Molecules and Cells

Minireview

Post ingestive systemic nutrient sensing for whole-body homeostasis

Gahbien Lee[1,†], Jiyeon Lee[1,†], Greg S.B. Suh[2], and Yangkyun Oh[1,*]

[1]Department of Life Science, College of Natural Sciences, Ewha Womans University, Seoul 03760, Republic of Korea, [2]Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon 34141, Republic of Korea

*Corresponding author. yangkyun@ewha.ac.kr

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ABSTRACT

Systemic nutrient sensing is a fundamental process that aligns nutrient availability with an organism's metabolic demands. This mini-review explores nutrient sensors in the intestine, pancreas, portal vein, and the brain—organs that detect and convey nutrient status to other tissues via neuronal and hormonal signaling. Unlike oral taste receptors that sense external nutrient inputs, these nutrient sensors monitor post ingestive levels of macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and essential trace elements such as calcium, magnesium, and zinc) within the body. We describe the specific mechanisms by which each organ discerns fluctuations in nutrient concentration and discuss how these signals integrate into endocrine and neural circuits to maintain whole-body nutrient balance. Finally, by comparing mammalian and invertebrate models such as *Drosophila*, we offer a comprehensive perspective on how organ-level nutrient sensing upholds metabolic homeostasis across diverse species.

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INTRODUCTION

Animals must consume proper nutrients to survive, including macronutrients—carbohydrates, proteins, and lipids—as well as micronutrients, such as vitamins and trace elements like calcium, magnesium, and zinc. Among macronutrients, carbohydrates and lipids are mainly used to produce adenosine triphosphate (ATP), the basic energy unit in most cells. They can also be stored as glycogen or fat to prepare for future energy shortages. Proteins, which are complexes of 20 amino acids, serve many roles inside cells, such as transport, enzymatic activity, signal transduction, cell recognition, and structural support (Honig and Shapiro, 2020; Kilberg et al., 2005). In some cases, proteins also function as an energy source when other nutrients are limited.

Because all cells require energy for survival, they have intrinsic nutrient-sensing mechanisms that allow them to detect and respond to changes in glucose, amino acids, and fatty acids (Efeyan et al., 2015; Sung et al., 2023). Previous studies have characterized these intracellular sensors in detail, showing how cells detect excess or limited nutrient levels and then adjust metabolic pathways accordingly in a cellular level (Efeyan et al., 2015; Sung et al., 2023). Expanding beyond the cellular level, this review highlights nutrient sensing from a physiological perspective at the level of the whole organism. Specifically, we examine how post ingestive nutrient levels are monitored across various organs and how these signals elicit physiological and behavioral responses to maintain whole-body homeostasis.

After an animal ingests food, specialized nutrient-sensing cells in multiple organs monitor the concentrations of essential nutrients, including carbohydrates, protein, and lipids (Kim et al., 2021a; Oh et al., 2019; Rasmussen et al., 2012). These sensors relay the nutrient information via neural or hormonal signals to the brain, liver, and other organs. Once the brain receives these signals, specific neuronal circuits become active and can alter feeding behavior or dietary preferences. Furthermore, internal metabolic processes adapt to changing nutrient status, mainly controlled by livers and other endocrine organs (Smith et al., 2018). Animals do have external nutrient sensors—mainly oral taste receptors—that allow to detect sweetness (mono- and disaccharide), umami (amino acids such as glutamate), saltiness (Na^+), sourness (H^+), or bitterness (various toxic chemical compounds) (Melis and Tomassini Barbarossa, 2017).

Instead of investigating how the oral taste receptors work before ingestion, our goal here is to examine how the nutrient receptors detect post ingestive nutrients and signal to maintain

† Gahbien Lee and Jiyeon Lee authors contributed equally.

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whole-body nutrient balance. We will examine how each organ can sense macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and trace elements) inside the gut lumen and internal organs, and then transfer signals to the brain and other organs to control feeding behavior and maintain the metabolic homeostasis (Redhai et al., 2020; Sung et al., 2023; Wang and Babitt, 2019). We named these external (gut lumen) and internal nutrient sensors as "systemic nutrient sensors" to describe these organ-based post ingestive nutrient-detecting groups of cells distributed across the intestine, blood vessel, liver, pancreas, and neuronal and glial cells in the peripheral and central nerve systems. First, we will outline how these sensors detect nutrients through various molecular pathways using taste, electric, or metabolic receptors and those downstream signaling pathways. Additionally, we will describe the post ingestive nutrient sensors that were recently found in the *Drosophila* model system and compare their nutrient-sensing mechanisms with those of mammals. We will discuss how these sensors detect nutrient levels, how they convert the cellular signals into the neural or endocrine signals, and ultimately influence target organs such as the brain and liver to coordinate behavior and metabolic responses, thereby maintaining metabolic homeostasis. Finally, we suggest future research directions to uncover how animals integrate post ingestive nutrient information in the brain or metabolic organs and respond with behavioral or metabolic changes. By focusing on the macroscopic, organism-level perspective of nutrient-sensing and responding mechanisms in animals, we hope to shed light on how balanced feeding patterns and whole-body energy homeostasis is maintained beyond the scope of the intercellular level of nutrient sensing.

SYSTEMIC NUTRIENT SENSOR: ORGAN-LEVEL NUTRIENT DETECTOR

All cells require nutrients to maintain cellular function and must detect the cellular nutrient level to regulate metabolic processes (Efeyan et al., 2015; Miyamoto et al., 2013). Animals generally use 2 broad strategies for nutrient detection. First, they rely on the oral taste receptors to evaluate food before ingestion, which allows them to estimate it's nutritive value and decide whether to consume it or not (Behrens and Meyerhof, 2011; Miyamoto et al., 2013). Second, post ingestive nutrient sensors monitor the type and amount of nutrients both while food remains in the digestive tract and after it is absorbed into the body. These sensors detect individual nutrient levels, stimulate gut hormone release to regulate food intake, and modulate nutrient-specific appetites in response to internal imbalances by acting through brain circuits, thereby contributing to metabolic homeostasis. Interestingly, some group of cells in the intestine also express taste receptors that function as post ingestive nutrient sensors (Behrens and Meyerhof, 2011; Jang et al., 2007). This review explores how post ingestive nutrient sensors detect nutrients, transmit signals to other organs, and regulate feeding behavior and metabolic homeostasis.

Every cell needs glucose to generate energy in the form of ATP, and specialized glucose transporters and downstream signaling cascades support the cellular glucose detection. For example, glucose can enter cells via glucose transporter type 2 (GLUT2) or sodium-glucose-linked transporter 1 (SGLT1) transporters and be phosphorylated by glucokinase (GCK), which then activates signaling cascades such as AMP-activated protein kinase (AMPK) (Fig. 1A) (Cani et al., 2007; Claret et al., 2007; Gorboulev et al., 2011). When glucose is scarce, AMPK activity increases, initiating a series of steps that suppress anabolic processes while promoting cell survival (Sung et al., 2023). Among the many cell types that utilize these basic sensing pathways, some serve as specialized "detector" cells that present the information of internal nutrient level to the other organs, including the brain and liver, using neuronal or hormonal signaling pathways. We refer to these detectors as "systemic glucose sensors," as they detect changes in glucose levels and communicate that information to other cells or organs through neural or hormonal signals, ultimately regulating whole-

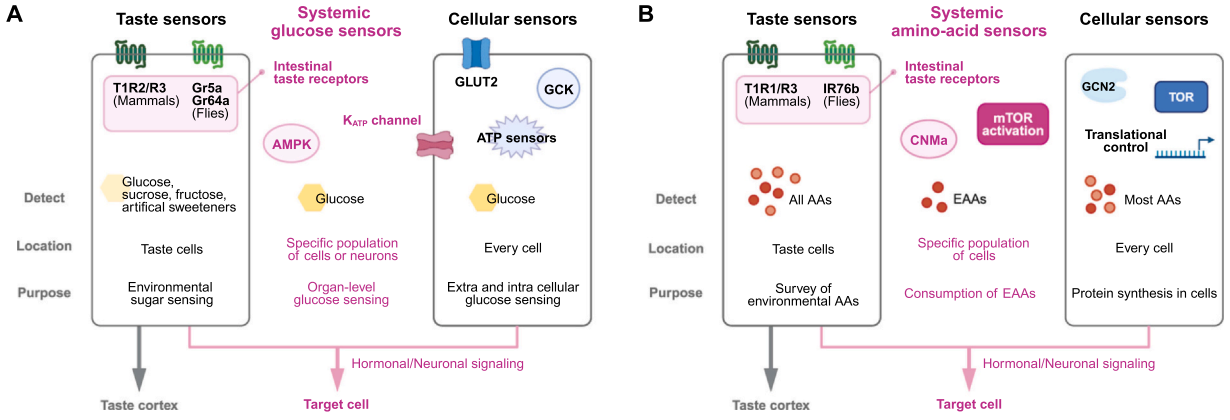


Fig. 1. Nutrient sensors in animals: from taste to systemic sensing. Overview of nutrient sensors for glucose (A) and amino acids (B). Nutrient sensors operate at multiple levels to maintain nutrient balance. Taste-level sensors, such as T1R2/T1R3 in mammals and Gr5a/Gr64a in *Drosophila*, detect environmental nutrients before ingestion. Cellular sensors (eg, GLUT2, AMPK, and K_{ATP} channels for glucose; GCN2, mTORC1, and CNMa for amino acids) monitor intracellular nutrient abundance to regulate cellular processes. Systemic nutrient sensors, found in specialized cells, detect circulating nutrient levels and initiate broader physiological responses through hormonal or neural signaling to maintain whole-body homeostasis. CNMa, CNMamide; GCN2, control nonderepressible 2; K_{ATP}, ATP-sensitive potassium.

body glucose availability and maintaining glucose homeostasis (Fig. 1A).

At the cellular level, amino acids or dipeptides enter cells via amino-acid transporter/receptors and activate various signaling pathways, including general control nonderepressible 2 (GCN2) and mechanistic target of rapamycin (mTOR)-related signaling pathways (Hara et al., 1998; Hundal and Taylor, 2009; Kim and Guan, 2011). When intracellular amino-acid availability is low, GCN2 detects the accumulation of uncharged tRNAs and modifies translational initiation to conserve resources (Hundal and Taylor, 2009; Kilberg et al., 2005). Conversely, sufficient levels of amino acids can activate mTOR, promoting anabolic processes such as protein synthesis (Kim and Guan, 2011). Through these mechanisms, cells dynamically sense and respond to changes in amino-acid levels, ultimately adjusting their metabolic activities to match current nutrient status (Fig. 1B). Several amino acids, including leucine, methionine, arginine, threonine, and glutamine, also have distinct cellular mechanisms to detect and respond to changes in their own levels (Sung et al., 2023). As with glucose: while many cells can detect amino-acid levels to regulate their own metabolism, specialized cell types in the intestine, blood vessels, liver, and brain function as amino-acid sensors by translating local fluctuations into signals that convey organism-wide amino-acid status and drive behavioral or metabolic responses (Fig. 1B) (Efeyan et al., 2015; Miyamoto et al., 2013; Yi and Xiong, 2025). Additionally, some amino-acid sensors only detect the increase or decrease of specific amino acids but do not respond to changes of the others (Chantranupong et al., 2016; Kim et al., 2021a; Wolfson et al., 2016). In this review, we group together these specialized detectors of amino-acid levels as “systemic amino-acid sensors” (Fig. 1B). We will define these organ-based sensors for each nutrient category and describe how they function in sending nutrient-related signals to the rest of the body.

INTESTINE SENSING OF MACRONUTRIENT

After food intake, the intestine is the first organ directly exposed to the nutritive molecules of the ingested food. Enteroendocrine cells (EECs) play a pivotal role in sensing nutritive molecules and secreting various hormones to maintain the nutritive balance of the body. Located primarily in the small intestine, EECs secrete various hormones in response to nutrient intake (Steinert and Beglinger, 2011). When carbohydrates -typically in the form of glucose -enter the intestinal lumen, they can be transported into EECs through membrane proteins such as SGLT1 and GLUT2. This transport triggers incretin secretion that subsequently promotes insulin release from pancreatic β-cells and maintains internal glucose homeostasis after carbohydrate ingestion (Cani et al., 2007; Gorboulev et al., 2011). Sweet taste receptors that detect sugars, particularly the heterodimeric complex of T1R2 and T1R3, are also expressed in the intestine. These receptors are expressed in EECs and have been suggested to promote glucagon-like peptide 1 (GLP-1) secretion in response to luminal sugars, thereby supporting insulin release and postprandial glycemic regulation (Jang et al., 2007). Although T1R2/T1R3 receptors were initially identified in the tongue, they have since been detected in various peripheral tissues, including the intestinal epithelium, indicating a broader role in nutrient sensing beyond the oral cavity (Behrens and Meyerhof, 2011). Sugar sensing via intestinal T1R receptors is part of the gut-brain axis, translating nutrient availability into endocrine and neural signals that regulate feeding behavior and maintain metabolic homeostasis (Raka et al., 2019).

Systemic amino-acid sensors located in the intestine can also detect the amino acid or dipeptide level after food ingestion (Bröer, 2023; Gao et al., 2024). EECs also detect amino acids derived from digested proteins in the small intestine. In particular, amino-acid availability in the intestine is sensed by GCN2 and mTORC1. Under amino-acid deficiency, GCN2 activation modulates mTORC1 activity, contributing to whole-body energy homeostasis and nutrient balance (Fig. 2B) (Ge et al., 2023; Ye et al., 2015). These cells recognize amino acids or peptides from ingested food within the gastrointestinal tract and, through endocrine signals, regulate various physiological responses such as appetite, gastric emptying, and the secretion of digestive enzymes (Gao et al., 2024; Liu et al., 2016). Amino-acid sensing in the intestine is mainly mediated by several types of G-protein-coupled receptors (GPCRs) expressed on the intestinal cell membranes (Liu et al., 2016). Notable receptors, including the calcium-sensing receptor (CaSR), metabotropic glutamate receptor 4 (mGluR4), and GPCR family C group 6 member A (GPRC6A), respond to specific amino acids, including L-phenylalanine and L-tryptophan, to promote hormone secretion (Raka et al., 2019).

Lipids—long-chain fatty acids, triacylglycerol, and glycerol—are also detected by EECs in the intestine. Lipid sensing in these cells is mainly mediated by cell surface receptors that respond to unsaturated fatty acids (Edfalk et al., 2008). Two key receptors involved in this process are G-protein receptor 120 (GPR120), also known as free fatty acid receptor 4 (FFAR4), and GPR40 (FFAR1), both of which are sensitive to long-chain unsaturated fatty acids (Liou et al., 2011; Oh et al., 2010). In addition, Cluster of Differentiation 36 (CD36), also known as fatty acid translocase, plays a crucial role in fatty acid uptake, facilitating fatty acid internalization and subsequent metabolism (Drover et al., 2005). Activation of these receptors promotes the secretion of hormones that help regulate digestion and nutrient distribution throughout the body.

In particular, EECs are further classified into L cells, I cells, and K cells, each of which detects macronutrients, including glucose, amino acids, and fatty acids, and secretes distinct hormones, including GLP-1, cholecystokinin (CCK), and peptide YY (PYY) that play important roles in maintaining whole-body nutrients homeostasis via the gut-brain axis (Fig. 2B) (Liu et al., 2016).

L cells, located in the ileum and colon, detect amino acids using GPCRs including CaSR and stimulate the secretion of GLP-1, GLP-2, and PYY (Raka et al., 2019; Reimann et al., 2012). L cells also express GPR40, GPR120, and GPR119. In these cells, activation by long-chain unsaturated fatty acids and lipid derivatives triggers the release of incretin hormones such as GLP-1, GLP-2, and PYY (Raka et al., 2019; Steinert and Beglinger, 2011). GLP-1 enhances insulin secretion from pancreatic β-cells, delays gastric emptying, and suppresses appetite. GLP-2 stimulates glucose and amino-acid absorption, while

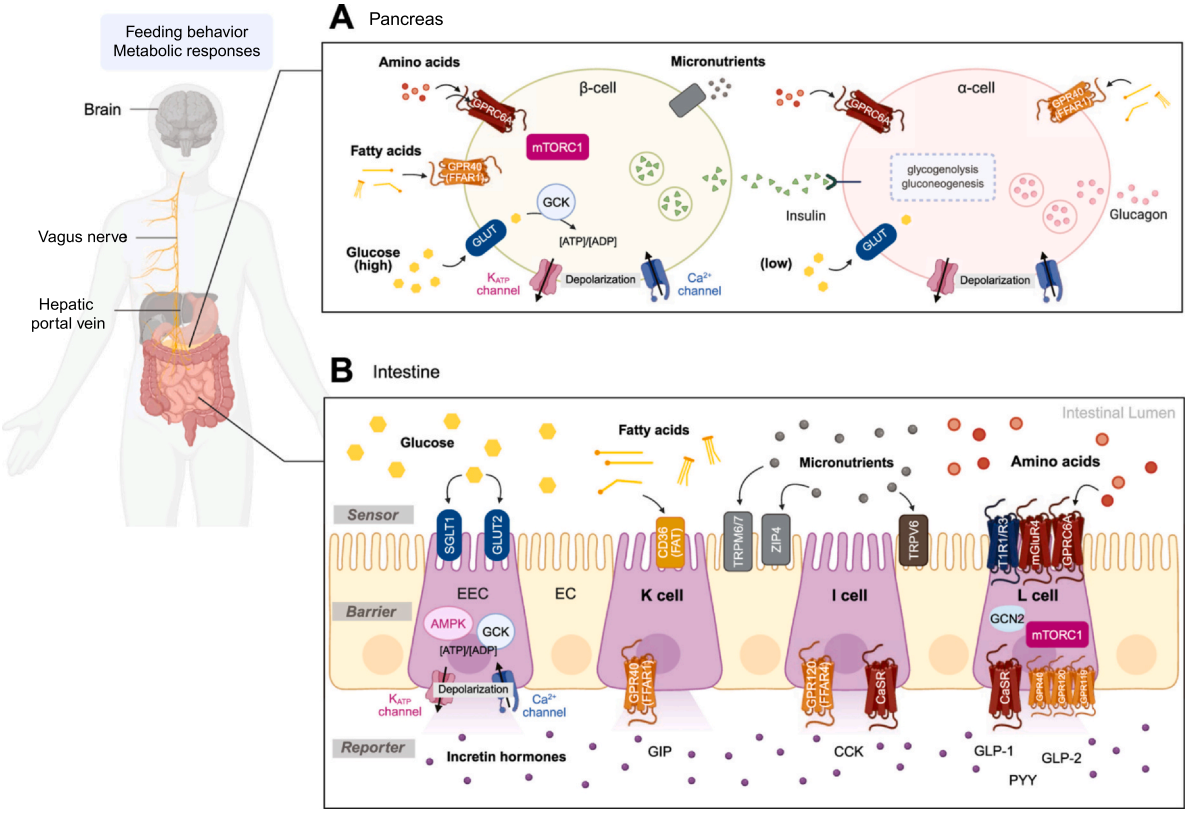


Fig. 2. Intestinal and pancreatic nutrient-sensing systems. (A) Pancreatic β- and α-cells act as key systemic nutrient sensors. β-cells detect elevated levels of glucose via sensors like GLUT, GCK, and K_{ATP} channels, triggering insulin secretion and respond to amino acids and fatty acids. α-Cells respond to low glucose or elevated amino-acid levels by releasing glucagon to raise blood sugar levels. (B) The intestinal epithelium contains multiple specialized cell types that detect post ingestive nutrients in the gut lumen and secrete various hormones in response to the nutrient status. Glucose uptake through transporters like SGLT1 and GLUT2 triggers the release of incretin hormones including GLP-1 and GIP. Amino acids are detected by G-protein-coupled receptors (GPCRs) like CaSR, mGluR4, and GPRC6A, leading to the secretion of PYY and CCK. Lipid sensing involves receptors such as CD36, GRP40 (FFAR1), and GPRR120 (FFAR4). These signals engage vagus nerve signaling and hepatic portal vein chemoreceptors to regulate feeding behavior and systemic metabolic homeostasis in a nutrient-dependent manner.

PYY enhances postprandial satiety and regulates gut motility (Steinert and Beglinger, 2011; Zheng et al., 2024). GPRC6A is expressed in G cells and L cells in the stomach and small intestine, respectively, and responds to a range of basic amino acids to contribute to GLP-1 release (Fig. 2B) (Haid et al., 2012; Oya et al., 2013).

I cells are predominantly found in the intestinal epithelium and are responsible for secreting CCK, a hormone that promotes the release of digestive enzymes and bile while delaying gastric emptying to induce a feeling of fullness (Rehfeld, 2017). Aromatic amino acids specifically activate CaSR in I cells, thereby enhancing CCK secretion and triggering neuroendocrine responses related to protein digestion (Raka et al., 2019). I cells are thought to detect lipids through a combination of lipid-sensitive GPRs (Liou et al., 2011; Reimann et al., 2012). When activated by fatty acids, these receptors induce the release of CCK, which stimulates the secretion of digestive enzymes and bile, and slows gastric emptying, thereby contributing to a feeling of fullness (Rehfeld, 2017; Reimann et al., 2012).

K cells, found predominantly in the duodenum and proximal jejunum, secrete glucose-dependent insulinotropic polypeptide (GIP) in response to sugars, including mono- and disaccharides, which plays a role in modulating insulin release under normal condition (Baggio and Drucker, 2007; Campbell and Drucker, 2013; Cho and Kieffer). Although their primary role is linked to carbohydrate-induced GIP secretion, emerging evidence suggests that dietary fats may also modulate GIP release via pathways involving receptors such as GPR40 and CD36 (Sundaresan and Abumrad, 2015).

Additionally, the nutritional status of the body can influence the macronutrient absorption efficiency of enterocytes (ECs). Studies have shown that PYY secreted by nutrient-sensing EECs can modulate glucose and dipeptide absorption by regulating ion transport in neighboring ECs (McCauley et al., 2020). Moreover, high-fat and high-sugar diets have been reported to adaptively alter the absorptive capacity of ECs in response to dietary conditions (Stojanović et al., 2021).

Collectively, the sugar-, amino acid–, and fatty acids–sensing systems of intestinal EECs, including L, I, and K cells, are not restricted only in nutrient absorption; they incorporate the information of complex nutrient molecules mixed with the post ingestive food and trigger the secretion of suitable hormones,

including GIP, GLP-1, GLP-2, PYY, and CCK, according to the internal macronutrient level. Those intestinal systemic sugar, amino acids, and fatty acids sensors convert the detection of the macronutrients in the intestine into neural and endocrine signals that are delivered to the brain and other organs. These neural and hormonal signals play a critical role in regulating digestive processes, nutrient absorption, feeding behaviors, and energy balance, thereby forming an essential part of the gut-brain axis in metabolic regulation (Duca et al., 2021).

INTESTINAL SENSING OF MICRONUTRIENT

In addition to macronutrient detection, the intestine participates in monitoring micronutrient levels such as minerals and vitamins. Although our understanding of how intestinal cells sense specific minerals is still developing, changes in absorption rates appear to be a direct mechanism by which this sensing occurs. For example, when blood calcium levels are low, activation of vitamin D promotes higher expression of calcium transporters, including transient receptor potential vanilloid 6 and calbindin, within ECs (Christakos et al., 2016). These transporters enhance calcium uptake, effectively adjusting internal calcium levels. Sodium homeostasis is primarily maintained by the kidneys and hormonal signals, but the small intestine can fine-tune the sodium absorption by coordinating with glucose transport (via SGLT1) or amino-acid transporters (Gorboulev et al., 2011). Similarly, trace elements such as magnesium and zinc are absorbed by specialized transporters like transient receptor potential melastatin 6 and 7 and zinc transporter ZIP4, which adjust their activity based on dietary intake and bodily requirements (Kambe et al., 2004; Schlingmann and Gudermann, 2005).

Vitamins are essential micronutrients that function primarily as enzyme cofactors and are required in trace amounts to sustain metabolic and physiological processes. Most vitamins are not synthesized in sufficient amounts endogenously and must be obtained through diet, although some are produced by commensal gut microbiota. Key examples include vitamin A (retinoic acid), B_1 (thiamine), B_2 (riboflavin), B_7 (biotin), C (ascorbic acid), and D (calciferols) (Hrubša et al., 2022; Pham et al., 2021). Vitamin B_1 (thiamine) uptake in the human small intestine primarily occurs in the duodenum and jejunum via both passive diffusion and carrier-mediated transport. Two specific transporters, thiamine transporter 1 (THTR-1, encoded by SLC19A2) and THTR-2 (encoded by SLC19A3), mediate thiamine absorption. Notably, THTR-2 located on the apical membrane of ECs is essential for thiamine uptake, while THTR-1 facilitates basolateral efflux into circulation (Reidling et al., 2010). Vitamin B_2 (riboflavin) sensing and absorption in animals are less well-characterized, but a *Caenorhabditis elegans* (*C. elegans*) study revealed that riboflavin deficiency modulates feeding behavior and physiology via TORC1 signaling linked to flavin adenine dinucleotide–dependent ATP levels, indicating a nutrient-specific entero-intestinal sensing pathway (Qi et al., 2017; Yerevanian et al., 2022). Vitamin B_7 (biotin) is not synthesized by humans and must be obtained from dietary and microbial sources. Biotin absorbed in the gut is taken up via the sodium-dependent multivitamin transporter (SLC5A6), which also transports pantothenic acid and lipoate. The human sodium-dependent multivitamin transporter is predominantly localized to the apical membrane of intestinal ECs and is adaptively upregulated under biotin deficiency via transcriptional mechanisms involving Kruppel-like factor 4 (Said, 2009). The vitamin D receptor (VDR), a nuclear receptor highly expressed in intestinal ECs, plays a central role in regulating gene expression involved in calcium absorption, immune modulation, and epithelial barrier integrity (Christakos et al., 2020; Liu et al., 2013).

Although mechanisms for detecting micronutrients and transferring information to hormonal secretion or neural signals are less thoroughly documented than those for macronutrients, there is growing evidence that at least some minerals, particularly calcium, trigger intracellular signaling cascades in ECs that can fine-tune their absorption efficiency (Christakos et al., 2020). As research advances, it appears that the intestinal epithelium not only manages the uptake of micronutrients but may also send regulatory signals to the rest of the body when these nutrients fluctuate outside of optimal ranges (Barton et al., 2023; Redhai et al., 2020). Such findings highlight the intestine's broad function as a barrier, sensor, and reporter to integrate diverse nutrient signals and relay the detected information to the brain or other organs to maintain overall metabolic stability (Fig. 2).

PANCREATIC Β- AND Α-CELLS

In the pancreas, β- and α-cells are vital for maintaining circulating blood glucose homeostasis. One of the key features of these cells is their reliance on GCK as a glucose sensor (Printz et al., 1993). Because GCK has a relatively high Km (Michaelis constant) value, it only becomes active when blood glucose levels surpass ~8 mM (Nordlie et al., 1999). At that point, GCK phosphorylates incoming glucose, which raises intracellular ATP levels as a result of the glycolysis process. This glucose influx and reaction of GCK in pancreatic β-cells alter the intracellular ATP-to-AMP ratio, influencing membrane potential by inhibiting ATP-sensitive potassium (K_{ATP}) channel that can detect cellular ATP level and triggering increases in cytosolic calcium levels mediated by L-type voltage-gated calcium channels in pancreatic β-cells. Elevated ATP leads to the closure of K_{ATP} channel on the β-cell membrane, causing membrane depolarization and subsequent opening of voltage-gated calcium channels. The influx of calcium ions triggers insulin-containing granules to fuse with the cell membrane and release insulin into circulation (Ashcroft and Rorsman, 2013). This cascade is so fundamental to β-cell physiology that many genetic variants affecting GCK activity can profoundly influence blood glucose regulation. By design, β-cells therefore serve as glucose "detectors" for the entire organism, converting changes in glucose concentration into insulin signals that modulate energy storage and utilization throughout the whole body (Pia et al., 2016).

In addition to glucose sensing, β-cells also respond directly to certain amino acids. Leucine and arginine, for instance, can potentiate insulin release either by entering β-cells and fueling ATP production or by activating mTORC1 or specific GPCRs such as GPRC6A (Sancak et al., 2008; Wauson et al., 2013).

This amino-acid-based stimulation often amplifies the cell's response to rising blood glucose levels, reinforcing the β-cell's role in orchestrating nutrient-triggered hormone secretion. Fatty acids are also relevant to β-cell function: receptors like GPR40 on the β-cell surface detect circulating free fatty acids, further enhancing insulin release when sufficient energy substrates are present (Itoh and Hinuma, 2005).

Notably, α-cells, which primarily secrete glucagon, respond to a drop in blood glucose levels or to increases in circulating amino acids, fatty acids, and hormones such as insulin or somatostatin (Ashcroft and Rorsman, 2013; Gromada et al., 2007; Lu and Li, 2018; Rorsman et al., 2008). While β-cells respond to high glucose by releasing insulin, α-cells generally become more active under low-glucose conditions, secreting glucagon to raise blood sugar through glycogenolysis and gluconeogenesis. There are 2 major hypotheses regarding the molecular mechanisms by which α-cells are activated to secrete glucagon in response to low blood glucose levels: one proposes direct sensing of a fall in blood glucose levels by α-cells, while the other suggests activation through external signals, including insulin, zinc, and inputs from innervating nerve terminals (Gromada et al., 2007; Ishihara et al., 2003; Kawamori et al., 2009; Miki et al., 2001). Amino acids can similarly modulate α-cell activity, providing additional layers of fine-tuned regulation to balance the metabolic needs of various tissues (Bennett et al., 2010).

Although the pancreas is best known for detecting and regulating macronutrient levels, it also interacts with micronutrients. β-cells, for example, contain high levels of zinc. Insulin is stored in crystalline form, stabilized by zinc ions, and secreted along with these ions upon β-cell stimulation (Li, 2014). While zinc is crucial for proper insulin storage and release, a dedicated "zinc sensor" mechanism in β-cells is less clearly defined in terms of systemic signaling; it remains primarily associated with maintaining insulin solubility and secretion efficiency.

Calcium is essential for β-cells because it triggers the release of insulin by helping vesicles fuse with the cell membrane (Pia et al., 2016). However, when considering organism-wide calcium balance, the parathyroid hormone-vitamin D axis is more important than the pancreas itself. Although the β-cell constantly uses calcium flux to drive insulin exocytosis, it does not serve as the principal organ-level sensor of plasma calcium levels (Ashcroft and Rorsman, 2013). Instead, the pancreas plays a supportive role in responding to changes in blood calcium that are largely managed by other endocrine organs. Together, the pancreas primarily governs macronutrient-related hormonal signals but also accommodates micronutrients crucial for optimized insulin and glucagon production and secretion.

HEPATIC PORTAL VEIN: CHEMORECEPTOR TO VAGUS NERVE

The hepatic portal vein is a specialized vessel that transports nutrients from the gastrointestinal tract to the liver, forming a distinct portal circulation separate from systemic venous return (Raybould, 2010). As the first site of contact for absorbed glucose, amino acids, fatty acids, and gut-derived hormones, it provides a rapid and accurate reflection of nutritional status (Grill and Hayes, 2009). Nutrient detection in this region is a key trigger for systemic metabolic responses. The portal area is densely innervated by vagal and sympathetic afferents that transmit nutrient signals to the brain, modulating feeding, satiety, and energy balance (Bacharach et al., 2023; Berthoud and Neuhuber, 2000). In addition, nutrient sensing occurs before hepatic processing, influencing insulin sensitivity, gluconeogenesis, and lipid metabolism (Tappy, 2021). Thus, the hepatic portal vein functions as a key nutrient-sensing hub within the brain-gut-liver axis (Berthoud, 2008).

Glucose sensing in the hepatic portal vein has attracted increasing interest, as evidence suggests that specialized chemoreceptors near the portal vein detect blood glucose levels and relay this information to the brain via the vagus nerve (Vahl et al., 2007). Some of these receptors appear to rely on GLUT2-expressing nerve fibers to gauge portal glucose concentrations (Burcelin et al., 2000). When the circulating glucose level surpasses a certain threshold, it enters the endothelial layer of hepatoportal vein via GLUT2, altering intracellular metabolism and triggering afferent signals along the vagus nerve (Burcelin et al., 2000). These signals ultimately reach the brain regions involved in metabolic regulation, such as the hypothalamus, and contribute to the control of feeding behavior and whole-body metabolic balance. Although most research focuses on glucose sensing, there is some evidence that the portal vein area may also sense other nutrient types including amino acids and short-chain fatty acids (Mithieux, 2014; Mithieux et al., 2005). However, the precise mechanisms are still not fully understood. Postprandial increases in amino acids and fatty acids may also activate vagal branches around the portal vein, and those neuronal signaling pathways report the fresh supply of energy substrates of the body to the brain (Raka et al., 2019). Investigators also proposed that local sensory neurons respond directly to fatty acid–responding GPCRs, including GPR120, or putative amino-acid receptors in the portal vein area (Li et al., 2022). These receptors could convert local nutrient-level alterations into neural signals that coordinate nutritive inputs among the liver, brain, and pancreas. However, the molecular details of such amino acid– or lipid-sensing pathways are still not thoroughly understood.

BRAIN: NUTRIENT-SENSING NEURONS AND RELATED CIRCUITS

The brain is the central integrator of nutrient information in animals, receiving hormonal and neural signals that reflect the body's internal nutrient status. Much of the input arrives through the brainstem and hypothalamus. The partial permeability of the blood-brain barrier in areas such as the median eminence, and some part of hypothalamus allows hormonal signals, including insulin, leptin, and GLP-1 to enter the neural tissue (Levin et al., 2004). At the same time, the vagus nerve carries direct sensory input from peripheral organs, relaying changes in glucose, amino acids, fatty acids, and other nutrients (Duca et al., 2021). In some cases, hormones can bind their specific receptors expressed on vagal afferent neurons, merging the endocrine and neural signaling pathways (Berthoud et al., 2011). By integrating these diverse inputs, the brain orchestrates adaptive responses that maintain the whole-body nutrient homeostasis.

Brain nutrient sensors are specialized neurons that detect changes in circulating nutrients, such as glucose, and help to regulate feeding behavior and energy homeostasis. The hypothesis that the brain contains neurons capable of sensing circulating blood glucose level was first proposed by Mayer (1953), and it was later supported by electrophysiological studies by Oomura et al. (1964), who identified glucose-excited neurons in the cat hypothalamus. These neurons use glucose not only as a fuel source but also as a signaling molecule, altering their membrane potential and firing rates in response to changes in extracellular glucose. Despite these early discoveries, the precise physiological roles of brain glucose-sensing neurons remained unclear for many years.

More recent research using mammalian models has provided further insight into the mechanisms of brain nutrient sensing. For example, studies involving genetically modified mice have shown that disruption of K_{ATP} channels in proopiomelanocortin neurons can impair glucose sensing, leading to altered glucose tolerance (Parton et al., 2007). In contrast, deletion of AMPK in proopiomelanocortin or agouti-related peptide neurons leads to distinct changes in body weight and feeding behavior, highlighting the complex and divergent roles of these neuronal populations in regulating whole-body energy balance (Claret et al., 2007). Studies in *Drosophila* have further elucidated the cellular and molecular mechanisms of nutrient sensing at the organismal level (Dus et al., 2015; Oh et al., 2019). These findings emphasize that brain nutrient sensors are essential for coordinating metabolic responses, such as maintaining glucose homeostasis and guiding animals toward nutritive food during starvation. However, a full understanding of their physiological roles still requires further investigation (Fig. 3).

Glucose-sensing neurons in the hypothalamus, especially in the ventromedial hypothalamus and the arcuate nucleus, can adapt their firing rates to the alteration of glucose level (Claret et al., 2007; Parton et al., 2007). Glucose-excited neurons typically respond to increased glucose by closing K_{ATP} channels, causing membrane depolarization and rise in neuronal activity (Parton et al., 2007). Conversely, glucose-inhibited neurons display the opposite physiological property, reducing firing when glucose is abundant. Through these mechanisms, the brain modulates appetite, autonomic functions, and overall metabolic balance, coordinating with peripheral organs to fine-tune energy intake and expenditure (Fig. 3).

The systemic amino-acid sensors in the brain detect the circulating level of specific amino acids and affect feeding pattern and metabolic balance. Specific amino acids, including leucine and glutamine, activate mTORC1 pathways in the specific hypothalamic neurons, influencing feeding behavior and energy usage (Sung et al., 2023; Wolfson et al., 2016). Additionally, populations of hypothalamic neurons detect long-chain fatty acids via enzymes and transporters such as carnitine palmitoyl transferase 1 and acyl-CoA synthetase family member 3 (Rasmussen et al., 2012). By monitoring fluctuations in fatty acid metabolism, these neurons can promote satiety signals or adapt metabolic responses. Micronutrient sensing is more subtle: while sodium levels are partly monitored by circumventricular organs like the subfornical organ or the organum vasculosum of the lamina terminalis, direct detection of other minerals, such as calcium and zinc, may involve brainstem regions like the nucleus of the solitary tract or hypothalamic metal ion transporters (Fig. 3) (Kambe et al., 2004; Miyamoto et al., 2013). However, the exact neuronal circuits sensing these micronutrients remain under investigation.

Altogether, the brain contains various systemic nutrient sensors to detect internal nutrient level and regulate feeding patterns, fluid balance, and whole-body metabolic processes. As signals from glucose, amino acids, and fatty acids and even certain micronutrients converge on neuronal signaling in the hypothalamus and brainstem, they are integrated and relayed to generate appropriate behavioral responses from the internal nutrient status (Cruciani-Guglielmacci and Fioramonti, 2019; Miyamoto et al., 2013). When these systems are

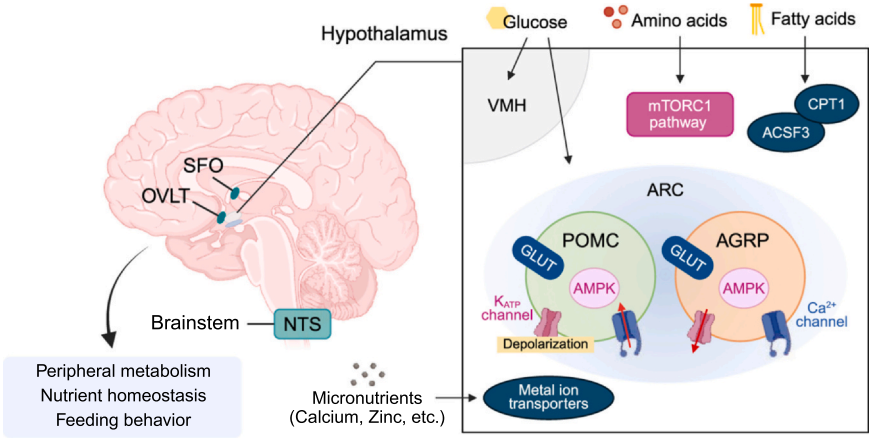


Fig. 3. Brain integration of nutrient signals. This figure illustrates how the brain integrates hormonal and neural signals reflecting the body's nutrient status. Specialized nutrient-sensing neurons across hypothalamic and brainstem regions (eg, ARC, VMH, NTS, and SFO) utilize cellular sensors (eg, AMPK, mTORC1, K_{ATP} channels, and CPT1) to detect nutrient changes. These pathways adjust appetite and energy expenditure accordingly through neuroendocrine and autonomic outputs. ACSF3, acyl-CoA synthetase family member 3; ARC, arcuate nucleus; CPT1, carnitine palmitoyl transferase 1; NTS, nucleus of the solitary tract; SFO, subfornical organ; VMH, ventromedial hypothalamus.

disrupted—through genetic manipulation, neuronal ablation, or metabolic disease—animals often show significant changes in food intake and body weight. By combining insights from simple models and mammalian studies, researchers continue to decipher the neural machinery that synchronizes nutrient sensing with whole-body energy homeostasis.

SYSTEMIC NUTRIENT SENSORS IN *DROSOPHILA*

Ongoing research in simple model organisms, such as the fruit fly *Drosophila melanogaster*, has revealed core principles of brain nutrient-sensing circuits and provides a foundation for exploring the physiological roles of systemic nutrient sensors. *Drosophila* possesses simple yet fully organized sensory, digestive, neuronal, and endocrine systems, with many functional features conserved with those of mammals. The major organ systems include the brain and ventral nerve cord, crop, midgut, hindgut, fat body (functionally analogous to the mammalian liver and adipose tissue), and endocrine components distributed across various organs (Kim et al., 2021b; Miguel-Aliaga et al., 2018; Strausfeld and Hirth, 2013). The EECs located in the midgut and the neuroendocrine cells located in the brain of the flies, which can detect the nutrients and secrete various hormones to respond post ingestive nutritive molecules. Although *Drosophila* already has highly organized external olfactory receptors and oral taste receptors (Yi and Xiong, 2025), we will focus on the post ingestive nutrient-sensing system in this review.

The fly intestinal system is a key digestive organ that plays an essential role in nutrient sensing and secretes neuropeptides in response to changes in the nutrient composition of ingested food (Chopra et al., 2022). After *Drosophila* consumes food, the first internal organ that the food reaches is its intestine, which is composed of the crop (analogous to the human stomach), the midgut (comparable to the small intestine), the hindgut (similar to the large intestine), and the Malpighian tubules (functioning like kidneys) (Miguel-Aliaga et al., 2018). Food is initially stored in the crop via the esophagus. The crop can expand significantly depending on the amount ingested, and this expansion is detected by mechanosensory Piezo channels, which help to prevent excessive feeding that could damage the gut (Min et al., 2021; Oh et al., 2021). After storage, food passes through the proventriculus (PV) and enters the midgut, which is subdivided into 5 regions (R1-R5) based on their morphology, physiology, and cellular composition (Fig. 4) (Miguel-Aliaga et al., 2018).

In each region, specialized EECs detect the ingested nutrient level and secrete hormones to regulate internal metabolic balance according to the nutritive molecules of the ingested food (Chopra et al., 2022). These hormones also play key roles in regulating the fly's feeding amount, food choice, and metabolism (Nässel, 2018). EECs also specifically detect amino acids and regulate protein appetite to maintain nutritive balance in flies. For example, during protein-rich feeding in adult flies, amino acids are sensed by EECs in the posterior midgut (R4 or R5), which secrete diuretic hormone 31 (DH31) in response. This hormone travels to the brain, where it suppresses feeding behavior and promotes male sexual behavior (Lin et al., 2022). Similarly, in

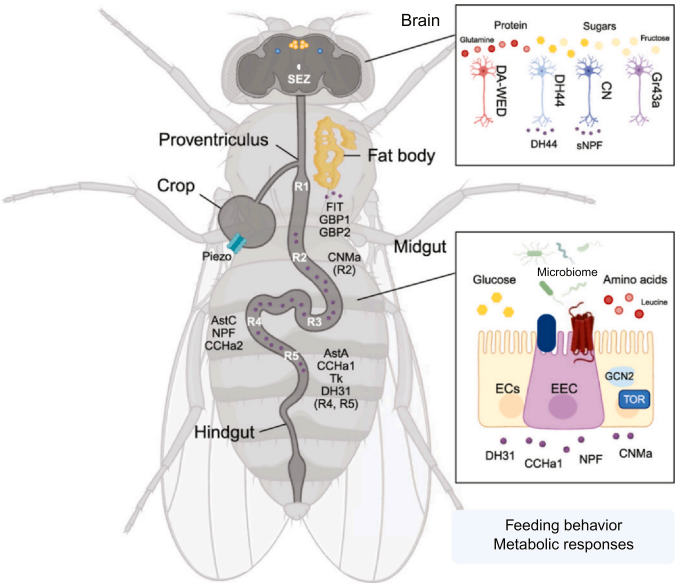


Fig. 4. Systemic nutrient sensing in *Drosophila*. In *Drosophila*, enteroendocrine cells (EECs) in the midgut sense dietary sugars and amino acids, releasing neuropeptides such as DH31, CCHa1, and CNMa. Nutrient-responsive neurons such as DH44 and CN neurons respond to circulating nutrients to modulate insulin production. Dopaminergic circuits like DA-WED are activated particularly during amino-acid deficiency to promote protein-specific feeding. Microbiome also contributes to nutrient sensing and homeostasis. Gut-brain communication dynamically coordinates behavior and physiology according to internal nutrient availability. CCHa1, CCHamide1; DH31, diuretic hormone 31; DH44, diuretic hormone 44; FIT, female-specific independent of transformer; GBP1 and GBP2, growth-blocking peptides.

larvae, a subset of EECs in the posterior midgut expressing DH31 and tachykinin is activated by dietary protein and amino acids, suggesting that protein sensing by EECs and DH31 signaling is conserved across developmental stages (Park et al., 2016). Additionally, the posterior EECs located in R4 and R5 detect protein-rich food and secrete peptide hormone CCHamide1, which is received by the specific population of enteric neurons, producing small neuropeptide F (NPF), then the downstream enteric neurocircuit induces nutrient-specific satiety by inhibiting gustatory receptor 43a (Gr43a) expressing taste sensory neurons (Yoshinari et al., 2024). Furthermore, when essential amino-acid intake is low, ECs in the R2 region detect reduced amino-acid levels through intracellular mechanisms involving GCN2 and mTOR, triggering the secretion of CNMamide (CNMa) peptide. CNMa is then conveyed to the brain, where it activates feeding behavior specific to essential amino acids (Kim et al., 2021a). Notably, if the fly contains *Acetobacter* species in its intestinal commensal microbes that produce leucine using its own metabolism, CNMa secretion is suppressed even during protein starvation (Fig. 4) (Kim et al., 2021a).

Moreover, in mated females, fluctuations in sugar and protein levels are detected by EECs in the R2 to R3 regions of the midgut and those EECs secrete NPF after the detection of nutritive changes. NPF functions by inhibiting adipokinetic hormone (which is similar to glucagon) to reduce sugar feeding

while promoting protein intake (Malita et al., 2022). In addition, L-glutamate can act via mGluR to suppress calcium oscillations in EECs, thereby reducing NPF secretion, leading to increased overall feeding and decreased gut motility (Fig. 4) (Gao et al., 2024). Furthermore, dopaminergic DA-WED neurons in the brain modulate protein-specific appetite under protein deprivation, particularly in response to glutamine (Liu et al., 2017). In mated females, upstream signals activate DA-WED neurons to increase protein feeding, and DA-WED neurons inhibited by other male-specific upstream signals to fine-tuning the protein preference to meet physiological need of mated female, virgin female, and male flies (Oh and Lee, 2025; Wu et al., 2024). Among the brain regions in flies, the subesophageal zone (SEZ) is best known for regulating feeding behavior. In fact, a circuit in the SEZ has been shown to activate protein-preference feeding behavior in response to protein deprivation. Through this circuit, flies increase their response to protein-rich foods and exhibit a preference for yeast-based diets when they are protein-deprived (Münch et al., 2022).

In the *Drosophila* midgut, the expression of sugar taste receptors appears to be limited to Gr64a and Gr43a, both of which are detected in ECs. While these receptors do not form heteromeric complexes in peripheral taste neurons, Gr43a alone functions as a dedicated fructose sensor (Miyamoto et al., 2012). Interestingly, Gr43a is also expressed in a specific subset of neurons located in the PV, a contractile organ that directs food from the crop to the midgut. These neurons project to both the SEZ, the brain region responsible for taste integration, and the gut epithelium. Although the physiological role of Gr43a in the midgut and PV remains to be fully elucidated, current evidence suggests that it may participate in the neural regulation of gut motility and nutrient flow (Miyamoto et al., 2013).

In addition to sensing sugars, ECs in the *Drosophila* midgut can also detect micronutrients such as vitamin D, exerting complex regulatory effects on gut physiology. In particular, VDR plays a critical role in maintaining intestinal homeostasis by modulating intestinal stem cell (ISC) activity and protecting against age-associated decline. The interaction between vitamin D and its receptor in ECs influences ISC proliferation, apoptosis, and differentiation. Notably, EC-specific knockdown of VDR leads to increased ISC proliferation, EC death, and accumulation of DNA damage, including centrosome amplification, hallmarks of intestinal aging. Conversely, vitamin D supplementation reduces age- and oxidative stress–induced ISC overproliferation and genomic instability. These findings collectively underscore the importance of the vitamin D/VDR axis and vitamin B_1 produced by gut microbiota as the key regulators of midgut integrity and stem cell aging in *Drosophila* (Park et al., 2024; Sannino et al., 2018).

Glucose-sensing neurons in the brain, including diuretic hormone 44 (DH44) neurons and CN neurons, are activated by circulating sugars. Sugars such as glucose, trehalose, and fructose stimulate DH44 neurons, triggering the secretion of the DH44 peptide. This peptide acts through its receptors—DH44-R1 in the brain and DH44-R2 in the midgut—to stimulate feeding and enhance gut motility, respectively (Dus et al., 2015). To prevent overconsumption of carbohydrate-rich foods, DH44 neuron activity is inhibited by mechanosensory Piezo channels in the crop and suppressed by glucose-activated hugin neurons in the ventral nerve cord when the fly is sated. These inhibitory signals are removed during starvation, and DH44 neurons can be activated by nutritive sugars only when these inhibitory signals are absent (Oh et al., 2021). Interestingly, DH44 neurons are also activated by specific amino acids, including glutamate, alanine, and aspartate, and promote feeding behavior after sensing those nonessential amino acids (Yang et al., 2018).

CN neurons, activated by sugars, including glucose, trehalose, and fructose, secrete small NPF to stimulate *Drosophila* insulin-like peptide 2 secretion on the insulin-producing cells (IPCs) and inhibit adipokinetic hormone secretion to prevent excessive blood sugar rises and maintain glucose homeostasis in flies (Oh et al., 2019). Other sugar sensors, such as Gr43a neurons in the dorsolateral brain, detect fructose levels and regulate feeding behavior according to the circulating amount of fructose (Miyamoto et al., 2012). Gr43a neurons are not activated by glucose or other sugars but are selectively responsive to fructose. Acting as narrowly tuned internal nutrient sensors, these neurons are both necessary and sufficient to detect hemolymph fructose concentrations and modulate feeding behavior. Notably, activation of Gr43a-expressing brain neurons promotes feeding in hungry flies but suppresses it in satiated flies, suggesting that they assign opposing valence to feeding depending on the animal's nutritional state.

The fat body in *Drosophila*, serving roles similar to the liver and adipose tissue, also plays an important role in regulating nutrient-specific feeding behavior and systemic metabolism in response to circulating nutrient levels. After the flies intake sufficient amount of protein, the fat body secretes female-specific independent of transformer as a protein-satiety hormone, which activates IPCs to secrete insulin for reducing protein feeding amount in flies (Fig. 4) (Sun et al., 2017). The fat body also senses amino acid via TOR signaling and produces growth-blocking peptides (GBP1 and GBP2), which promote *Drosophila* insulin-like peptide 2 secretion from IPCs. Loss of these peptides reduces growth, revealing how the fat body conveys nutritional status to regulate body size (Koyama and Mirth, 2016).

CONCLUSION AND PERSPECTIVES

In this review, we explored how animals sense a wide range of nutrients inside of their body at the organismal level. We have shown how macronutrients (carbohydrates, proteins, and lipids) and micronutrients (vitamins and trace elements) are detected by specialized systemic nutrient sensors in different organs—such as the intestine, pancreas, portal vein, and brain—and then we showed how those detected information of nutrients translated into neural or hormonal signals. Through these pathways, the body maintains internal nutrient balance by adjusting feeding behavior, energy storage, and metabolic balance. By defining certain organ-level nutrient detectors as "systemic nutrient sensors," we highlighted the importance of specialized cells or tissues that detect whole-body nutritive status and impact the function of multiple organ systems.

So far, much of the work on nutrient sensors has centered on understanding mechanisms at the cellular level. While this foundation is crucial, there remains a need for deeper investigation into organ-level nutrient sensing and the ways in which signals from these local detectors shape global metabolic outcomes. At this point of view, the systemic nutrient sensor is not just a chemical detector of nutrient molecules but also signal producer, including neuronal and hormonal signaling, to send the nutritive information to the other tissues or organs. In this review, we propose that certain groups of cells, which utilize post ingestive taste or cellular sensing mechanisms but additionally send outputs via neural or hormonal routes to distant organs, should be viewed as "systemic nutrient sensors." These sensors orchestrate interorgan communication that ultimately allows the body to adapt to nutrient imbalances.

Further research is essential to fully understand how systemic nutrient sensors function within their organs and how they communicate with central brain circuits that regulate behavior and metabolism. Such research will also be critical for elucidating the mechanisms underlying behavioral and metabolic disorders associated with nutrient imbalance, which are increasingly prevalent in modern society. Specifically, unraveling how these organ-level sensors detect nutritional states, and direct behavioral changes and metabolic responses, will help scientists and clinicians design better interventions for obesity, diabetes, and other diet-related metabolic diseases. A deeper appreciation of systemic nutrient sensing also holds promise for improving therapies already in use, such as GLP-1 receptor agonists for obesity and metabolic syndrome. By uncovering how organ-based sensors communicate with brain reward centers and energy-regulating circuits, we may discover new pharmacological targets or refine existing therapies to restore nutrient balance more effectively. In this sense, the emerging concept of "systemic nutrient sensors" will be pivotal to the next generation of research aiming to treat and prevent metabolic disease.

AUTHOR CONTRIBUTIONS

Gahbien Lee: Writing – review & editing, Writing – original draft. **Yangkyun Oh:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Greg S.B. Suh:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Jiyeon Lee:** Writing – review & editing, Writing – original draft.

DECLARATION OF COMPETING INTERESTS

The authors declare no competing interests.

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ORCID

Gahbien Lee https://orcid.org/0009-0003-0406-559X
Jiyeon Lee https://orcid.org/0009-0000-6628-6636
Greg S.B. Suh https://orcid.org/0000-0003-4381-658X
Yangkyun Oh https://orcid.org/0000-0003-4070-7601

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REFERENCES

Ashcroft, F.M., and Rorsman, P. (2013). K_{ATP} channels and islet hormone secretion: new insights and controversies. Nat. Rev. Endocrinol. *9*, 660-669.

Bacharach, S.Z., Tordoff, M.G., and Alhadeff, A.L. (2023). Glucose sensing in the hepatic portal vein and its role in food intake and reward. Cell. Mol. Gastroenterol. Hepatol. *16*, 189-199.

Baggio, L.L., and Drucker, D.J. (2007). Biology of incretins: GLP-1 and GIP. Gastroenterology, *132*, 2131-2157.

Barton, J.R., Londregan, A.K., Alexander, T.D., Entezari, A.A., Covarrubias, M., and Waldman, S.A. (2023). Enteroendocrine cell regulation of the gut-brain axis. Front. Neurosci. *17*, 1272955.

Behrens, M., and Meyerhof, W. (2011). Gustatory and extragustatory functions of mammalian taste receptors. Physiol. Behav. *105*, 4-13.

Bennett, K., James, C., and Hussain, K. (2010). Pancreatic β-cell K_{ATP} channels: hypoglycaemia and hyperglycaemia. Rev. Endocr. Metab. Disord. *11*, 157-163.

Berthoud, H.-R., and Neuhuber, W.L. (2000). Functional and chemical anatomy of the afferent vagal system. Auton. Neurosci. *85*, 1-17.

Berthoud, H.-R., Shin, A.C., and Zheng, H. (2011). Obesity surgery and gut–brain communication. Physiol. Behav. *105*, 106-119.

Berthoud, H.R. (2008). The vagus nerve, food intake and obesity. Regul. Pept. *149*, 15-25.

Bröer, S. (2023). Intestinal amino acid transport and metabolic health. Annu. Rev. Nutr. *43*, 73-99.

Burcelin, R., Dolci, W., and Thorens, B. (2000). Glucose sensing by the hepatoportal sensor is GLUT2-dependent: in vivo analysis in GLUT2-null mice. Diabetes, *49*, 1643-1648.

Campbell, J.E., and Drucker, D.J. (2013). Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab. *17*, 819-837.

Cani, P.D., Holst, J.J., Drucker, D.J., Delzenne, N.M., Thorens, B., Burcelin, R., and Knauf, C. (2007). GLUT2 and the incretin receptors are involved in glucose-induced incretin secretion. Mol. Cell Endocrinol. *276*, 18-23.

Chantranupong, L., Scaria, S.M., Saxton, R.A., Gygi, M.P., Shen, K., Wyant, G.A., Wang, T., Harper, J.W., Gygi, S.P., and Sabatini, D.M. (2016). The CASTOR proteins are arginine sensors for the mTORC1 pathway. Cell, *165*, 153-164.

Cho, Y.M., and Kieffer, T.J. (2010). Chapter four - K-cells and glucose-dependent insulinotropic polypeptide in health and disease. In Vitamins Hormones, G. Litwack, ed. (Cambridge, MA: Academic Press). pp. 111-150.

Chopra, G., Kaushik, S., and Kain, P. (2022). Nutrient sensing via gut in *Drosophila melanogaster*. Int. J. Mol. Sci. *23*, 2694.

Christakos, S., Dhawan, P., Verstuyf, A., Verlinden, L., and Carmeliet, G. (2016). Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol. Rev. *96*, 365-408.

Christakos, S., Li, S., De La Cruz, J., Shroyer, N.F., Criss, Z.K., Verzi, M.P., and Fleet, J.C. (2020). Vitamin D and the intestine: review and update. J. Steroid Biochem. Mol. Biol. *196*, Article 105501.

Claret, M., Smith, M.A., Batterham, R.L., Selman, C., Choudhury, A.I., Fryer, L.G.D., Clements, M., Al-Qassab, H., Heffron, H., Xu, A.W., et al. (2007). AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. J. Clin. Invest. *117*, 2325-2336.

Cruciani-Guglielmacci, C., and Fioramonti, X. (2019). Brain nutrient sensing in the control of energy balance: New insights and perspectives. Front. Physiol. *10*, 51.

Drover, V.A., Ajmal, M., Nassir, F., Davidson, N.O., Nauli, A.M., Sahoo, D., Tso, P., and Abumrad, N.A. (2005). CD36 deficiency impairs intestinal lipid secretion and clearance of chylomicrons from the blood. J. Clin. Invest. *115*, 1290-1297.

Duca, F.A., Waise, T.M.Z., Peppler, W.T., and Lam, T.K.T. (2021). The metabolic impact of small intestinal nutrient sensing. Nat. Commun. *12*, 903.

Dus, M., Lai, J.S.-Y., Gunapala, K.M., Min, S., Tayler, T.D., Hergarden, A.C., Geraud, E., Joseph, C.M., and Suh, G.S.B. (2015). Nutrient sensor in the brain directs the action of the brain-gut axis in *Drosophila*. Neuron, *87*, 139-151.

Edfalk, S., Steneberg, Pr, and Edlund, H. (2008). Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes, *57*, 2280-2287.

Efeyan, A., Comb, W.C., and Sabatini, D.M. (2015). Nutrient-sensing mechanisms and pathways. Nature, *517*, 302-310.

Gao, J., Zhang, S., Deng, P., Wu, Z., Lemaitre, B., Zhai, Z., and Guo, Z. (2024). Dietary L-Glu sensing by enteroendocrine cells adjusts food intake via modulating gut PYY/NPF secretion. Nat. Commun. *15*, 3514.

Ge, M.-K., Zhang, C., Zhang, N., He, P., Cai, H.-Y., Li, S., Wu, S., Chu, X.-L., Zhang, Y.-X., Ma, H.-M., et al. (2023). The tRNA-GCN2-FBXO22-axis-mediated mTOR ubiquitination senses amino acid insufficiency. Cell Metab. *35*, 2216-2230.

Gorboulev, V., Schürmann, A., Vallon, V., Kipp, H., Jaschke, A., Klessen, D., Friedrich, A., Scherneck, S., Rieg, T., Cunard, R., et al. (2011). Na^+-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes, *61*, 187-196.

Grill, H.J., and Hayes, M.R. (2009). The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. Int. J. Obes. *33*, S11-S15.

Gromada, J., Franklin, I., and Wollheim, C.B. (2007). α-cells of the endocrine pancreas: 35 years of research but the enigma remains. Endocr. Rev. *28*, 84-116.

Haid, D.C., Jordan-Biegger, C., Widmayer, P., and Breer, H. (2012). Receptors responsive to protein breakdown products in G-cells and D-cells of mouse, swine and human. Front. Physiol. *3*, 65.

Hara, K., Yonezawa, K., Weng, Q.-P., Kozlowski, M.T., Belham, C., and Avruch, J. (1998). Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 through a common effector mechanism. J. Biol. Chem. *273*, 14484-14494.

Honig, B., and Shapiro, L. (2020). Adhesion protein structure, molecular affinities, and principles of cell-cell recognition. Cell, *181*, 520-535.

Hrubša, M., Siatka, T., Nejmanová, I., Vopršalová, M., Kujovská Krčmová, L., Matoušová, K., Javorská, L., Macáková, K., Mercolini, L., Remião, F., et al. (2022). Biological properties of vitamins of the B-Complex, Part 1: Vitamins B(1), B(2), B(3), and B(5). Nutrients, *14*, 484.

Hundal, H.S., and Taylor, P.M. (2009). Amino acid transceptors: gate keepers of nutrient exchange and regulators of nutrient signaling. Am. J. Physiol. Endocrinol. Metab. *296*, E603-E613.

Ishihara, H., Maechler, P., Gjinovci, A., Herrera, P.-L., and Wollheim, C.B. (2003). Islet β-cell secretion determines glucagon release from neighbouring α-cells. Nat. Cell Biol. *5*, 330-335.

Itoh, Y., and Hinuma, S. (2005). GPR40, a free fatty acid receptor on pancreatic β cells, regulates insulin secretion. Hepatol. Res. *33*, 171-173.

Jang, H.-J., Kokrashvili, Z., Theodorakis, M.J., Carlson, O.D., Kim, B.-J., Zhou, J., Kim, H.H., Xu, X., Chan, S.L., Juhaszova, M., et al. (2007). Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc. Natl. Acad. Sci. U.S.A. *104*, 15069-15074.

Kambe, T., Yamaguchi-Iwai, Y., Sasaki, R., and Nagao, M. (2004). Overview of mammalian zinc transporters. CMLS, *61*, 49-68.

Kawamori, D., Kurpad, A.J., Hu, J., Liew, C.W., Shih, J.L., Ford, E.L., Herrera, P.L., Polonsky, K.S., McGuinness, O.P., and Kulkarni, R.N. (2009). Insulin signaling in α cells modulates glucagon secretion in vivo. Cell Metab. *9*, 350-361.

Kilberg, M.S., Pan, Y.-X., Chen, H., and Leung-Pineda, V. (2005). Nutritional control of gene expression: how mammalian cells respond to amino acid limitation. Annu. Rev. Nutr. *25*, 59-85.

Kim, B., Kanai, M.I., Oh, Y., Kyung, M., Kim, E.K., Jang, I.H., Lee, J.H., Kim, S.G., Suh, G.S.B., and Lee, W.J. (2021a). Response of the microbiome-gut-brain axis in *Drosophila* to amino acid deficit. Nature, *593*, 570-574.

Kim, J., and Guan, K.-L. (2011). Amino acid signaling in TOR activation. Annu. Rev. Nutr. *80*, 1001-1032.

Kim, S.K., Tsao, D.D., Suh, G.S.B., and Miguel-Aliaga, I. (2021b). Discovering signaling mechanisms governing metabolism and metabolic diseases with *Drosophila*. Cell Metab. *33*, 1279-1292.

Koyama, T., and Mirth, C.K. (2016). Growth-blocking peptides as nutrition-sensitive signals for insulin secretion and body size regulation. PLoS Biol. *14*, Article e1002392.

Levin, B.E., Routh, V.H., Kang, L., Sanders, N.M., and Dunn-Meynell, A.A. (2004). Neuronal glucosensing: what do we know after 50 years? Diabetes, *53*, 2521-2528.

Li, M., Tan, H.-E., Lu, Z., Tsang, K.S., Chung, A.J., and Zuker, C.S. (2022). Gut–brain circuits for fat preference. Nature, *610*, 722-730.

Li, Y.V. (2014). Zinc and insulin in pancreatic beta-cells. Endocrine, *45*, 178-189.

Lin, H.-H., Kuang, M.C., Hossain, I., Xuan, Y., Beebe, L., Shepherd, A.K., Rolandi, M., and Wang, J.W. (2022). A nutrient-specific gut hormone arbitrates between courtship and feeding. Nature, *602*, 632-638.

Liou, A.P., Lu, X., Sei, Y., Zhao, X., Pechhold, S., Carrero, R.J., Raybould, H.E., and Wank, S. (2011). The G-protein−coupled receptor GPR40 directly mediates long-chain fatty acid−induced secretion of cholecystokinin. Gastroenterology, *140*, 903-912.

Liu, J., Yu, K., and Zhu, W. (2016). Amino acid sensing in the gut and its mediation in gut-brain signal transduction. Anim. Nutr. *2*, 69-73.

Liu, Q., Tabuchi, M., Liu, S., Kodama, L., Horiuchi, W., Daniels, J., Chiu, L., Baldoni, D., and Wu, M.N. (2017). Branch-specific plasticity of a bifunctional dopamine circuit encodes protein hunger. Science, *356*, 534-539.

Liu, W., Chen, Y., Golan, M.A., Annunziata, M.L., Du, J., Dougherty, U., Kong, J., Musch, M., Huang, Y., Pekow, J., et al. (2013). Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. J. Clin. Invest. *123*, 3983-3996.

Lu, M., and Li, C. (2018). Nutrient sensing in pancreatic islets: lessons from congenital hyperinsulinism and monogenic diabetes. Ann. N. Y. Acad. Sci. *1411*, 65-82.

Malita, A., Kubrak, O., Koyama, T., Ahrentløv, N., Texada, M.J., Nagy, S., Halberg, K.V., and Rewitz, K. (2022). A gut-derived hormone suppresses sugar appetite and regulates food choice in *Drosophila*. Nat. Metab. *4*, 1532-1550.

Mayer, J. (1953). Glucostatic mechanism of regulation of food intake. N. Engl. J. Med. *249*, 13-16.

McCauley, H.A., Matthis, A.L., Enriquez, J.R., Nichol, J.T., Sanchez, J.G., Stone, W.J., Sundaram, N., Helmrath, M.A., Montrose, M.H., Aihara, E., et al. (2020). Enteroendocrine cells couple nutrient sensing to nutrient absorption by regulating ion transport. Nat. Commun. *11*, 4791.

Melis, M., and Tomassini Barbarossa, I. (2017). Taste perception of sweet, sour, salty, bitter, and umami and changes due to L-arginine supplementation, as a function of genetic ability to taste 6-n-propylthiouracil. Nutrients, *9*, 541.

Miguel-Aliaga, I., Jasper, H., and Lemaitre, B. (2018). Anatomy and physiology of the digestive tract of *Drosophila melanogaster*. Genetics, *210*, 357-396.

Miki, T., Liss, B., Minami, K., Shiuchi, T., Saraya, A., Kashima, Y., Horiuchi, M., Ashcroft, F., Minokoshi, Y., Roeper, J., et al. (2001). ATP-sensitive K+ channels in the hypothalamus are essential for the maintenance of glucose homeostasis. Nat. Neurosci. *4*, 507-512.

Min, S., Oh, Y., Verma, P., Whitehead, S.C., Yapici, N., Van Vactor, D., Suh, G.S.B., and Liberles, S. (2021). Control of feeding by Piezo-mediated gut mechanosensation in *Drosophila*. eLife, *10*, Article e63049.

Mithieux, G. (2014). Metabolic effects of portal vein sensing. Diabetes Obes. Metab. *16*, 56-60.

Mithieux, G., Misery, P., Magnan, C., Pillot, B., Gautier-Stein, A., Bernard, C., Rajas, F., and Zitoun, C. (2005). Portal sensing of intestinal gluconeogenesis is a mechanistic link in the diminution of food intake induced by diet protein. Cell Metab. *2*, 321-329.

Miyamoto, T., Slone, J., Song, X., and Amrein, H. (2012). A fructose receptor functions as a nutrient sensor in the *Drosophila* brain. Cell, *151*, 1113-1125.

Miyamoto, T., Wright, G., and Amrein, H. (2013). Nutrient sensors. Curr. Biol. *23*, R369-R373.

Münch, D., Goldschmidt, D., and Ribeiro, C. (2022). The neuronal logic of how internal states control food choice. Nature, *607*, 747-755.

Nässel, D.R. (2018). Substrates for neuronal cotransmission with neuropeptides and small molecule neurotransmitters in *Drosophila*. Front. Cell. Neurosci. *12*, 83.

Nordlie, R.C., Foster, J.D., and Lange, A.J. (1999). Regulation of glucose production by the liver. Annu. Rev. Nutr. *19*, 379-406.

Oh, D.Y., Talukdar, S., Bae, E.J., Imamura, T., Morinaga, H., Fan, W., Li, P., Lu, W.J., Watkins, S.M., and Olefsky, J.M. (2010). GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell, *142*, 687-698.

Oh, Y., Lai, J.S.-Y., Mills, H.J., Erdjument-Bromage, H., Giammarinaro, B., Saadipour, K., Wang, J.G., Abu, F., Neubert, T.A., and Suh, G.S.B. (2019). A glucose-sensing neuron pair regulates insulin and glucagon in *Drosophila*. Nature, *574*, 559-564.

Oh, Y., Lai, J.S.-Y., Min, S., Huang, H.-W., Liberles, S.D., Ryoo, H.D., and Suh, G.S.B. (2021). Periphery signals generated by Piezo-mediated stomach stretch and Neuromedin-mediated glucose load regulate the *Drosophila* brain nutrient sensor. Neuron, *109*, 1979-1995.

Oh, Y., and Lee, W.-J. (2025). Fine-tuning protein hunger: sex- and mating-dependent setpoint control. Cell Res. *35*, 161-162.

Oomura, Y., Kimura, K., Ooyama, H., Maeno, T., Iki, M., and Kuniyoshi, M. (1964). Reciprocal activities of the ventromedial and lateral hypothalamic areas of cats. Science, *143*, 484-485.

Oya, M., Kitaguchi, T., Pais, R., Reimann, F., Gribble, F., and Tsuboi, T. (2013). The G protein-coupled receptor family C group 6 subtype A (GPRC6A) receptor is involved in amino acid-induced glucagon-like peptide-1 secretion from GLUTag cells. J. Biol. Chem. *288*, 4513-4521.

Park, J.-H., Chen, J., Jang, S., Ahn, T.J., Kang, K., Choi, M.S., and Kwon, J.Y. (2016). A subset of enteroendocrine cells is activated by amino acids in the *Drosophila* midgut. FEBS Lett. *590*, 493-500.

Park, J.-S., Na, H.-J., and Kim, Y.-J. (2024). The anti-aging effect of vitamin D and vitamin D receptor in *Drosophila* midgut. Aging, *16*, 2005-2025.

Parton, L.E., Ye, C.P., Coppari, R., Enriori, P.J., Choi, B., Zhang, C.-Y., Xu, C., Vianna, C.R., Balthasar, N., Lee, C.E., et al. (2007). Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. Nature, *449*, 228-232.

Pham, V.T., Dold, S., Rehman, A., Bird, J.K., and Steinert, R.E. (2021). Vitamins, the gut microbiome and gastrointestinal health in humans. Nutr. Res. *95*, 35-53.

Pia, V.R., Bingbing, W., Yixian, L., and Weiping, H. (2016). Pancreatic regulation of glucose homeostasis. Exp. Mol. Med. *48*, e219.

Printz, R.L., Magnuson, M.A., and Granner, D.K. (1993). Mammalian glucokinase. Annu. Rev. Nutr. *13*, 463-496.

Qi, B., Kniazeva, M., and Han, M. (2017). A vitamin-B2-sensing mechanism that regulates gut protease activity to impact animal's food behavior and growth. eLife, *6*, Article e26243.

Raka, F., Farr, S., Kelly, J., Stoianov, A., and Adeli, K. (2019). Metabolic control via nutrient-sensing mechanisms: role of taste receptors and the gut-brain neuroendocrine axis. Am. J. Physiol. Endocrinol. Metab. *317*, E559-E572.

Rasmussen, B.A., Breen, D.M., and Lam, T.K.T. (2012). Lipid sensing in the gut, brain and liver. TEM, *23*, 49-55.

Raybould, H.E. (2010). Gut chemosensing: interactions between gut endocrine cells and visceral afferents. Auton. Neurosci. *153*, 41-46.

Redhai, S., Pilgrim, C., Gaspar, P., Giesen, Lv, Lopes, T., Riabinina, O., Grenier, T., Milona, A., Chanana, B., Swadling, J.B., et al. (2020). An intestinal zinc sensor regulates food intake and developmental growth. Nature, *580*, 263-268.

Rehfeld, J.F. (2017). Cholecystokinin—from local gut hormone to ubiquitous messenger. Front. Endocrinol, *8*, 47.

Reidling, J.C., Lambrecht, N., Kassir, M., and Said, H.M. (2010). Impaired intestinal vitamin B1 (Thiamin) uptake in thiamin transporter-2–deficient mice. Gastroenterology, *138*, 1802-1809.

Reimann, F., Tolhurst, G., and Gribble, F.M. (2012). G-protein-coupled receptors in intestinal chemosensation. Cell Metab. *15*, 421-431.

Rorsman, P., Salehi, S.A., Abdulkader, F., Braun, M., and MacDonald, P.E. (2008). K_{ATP}-channels and glucose-regulated glucagon secretion. Trends Endocrinol. Metab. *19*, 277-284.

Said, H.M. (2009). Cell and molecular aspects of human intestinal biotin absorption. J. Nutr. *139*, 158-162.

Sancak, Y., Peterson, T.R., Shaul, Y.D., Lindquist, R.A., Thoreen, C.C., Bar-Peled, L., and Sabatini, D.M. (2008). The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science, *320*, 1496-1501.

Sannino, D.R., Dobson Adam, J., Edwards, K., Angert Esther, R., and Buchon, N. (2018). The *Drosophila melanogaster* gut microbiota provisions thiamine to its host. mBio, e00155-18.

Schlingmann, K.P., and Gudermann, T. (2005). A critical role of TRPM channel-kinase for human magnesium transport. J. Physiol. *566*, 301-308.

Smith, R.L., Soeters, M.R., Wüst, R.C.I., and Houtkooper, R.H. (2018). Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. Endocr. Rev. *39*, 489-517.

Steinert, R.E., and Beglinger, C. (2011). Nutrient sensing in the gut: interactions between chemosensory cells, visceral afferents and the secretion of satiation peptides. Physiol. Behav. *105*, 62-70.

Stojanović, O., Altirriba, J., Rigo, D., Spiljar, M., Evrard, E., Roska, B., Fabbiano, S., Zamboni, N., Maechler, P., Rohner-Jeanrenaud, F., et al. (2021). Dietary excess regulates absorption and surface of gut epithelium through intestinal PPARα. Nat. Commun. *12*, 7031.

Strausfeld, N.J., and Hirth, F. (2013). Deep homology of arthropod central complex and vertebrate basal ganglia. Science, *340*, 157-161.

Sun, J., Liu, C., Bai, X., Li, X., Li, J., Zhang, Z., Zhang, Y., Guo, J., and Li, Y. (2017). *Drosophila* FIT is a protein-specific satiety hormone essential for feeding control. Nat. Commun. *8*, Article 14161.

Sundaresan, S., and Abumrad, N.A. (2015). Dietary lipids inform the gut and brain about meal arrival via CD36-mediated signal transduction. J. Nutr. *145*, 2195-2200.

Sung, Y., Yu, Y.C., and Han, J.M. (2023). Nutrient sensors and their crosstalk. Exp. Mol. Med. *55*, 1076-1089.

Tappy, L. (2021). Metabolism of sugars: a window to the regulation of glucose and lipid homeostasis by splanchnic organs. Clin. Nutr. *40*, 1691-1698.

Vahl, T.P., Tauchi, M., Durler, T.S., Elfers, E.E., Fernandes, T.M., Bitner, R.D., Ellis, K.S., Woods, S.C., Seeley, R.J., Herman, J.P., et al. (2007). Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. Endocrinology, *148*, 4965-4973.

Wang, C.-Y., and Babitt, J.L. (2019). Liver iron sensing and body iron homeostasis. Blood, *133*, 18-29.

Wauson, E.M., Lorente-Rodríguez, A., and Cobb, M.H. (2013). Minireview: nutrient sensing by G protein-coupled receptors. Mol. Endocrinol. *27*, 1188-1197.

Wolfson, R.L., Chantranupong, L., Saxton, R.A., Shen, K., Scaria, S.M., Cantor, J.R., and Sabatini, D.M. (2016). Sestrin2 is a leucine sensor for the mTORC1 pathway. Science, *351*, 43-48.

Wu, G., Ma, T., Hancock, C.E., Gonzalez, S., Aryal, B., Vaz, S., Chan, G., Palarca-Wong, M., Allen, N., Chung, C.-I., et al. (2024). Opposing GPCR signaling programs protein intake setpoint in *Drosophila*. Cell, *187*, 5376-5392.

Yang, Z., Huang, R., Fu, X., Wang, G., Qi, W., Mao, D., Shi, Z., Shen, W.L., and Wang, L. (2018). A post-ingestive amino acid sensor promotes food consumption in *Drosophila*. Cell Res. *28*, 1013-1025.

Ye, J., Palm, W., Peng, M., King, B., Lindsten, T., Li, M.O., Koumenis, C., and Thompson, C.B. (2015). GCN2 sustains mTORC1 suppression upon amino acid deprivation by inducing Sestrin2. Genes Dev. *29*, 2331-2336.

Yerevanian, A., Murphy, L.M., Emans, S., Zhou, Y., Ahsan, F.M., Baker, D., Li, S., Adedoja, A., Cedillo, L., Stuhr, N.L., et al. (2022). Riboflavin depletion promotes longevity and metabolic hormesis in *Caenorhabditis elegans*. Aging Cell, *21*, Article e13718.

Yi, Q., and Xiong, L. (2025). From sensory organs to internal pathways: a comprehensive review of amino acid sensing in *Drosophila*. Comp. Biochem. Physiol. Part A Mol. Integr. Physiol, *303*, Article 111828.

Yoshinari, Y., Nishimura, T., Yoshii, T., Kondo, S., Tanimoto, H., Kobayashi, T., Matsuyama, M., and Niwa, R. (2024). A high-protein diet-responsive gut hormone regulates behavioral and metabolic optimization in *Drosophila melanogaster*. Nat. Commun. *15*, Article 10819.

Zheng, Z., Zong, Y., Ma, Y., Tian, Y., Pang, Y., Zhang, C., and Gao, J. (2024). Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct. Target. Ther. *9*, 234.