essential to a normal functioning of the brain and critical to life. Although there have been many studies and reviews on slowly digestible starch (SDS) and SDC, the mechanisms of its slow digestion and absorption were mostly investigated from the material side without considering the physiological processes of its *in vivo* digestion, absorption, and most importantly interactions with other food components and the gastrointestinal tract. In this article, the physiological processes modulating the bioavailability of carbohydrate, specifically its rate and extent of digestion and absorption as well as the related locations, in a whole food context will be discussed by focusing on the activities of the gastrointestinal tract including glycolytic enzymes and glucose release, sugar sensing, gut hormones, and neurohormonal negative feedback mechanisms. It is hoped that a deep understanding of these physiological processes will facilitate the development of innovative dietary approaches to achieve desired carbohydrate or glucose bioavailability for improved health.

Key words: slowly digestible starch (SDS), slowly digestible carbohydrate (SDC), ileal brake, sugar sensing, gastric emptying, gut hormones

Introduction

Glucose, as the preferred energy source for the central nervous system [1] and the starting material for a variety of synthetic reactions, is critical to life and the normal physiological functioning of the body. Glucose also acts as a signal molecule participating in energy metabolism including insulin secretion, glucose utilization, and gluconeogenesis. Accordingly, the concentration of plasma glucose, in contrast to other macronutrients of fat and protein, is tightly regulated. Although glucose can be synthesized through gluconeogenesis, dietary glycemic carbohydrate, as one important macronutrient in foods providing glucose, is essential to the maintenance of glucose homeostasis. A highly sophisticated and coordinated digestive system with various types of hydrolytic enzymes and neurohormonal feedback machinery can efficiently maximize the assimilation of various nutrients from foods. Regarding glycemic dietary carbohydrates, glucose release from their digestion in the gastrointestinal tract is not only the starting point of the glucose homeostasis regulation cascade, but includes also the function of glucose as a signal molecule to regulate its absorption, deposition and metabolism.

The rate and extent of dietary carbohydrate digestion have been shown to vary considerably, which is the basis for the concept of glycemic index (GI) [2] classifying foods according to their postprandial glycemic response in human subjects. In the meantime, the main dietary carbohydrate of starch has been categorized into rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS) that are expressed as the percentages of total starch amount [3], and the content of SDS is often negatively correlated to that of RDS in starch materials[4]. SDS, which has a slow digestion property, is the material basis for most cereal-sourced low-GI foods since GI values are positively correlated to the contents of RDS in foods[5], and high amount of SDS, thus, is necessary to reduce the GI values of cereal-sourced foods. The concept of RDS and SDS can also be expanded to rapidly digestible carbohydrate (RDC) and slowly digestible carbohydrate (SDC) by excluding the non-glycemic fructose

that has opposed effect to glucose on carbohydrate metabolism[6]. Thus, SDC and low-GI carbohydrate, based on our understanding, are interchangeable terms from the perspective of carbohydrate nutrition. Carbohydrates of RDC including RDS and simple sugars of maltose and glucose, and maltodextrins, which belong to the category of high-GI carbohydrate, are the most common glycemic carbohydrates in foods. Their rapid digestion and absorption in the duodenum and upper jejunum of the small intestine lead to a rapid elevation of blood glucose and often a subsequent episode of hypoglycemia due to a high rate of insulin secretion stimulated by absorbed glucose. This large fluctuation of blood glucose is a stress to the regulatory system of glucose homeostasis [7], which could lead to cell, tissue, and organ damages in the long run [8]. Such postprandial glycemic fluctuations can also generate a high level of reactive oxygen species that are a causative factor for many chronic diseases [9], and even a transient hyperglycemia in human might produce longstanding deleterious effects of diabetic complications through epigenetic mechanisms [10]. Furthermore, a high level of plasma insulin induced by RDC promotes cellular absorption of glucose and potentiates fat synthesis. For individuals with susceptible genetic background, long-term consumption of refined foods with high amount of RDC, on the contrary to the body-weight loss effect of 'low-carbohydrate food' by meta-analysis [11] or the short-term weight loss effect from low-carbohydrate food from a recent meta-study[12] , might be a risk factor of obesity [13] and insulin resistance, which is a common property of metabolic diseases of type 2 diabetes, cardiovascular disease, and possibly cancer [7]. Persistent high level of insulin is also related to reduced life-span and unhealthy ageing [14] from studies in *Caenorhabditis elegans* and *Drosophila* [15]. Thus, long term consumption of RDC is likely one important risk factor of metabolic diseases.

In contrast to RDC or RDS, slowly digestible carbohydrate (SDC) or slowly digestible starch (SDS) often produces a moderate or flat postprandial glycemic response that might be beneficial to health [16]. However, both the definitions of SDC or SDS and glycemic index are methodology-oriented

terms, and no information about the structure of carbohydrate and the food property is provided, making it difficult to fabricate carbohydrate materials with low-GI properties. Since carbohydrate assimilation profile is influenced by both its intrinsic digestibility, which is determined by the structural properties of carbohydrate materials, and neurohormonal feedback regulations in the gastrointestinal tract, it is necessary to take both sides into consideration to develop dietary approaches for desired profiles of glucose bioavailability, which is the rate and extent of glucose release (from carbohydrate digestion) and absorption as well as the associated locations in the gastrointestinal tract. We have previously, in a review paper, described the structure of starch molecules (the major glycemic carbohydrate) and food matrix related to the slow digestion property of starch [17]. In the current article, a slow glucose bioavailability within a whole food context will be discussed from the viewpoint of digestion physiology involving both the hydrolytic enzymes and activities of the gastrointestinal tract upon contact with luminal nutrients. Due to the noted difficulty of producing SDC through food or carbohydrate structural changes and a scarcity of SDC in common foods, it is expected the information provided in the current article will facilitate the development of novel dietary strategies to achieve an optimum rate of *in vivo* glucose release and absorption, and possibly an extended and location-specific glucose deposition for improved health.

1. Coordination of Carbohydrate Property and Enzyme Activity

Dietary carbohydrate digestion in the gastrointestinal tract involves multiple hydrolytic enzymes. The luminal salivary pancreatic α-amylases and the brush border glucogenic enzymes of maltase-glucoamylase (MGAM)[18] and sucrase-isomaltase (SI) (Figure 1) [19] are the major enzymes for glucose liberation from glycemic carbohydrates. After starch or starch-derived product is released from the stomach, large starch molecules are first hydrolyzed by α-amylase to generate glucose-containing oligosaccharides or α-limit dextrins, which are then cleaved by the brush border enzymes into glucose

for absorption (sucrose is hydrolyzed by sucrase to glucose and fructose) [20]. α-Amylase is efficient in hydrolyzing large molecules as observed from a decreased apparent *K*m (more affinity to substrate) with increased glucose units in the substrates [21]. Carbohydrate concentration also affects the molecular structures of α-amylase generated oligosaccharides or dextrins that are substrates for brush border glucogenic enzymes, indicating a coordination between the activity of α-amylase and small intestine α-glucosidases [22]. Increased starch digestion rate by MGAM and SI after α-amylase pretreatment[23] also supports their coordination, and the important role played by α-amylase in carbohydrate digestion. However, the brush border enzymes of MGAM and SI are the ultimate players to fulfill the task of transforming glycemic carbohydrates into absorbable glucose, as well as fructose and galactose, depending on the carbohydrate sources.

Brush border enzymes of MGAM and SI are complementary to each other [18] during the digestion of α-limit dextrins, oligoglucans, and sucrose with different glycosidic linkages and patterns (Table 1). Both MGAM and SI display α-1,4 exo-glucosidic activity from the non-reducing ends of linear chains of the α-amylase degradation products to release glucose. The hydrolytic action on branched α-1,6 linkages shown by isomaltase activity of N-terminal SI (NtSI) is complementary to the hydrolytic activity on α-1,4 linkages shown by both MGAM and SI with certain degree of substrate overlap, and the C-terminal SI (CtSI) also displays specific activity on α-1,2 linkage for sucrose digestion. For N-terminal MGAM (NtMGAM) and C-terminal MGAM (CtMGAM) with 40% sequence identity, their substrate specificities are different due to the latter having both higher maltase and glucoamylase activities[24]. Comparing the contribution of MGAM and SI to carbohydrate digestion, recent research shows that, at low oligomer concentrations, MGAM is ten times more active than SI, but at high concentrations, MGAM experiences substrate inhibition while SI is not affected [25]. Maltotriose, maltotetrose, and maltopentose all display a fairly strong substrate ‘‘brake’’ effect on MGAM activity [26] through the

CtMGAM's "glucoamylase" subunit [27]. This substrate 'brake' effect suggests that total digestion rate of carbohydrate by MGAM can be regulated, and carbohydrate with certain molecular structures might be used to modulate carbohydrate digestion to achieve desired rate of glucose release. The same group also showed that MGAM is crucial for carbohydrate digestion and postprandial glucose homeostasis in mice [28]. The importance of MGAM and SI to carbohydrate digestion is further manifested by the disease of congenital sucrase-isomaltase deficiency [29] in which only the MGAM is present as the α-glucosidase. With the finding of the dominant role played by SI in mucosal maltase activity and early rate of starch digestion[30], the loss of debranching activity of isomaltase of SI makes it difficult to produce linear maltooligosaccharides that can be rapidly digested by MGAM. The SI deficiency also causes the malabsorption of sucrose. Thus, the complementary roles played by SI and MGAM are essential to the complete conversion of carbohydrate to absorbable monosaccharides.

The brush border enzyme activity was also affected by the structure and property of the carbohydrate or oligomer substrate. An *in vivo* study (unpublished results) in our laboratory using a fabricated SDS sample of alginate-based starch-entrapped microsphere [31] in an animal model of mice showed that, compared to the control of a rapidly digestible starch (RDS) sample, the glucose release and absorption from the SDS were suppressed and the activities of jejunal SI and MGAM were also decreased. Consistent to this, resistant starch (RS) feeding to rats decreased the expression of MGAM at the transcription level through an epigenetically reduced acetylation of histone H3 and H4 on the MGAM gene [32]. Similarly, a study using a mouse model showed that Miglitol, an inhibitor of α-glucosidase, reduced the enzyme activity of SI and MGAM (maltase) in the upper jejunum, but increased their activities in the lower jejunum and ileum [33]. On the contrary, when feeding a high RDS/low fat diet, MGAM activity was significantly increased due to its high expression at the mRNA level with observed histone acetylation and binding of transcription factors of CREBP, CDX2 and

HNF1 in the promoter/enhancer regions of the MGAM gene [34]. In our laboratory, maltose promoted the post-translational glycosylation of SI of Caco-2 cells while isomaltose, sucrose and monosaccharide had no effect on SI maturation [35]. These studies indicate a regulatory role of carbohydrate substrate on gene expression and activities of MGAM and SI, and suggest the existence of a sugar sensing mechanism.

2. Glucose Release and Absorption

Glucose release from carbohydrate digestion and its absorption are important steps for the assimilation of carbohydrate. Although the activity of brush border enzymes and substrate property are coordinated to maximize glucogenesis, the absorption of glucose is an important step that affects glucose bioavailability. The liberated glucose is largely absorbed by a Na^+-K^+ co-transporter (also called type 1 sodium-glucose-linked transporter (SGLT)) in the small intestine and then is diffused out from the basolateral side of the enterocyte through glucose transporter 2 (GLUT2). Glucose release and absorption are coordinated processes as evidenced by the co-activation of SI [36] and SGLT-1 [37]in mice fed a high carbohydrate diet, as well as shifted peak of gene expression of SGLT-1 from the jejunum to ileum when a RS-containing diet was fed [38]. Similarly, fructose absorption (expression of glucose transporter 5 (GLUT5)) and SI activity (gene transcription) in the jejunum of the rat small intestine were significantly and positively correlated, which also supports a coordination between carbohydrate digestion and absorption [39].

Glucose absorption is intimately associated with the activity and abundance of SGLT-1, which is another control point for glucose bioavailability modulation. SGLT-1 is known to be affected by several hormones. Peptide Y (PYY) increased the absorption of glucose in a mouse study [40], while leptin significantly decreased the abundance of SGLT-1 leading to a slow absorption of glucose in an *ex vivo* study using rat jejunal mucosa [41]. Pyroglutaminated apelin-13 isoform, a peptide secreted from the proximal region of the small intestine upon stimulation by glucose, also promotes the absorption of

glucose in mice by increasing the GLUT2/SGLT-1 protein ratio in the brush border membrane [42]. Patients after Roux-en-Y gastric bypass (RYGB) surgery, which causes a exaggerated release of incretin hormone of GLP-1[43], also showed increased expression of SGLT-1 and increased glucose absorption [44]. In a whole food matrix, other food components also affect the glucose absorption. Tea catechin, a bioactive phytochemical, reduced the rate of glucose absorption due to competitive inhibition of the activity of SGLT-1 in the brush border membrane vesicles observed from an animal model of rabbit [45]. High carbohydrate diet, on the other hand, increased the abundance of SGLT-1 in weaning piglets when fed >50% digestible carbohydrate[46]. Guar gum, with its effect on viscosity of luminal digesta lowered the rate of glucose absorption in a piglet study [47]. In a human study, decreased glucose absorption by adding guar gum (2%) was associated with improved satiety, which was not related to gastric emptying, but speculated to be mediated by glucose-stimulated secretion of satiety signals [48]. A fermentable rhubarb fiber in a rat study also showed a slow absorption of glucose although the total uptake glucose was not affected [49]. These literature reports show the complexity of glucose absorption and suggest opportunities of modulating glucose uptake for desired profiles of glucose bioavailability.

3. Glucose Release and Sugar Sensing

During the processes of carbohydrate digestion and absorption, the regulatory effect of carbohydrate on the expression and activity of pancreatic α-amylase [50],brush border enzymes of MGAM [34] and SI [36, 51], as well as SGLT-1[37] in rat-based studies indicates there is a sugar sensing mechanism, especially glucose sensing. This is also indicative of glucose's function as a signal molecule to regulate its digestion and absorption[52]. From what has been known so far, sugar sensing is a complex process that includes sugar transport, sugar metabolites, receptors on cell membranes, and secretion of gut hormones, as well as the vagal afferent nerves[53]. GLUT2, as a basolateral transporter for monosaccharide exiting the enterocytes and entering into the blood stream, is a sugar sensor that can

lead to a high expression of SI (at the mRNA level), which is termed as the GLUT2-dependent signaling pathway described in a mouse study [54]. The glucose-induced GLP-1 secretion also needs the function of GLUT2[55]. Another major type of sugar sensor is the sweet taste receptor of type 1 G-protein-coupled receptors (T1R) including members of T1R1, T1R2 and T1R3 that are coupled with G-protein gustducin [56]. Sweet taste receptors have been demonstrated in the small intestine of various species. T1R3 and the G-protein gustducin ($G\alpha_{gust}$) on the enteroendocrine cells of the gastrointestinal tract of mice can bind sucrose, artificial sweeteners (e.g., sucralose), and other sugars to stimulate glucose absorption by increasing the expression of SGLT-1 through the function of hormones including GIP and GLP-1 [57]. A later study also showed the existence of T1R3, T1R2 and G-protein gustducin in the enterocytes of rats that can sense sugar molecules and stimulate glucose absorption through apical GLUT2 [58]. In the enteroendocrine cells of piglet intestine, T1R2, T1R3, and gustducin have also been shown co-expressed in response to dietary carbohydrate or artificial sweetener, and T1R and gustducin were co-expressed with GIP and GLP-1 [59]. As for large carbohydrate molecules such as the maltodextrin Polycose™, behavior studies of rodents showed that starch taste (including starch-derived maltooligosaccharide) is distinct from sugar (mainly sucrose) taste [60], and a recent study [61] in mice showed that T1R3, as a sugar receptor, is critical for sucrose sensing, but had no effect on Polycose™ sensing. Our recent study [35] in which only maltose treatment induced the maturation of SI in Caco2 cells (higher molecular band) indicates there might be a maltose sensing mechanism (Figure 2).

Sugar sensing is the basis for gastrointestinal activity modulation through the neurohormonal feedback mechanisms of the ileal brake and gut-brain axis. Liberated glucose from carbohydrate digestion stimulates the secretion of gut hormones through glucose sensing, and the gut hormones may directly or indirectly regulate gastrointestinal activity including digestion, nutrient absorption, gastric emptying and intestinal motility leading to certain health effects such as appetite control[62 63]. In addition

to gut hormones, the vagal nerve, enteric nervous system (ENS), and central nervous system (CNS) are also involved. Thus, the gastrointestinal tract, as a highly sophisticated system, is a link between nutrient status in the gut and health outcomes of satiety and energy balance, and nutrient sensing is the critical player in this linkage. Luminal glucose, as an example, can influence food intake, gastrointestinal motility, and secretory function of the digestive system. A recent *in vivo* study in rats[64] showed that glucose's regulatory function is realized through the gut-brain pathway activated by glucose-stimulated secretion of gut hormones of GLP-1 and 5-hydroxytryptamine (5-HT) from enteroendocrine and enterochromaffin cells (EC), respectively. Specifically, glucose sensing by SGLT-3 on the EC cells induced the release of 5-HT, and the binding of 5-HT to its receptors on vagal afferent endings transmitted the signal to the CNS to initiate changes in gastrointestinal functions. Thus, glucose sensing is a good example of a neurohormonal feedback mechanism by activating intrinsic and extrinsic neuronal pathways to exert its regulatory functions[65]. Hence, carbohydrate or glucose sensing is another potential target to modulate glucose bioavailability.

4. Neural and Hormonal Signals in Gastrointestinal Tract

The gastrointestinal tract is a highly coordinated system for maximizing assimilation of nutrients from diets. Both the vagal nerve[66] and gut hormones[63] are important players in the distal- proximal feedback loop through gut-brain axis[67] to coordinate gastrointestinal tract activity. The vagus nerve is one type of cranial nerve carrying a variety of neural signals for instinctive responses in the body. Concerning the digestive system, it is the communication route[67] between the central nervous system (CNS) and the enteric nervous system (ENS) comprised of efferent neurons, afferent neurons, and inter-neurons that are responsible for a proper function of the digestive tract (such as motility, enzyme secretion, and nutrient sensing). The vagal afferents can transmit the signals or stimuli (mechanical or chemical) sensed by the ENS to the CNS, and transfer neural signals from CNS to ENS to affect the

gastrointestinal activity. The regulatory functions of gut hormones, which are produced in response to chemical and mechanical stimuli in the gut, on gastrointestinal tract activity such as gastric emptying is mediated by the long vago-vagal reflexes triggered by the binding of gut hormones to their receptors on the vagal efferent neurons[67]. Thus, in the distal-proximal feedback loop, both vagus nerve signaling and hormonal signaling are important to maximize the assimilation of nutrients and to maintain the proper function of the digestive system. An understanding of this neurohormonal feedback mechanism related to food intake is important to develop dietary approaches for glucose bioavailability modulation or energy intake control.

The gastrointestinal tract, as said before, is a highly coordinated system and the enteroendocrine cells such as the CCK-secretion I cell, the glucose-dependent insulinotropic peptide (GIP) secretion K cell, and the GLP-1 and PYY secretion L-cell are important components of the gastrointestinal endocrine system[68] that is important for chemosensing and gastrointestinal activity regulation. In order to have a better understanding of this system, the enteroendocrine cells need first to be evaluated regarding their distribution in the gut and anatomical structures. Enteroendocrine I and K cells and other sensing cells in the stomach are mainly located in the proximal region of the gut, and are always active during food intake. The L-cells, on the other hand, are mostly located in the distal region of the small intestine and colon, and rarely activated by common foods that are rapidly digested and absorbed in the proximal regions of the gut, indicating they are one of the most important players in the negative feed-back loop. L-cells differ morphologically in ileum and colon (Figure 3), and for ileal L-cells, they have long extending basal processes with synapse-like terminal endings with a minimal contact to the gut lumen, and for the colonic counterpart, they adopt a spindle-like shape and maintain a substantial contact with the lumen and lamina propria suggesting a dual function of nutrient monitoring and hormone secretion based on a study using a transgenic mouse model [69]. The cytoplasmic granules

containing GLP-1 and PYY are confined to the base of the L-cells in both cases (Figure 3). Concerning the distribution and abundance of L-cells, there are significant variations among species[70]. In the pig and human, a large number of cells are positioned at the distal jejunum and ileum of the small intestine, and the cell numbers continuously increase from the proximal to the distal colon with highest numbers in the rectum. For rat, highest cell density was found in the ileum, while similar to the pig and human, cell density in colon increased from proximal to distal regions[70]. Apparently, the location and distribution as well as the morphological properties of L-cells reflect their different functions in sensing slowly digested or indigestible nutrients to maximize assimilation of food materials.

4.1. Gut hormones involved in feedback

4.1.1 Cholecystokinin(CCK)

CCK is a major gut hormone released from endocrine I cells concentrated in the proximal region of duodenal and jejunal mucosa in the small intestine[71]. CCK is also produced by various neurons in the gastrointestinal tract and central nervous system [72] as a neurotransmitter with a variety of functions. There are multiple molecular forms of CCK resulting from posttranslational processing, such as CCK-58, CCK-33, and CCK-8. Two types of CCK receptors (CCK_A and CCK_B) have been discovered to mediate its action in coordinating the activity of the gastrointestinal tract, and it is likely the first important player in the negative feedback loop in the gastrointestinal tract to maximize the assimilation of food nutrients.

The secretion of CCK in the small intestine is intimately associated with the food components during the intestinal phase of the postprandial state. An early rat study using duodenal perfusion of food found that unhydrolyzed protein and free fatty acid (acyl chain length should be over 12 carbons) are potent stimulators of CCK secretion while glucose, casein hydrolysate, and intact fat had little effect [73]. A human study also showed that the chain length of the fatty acid needs to be over 12 to stimulate the

306 secretion of CCK [74]. There also exists a high degree of selectivity on the structure of free fatty acids for
307 CCK secretion [75], and conjugated linoleic acids are the most potent CCK secretagogues when tested
308 using the CCK-secretion STC-1 cells[76]. The potent stimulation effect of protein and amino acids on the
309 secretion of CCK have also been shown in the human while glucose only caused a small but significant
310 elevation of CCK [77]. Although dietary nutrients are the prerequisite for CCK release, a nutrient sensing
311 mechanism through receptors of lipid [78], and protein [79] is also required for its release through receptor-
312 coupled Ca^{2+} signaling.

313 CCK in the duodenum plays an important role in coordinating food digestion and nutrient
314 absorption through controlling the motility of the gastrointestinal tract and enzyme secretion. CCK
315 stimulates gallbladder contraction and pancreatic enzyme secretion [80], as well as the intestinal motor
316 activity that is important for gastric emptying. These functions make CCK an important hormonal
317 signal related to food intake and satiety [81]. Further study using a rat model showed that low dose of CCK
318 directly activates the vagal afferent fibers providing a negative feedback signal to the brain leading to a
319 food intake inhibition [82], and a high dose of CCK might indirectly interact with a localized CCK_A
320 receptor in the circular muscle and pyloric sphincter leading to pyloric contraction and a slow gastric
321 emptying in rat [83]. The presence of a positive leptin-CCK feedback loop in which "leptin and CCK may
322 potentiate their own effects by cross-stimulating their secretion" observed in rats by duodenal infusion
323 of leptin also supports the hormonal action of CCK on satiety[84]. Human studies further confirm CCK's
324 function in delaying gastric emptying[85] and pancreatic secretion[86]

325 Although CCK is an important gut hormone, limited information on the effect of carbohydrate
326 on CCK secretion is available [87]. No relationship was found between glucose release rate and the
327 postprandial level of CCK when a barley meal was used as the diet [88]. However, duodenal glucose loads
328 (perfused at 2 or 4 kcal/min, but not 1 kcal/min) affected the secretion of CCK in a human study[89],

329 indicating that both the quantity and sustained time might be important in stimulating CCK secretion by
330 glucose. Additionally, a human glucose perfusing study showed CCK reduced the postprandial
331 hyperglycemia through delaying gastric emptying [90]. CCK are also involved in insulin secretion and
332 glucose tolerance in mice fed with a high fat diet [91]. The anti-diabetogenic action of CCK-8[92] as well as
333 the insulinotropic effect of CCK-8 mediated through Ca^{2+}-independent phospholipase A2 signaling
334 pathway [93] also indicate important function of CCK in glucose homeostasis.

335 **4.1.2. Glucagon-like peptide-1 (GLP-1)**

336 The distal distribution of L-cells in the small intestine suggests the importance of the associated
337 gut hormones of GLP-1 and PYY as the final guard for nutrient assimilation. Endogenous GLP-1 has a
338 very short half-life of less than 2 min due to its rapid degradation by the enzyme of dipeptidyl peptidase-
339 4 (DPP-4). The known functions[94] of GLP-1 including glucose-dependent insulin secretion, reducing
340 glucagon secretion, and improvement of insulin sensitivity (pancreas), make GLP-1 a good candidate for
341 diabetes treatment and glucose homeostasis maintenance [95]. GLP-1 also inhibits gastric emptying and
342 increases satiety through the gut-brain axis, which is beneficial to food intake control and obesity
343 prevention. Pharmacologically, GLP-1 receptor agonists (RAs) have been produced to mimic the
344 function of GLP-1, but the long-lasting action of RAs could cause tachyphylaxis and a loss of certain
345 function of GLP-1. Thus, the pattern of RA application needs to be test for different RAs for desired
346 outcomes[96].

347 GLP-1 secretion (Figure 4) is potently stimulated by the nutrients of glucose, fatty acids,
348 essential amino acids, and other endocrine hormones, as well as neurotransmitters via receptor-coupled
349 signaling pathways [97]. The secretion of GLP-1 generally shows a biphasic pattern after meal ingestion:
350 the early phase (10-15 min) is mediated by the vagus nerve and neurotransmitters such as gastrin-
351 releasing peptide (GRP) and acetylcholine, and a second phase (30-60 min) is likely via direct contact

with the L-cells as observed in rats [98]. For unsaturated free fatty acids studied in vivo and in vitro, GPR120, a G-protein-coupled receptor was required for GLP-1 secretion [99]. Glucose-induced GLP-1 secretion is associated with ATP-sensitive K_{ATP} channel closure via the SGLT-1 transporter upon electrogenic sugar entry observed in a L-cell model of GLUTag cells [100], and the α-gustducin-coupled sweet taste receptor as observed in human L-cell line NCI-H716 and a transgenic mouse model [101, 102]. As studied in the rat small intestine, GLUT2 also plays an important role in glucose-induced secretion of GLP-1 and other gut peptide by affecting membrane depolarization through closure of K_{ATP} channels[103]. Fermentable dietary fiber stimulated the secretion of GLP-1 in the distal region of the intestinal tract and proximal colon of healthy dogs [104] through receptors of FFAR2 (GPR43) and FFAR3 (GPR41) for short chain fatty acids (SCFAs).

In addition to nutrient-stimulated GLP-1 secretion, other endocrine hormones and neural factors also induce the secretion of GLP-1. GLP-1 secretion is activated by leptin, and high fat induced obese mice are associated with leptin resistance with a decreased level of GLP-1[105]. A study using L-cell models of murine GLUTag, human NCI-H716, and fetal rat intestinal cells as well as MKR mice with a chronic hyperinsulinemia showed that insulin also promotes the secretion of GLP-1 through activating the phosphatidylinositol 3 kinase-Akt and MAPK kinase (MEK)-ERK1/2 pathways, and insulin resistance leads to a decreased secretion of GLP-1 [106]. Glucose insulinotropic peptide (GIP), produced by K-cells in the proximal region of small intestine, also stimulates glucose-independent GLP-1 secretion in the ileum observed from canine L-cells [107]. This proximal-distal regulation is mediated by a neuro-endocrine loop involving the enteric nervous system and vagus nerve as studied in an in situ model of the rat gastrointestinal system [108] since infusion of a gastrin-releasing peptide (GRP), a neurotransmitter within the enteric nervous system, stimulates the secretion of GLP-1 via activation of phospholipase C and protein kinase C triggering Ca^{2+} release in the distal region of rat intestinal tract [109].

GRP is distributed in both the gastrointestinal tract and brain, especially the hypothalamic feeding center, and GRP is likely a bridge between the gastrointestinal tract and brain to modulate food intake [110].

The main functions of GLP-1 (i.e., glucose-dependent insulin secretion, expansion of β-cell mass, peripheral glucose disposal, gastric emptying inhibition) are related to glucose homeostasis. GLP-1 is a vital incretin hormone specializing in regulating carbohydrate metabolism and glucose homeostasis, and impaired GLP-1 secretion is found in type 2 diabetics [111]. GLP-1 also exerts an important function of modulating energy intake, promoting satiety, and regulating fat metabolism in the central nervous system [112]. A decreased food intake and antidiabetic effect by inulin and oligofructose in rats were related to increased secretion of GLP-1 [113]. The satiety promotion effect on rats fed with a high fat diet was also related to oligofructose fermentation and increased secretion of GLP-1 in the proximal colon [114]. GLP-1's inhibition on food intake provides a theoretic basis for body weight control mediated by a cooperatively organized peripheral and central GLP-1 sensing pathways [115]. Another study [116] in human on raw corn starch (a type of SDS) showed significant increase in GLP-1 and GIP secretion compared with the rapidly available glucose; GIP secreted within 15-30 min was correlated with postprandial glycemia while GLP-1 increased significantly from 180-300 min after consumption the SDS indicating a distal secretion pattern. Certainly, the importance of GLP-1 to carbohydrate and energy metabolism not only supports the critical role of glucose to life, but also shows promises for preventing or treating chronic diseases related to impaired energy and glucose metabolism.

4.1.3 Peptide tyrosine tyrosine (PYY)

PYY is also called peptide Y, PYY_{3-36} and PYY_{1-36} are two main endogenous forms of PYY, and PYY_{3-36} , as the predominant form in circulation, is produced from the cleavage of PYY_{1-36} by dipeptidyl peptidase IV (DPP IV) after secretion from endocrine L-cells. PYY is mainly produced in the

ileum and colon, but PYY is also found in the central nervous system of the hypothalamus, pons, medulla and spinal cord and enteric nervous system[117] and thus is considered a neuropeptide. Structurally, PYY is similar to orexigenic neuropeptide Y (NPY) that is a potent stimulator of food intake [118]. As PYY and GLP-1 are co-synthesized in distal L-cells, PYY is also a gut hormone like GLP-1 secreted in a biphasic fashion after a meal, and proximal signals such as GIP and neurotransmitters [119] can also indirectly simulate its distal secretion [120].

Luminal nutrients with certain structural properties are required for PYY secretion through different mechanisms. Perfusion to the isolated rat ileum showed that glucose (250 mM) and peptone (5%) produced a pronounced and sustained release of both GLP-1 and PYY, while an early and transient release was shown for short chain fatty acids (20 mM) while intact cellulose or pectin did not show any effect [121]. Regarding the effect of lipid on PYY secretion, ileal fat infusion in human subjects did not show any effect on PYY secretion indicating lipid digestion is required for PYY secretion [122], and the fat hydrolysis products of free fatty acids in proximal small intestine can invoke release of CCK, and CCK, mediated by its receptor, can then stimulate the secretion of PYY [123] through an atropine-sensitive, cholinergic pathway[124]. Glucose-stimulated PYY secretion was shown to involve the sweet taste receptor, which is similar to secretion of GLP-1 in a human study [125]. Capability of amino acids to induce PYY secretion is not consistent in studies and also showed difference among species as well as different potencies in the colon and ileum [126].

PYY can be secreted by both ileal and colonic L-cells, but the dietary triggering mechanisms are different, which indicates the existence of regional difference of PYY secretion. The elevation of PYY in the colon after ingestion of resistant starch shown in rodent animal model was related to SCFA produced from its fermentation [127] , but SCFA in the ileum did not induce PYY secretion observed from an in vitro study using intestine tissue from pig [128] and rat[129]. Thus, the regional difference is another

aspect that has been investigated systematically in a rat study involving different nutrients[129]. Using oleic acid perfusion, the order of potency was: the colon < ileum < duodenum; glucose was effective in releasing PYY in the ileum and colon, but not the duodenum; and amino acids and SCFAs were only effective in the colon. L-cells in the ileum, with limited contact with the gut lumen, seems only respond to a few luminal stimuli [such as oleic and bile acid] through hormonal (such as CCK, GIP) and neural pathways for PYY secretion [130]. In contrast, the endocrine L cells in the colon can respond to a broad range of luminal stimuli as these L-cells have large area of direct contact to gut lumen [126], which reflects the relationship between anatomic structure of L-cells and their functions in ileum and colon.

The physiological function of PYY is mediated through its G-protein-coupled receptors including Y1, Y2, Y4 and Y5 subtypes in humans. PYY_{1-36} show high affinity to all receptors, while only PYY_{3-36} shows high specificity to receptor Y2 that was considered as the major functional receptor mediating many processes. These receptors are distributed in a wide range of tissues and organs: PYY preferring binding sites in the crypt cells in the small intestine[131], epithelial and nonepithelial tissue of the small or large intestine [132], human gastrointestinal tract muscle cells [133], differential and discrete distribution in the central nervous system [134], pancreas for secretion inhibition [135], human fat cells [136] for anti-lipolytic effects, the kidney for renal vasoconstriction and sodium execration [137], and ventricular arteries of heart [138]. This wide range distribution of PYY receptor is associated with multiple functions of PYY.

The impact of PYY on gastrointestinal tract activity (secretion, gastric emptying) is mediated by its receptor Y2. The function of inhibiting small intestinal secretion is mediated by the peripheral receptor Y2 located in crypt cells to decrease cAMP production and increase intracellular Ca^{2+} [139]. In dogs, pancreatic secretion inhibition was also shown to be mediated by PYY_{3-36} preferring subtype Y2 [140]. In smooth muscle cells, the Y2 receptor can activate G-protein Gq and stimulate IPs formation to

induce IP_3-depemdent Ca^{2+} release and muscle contraction [141] that is related to gastrointestinal transit time and gastric emptying. A similar study showed that the Y2 receptor present in the dorsal vagal complex (DVC) is responsible for slow gastric emptying through vagal reflex control circuits (vagus nerve), while Y1 receptor (binding with NPY) promotes gastric emptying [142] . The motility of the colon is also affected by PYY through the Y2 receptor as it was reported that PYY injected intraperitoneally into mice inhibited fecal pellet output by ~90%, and higherY2 mRNA expression observed in the colon mucosa also suggested a Y2-mediated effect on propulsive colonic motor function by PYY_{3-36} [143]. Consistently, the Y2 agonist PYY_{3-36} was shown to inhibit diarrhea by reducing intestinal fluid secretion and slowing colonic transit in mice [144]. Although CCK can mediate the distal release of PYY , PYY, on the other hand, inhibits the CCK-8 stimulated contraction of ileal muscle and gallbladder smooth muscle by inhibiting the release of acetylcholine from cholinergic nerve terminals [145].

Additional to the regulatory functions on the activity of the gastrointestinal tract, the function of decreasing appetite and promoting weight loss through Y2 has been extensively investigated with its potential to decrease food intake and obesity. Food intake is controlled by a key brain area of hypothalamus including the melanocortin and NPY system in the arcuate nucleus, and is regulated through access to peripheral nutrients and hormones. Food intake and appetite in both rodent and human were inhibited by either peripheral administration or direct intra-arcuate administration of PYY_{3-36} at a level matching the postprandial stage [146, 147], and indicated PYY's function in appetite control without changes in gastric emptying, plasma levels of insulin and leptin. Another study in 2006 [148] was the first report demonstrating that reduced food intake by PYY administration can be sustained over an extended time period by utilizing a chronic dosage pattern of one-hour intravenous infusions of PYY_{3-36} every other hour for 10 days. Later on, the same group [149] studied the effect of PYY on obese rats using an intermittent delivery paradigm (two 3-h ip infusions during the dark phase) of varying doses of PYY_{3-36}

for a period of 21 days. They also found a sustained food intake reduction and decreased fat deposition in high fat diet induced obese rats. As there exists compensatory hyperphagia and receptor tachyphylaxis for sustained elevation of PYY, the experimental paradigm is likely of great importance for a sustained result [150]. Since peripheral administration of PYY_{3-36} increased c-Fos immunoreactivity and reduced the expression of hypothalamic NPY through a Y2 mediated signaling pathway, a Y2-dependent gut-hypothalamus pathway is likely the mechanism for PYY_{3-36}'s function of decreasing food intake. The experimental result of Y2 null mice also proves the importance of the Y2 receptor for PYY_{3-36}'s action on food intake and appetite control [146, 147]. Beyond inhibition of food intake, PYY_{3-36} also alter substrate partitioning favoring fat oxidation and energy expenditure [151].

4.2 Ileal brake and gastric emptying

The coordination of the gastrointestinal tract in food digestion and nutrient absorption requires a balance of different processes. The ileal brake is a term describing a specific status of gastrointestinal activity (such as slow contraction, secretion inhibition) resulting from undigested nutrients reaching the ileum under normal physiological situations, and it is defined as "the primary inhibitory feedback mechanism to control transit of a meal through the gastrointestinal tract in order to optimize nutrient digestion and absorption" [152]. The ileal brake generates a distal to proximal feedback loop that inhibits upper gut motility including gastric emptying and intestinal transit (propagative to non-propagative motility), which could lead to a suppression of short-term food intake. Actually, ileal brake is just one type brake mechanism in the gastrointestinal tract in response to unabsorbed nutrients. Other types of brakes are also present such as the jejunal brake [153], duodenal brake [154], and PYY-mediated colonic brake [155, 156]. Thus, the ileal brake represents the negative feedback system in the digestive system to tune the assimilation of nutrients.

Gastric emptying refers to the transferring of a bolus of food from the stomach to the small intestine for digestion, and the rate of this transmission is the first control point for nutrient assimilation. The gut hormone CCK, secreted right after gastric emptying is used to coordinate food digestion, and it also acts as a feedback signal to regulate gastric emptying rate [85]. An observed slow glucose absorption by guar gum, due to a reverse relationship between glycemic response and satiety and CCK [157], indicates that a short-term satiety is likely associated with CCK.

Nutrient sensing in the distal gastrointestinal tract can stimulate the secretion of PYY and GLP-1 that can activate the neurohormonal pathway [158] to result in the ileal brake that has been shown to be beneficial to the control of food intake and appetite[159]. This is consistent with the physiological effect of these hormones as described above. Secretion of GLP-1 from the L-cells is almost equally sensitive to carbohydrate and fat exposure in the ileum [160]. For PYY, fatty acids are the most potent stimulator for its secretion compared to protein and carbohydrate. Fermentable fiber, from which SCFAs are produced, is an important nutrient that regulates the gastrointestinal motility and slows gastric emptying [161] through its ability of promoting the secretion of PYY and GLP-1[162]. In our study on the gastric emptying of starch-entrapped alginate-based microbeads, which have been shown to be a good example of slowly digestible starch[163], showed an increase of starch content in the rat stomach at 2 h after gavage (Figure 5, unpublished data), and this result appeared to be related to the ileal brake mechanism. This ileal brake might also be related to a decreased food intake and the down-regulated expression of NPY after 8-week feeding on the microbeads (data not shown), which is consistent with literature studies regarding the ileal brake and appetite control [164].

5. Locality of Nutrient Deposition

Gut hormones are the critical player to modulate the activity of the gastrointestinal tract. Gastric emptying delay through gut hormone-mediated ileal brake and the coordination between carbohydrate

substrate and enzyme activities are both for the purpose of maximal assimilation of food nutrients by matching the absorption capacity of the body. Since the distribution of enteroendocrine cells along the gastrointestinal tract are location-specific, there might require different nutrient stimuli at different locations in the gastrointestinal tract to stimulate specific gut hormone secretion. This is what we refer to as the locality of nutrient deposition representing an opportunity to design foods which meet location-specific requirements for nutrient exposure by endocrine cells. Here, we focus especially on the GLP-1 and PYY-secreting L-cells that are predominantly located at the distal region of the gastrointestinal tract. However, the fact that most of the food materials are digested and absorbed in the proximal region of the gastrointestinal tract indicates there needs to be food components with target-specific deposition in the gastrointestinal tract to activate the feedback regulation machinery to slow the nutrient or glucose bioavailability for improved health. Additionally, the length of time period of nutrient exposure is also of great importance as shown from the study [165] that a length of small intestine segment with 60 cm is required to elicit glucose-stimulated secretion of GLP-1. The load of nutrient exposure might be another factor that needs to be considered as shown from a human study that variations in duodenal glucose loads differentially affect the secretion of CCK,GLP-1, and GIP [89], and health related parameters of blood glucose and energy intake.

How to make food products with properties of target deposition location and quantity in the gastrointestinal tract is a great challenge to both academic research and food industry. Although slowly digestible starch (SDS) or low-GI food is assumed to provide a prolonged and slow release of glucose, there is no information on the concentration of glucose and its absorption location during the process of digestion. A recent study in pigs on SDS (raw normal corn starch) showed that the starch was completely digested before reaching the middle of the small intestine [166]. So, at least with this SDS material, it is not likely possible to induce a high level production of GLP-1 as the L-cells are mainly

located in the ileum. Therefore, a combination of different food ingredients such as proteins, fat with specific composition of fatty acids, resistant starch or fermentable dietary fiber, and other hormonal stimuli might be needed to trigger the release of these gut hormones so that the function of the ileal brake and gut-brain axis can be activated for improved health. Apparently, the food form and composition are the most important part to achieve a location-specific deposition of nutrients in the gastrointestinal tract.

Conclusion: Slow Carbohydrate Bioavailability – Physiological Perspective in a Context of Whole Food

Gut hormone induced ileal brake can cause delayed gastric emptying, and delayed gastric emptying would lead to decreased accessibility and availability of nutrients to digestive enzymes. The concomitant pancreatic secretion inhibition also decreases the concentration of digestion enzymes. For available carbohydrates, the net result is a slow carbohydrate bioavailability generated through a physiological way. For this to happen, though, an ileal brake inducer should be there either before or at the time of diet consumption.

Since the ileal brake is mediated by the hormones CCK, GLP-1 and PYY, direct administration of hormones or a hormonal agonist will cause ileal brake. But ileal exposure of a nutritional inducer would though be preferred and should be a natural choice to slow carbohydrate bioavailability. Indeed, a preload of whey protein, which is an inducer of GLP-1 secretion, showed significant improvement of postprandial glycemic response with high level of GLP-1 and significant delayed gastric emptying when a rapidly digestible carbohydrate meal (mash potato) was ingested later [167] . Similarly, a pre-loading of olive oil (30 min before eating) (Figure 6) also significantly increased the level of GLP-1, flattened postprandial blood glucose and decreased gastric emptying with highest carbohydrate retention in the distal stomach [168]. Obviously, proteins are not all equal to stimulate the secretion of gut hormones

558 evidenced by the fact that casein is much less effective in stimulating CCK and GLP-1 release and the
559 resulted satiating effect [169]. Unsaturated fat is more effective than saturated fat in stimulating secretion
560 of gut hormone GLP-1 [170]. Monounsaturated fat also improved glucose tolerance with its ability to
561 induce GLP-1 secretion [171]. The effect of fiber on glucose homeostasis with increased production of
562 GLP-1 is also well known, and certainly, it can also act as GLP-1 inducer to be ingested[172]. Food-
563 sourced inhibitors of SGLT-1, which leads to a high concentration of glucose in the gut lumen, might
564 also be used to induce the secretion of GLP-1 evidenced by a high level of serum GLP-1 in SGLT-1
565 knockout mice or treated by SGLT-1 inhibitor of LX4211[173]. Thus, when a GLP-1 inducer is preloaded,
566 available carbohydrates, including even rapidly digestible carbohydrates in the diet will naturally
567 become slowly available carbohydrate. Slowly digestible carbohydrate itself, if such materials can be
568 identified and verified to provide ileal location digestion, is also potentially a good dietary ingredient for
569 accentuating the ileal break. Thus, if a structure-based SDC material that has a property of targeted
570 ileum deposition is consumed as the carbohydrate component, the effect of slow digestion might become
571 more significant by adding the amplifying effect of delayed gastric emptying.

572 The production of GLP-1 and PYY not only mediates ileal brake, but also improves other
573 physiological processes that may have a wide range of health-related physiological functions. These can
574 be well illustrated by the effects of gastric bypass surgery, such as improvement of glucose tolerance for
575 diabetics and increased insulin sensitivity due to changes of gastrointestinal tract activity with a high
576 secretion of GLP-1 and PYY [174] and less production of ghrelin [175]. Dietary approaches with a location-
577 specific deposition of specific macronutrients with enough quantity [176] to activate the neurohormonal
578 feedback mechanisms might be the way to achieve not only a slow carbohydrate bioavailability but also
579 similar outcomes of gastric bypass surgery for improved health.

580

Acknowledgments

Funding: Financial support was provided by the National Natural Science Foundation of China (Project 31471585) and the Ministry of Science and Technology of People's Republic of China Infrastructure Program (Project 2012BAD33B05).

Declaration of interest. The authors have no relevant interests to declare.

601
602

603 Table 1. Variable sensitivities of mucosal enzymes on carbohydrate substrates with different glycosidic
604 linkages, and more + indicates high sensitivity.

	Linkages with glucose + glucose					Linkages with glucose + fructose	
	Trehalose (α-1,1)	Kojibiose (α-1,2)	Nigerose (α-1,3)	Maltose (α-1,4)	Isomaltose (α-1,6)	Sucrose (α-1,2)	Palatinose (α-1,6)
C-MGAM	-	++	++	++++	+	*	*
N-MGAM	-	+	+	+++	+	-	*
C-SI	-	++	++	+++	+	**	*
N-SI	-	++	++	+++	+++	-	***

605 Note: - : no activity

606

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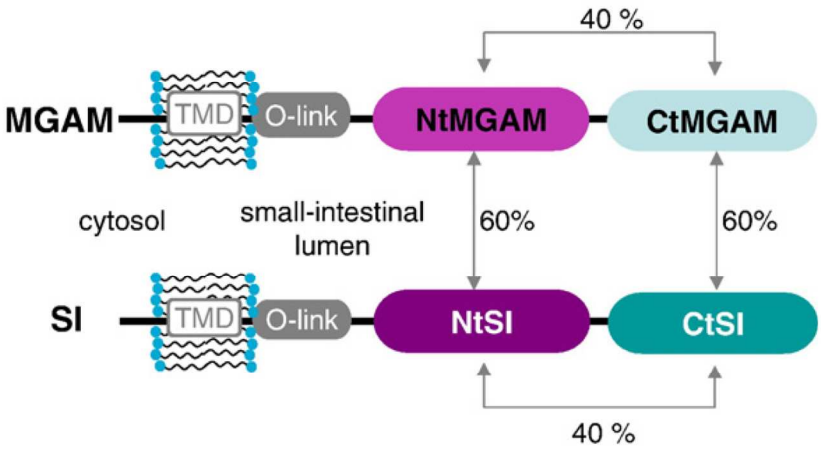

Figure 1. Digram of brush border enzymes of MGAM and SI. Nt: N-terminal, Ct: C-terminal.[177] (*Permission granted by thepulisherr*).

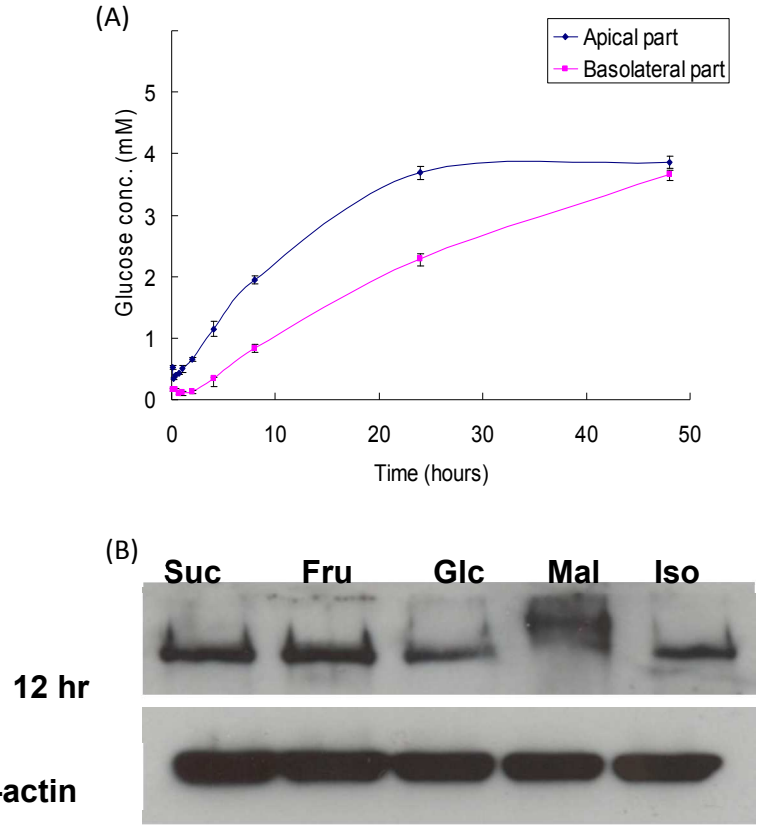

Figure 2. The concentration of liberated glucose along the treatment time with maltose (A), and Western blot of sucrase isomaltase (SI) enzymes under different sugars after 12 hours treatment. Only maltose showed a band with a higher molecular weight, which is likely the active form of SI that can digest maltose.

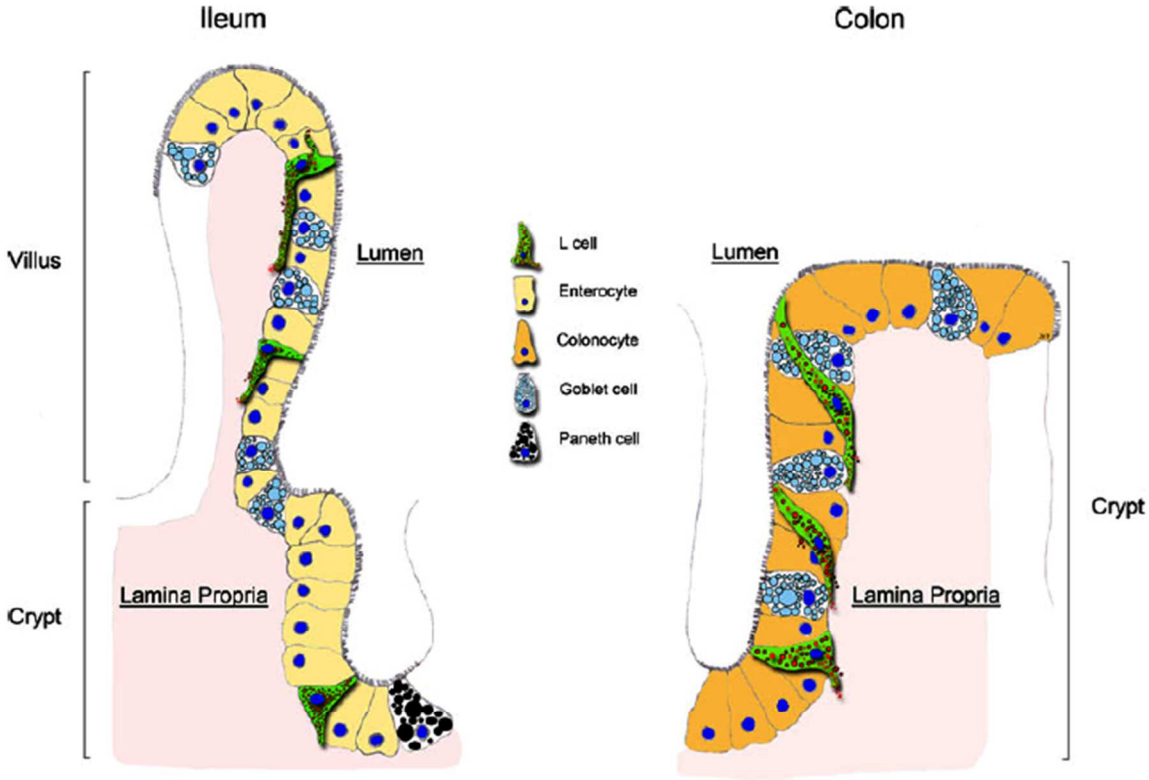

Figure 3. The anatomy of L-cell in the ileum and colon of rats[69]. (*permittion was granted by the publisher*)

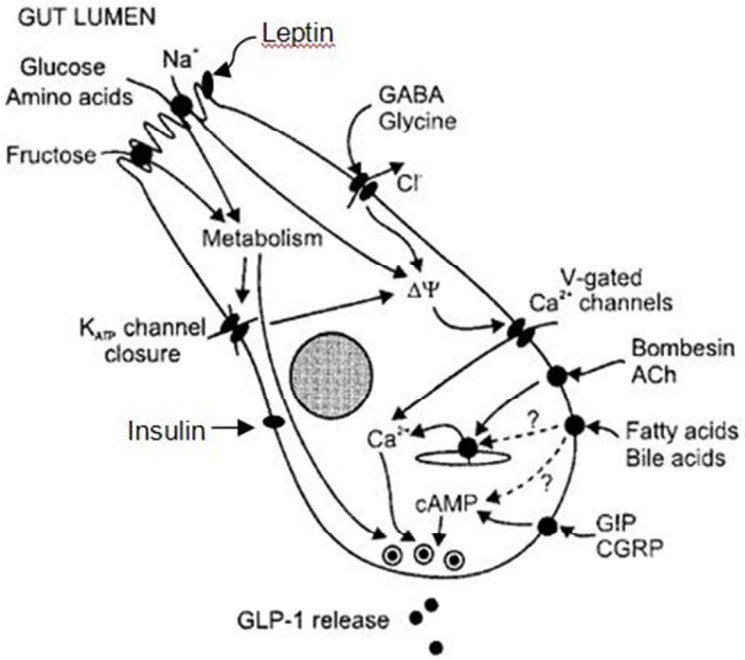

Figure 4. Digram of GLP-1 secretion from L-cells stimulated by nutrients, endocrin hormones and neurotransmetters through receptor-coupled signling pathways to produce cAMP, Ca^{2+} release and membrane depolarmizaiton trggering GLP-1 release. (*derived from Reimann etal (2006)* [178])

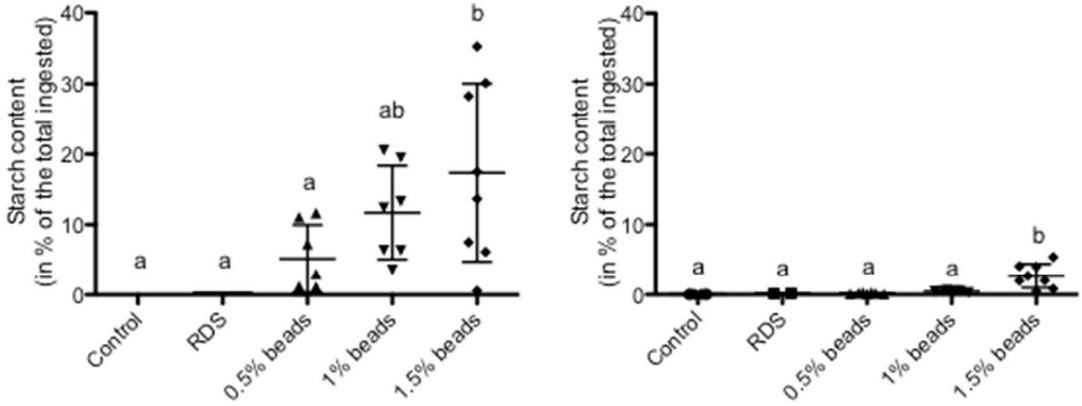

Figure 5. Starch content (in % of the total amount ingested) in stomach (left), and distal small intestine (right) after oral gavaging for 2 hrs. 0.5%, 1%, and 1.5% represent alginate concentration when making the alginate-trapped starch beads.

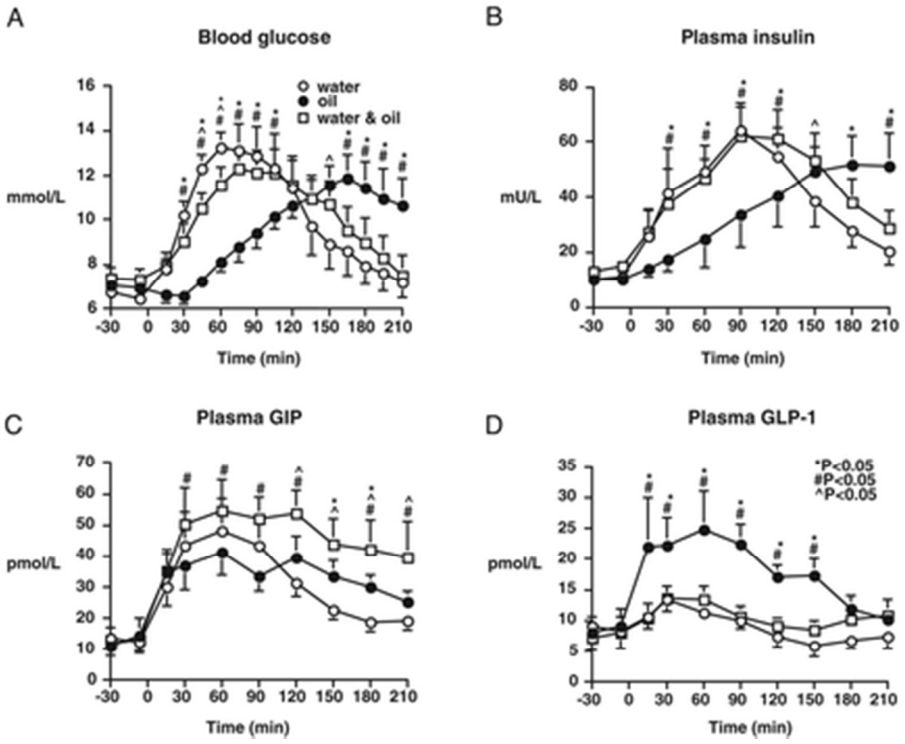

Figure 6. The concentration of blood glucose (A), insulin (B), GIP (C), and GLP-1 after ingestion of a mashed potato meal when either 30 ml olive oil was consumed before the meal (30 min), water or water &oil [168] (*permission granted by the publisher*).

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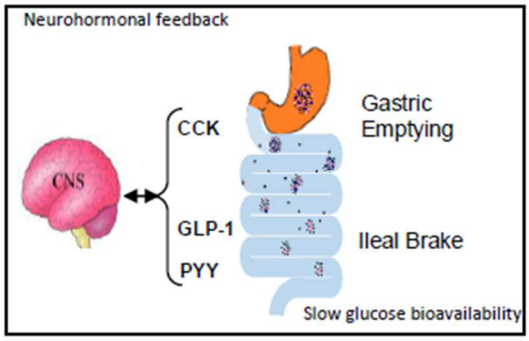
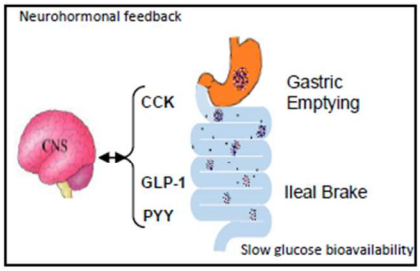


Slow glucose bioavailability through neurohormonal feedback activated by location-specific nutrient deposition



Slow glucose bioavailability through neurohormonal feedback activated by location-specific nutrient deposition

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