Chapter

Glucose or Sucrose Intakes and Plasma Levels of Essential and Nonessential Amino Acids

Akikazu Takada, Fumiko Shimizu, Yukie Ishii, Mutsumi Ogawa and Tetsuya Takao

Abstract

It is not known whether the administration of glucose or sucrose influences plasma levels of amino acids. We want to know whether plasma levels of amino acids and if the administration of glucose or sucrose are different in young and old men and are influenced by the administration of glucose or sucrose. We found that the levels of most amino acids in plasma are lower in old men than young men. When sucrose was administered to old men, levels of total amino acids decreased significantly in old men. In both old and young men plasma levels of total nonessential amino acids significantly decreased at 120 min. after the administration of glucose but not sucrose. On the other hand, total essential and branched amino acids levels decreased significantly after the administration of both glucose and sucrose in young and old men. From these results, responses to the administration of glucose were different from the response to sucrose between young and old men. Also glucose was more effective in decreasing plasma levels of various amino acids. These results seem to suggest that glucose was more effective in stimulating insulin release and young men were more responsive to sugar than old men in stimulating insulin release.

Keywords: amino acids, branched chain amino acids, tryptophan, serotonin, leucine, appetite, feeding

1. Introduction

Globally the prevalence of obesity nearly tripled between 1975 and 2016 (the World Health Organization) [1]. Foods such as fats, carbohydrates, or sugar are causes of such increase in alarming obesity pandemic. Carbohydrates were blamed for increase in obesity because consumption of carbohydrates results in increase in the release of insulin, and that insulin levels affect fat storage. Insulin secretion suppresses the release of fatty acids into circulation, thus storage of fat in fat cells.

According to the carbohydrate insulin model, decrease in the proportion of dietary carbohydrate to fat without changing protein or calories may reduce insulin secretion, mobilize fat from adipose tissue, and cause oxidation of circulating free fatty acids.

Recently, various data were presented to object to this theory. The intakes of isocaloric ketogenic diet were not shown to result in body fat loss and relatively small increases in energy expenditure [2].

The presence of signals about energetic value of food between gut and brain was proposed by experiments in which rodents were given isocaloric diets that varied in volume and rodents accurately took the volume of food consumed to maintain constant caloric intake across days [3].

The volumes and contents of foods we take will be conveyed to the brain by a gut-brain circuit [4], and it is proposed that intake of highly processed foods disturbs the circuitry resulting in the confusion of the processing of foods information in the brain. This may be the reason of overeating and obesity by the intakes of highly processed foods [1, 4].

We recently gave sucrose or glucose to healthy men and measured changes in plasma levels of various amino acids [5] and changes in body mass index [6]. We now review the results and discuss roles of sugar in maintaining plasma levels of amino acids. We also report that sugar intake did not result in increase in body mass index unless overtaken.

Many researchers paid attention to the central control of appetite and gut motor and hormonal functions [7–9]. Many studies have been performed on roles of tryptophan and leucine in the regulation of food intake and appetite [7–9]. Since serotonin is derived from tryptophan roles of serotonin in the regulation of appetite have been studied well (Review [10]).

Since intakes of carbohydrates considered to increase the release of insulin, which increase fat deposition, thus obesity, low carbohydrate diet has been popular in Japan lately. According to Noto et al. [11], high mortality rate was shown among people using low-carbohydrate-high protein diet.

Robert Atkins first proposed that intakes of meat may result decrease of fat, thus prevent obesity. He died by a serious head injury when he toppled down [12], the impaired muscle functions has been suspected for the results of low carbohydrate diet.

The ability of insulin to stimulate glucose uptake and to suppress protein degradation in skeletal muscle is increased after exercise. Decrease in amino acid availability may prevent the stimulatory effect of insulin on muscle protein synthesis after exercise.

Insulin is considered to regulate the metabolism of carbohydrate, lipid, protein, and amino acids [13]. Insulin inhibits protein degradation and the release of amino acids, and stimulates protein synthesis and amino acids uptake in skeletal muscles [14, 15]. When insulin levels were high, protein synthesis was stimulated in skeletal muscles [16]. In hyperglycemia plasma levels of alanine, phenylalanine, valine, leucine, isoleucine and tyrosine were shown to increase and the levels of histidine and glutamine decreased [17].

It is shown that when plasma levels of tryptophan were raised by taking tryptophan in foods or by injection of insulin, serotonin and tryptophan in the brain increased [18, 19]. It is also shown that intake of carbohydrate resulted in secretion of insulin, which increased plasma levels of tryptophan and lowered the plasma levels of competing amino acids such as branched neutral amino acids in rats [19]. Carbohydrate intake was shown to decrease plasma levels of free amino acids and glucose intake resulted in a decrease in large neutral amino acids such as methionine, phenylalanine, tyrosine, and tryptophan [20, 21]. Possibly plasma glucose and insulin may stimulate transporters of some amino acids of peripheral tissues, especially muscles, resulting in decrease in the concentration of such amino acids in plasma.

We administered glucose or sucrose solution to young and old men and examined plasma levels of various amino acids. In the present review we report the results [22, 23], and propose possible mechanisms with regard to the regulation of appetite.

2. Methods

We asked men older than 50 years old and men college students to participate in the experiments. We checked their health carefully and recruited them if there were no health problems such as diabetes, hypertension nor serious diseases experienced in the past. They did not smoke in the past. We also excluded people who took drugs for dyslipidemia, hyperglycemia, or hypertension.

Participants were randomly assigned to groups after fasting overnight. Depending on their group, each participant received a 550-mL solution containing 50 g of glucose or sucrose (or 500 mL water as a control). Either 50 g of glucose or sucrose was added and dissolved in each bottle containing 500 mL of water. Between 9:00 AM and 10:00 AM, blood was taken using a syringe, and participants were given either glucose or sucrose solution or water as a control. We measured blood glucose using a finger stick (TERUMO kit) before and 120 min after the administration of glucose or sucrose. Furthermore, other plasma factors were measured after plasma was separated from blood. Ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant.

Blood was centrifuged to obtain plasma. The amino acid and insulin levels were measured for backgrounds of these participants.

To know energy intakes of various foods we used BDHQ (brief-type self-administered diet history questionnaires). From these questionnaires, we calculated the intake of energy, carbohydrate, fat and protein.

The samples were analyzed by SRL, Inc. (Tokyo Japan) using the UF-Amino Station®, which is a liquid chromatography-mass spectrometry system with an automated pre-column derivatization for simultaneous determination of amino acids (Shimadzu Corporation, Kyoto, Japan). The original concept of this system was developed by Ajinomoto Co., Inc. (Tokyo Japan) as an automated method of analyzing major free amino acids in human plasma in the field of clinical chemistry.

The human plasma samples were cryopreserved with EDTANa2 before the analysis. The thawed samples were deproteinized with acetonitrile followed by the amino acid analysis. Pre-column derivatization in the UF-Amino Station was automatically performed using an automated sample injector with the regent APDSTAG® (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Target free amino acids as derivatized compounds were separated under a reversed phase ultrahigh-performance liquid chromatography condition and determined by the liquid chromatograph mass spectrometer.

Insulin was measured by the CLEIA (chemiluminescent immunoassay) method.

3. Ethics

This work was approved by the ethical committees of Showa Women's University and the NPO "International projects on food and health" and was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments.

4. Statistics

The results are presented as means ± SD. Statistical significance of the differences between groups was calculated according by one-way ANOVA. When ANOVA indicated a significant difference ($P < 0.05$), the mean values of the treatment were compared using Tukey's least significant difference test at $P < 0.05$.

5. Results

5.1 Measurements of plasma levels of amino acids in old and young men

Table 1 shows the background of participants. There was no difference on energy intake between young and old men. Young men take more lipids and old men take more carbohydrate.

Table 2 shows plasma levels of amino acids of young and old men. Plasma levels of nonessential amino acids were higher in old men than young men. No differences were shown in plasma levels of total amino acids, and total essential and branched amino acids between young and old men.

Levels of phenylalanine, tyrosine, alanine, A-aminobutyric acid, citrulline, cysteine, glutamic acid, ornithine, and taurine were higher in old men, and serine were higher in young men.

5.2 The administration of glucose or sucrose in young and old men

Blood was taken before the experiments from old men and amino acids levels were measured at 0 min and 120 min after the administration of glucose (15 men) or sucrose (16 men) or water as a control (13 men). Amino acids levels of all blood samples were measured. Compared with the control group, essential amino acids (EAAs) such as histidine, lysine, methionine, phenylalanine, threonine, tryptophan, leucine, isoleucine, and valine and branched amino acids (BAAs) such as leucine, isoleucine, and valine decreased significantly 120 min after the administration or glucose or sucrose in old men. Nonessential amino acid (NEAA) levels decreased at 120 min after the administration of glucose only compared with the control group.

In 36 young men, amino acids levels in plasma were measured at 0 min and 120 min after the administration of glucose (12 men) or sucrose (13 men), with 11 men of a control group taking water only. Similarly, the EAA and BCAA levels decreased in comparison with the control group (11 men) after the administration of glucose or sucrose to young men. EAAs such as histidine, lysine, methionine, phenylalanine, threonine, tryptophan, leucine, isoleucine, and valine and BCAAs such as leucine, isoleucine, and valine decreased significantly after the

Subjects	Young (n = 36)	Old (n = 44)	ss
Age (years)	20.8±1.6	62.4±9.6	**
Height (m)	1.72±0.06	1.68±0.07	*
BMI	22.2±3.3	24.3±3.2	*
Energy intake(kcal/day)	1988±591.8	2115.1±460.2	
Protein intake (g/day)	69.3±25.1	66.6±28.8	
Lipid intake (g/day)	60.4±24.8	49.1±22.6	*
Carbohydrate intake (g/day)	78.9±13.1	198.6±89.4	**
Insulin (μU/ml)	6.87±4.19	6.19±3.79	

*$P<0.05$.
**$P<0.01$.

Table 1.
Background of participants.

Amino acids	Young men (n = 36)	Old men (n = 44)	ss
Histidine	78.5±7.7	78.7±7.5	
Lysine	185.9±28.6	190.9±28.7	
Methionine	27.3±3.6	27.6±4.9	
Phenylalanine	56.9±7.0	65.4±8.8	**
Threonine	131.4±21.5	136.5±27.4	
Tryptophan	65.8±9.1	58.7±9.2	
Isoleucine	67.9±11.2	67.5±8.5	
Leucine	129.8±16.8	133.8±17.5	
Valine	221.9±16.3	228.1±30.6	
Tyrosine	58.2±8.7	70.3±12.0	**
Alanine	356.0±68.8	415.9±75.7	**
A-Aminobutyric acid	20.9±5.3	21.7±6.5	**
Arginine	77.6±15.0	79.3±17.6	
Asparagine	45.0±6.1	47.3±5.7	
Aspartic acid	3.4±1.4	3.4±0.7	
Citrulline	22.2±3.6	27.0±6.2	**
Cysteine	14.1±4.1	23.6±6.7	**
Glutamic acid	37.0±11.6	45.0±16.	**
Glutamine	548.5±64.0	575.6±53.0	
Glycine	213.5±25.9	198.5±28.6	
Monoethanolamine	8.5±1.2	8.8±1.3	
Ornithine	59.4±12.5	72.5±13.9	**
Proline	172.8±58.4	169.2±56.9	
Serine	124.6±17.2	105.5±18.2	**
Taurine	49.9±1.5	67.7±3.1	**
Total amino acids	2751.7±215	2891.4±201.6	
Total essential AAs	695.3±89.0	985.4±94.9	
Total nonessential AAs	1786.4±153.3	1960.4±166.0	**
Total branched chain AAs	419.5±48.3	427.5±52.3	
Fisher ratio	3.7±0.4	3.2±0.4	

AAs: amino acids, ss: statistical significance.
***P < 0.01.*

Table 2.
Plasma levels of amino acids in young and old men in Japan (nM).

administration of glucose or sucrose in young groups too. NEAA levels decreased after the administration of glucose in old and young men.

In **Figure 1**, changes in the levels of total amino acids at 120 min in old and young men after the administration of glucose or sucrose were compared to those levels in the control group. When glucose was taken the amounts of total amino acids significantly decreased in young and aged people. Sucrose administration resulted in a significant decrease in the total amino acids only in old men (**Figure 1**).

Decrease in plasma levels of total essential amino acids at 120 min after the administration of solutions containing 50 g of glucose or sucrose in young and old men were calculated.

Figure 2 shows changes in the decrease of total EAA levels at 120 min compared with the control group after glucose or sucrose administration in aged and young men. After the administration of both glucose and sucrose administration total EAAs significantly decreased in young and aged men at 120 min after the administration compared with the control group.

Figure 3 shows decrease in total NEAA levels at 120 min compared with the control group after glucose or sucrose administration in aged men. Glucose intake resulted in a significant decrease in the amounts of total NEAA levels in aged men. There was practically no further decrease in the total NEAAs after the administration of sucrose compared with the control group in either old or young men.

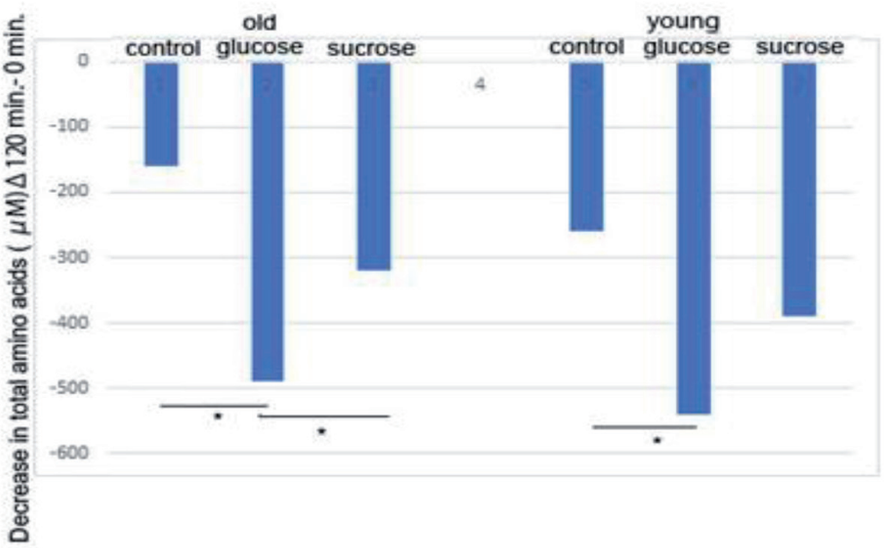

Figure 1.
Changes in total amino acids after the administration of glucose or sucrose in young and old men.

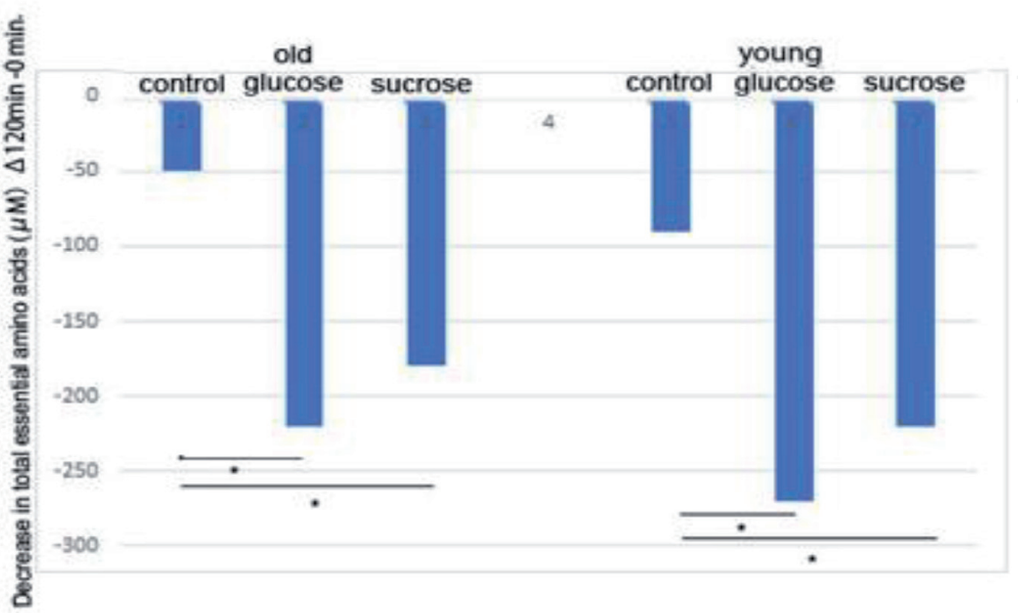

Figure 2.
Changes in total essential amino acids levels after the administration of glucose or sucrose in young and old men.

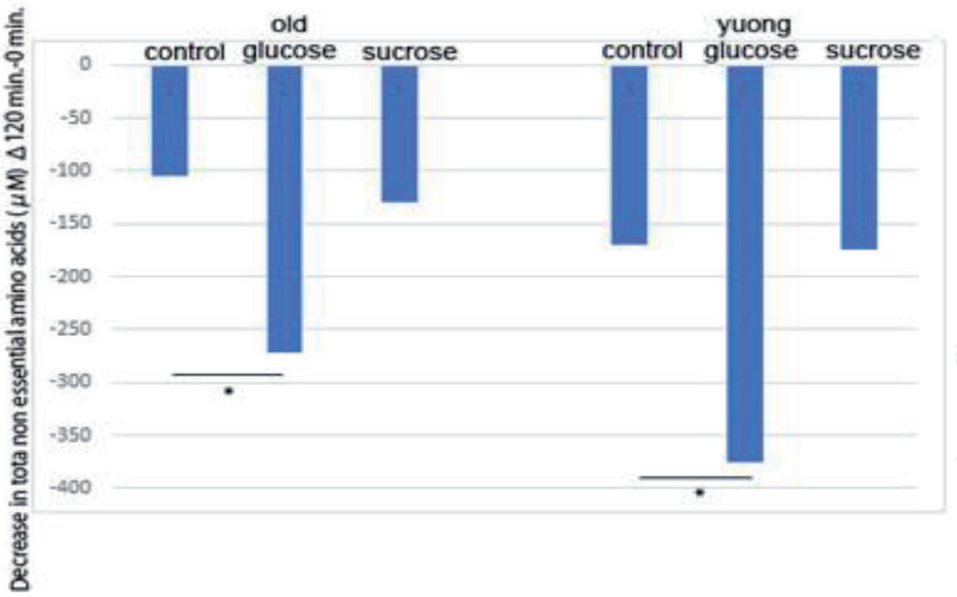

Figure 3.
Changes in total nonessential amino acids (NEAAs) after the administration of glucose or sucrose in young and old men.

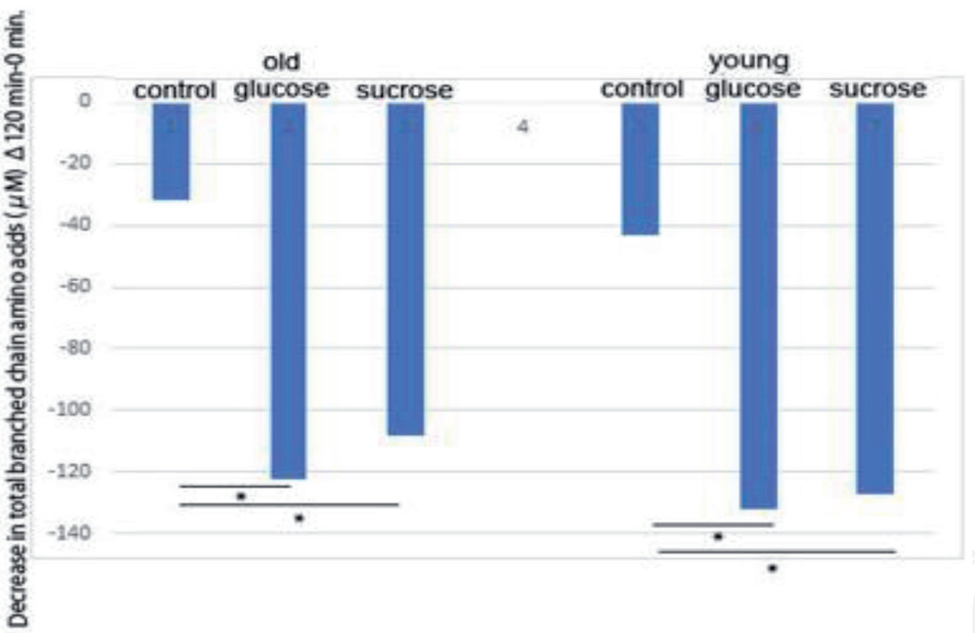

Figure 4.
Changes in total branched chain amino acids after the administration of glucose or sucrose in young and old men.

Figure 4 shows a decrease in the plasma levels of total BCAAs at 120 min after the administration of glucose or sucrose to old and young men. Both glucose and sucrose administrations significantly decreased total BCAA (leucine, isoleucine, and valine) levels in young and aged men at 120 min after the administration compared with the control group.

6. Discussion

Is carbohydrate needed for the transportation of amino acids from blood to the brain or peripheral organs.

As indicated by Burtman's group [18, 19], insulin is needed for the transportation of tryptophan to the brain.

Figure 5 illustrates the transportation of tryptophan from the blood to the brain. Insulin released upon intake of sugar facilitates the transportation of tryptophan. Burtman's group proposed that tryptophan competes with other long neutral amino acids for the transportation to the brain and that in the presence of insulin long neutral amino acids except for tryptophan are transported to the peripheral organ so that remaining tryptophan is now transported to the brain.

Figure 6 shows the hypothesis that in the presence of insulin long neutral amino acids are mainly transported to the peripheral organs and tryptophan is now transported to the brain.

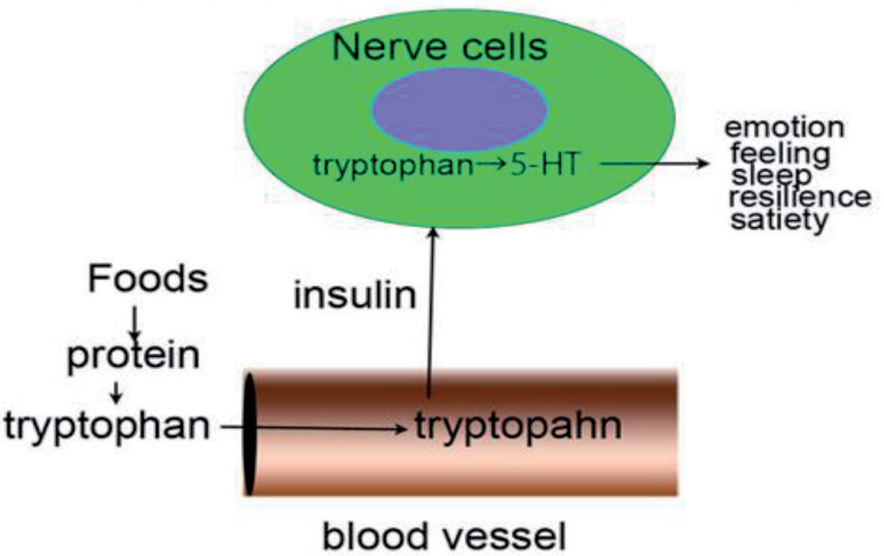

Figure 5.
The transportation of tryptophan from the blood to the brain.

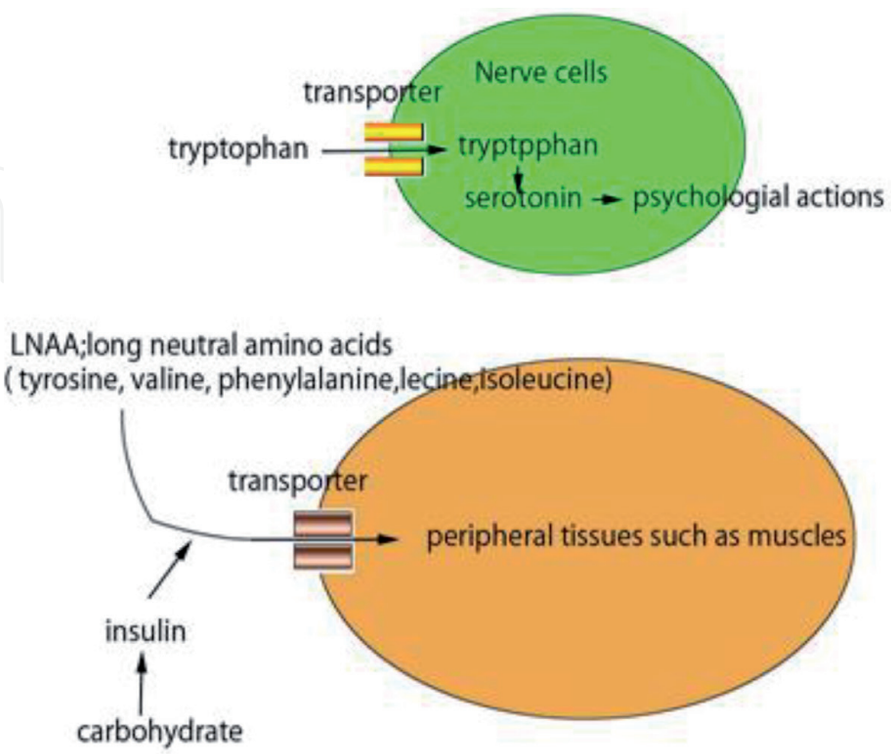

Figure 6.
Transportation of long neutral amino acids to the peripheral organs.

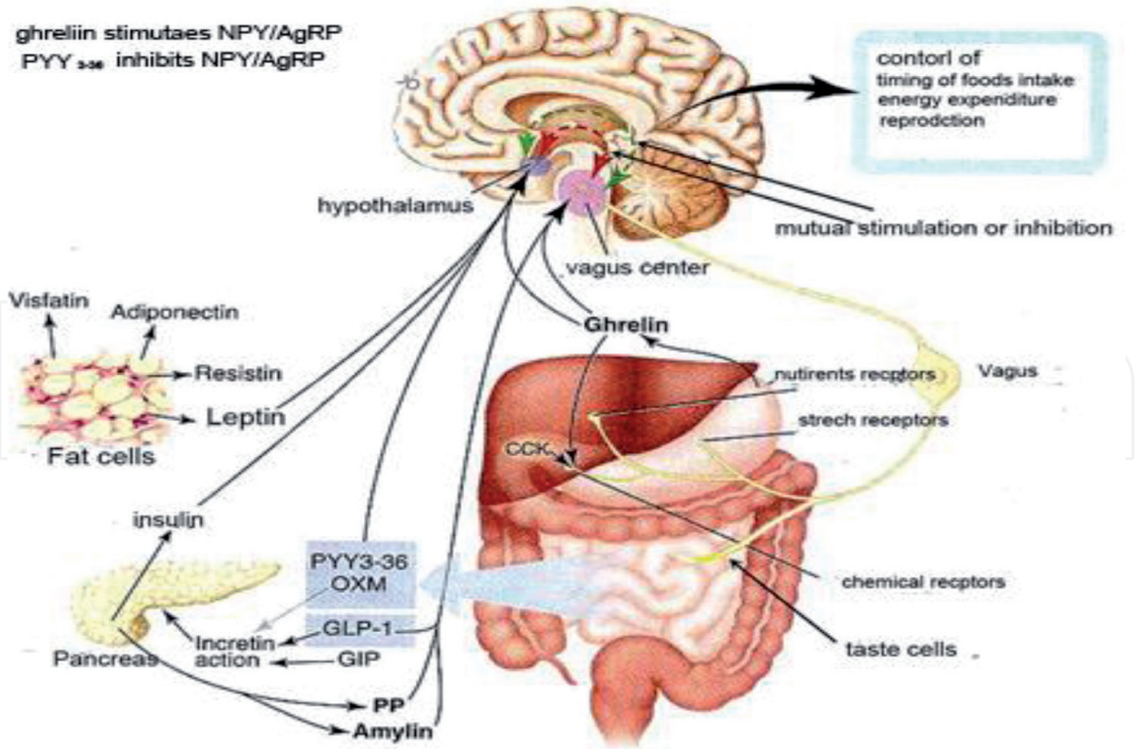

Figure 7.
Central and peripheral mechanisms of food intakes.

Intake of glucose or sucrose was shown to result in decrease in plasma levels of essential amino acids. Since insulin stimulate protein synthesis of the muscle [16] essential amino acids transported to the muscle are used muscular protein synthesis. This hypothesis explains why decrease in plasma levels of amino acids, especially essential amino acids after the administration of glucose or sucrose in men may be explained by this hypothesis.

Tryptophan is important for the stability of emotion, sleep and satiety.

There are many factors controlling hunger and satiety. As shown in **Figure 7**, ghrelin released from the stomach enhances foods intakes by stimulating NPY/AgRP NPY (neuropeptide Y)/AgRP (Agouti related peptide) in the arcuate nucleus. On the other hand $PYY_{3–36}$ released from the colon inhibits NPY/AgRP. Leptin from fatty cells and insulin from the pancreas inhibit NPY/AgRP and stimulate melanocortin-producing cells. Serotonin and leucine have been proposed to inhibit hunger.

In view of roles of tryptophan, thus serotonin in appetite controlling mechanisms, intakes of carbohydrates must be paid much attention.

Recently volumes and contents of intake amino acids are paid attention to.

7. Sensing of amino acids in the central nervous system

Ensuring sufficient consumption of proteins is needed for growth, reproduction, and species survival [24]. Evolutionally animals had mechanisms to keep adequate protein intake. Detection of decrease or increase of single amino acids can profoundly influence feeding behavior and food preference [24–27].

Hundred years ago, the marked reduction in energy intake and growth of animals maintained on diets containing very low protein amounts or imbalanced EAA ratios was first described. Harper and colleagues showed that the anorectic response to imbalanced amino acid diets is the cause rather than the consequence of growth failure. This suggestion supports the idea that dietary amino acids are important in the regulation of food intake [28–31].

Work by two independent groups demonstrated that mice could detect rapidly dietary EAA deficiency within the APC (anterior piriform cortex) occurs via a GCN2 (general control nonderepressible 2)-dependent mechanism; this pathway is also required for rejection of for EAA-imbalanced diets in drosophila [32]. The GCN2 pathway is an evolutionarily conserved pathway identified in yeast to mediate the detection of amino acid deficiency [33, 34].

From these observations, Hooley and Blouet [35] proposed a mechanism by which animals are able to detect lack or excess of protein. In these networks, leucine and tryptophan are considered a pivotal role in the regulation of feeding behaviors.

Figure 8 illustrates proposed protein sensing sites. APC is proposed to be a site to sense protein deficits and NTS (Nucleus tractus solitarius) is proposed to be a site to sense protein excess.

We here indicate that insulin, thus intake of carbohydrate is essential for the health of brain and peripheral organs. Especially insulin is needed for the transport of tryptophan to the brain. Tryptophan is important for feeding behavior and the production of serotonin, which is needed for emotion. Serotonin is further converted to melatonin in the pineal body. Melatonin is important for sleep. APC and NTS are sites to sense the excess and deficit of proteins. Tryptophan and leucine play important roles there.

In Section 1, we indicate that highly processed foods disturb the gut-brain circuitry so that the nutritional content in the processed foods is not accurately conveyed to the brain. It is possible that the way foods are processed and prepared

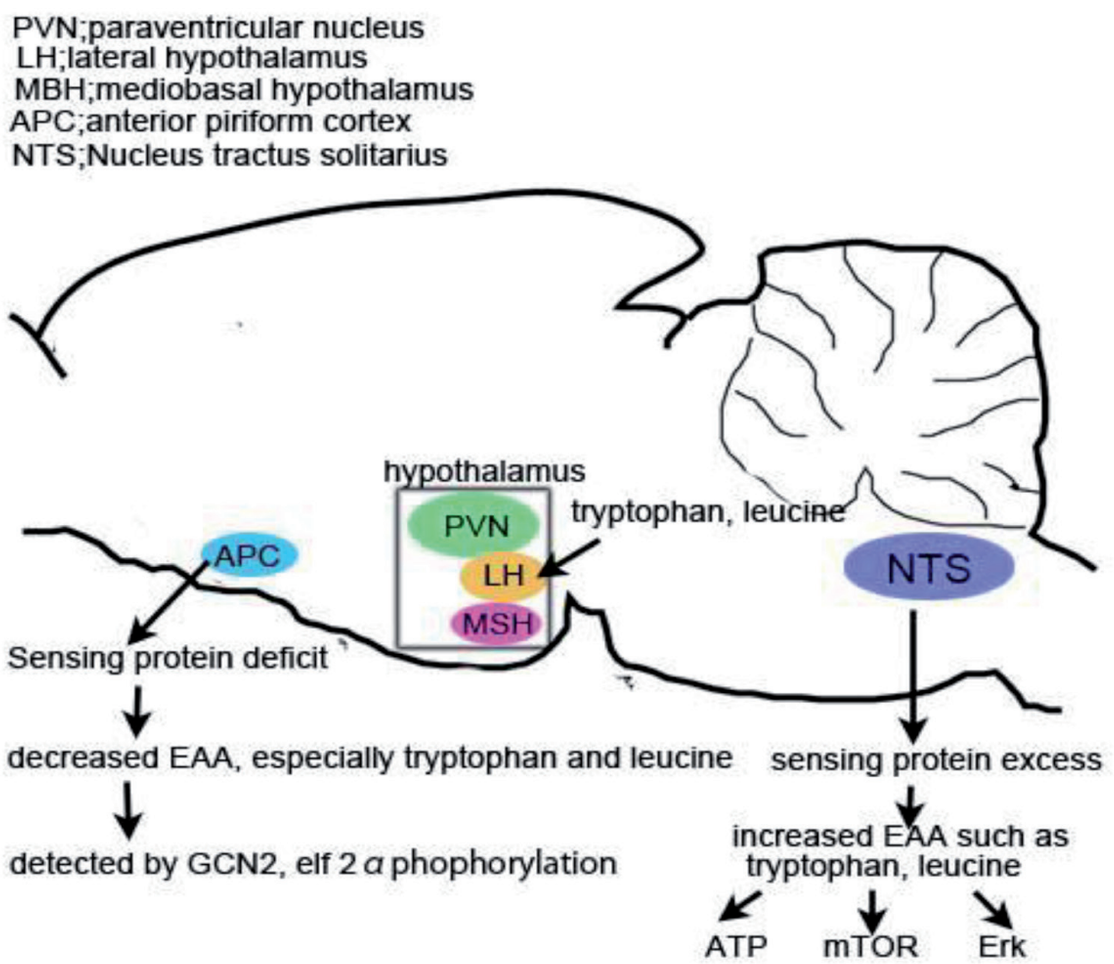

Figure 8.
Protein sensing sites.

affects physiology beyond the energy density or palatability of the foods, and that these disturbances promote overeating and metabolic dysfunction.

Small and DiFeliceantonio [4] proposed that information of carbohydrates after oxidation of glucose is conveyed to the midbrain and further to the cortex and that information of fat through PPAR γ is conveyed through vagus nerve and transmitted to the substantia nigra, further to the cortex, where unusual amounts of dopamine are released, leading to overeating.

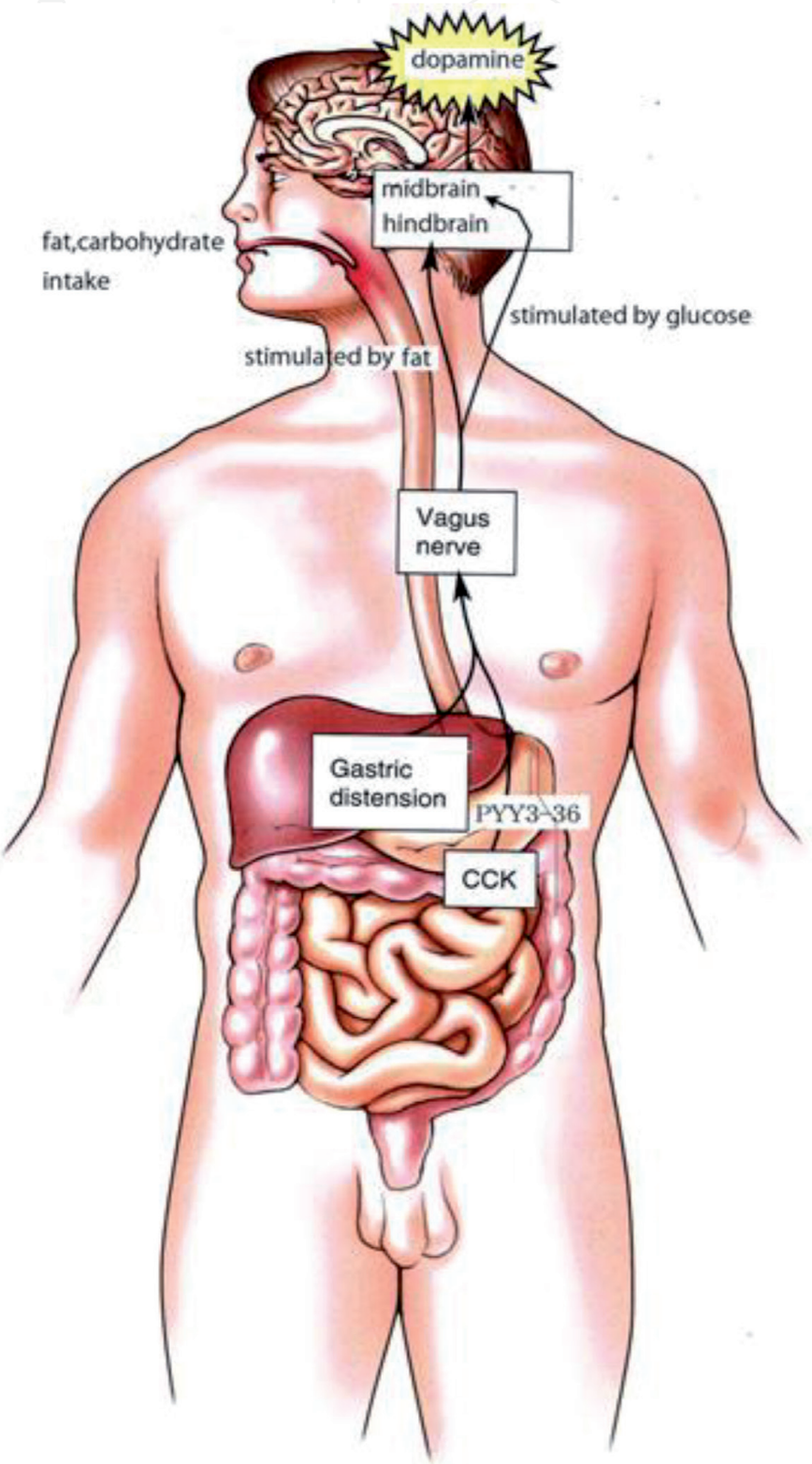

Figure 9.
Gut-brain circuitry of foods contents.

We propose that information of carbohydrates and fats in the processed foods is sent to the brain through vagus nerve, causing unexpected amounts of dopamine release. This may cause overeating.

Figure 9 shows our hypothesis. We propose that information of food intake is conveyed mainly through the vagus nerve to the brain. We report this hypothesis elsewhere.

Conflict of interest

No conflict of interest for any author in the project.

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