

# Plasma Levels of Amino Acids in Japanese Men and Their Changes after the Administration of Glucose and Sucrose

Akikazu Takada<sup>1\*</sup>, Fumiko Shimizu<sup>2</sup>, Yukie Ishii<sup>2</sup>, Mutsumi Ogawa<sup>2</sup>, Tetsuya Takao<sup>2</sup>

<sup>1</sup>International Projects on Food and Health (NPO), Tokyo, Japan

<sup>2</sup>Faculty of Human Life and Environmental Sciences, Showa Women's University, Tokyo, Japan

Email: \*takadaa@mwd.biglobe.ne.jp

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## Abstract

**Background:** It is not known whether plasma amino acids levels are different between young and old men in Japan. No research has been reported about changes in plasma levels of amino acids after the administration of glucose or sucrose to young and aged men. **Objective:** We want to know whether there are age differences in plasma levels of amino acids and if the administration of glucose or sucrose influences their levels. **Results:** Old people had lower plasma levels of most of amino acids, especially essential and branched-chain amino acids than young men. Plasma levels of amino acids were measured after the administration of 50 grams of glucose or sucrose to young (18 - 22 years old) and aged ( $\geq 50$  years old) male adults. Plasma levels of total amino acids decreased after the administration of glucose. Decrease in the total amino acid levels was significant in aged men after the administration of sucrose. A significant decrease in plasma levels of total non-essential amino acids was observed at 120 min after the administration of glucose but not sucrose in both aged and young men. Both glucose and sucrose administrations resulted in a significant decrease in the plasma levels of the total essential amino acid levels and branched amino acids in young and aged men. **Conclusion:** These results suggest that there are age differences in plasma levels of amino acids. Upon the administration of glucose or sucrose amino acids, particularly essential amino acids, decreased in plasma. These amino acids may be transported from the blood soon after the administration of sugar (glucose or sucrose) to the tissues, such as muscles, possibly due to an increase in the insulin levels.

## Keywords

Amino Acids, Branched Chain Amino Acids, Tryptophan, Serotonin,

## 1. Introduction

The Global Burden of Disease (GBD) indicated that the global obesity epidemic is worsening in most parts of the world [1].

It has been shown that the prevalence of obesity has more than doubled since 1980 and is now 5% in children and 12% in adults. Strangely, despite of increase in obesity, the effects of high body mass index (BMI) on population-levels of age-adjusted rates of death and disability have not increased, suggesting that obese persons are healthier and live longer than in previous decades due to better care and risk factor management [1].

The control of appetite centrally and gut motor and hormonal functions have been paid attention to by many researchers [2] [3] [4].

Among many amino acids, roles of tryptophan and leucine in the regulation of food intake and appetite have been studied extensively [2] [3] [4]. Especially, roles of serotonin, thus tryptophan in the regulation of appetite have been extensively studied (Review [5]).

Recently, low carbohydrate diet is very popular in Japan. Noto *et al.* [6] reported, however, that a high mortality rate has been shown among those using low carbohydrate-high protein diets.

Since Robert Atkins who advocated low carbohydrate diet died by a serious head injury when he toppled down [7], the impaired muscle functions are considered to be the results of low carbohydrate diet.

Insulin has been shown to regulate carbohydrate, lipid, protein, amino acids metabolism [8]. Insulin inhibits proteolysis and associated release of amino acids and stimulates amino acid intake and protein synthesis in skeletal muscle [9] [10]. High insulin levels were shown to stimulate skeletal muscle protein synthesis [11]. As to individual amino acids, plasma levels of alanine, phenylalanine, valine, leucine, isoleucine, and tyrosine were shown to increase and the levels of histidine and glutamine decreased in hyperglycemia [12].

Fernstrom, J.D. and Wurtman R.J. Indicated 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 [13] [14]. They indicated that carbohydrate ingestion increased the secretion of insulin which raised plasma levels of tryptophan and lowered the concentrations of the competing amino acids such as branched neutral amino acids in rats [14]. Carbohydrate ingestion 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 [15] [16]. These results suggest that increase in plasma levels of glucose or insulin may increase the transport of some amino acids using transporters and decrease in the concentration of such amino acids.

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 [17] [18], and propose possible mechanisms with regards to the regulation of appetite.

## 2. Methods

We asked men older than 50 years old and men college students to participate in the experiments, 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.

After fasting overnight, participants were randomly assigned to groups. 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 sampled 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.

Plasma was obtained by centrifuging the blood samples, and the amino acid and insulin levels were measured for backgrounds of these participants.

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 reagent 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.

### 2.1. 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.

## 2.2. Statistics

The results are presented as means  $\pm$  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  $P < 0.05$ .

## 3. Results and Discussion

1) Measurements of plasma levels of amino acids in old and young men.

a) Background of participants.

**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.

b) Plasma levels of amino acids.

**Table 2** shows plasma levels of amino acids of young and old men. Although there were no differences in plasma levels of total amino acids and total essential and branched amino acids between young and old men, plasma levels of nonessential amino acids were higher in old men.

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

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). Blood samples were collected and amino acids levels were measured. Essential amino acids (EAA) such as histidine, lysine, methionine, phenylalanine, threonine, tryptophan, leucine, isoleucine, and valine) and branched amino acids (BAA) such as leucine, isoleucine, and valine decreased significantly 120 min after the administration or

**Table 1.** Background of Participants.

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

\* $p < 0.05$ , \*\* $p < 0.01$ .

**Table 2.** Amino acids levels of young and old men.

Plasma levels of amino acids in young and old men in Japan (nM)			
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	**
Cystine	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	

AA; amino acids, ss; statistical significance, \*\*p < 0.01.

glucose or sucrose in old men compared with the control group. Non-essential amino acid (NEAA) levels decreased at 120 min after the administration of glucose only compared with the control group.

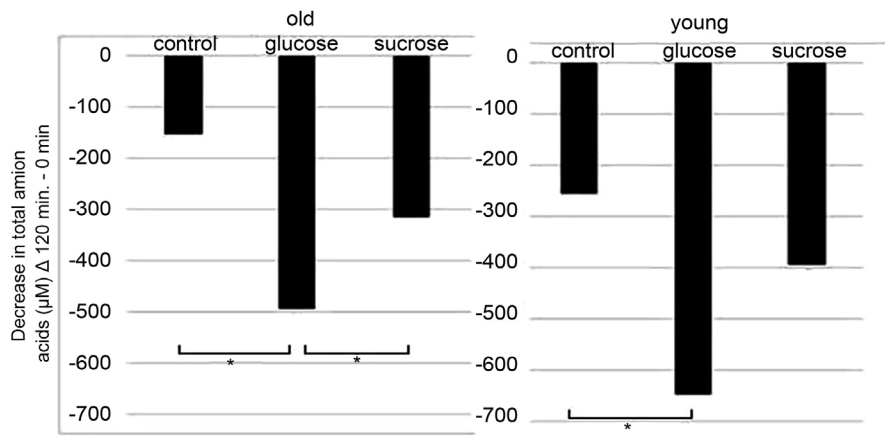
Amino acids levels in plasma of 36 young men at 0 min and 120 min after the administration of glucose (12 men) or sucrose (13 men) were measured with 11 men of a control group taking water only. Similarly, a decrease in the EAAs and BCAAs levels was observed compared with the control group (11 men) after 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 administration of glucose or sucrose in young groups too. NEAA levels decreased after the administration of glucose in aged and young men.

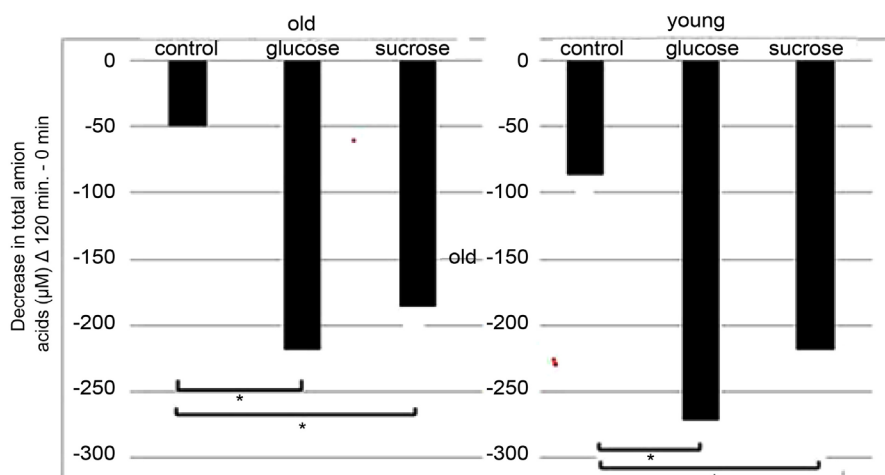
Changes in the levels of total amino acids at 120 min in old and young men after the administration of glucose or sucrose were compared to those levels in the control group. Glucose intake resulted in a significant decrease in the amounts of total amino acids in young and aged people. Sucrose administration 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



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

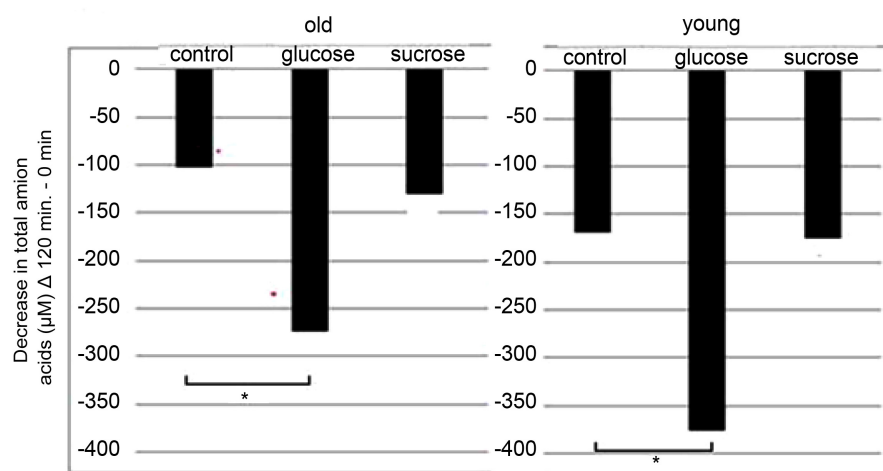


**Figure 2.** Changes in total essential amino acids levels after the administration of glucose or sucrose in young and old men.

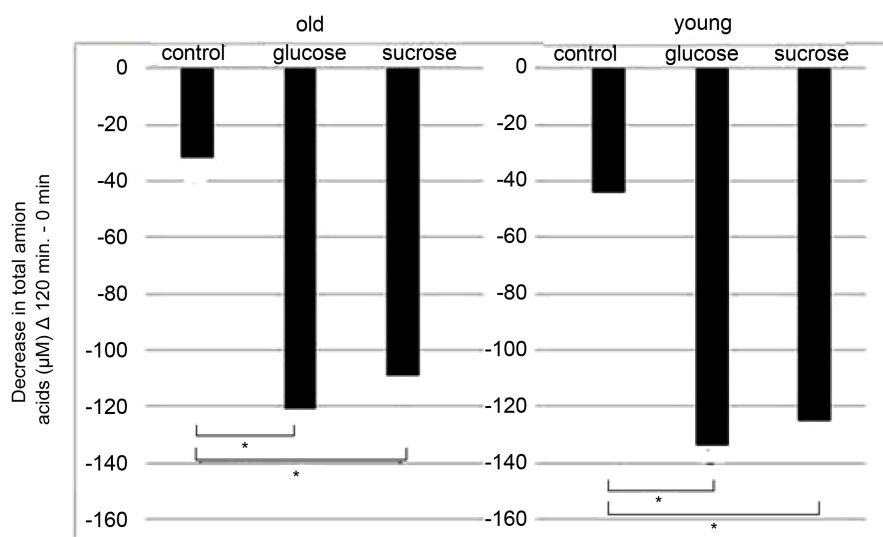
compared with the control group after glucose or sucrose administration in aged and young men. Both glucose and sucrose administration significantly decreased total EAAs in young and aged men at 120 min after the administration compared with the control group.

**Figure 3** shows decrease in total NEAAs 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 NEAAs 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 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



**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.

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.

3) The transport of amino acids from the blood to brain and peripheral organs.

As indicated by Burtman's group [13] [14] [15] [16] insulin plays an important role in the transport of essential amino acids to the brain and peripheral organ.

**Figure 5** shows that insulin, thus carbohydrate intake, is necessary for the transport of tryptophan to the brain. Insulin is needed for the transport of tryptophan from the blood to the brain. Tryptophan is then converted to serotonin, important for the regulation of emotion and feeling. Serotonin is then converted to melatonin in the pineal body.

Serotonin is an important regulator of feeding.

Leucine is also important in the feeding behavior.

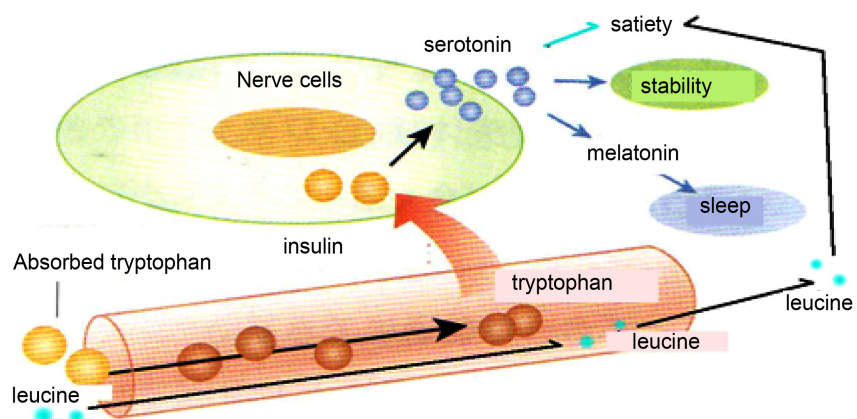
Essential amino acids, especially long chain neutral amino acids are transported to the peripheral organs such as muscles. Our data shown in **Figures 1-4** show that intake of glucose or sucrose decreases in plasma levels of essential amino acids in men. Since insulin enhances protein synthesis of the muscle [11] essential amino acids transported to the muscle are used muscular protein synthesis. This hypothesis explains why plasma levels of amino acids, especially essential amino acids decreased after the administration of glucose or sucrose in men.

**Figure 6** illustrates the mechanisms of transport of amino acids in the presence of insulin.

Long neutral amino acids such as tyrosine, phenylalanine, valine, leucine and isoleucine are transported to peripheral tissues such as muscles in the presence of insulin while tryptophan is transported to the brain.

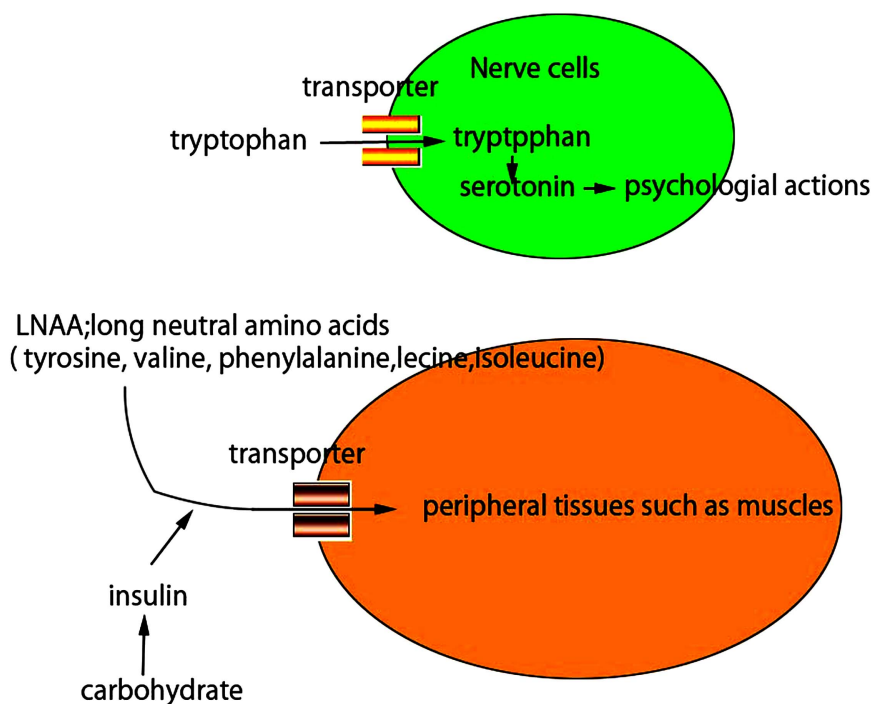
4) Roles of amino acids, tryptophan and leucine in the regulation of appetite and feeding behavior.

**Figure 7** shows that peripherally generated in the periphery are also important

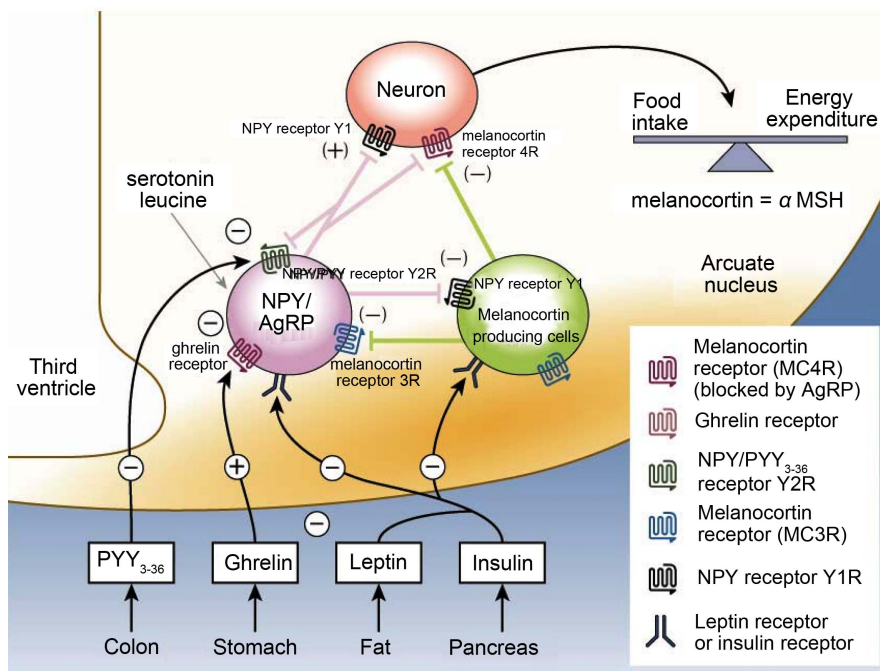


**Figure 5.** Transport of tryptophan to the brain.





**Figure 6.** Transport of tryptophan and other long chain neutral amino acids to the brain and the peripheral tissues.



**Figure 7.** Factors involved in the regulation of feeding.

in the regulation of feeding. PYY (peptide YY)<sub>3-36</sub> released from the colon inhibits hunger. On the other hand, ghrelin released from the stomach stimulates feeding desire. Leptin released from the fatty tissues and insulin released from the pancreas inhibits the hunger by stimulating NPY (neuropeptide Y)/AgRP

(Agouti related peptide) cells in the arcuate nucleus of the hypothalamus and inhibit melanocortin producing cells.

Informations from NPY/AgRP cells stimulate higher feeding center to increase food intake. On the other hand, melanocortin producing cells inhibit higher feeding centers to stop feeding.

Serotonin and leucine are implicated to be involved in these networks, inhibiting feeding behaviors.

#### 5) Sensing of amino acids in the central nervous system.

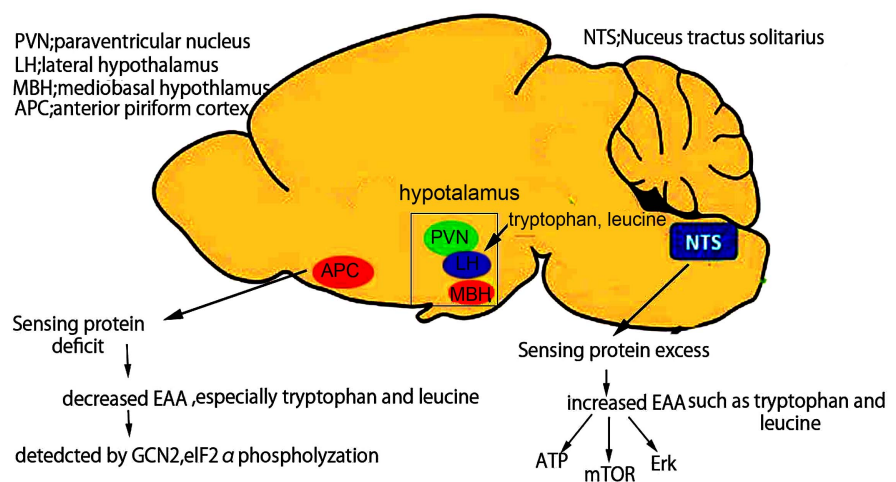
Ensuring sufficient consumption of proteins is needed for growth, reproduction, and species survival. [19]. Animals evolved mechanisms to ensure adequate protein intake. Detection of decrease or increase of single amino acids can have profound effects on feeding behavior and food preference [19] [20] [21] [22].

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 over 100 years ago. Harper and colleagues demonstrated that the anorectic response to imbalanced amino acid diets is the cause rather than the consequence of growth failure, supporting a direct role for dietary amino acids in the regulation of food intake [23] [24] [25] [26].

Work by two independent groups demonstrated that the rapid detection of dietary EAA deficiency within the APC (anterior piriform cortex) occurs via a GCN2 (general control nonderepressible 2)-dependent mechanism in mice; this pathway is also required for rejection of for EAA imbalanced diets in drosophila [27]. The GCN2 pathway is an evolutionarily conserved pathway identified in yeast to mediate the detection of amino acid deficiency [28] [29].

From these observations, Hooley N. and Blouet C. [30] proposed a mechanism by which animals 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



**Figure 8.** Protein sensing sites.

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.

## 4. Conclusions

We have found that glucose or sucrose administration to health young and old men resulted significant decrease in plasma levels of amino acids, especially essential amino acids. We propose that this observation was brought about by increasing in transport of essential amino acids from the blood to the peripheral tissues, especially muscles.

Carbohydrate restricted diets may be hazardous for our health not only due to the damage to the brain but to muscles.

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Experiments were designed and performed by all of the authors. AT wrote a manuscript. Statistical analyses were done by TT. All authors read the manuscript and approved the final version. All the authors had responsibilities for the final content.

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## Conflicts of Interest

No conflicts of interest for any author.

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