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Energy intake, metabolic homeostasis, and human health

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Abstract

The energy substances (mainly carbohydrates and fats) are the basis and guarantee of life activity, especially the oxidative phosphorylation for energy supply. However, excessive absorption and accumulation of these substances can lead to metabolic diseases such as obesity, hyperlipidemia, diabetes, and cancers. A large amount of studies demonstrate that G protein-coupled receptors (GPCRs) play a key role in identification and absorption of energy substances, and the signaling network of nerves, immune, and endocrine regulates their storage and utilization. The gastrointestinal mucus layer not only identifies these substances through identification in diet components but also transfers immune, metabolic, and endocrine signals of hormones, cytokines, and chemokines by promoting interactions between receptors and ligands. These signaling molecules are transferred to corresponding organs, tissues, and cells by the circulatory system, and cell activity is regulated by amplifying of cell signals that constitute the wireless communication network among cells in the body. Absorption, accumulation, and utilization of energy substances in the body obey the law of energy conservation. Energy is stored in the form of fat, and meets the demand of body *via* two coupled mechanisms: catabolism and oxidative phosphorylation. Under normal physiological conditions, fat consumption involves ketone body metabolism through the circulatory system and glucose consumption requires blood lactic acid cycle. Accumulation of excessive energy leads to the abnormal activation of mammalian target of rapamycin (mTOR), thus promoting the excretion of glucose or glycogen in the form of blood glucose and urine glucose. Alternatively, the body cancels the intercellular contact inhibition and promotes cell proliferation to induce carcinogenesis, which can induce the consumption of large amounts of glucose. Intercellular communication is performed by signaling molecules *via* sensing, absorption, accumulation, and utilization of energy substances, and anabolism and catabolism are controlled by the central metabolic pathway. Therefore, slower catabolism will result in longer life expectancy, whereas faster catabolism results in shorter life expectancy. Energy substances in diet influence the balance between energy and metabolism in the body through the sensing function of the gastrointestinal system at two levels: cellular communication network and metabolic network. The present review of studies aims to strengthen our knowledge on cellular communication and metabolic networks to offer a dietary guidance on the metabolism and communication role of various foods.
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Keywords: Energy substance; Metabolism balance; Metabolic syndrome; Wireless intercellular communication network; Metabolic network; Human health

1. Introduction

Basic nutrients, such as carbohydrates, fats, and proteins, are the foundation of all life activities. They constitute the carbon skeleton (intermediate metabolites) of various functional molecules, and provide energy through oxidative decomposition. Traditionally, the main aim of nutrition is prevent and treat nutritional deficiencies. However, when nutrition is adequate or excessive, the body faces the problems of quantitative control of the nutrients absorption and storage. Overnutrition, especially absorption and storage of energy, can not only affect health but also cause many diseases such as diabetes, cardiovascular diseases, obesity, hypertension, and hyperlipidemia. Further, overnutrition reduces reproductive capacity and promotes the development of various cancers that will seriously affect quality of life, survival, and reproduction in human beings.

Because of overnutrition, nutriology based on nutritional requirements cannot make recommendations for nutrient intake

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in daily life because nutrient absorption, energy storage, and oxidative energy supply control vary from person to person. Even during evolution, nutritional experience seems to be recorded in the nucleosomes and DNA, which involves all aspects of nutrient sensing, cell communication, metabolic regulation, gene expression, and epigenetic modifications. However, food intake is a fundamental activity of the human body and is a source of energy. This study reviews the relationship among energy absorption, metabolism, and human health to systematically analyze and discuss signaling processes, metabolic control mechanisms, and corresponding diseases due to overnutrition. This review also highlights the key problems that need to be resolved and puts forth views for future development.

2. Sensing and quantification of energy substances

In 2012, the Nobel Prize in Chemistry was awarded to two American scientists Robert J. Lefkowitz and Brian K. Kobilka for their outstanding contribution to our understanding of G protein-coupled receptors (GPCRs). Absorption and quantification of nutrients mainly occurs *via* the sensing function of GPCRs. The GPCR superfamily includes many receptors that sense all nutritional components, especially energy substances. GPCRs are highly conserved molecules from microorganisms to humans. GPCRs are coupled to G protein cascade activation and signal transduction to transfer structural and functional information of nutrients, non-nutrients, and food safety to the body by taste and smell and the gastrointestinal (GI) system, thus forming the physiological basis of nutrient absorption and quantitative control, safety and defense, and stress and relaxation [1].

Due to their transmission function of smell, taste, light, sound, signal as well as immunity, hormone, defense and other physiological functions, the GPCR family members are the most important screening target of medicine, functional foods, and food additives. Previous studies have described that GPCRs are involved in multiple signaling pathways by coupling with G proteins and perform various physiological and pathological functions by controlling the signaling pathway of mammalian target of rapamycin (mTOR). MTOR not only controls synthesis and catabolism but also controls energy operation, substance distribution, endocrine function, storage, energy oxidation, cell cycle, growth, development, differentiation, reproduction, apoptosis, autophagy, carcinogenesis, and lifespan. MTOR is an important molecule that senses, quantifies, and responds to basic nutrients such as glucose, amino acids, and fatty acids [2].

2.1. Sensing effect of the GI receptor system on nutrition

Higher animals successively have various receptor systems that can recognize sense, quantify, and transfer various signals to the body to initiate ordered physiological activities sequentially from the first exposure to foods to absorption. The receptor system is classified into two types. The first type of receptors include visual, auditory, olfactory, and taste receptors and the stomach, which quickly respond and transfer neural and endocrine signals to control appetite and to select foods. The second type includes the intestinal system that identifies the functions and molecular structures of different nutritional components in foods and delivers biochemical signals involving various cytokines, chemokines, and hormones to recognize the quality and quantity of ingredients in foods [3]. Several investigations have proven that the body uses this complex nutritional or non-nutritional sensing system to control food choice, food intake, digestion, and absorption qualitatively and quantitatively, indicating that this sensing system allows adaptation to different nutritional environments. Inappropriate control results in nutritional defects or overnutrition, subsequently leading to various diseases.

2.1.1. Taste sense: quantitative detection of nutrition in the human body

The taste sense can identify nutrient categories and determines their absorption. Humans have five taste senses, namely, sweet, salty, delicious, bitter, and sour. Sweet foods imply carbohydrates and energy substances; salty foods include Na^+ and other salts required for life activities; delicious foods include proteins, amino acids, and nucleotides; bitter foods include bitter-tasting substances, including convergent and antinutrient substances; and sour foods include substances that undergo anaerobic fermentation to produce short-chain fatty acids (SCFAs). Because fat is associated with fragrance and is an important energy substance, some researchers have suggested the flavor of fat as the sixth taste sense, *i.e.*, fragrance [4]. Throughout evolution, this receptor sensing system has ensured abundant supply and proper storage of nutrients, thus preventing unfavorable nutrient uptake or unsafe food intake.

2.1.2. Taste bud cells and their sensing functions

Taste receptor cells (TRCs) in taste buds interact with each other and transmit electrochemical signals that are amplified by the G protein signaling system. When these electrochemical signals reach a threshold of nerve stimulation, TRCs transfer signals to specific taste perception areas in the brain through afferent nerves. TRCs are classified into four types according to their morphological characteristics [5]. Type I glia-like cells transmit signals for saltiness while type II cells transmit signals for sweetness, deliciousness, and bitterness. Type III cells sense sourness while type IV cells are stem/progenitor cells of taste. Members of TAS1R family are heterodimers that directly sense sweetness (TAS1R2–TAS1R3) and deliciousness (TAS1R1–TAS1R3). TAS2R receptor family includes >25 members that directly sense bitterness [6]. Fat-sensing receptors such as FFAR1 and GPR120 are expressed by type I and II cells, respectively [7]. Taste receptors are not only present in cells of the taste buds but also in cells of the GI tract, respiratory tract, pancreas, brain, and other organs. The complex of tastants such as sweetness, fatty, bitter, and delicious substances initiate the release of second messengers, which then initiate cascade amplification to accelerate the release of peptides or neurotransmitters (electrical signals). Some peptides contribute to taste sensing; for example, α-peptides can not only recognize bitterness and sweetness but also partially recognize fat flavor [8]. These α-peptides affect cAMP and cGMP and activate phosphatase Cβ2 (PLCβ2) through the flavor peptide $\beta\gamma$ ($\beta 3\gamma 13$) to transfer quantitative signals, which can induce the IP3-mediated

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