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Nutrient Sensing: A New Emerging Pathway

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Abstract:

Nutrients are the compound present in foods and essential for health and provide us energy; act as building blocks and essential component of cells and organs. They help us to regulate various chemical processes in the body. Nutrient Sensing is a cell's ability to recognize and respond to fuel substances such as protein, carbohydrates and lipids. One of the most serious problems in the present world is the increasing number of overweight and obese people around the world. Nutrient Sensing has become a major focus in scientific research over the past few decades as it enables us to understand mechanism of nutrient metabolism and feeding process. By studying the basic metabolic pathway and uptake of nutrients by the cells, which ultimately control the feeding process; it enables us to understand the physiological processes which are disrupted by diseases such as- diabetes, cardiovascular diseases and obesity. Nutrient Sensing is the basic mechanism which not only helps us to maintain balance between stored energy and calorie intake but also regulate various metabolic pathways in our body. If nutrient sensing is disrupted it leads to several chronic lifestyle diseases, hence understanding and restoring the proper nutrient diet would enable us to lead a healthy and less disease prone life. In consideration of nutrient homeostasis, particularly in human and also in all living organisms, our aim is to provide an outlook of nutrient sensing mechanism as our present knowledge in this domain is scarce.

Keywords: Nutrient sensing, sensor, receptor, transporter, metabolism, glucose, amino acid, lipid, nutrient homeostasis.

Abbreviation:

T1R2	Human taste type 1 receptor 2
T1R3	Human taste type 1 receptor 3
T1R1	Taste receptor type 1 member 1
T2RS	Human bitter taste receptor
GLUT2	Glucose transporter 2
ATP	Adenosine Triphosphate
GLUT4	Glucose transporter type 4
GPR40	G-protein coupled receptor 40
GPR120	G-protein coupled receptor 120
GLP1	Glucagon like peptide 1
PIK3/AKT	Phosphatidylinositol-3-kinase/ Protein kinase B
SREBP1	Sterol regulatory element binding protein-1
TRP	Trasient Receptor Protein
mTorc1	Mammalian target of rapamycin complex 1

1. Introduction:

1.1 Understanding Nutrients:

Nutrients can be classified into two main classes- Macronutrients which include- carbohydrate, protein and lipid and Micronutrients which include- vitamins and minerals. In macronutrients carbohydrate are the main source of energy in the body, where as proteins act as structural components and help to produce tissues, enzymes etc and are essential for growth and development. Fats are essential component of hormones and various other molecules. In micronutrients vitamin and minerals are essential components for body functioning and maintenance and their absence produces various deficiency diseases. Various vitamins act as cofactors of enzymes. Many minerals play important role in various enzymatic processes. Macronutrients are needed in large at regular intervals, where as micronutrients are needed in very small quantities but very much essential for growth and development. Beside these, water is an essential component which is needed in large quantities and on a daily basis. Though water is not considered as a 'nutrient' but it is essential for maintaining body in optimal and healthy condition [1]. Nutrient scarcity compelled our body for producing a strong pressure for selecting more efficient pathway of nutrient sensing in all organisms [2].

Nutrient sensing mechanism involves direct and indirect mechanism. In direct nutrient sensing mechanism sense molecules bind to the sensor directly. On the contrary, indirect nutrient sensing mechanism depends on surrogative molecules which reflect nutrient abundance. Beside the normal process of nutrient sensing, we will consider the specific molecules to which sense molecules bind as 'sensors', if only the affinity constant of the sensor is in the range of physiological changes of the nutrient's or its surrogate molecule's concentration.

Multicellular organisms are not directly exposed to changes in environmental nutrients and maintain its intracellular and extracellular nutrient levels through homeostatic mechanisms. But in case of mammals, as their internal nutrient level fluctuates, so intracellular and extracellular mechanism both exists. In multicellular organism, nutrient triggers the release of hormones which help to coordinate various coherent processes [2].

1.2. External Nutrient Sensing: Taste Receptors for Sugar, Amino Acids and Salts:

Every nutrient has different taste and different sensory mechanism. The two main component of food that is carbohydrate and protein, have an intrinsic hedonic taste quality: and in case of humans salts, especially sodium salt, also has a desirable taste. So the main reason of consuming these nutrients is their pleasant taste, mediated via taste sensory system. Other two taste qualities, bitter and sour are made up of chemicals that do not have any nutritional quality. So they cause feeding suppression or avoidance.

In mammals the main taste structures are taste buds which located on the tongue, and contain large number of chemosensory taste cells. In oral cavity other structures such as-epiglottis and soft palate which contain limited amounts of taste buds. Sugar sensing in human occurs via a single taste receptor which is a heterodimer composed of two G – Protein Couple Receptor (GPCRs) – Human taste type 1 receptor 2 (T1R2) and Human taste type 1 receptor 3 (T1R3). These proteins are encoded with specific genes and co expressed through many taste cells. Three main dietary component of sugar such as fructose, glucose and sucrose along with many artificial sweeteners activate T1R2 or T1R3. T1R3 along with Taste receptor type 1 member1 (T1R1) are expressed by specific taste cells which in turn are activated by L-amino acids, specially L-Glutamate. NaCl sensing is mediated by another group of taste cells. The taste cells express an epithelial sodium channel through which low sodium concentration can be detected. The receptors of other taste qualities such as bitter and sour are Human bitter taste receptor (T2RS) and KDL family of TRP (Transient receptor protein) channels. As these two tasting qualities are associated with non-nutritious chemicals so these receptors are not considered as nutrient sensor [1].

1.3. Nutrient Sensing In the Intestine:

Nutrient Sensing mechanism also present in the intestine. Here the content of food is re-examined for nutritive value and harmful content are discarded through excretory systems. Firstly, nutrients are sensed and then broken down. The broken molecules are then taken up by the intestine. Different nutrients have different mechanisms. Absorption of major classes of nutrients occurs actively. They first transported to cells and then released into blood circulation. The transport occurs through various transporters which play important role in nutrient sensing by affecting target cells [1].

1.4. Post ingestive Nutrient Sensing:

Every nutrient has different and distinct function in the body. After digestion nutrients absorbed into the blood and circulated throughout the body and different cells. After reaching specific site they perform their specific functions such as-provide energy (carbohydrate), building blocks for growth and development (proteins), and act as important component of essential cellular materials (lipid) [1]. These are all sense cells of the body as well as organs which ultimately control nutrient intake and metabolism.

1.4.1. Sugars:

Each and every cells of the body (particularly brain and heart cells) require ready source of energy for their functioning. Glucose is usually simple and readily absorbed by the intestine and extremely essential for our body functioning. Most important way of glucose sensing is through metabolic nutrient sensors such as- AMP-activated Protein Kinase (AMPK), which is activated when intracellular ATP drop, which initiates glucose breakdown and inhibits carbohydrate and lipid anabolism. The central glucose sensing organ is pancreas which maintains glucose level in blood. Glucose Transpoter 2 (GLUT2) is act as a transporter through which glucose enters in the pancreatic β cells. Through several biochemical processes nutrient sensing is mediated involving the production of Glucose-6-Phosphate and ATP (Adenosine Triphosphate) that ultimately results in the increase of intracellular Ca^{2+}.

Then the secreted insulin acts on the liver, adipose tissue and muscles. Thus it increases glucose uptake via a second transporter, Glucose Transpoter Type 4 (GLUT4) and thus lowering blood glucose levels. Insulin helps to maintain glucose level and makes sure the level should not exceed in blood (~100 mg/dl). On the other hand, another hormone, glucagon is secreted by α cells of the pancreas. Glucagon works in opposition to insulin, and when glucose levels in blood falls from its normal level, glucagon releases from α cells. Glucagon helps to break down glycogen store in liver cells and thus glucose is released in blood. Still it is poorly understand how α and β cells regulate glucose level in blood [1].

In the brain, neurons of hypothalamus and brainstem respond to glucose levels, thus may regulate appetite and feeding behaviors. They also regulate pancreatic hormone release as well as blood level by feedback mechanism. For example-Type 2 Diabetes is caused by glucose-excited Proopiomelanocortin (POMC) sensing. In these cells glucose sensing involves intracellular metabolic pancreas. Intracellular ATP level is increased by GLUT2 mediated glucose transport which leads to signaling through ATP dependant K+ channels. Glucose also suppresses activity of various neurons in the hypothalamus and other parts of brain but the mechanism is not well understood. For example-external nutrient sensing mechanism such as-Na+ glucose co-transporters or TRP channels rather than intracellular metabolic process [1].

1.4.2. Amino Acids:

Amino acids are essential component of proteins. They act as building blocks of the body. They help to produce muscles, tissues, and hormones and are also precursors of many important neurotransmitters such as dopamine, serotonin, etc. Excess of them converted to energy and storage proteins.

Amino acid regulation in blood is occurred through the activity of the neurons in the hypothalamus. These neurons respond to amino acid flux via intracellular metabolic nutrient sensors such as- TOR. Though TOR mainly is activated by essential amino acids (such as- leucine) but its activation depends on intracellular ATP levels. So, it was seen TOR is act as sensor for both carbohydrates and amino acids [1]

Mice can sense one or more dietary amino acids in the brain. When they are fed an amino acid diet deficit in one or more essential amino acids, they started to reduce feeding within 20 minutes. This rapid response may prevent protein degradation. This mechanism helps to release missing amino acids from stored proteins. On the other hand, when animals fed with a diet deficit in an essential amino acid, an increased taste preference to this amino acid is developed by them [1]. Proper sensing of the amino acid level is the most important factor in controlling food intake. By proper sensing of amino acid, protein and amino acid synthesis as well as catabolism can be regulated [2].

1.4.3. Lipid Sensing:

Lipids are chemically diverse group of compounds (e.g. fatty acids or cholesterol) and their biological functions are as diverse as their chemistry. Lipids are characterized by hydrophobic carbon backbones which is their defining features (do not dissolve in water) and these are used for energy storage and membrane biosynthesis. Fats are principle stored form of energy in many organisms. Lipid molecules rarely found free in a soluble form in organism. They bound to other molecules producing lipoproteins or chylomicrons or albumin in the serum as they are non polar in nature. In obese states, morbidity rates are increasing due to high consumption of lipid and malfunctioned lipid storage mechanism but we know relatively little about lipid sensing mechanism.

1.4.3.1 Fatty Acid Signaling:

G-protein coupled receptor 40 (GPR40) and G-protein coupled receptor 120 (GPR120) which are family of G-protein coupled receptor found to detect long chain unsaturated fatty acid (FA). GPR40 present at plasma membrane of β cells of pancreas which stimulated by free fatty acids and on the other hand stimulate glucose induced insulin release[3]. GPR120 also induce insulin secretion. By an indirect mechanism GPR120 involves in the production of GLP1 which belongs to a group of gastrointestinal hormone named Incretins that in turn induces insulin secretion in β cells [4]. By these examples it was understood that increase in one particular nutrient (fatty acids) can also induces increase of another nutrient (glucose). In addition at the plasma membrane of white adipocyte cells activation of GPR120 occurs which produces a signal transduction cascade that in turn activates Phosphatidylinositol-3-kinase/ Protein kinase B (PlK3/AKT). By this, glucose uptake is increased by the cells [5]. It was seen that in case of obese human genetic mutation occurs that disrupt GPR120 function and removal of GPR120 in mice produces diet-induced obesity in them. So, from these it is seen that this pathway plays an important role in maintaining nutrient homeostasis [6].

1.4.3.2. Cholesterol Sensing:

Cholesterol is a very important component of cell membrane. It helps to maintain membrane fluidity and involved in the synthesis of steroid hormones. Diet is the main source of cholesterol. Internal cholesterol sensing helps to control the demanding cholesterol biosynthetic pathway. So, when external supply and internal cholesterol levels are low, then it becomes activated to maintain a normal level of cholesterol. Hence, cholesterol biosynthetic pathway is regulated by cholesterol sensing mechanism [2].

On the Endoplasmic Reticulum (ER) a bound complex is produced by the cholesterol sensing protein and transcription factor. They help in the process of cholesterol biosynthetic pathway by inducing the expression of the enzymes. Cholesterol is bound by the cholesterol sensing protein SCAP (SREBP1 cleavage activating protein) via a particular region. SCAP is constitutively bound to Sterol Regulatory Element-Binding Protein-1 (SREBP1). This in turn transactivates gene needed for cholesterol synthesis [2].

Some evidences shown that there is another sterol sensing event present. This occurs within the ER, by the enzyme HMG-CoA Reductase. Rate limiting step of de novo synthesis is catalyzed by this enzyme and is a transcriptional target of SREBP1, when cholesterol level becomes low [2].

1.4.4. Sensors Upstream of Adipokinase:

Adipokinase hormones which are secreted from adipocytes help to regulate appetite, energy expenditure and many other process of nutrient homeostasis. Though lipid levels are not reflected by their levels but some report on organismal lipid storage [7] and some adipokinase, as LEPTIN may be considered as indicator of lipid levels. LEPTIN receptors are expressed in the central nervous system and peripheral tissues. Activation of LEPTIN coordinates food intake and metabolism. Besides LEPTIN, another hormone, called Adiponectin (also known as ADIPOQ) [8, 9] also synthesized by adipocytes. But regulation of its production is not well understood [10].

1.5. Autophagy:

Nutrient sources are intermittent in the environment. So, cells and organisms evolved different pathways of storing nutrient during abundance. This occurs in unicellular organism. But it is more structured in animals and multicellular organism, as their organs have special mechanism for nutrient storage such as- liver, tissues and skeletal muscle. Glucose is stored as glycogen in the mammalian cell where as lipids stored within lipid droplets and internal membranes and amino acids in protein and organelles. These stored nutrients support organisms during period of nutrient limitation. Cells have different processes to obtain these nutrients from internal stores, including autophagy. In this process, cellular constituents which are stored within a double membrane structure are recycled. Autophagy is a unique process as it targets any cell or nutrient storage and act as an important source under scarcity and regulated by nutrient and nutrient signaling [2].

2. Conclusion:

We are just having started to understand function and role of internal nutrient sensing. Nutrient is needed by each and every cells of the body and all have internal metabolic pathway that can act as nutrient sensing devices. Moreover, many tissues including- brain and gut can detect nutrient even when it is in the blood or midgut, as they have internal sensors that help them to detect nutrients early. These additional nutritional sensations may help to maintain nutrient homeostasis. ‘Transreceptors’ can play an important role in maintaining cellular and organismal homeostasis as they can sense internal and external level of nutrients. Various researches will be done in the future that may discover nutrient signaling pathway that can detect multiple nutrient signals simultaneously. As we are just have started to understand about nutrient sensing mechanism so various aspect of this mechanism is still unclear to us. For example, relation between level of storage lipid and LEPTIN synthesis and release is yet not well understood. On the other hand, about the glucose and amino acid sensors upstream of mTORC1 is still unclear. Cross regulation between different nutrient sensing pathways is important to understand complete nutrient sensing mechanism, and it also includes incorporating regulation by other signaling events. Lastly, nutrient abundance, not only hasten to onset of Diabetes but also increases the risk of cancer development and aging process. Nutrient Sensing is the mechanism which not only helps to maintain balance between stored energy and calorie intake, but also regulate various metabolic pathways. Hence, understanding normal nutrient sensing mechanism is most important factor for future inventions against degenerative lifestyle diseases.

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