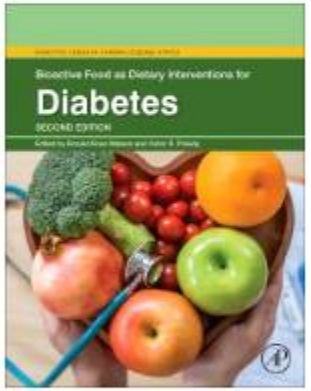

Bioactive Food as Dietary Interventions for Diabetes

2nd Edition

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16. Magnesium and Relationship with Diabetes **249**

Jesse Bertinato

1 Magnesium 249
2 Diabetes 250
3 Mg Deficiency in the General Population, Chronically Ill and Diabetics 251
4 Mg Intakes and Serum Mg Concentrations Are Inversely Associated With Diabetes Risk and Abnormal Glucose Metabolism 252
5 Mg Supplementation and Glucose Metabolism: Results From RCT 254
6 Mg Deficiency and Insulin Sensitivity: Molecular Mechanisms 255
7 Mg Intake and Diabetes 257
8 Type 2 Diabetes for Setting Dietary Reference Values for Mg and a Reference Interval for Total Serum Mg Concentration 259
9 Conclusions and Future Directions 260
References 260

17. Plasma Levels of Tryptophan Metabolites in Patients of Type 2 Diabetes Mellitus **265**

A. Takada, F. Shimizu, J. Masuda, K. Matsuoka

1 Introduction 265
2 Ethics 266
3 Statistics 266
4 Methods 266
5 Results 269
6 Discussion 273
Acknowledgments 275
Financial Support 275
References 275
Further Reading 276

18. Effect of Magnesium Supplementation on Lipid Profile: A Systematic Review of Randomized Clinical Trials **277**

Fernando Guerrero-Romero, Claudia I. Gamboa-Gómez, Luis E. Simental-Mendía, Martha Rodríguez-Morán

1 Lipids and Cardiovascular Risk 277
2 Metabolic Pathways of Magnesium in the Lipid Profile 278
3 Magnesium Supplementation in the Improvement of Lipid Profile 281
References 283
Further reading 286

CHAPTER 17

Plasma Levels of Tryptophan Metabolites in Patients of Type 2 Diabetes Mellitus

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1. INTRODUCTION

Tryptophan (TRP) is an essential amino acid important for protein synthesis, but it also serves as substrate for the generation of several bioactive compounds with important physiological roles. TRP is converted to serotonin (5-hydroxytryptamine), an important neurotransmitter involved in the control of many responses in the central nervous system (CNS) and linked to alterations in mood, anxiety, or cognition.[1] Serotonin can be further converted to *N*-acetylserotonin (NAS) and melatonin, influencing control over circadian rhythmicity to the list of biological roles for TRP metabolites.[2] It is known that in mammals, the majority of free TRP is degraded through the kynurenine pathway (KP) and generates many metabolites involved in inflammation, immune response, and excitatory neurotransmission.[3]

We have shown that foot shock applied to rats resulted in increase of not only brain serotonin levels but also kynurenine (KN) in plasma, kidney, liver, and every part of the brain.[4–6]

Several TRP metabolites have been shown to exhibit neuroexcitatory, convulsant, and toxic properties.[7,8]

In the periphery, only 1% of dietary TRP was converted to serotonin and more than 95% was metabolized to KNs.[9,10]

We thought that TRP metabolism may have been changed in diabetic patients because of various stresses both physiological and psychological including self-care. So, we measured plasma level of serotonin, 3-hydxyindole acetic acid, and KN metabolites, and showed that TRP metabolites increased in plasma of patients of type 2 diabetes mellitus (T2DM).[11]

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In this chapter, we report in detail the plasma levels of TRP metabolites and also show relationship between obesity measured by body mass index (BMI) and the plasma levels of various TRP metabolites.

2. ETHICS

This work has been approved by the Ethical Committees of Showa Women's University and nonprofit organization (NPO) "International Projects on Food and Health" and has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments.

3. STATISTICS

The results are presented as means ± SEM. Statistical significance of the differences between groups was calculated accordingly by one-way analysis of variance (ANOVA). When ANOVA indicated a significant difference ($P < .05$), the mean values were compared using the Turkey's least significant difference test at $P < .05$. The Spearman's correlation tests were used to examine statistical significance.

4. METHODS

We asked male acquaintances older than 50 years to participate in the experiments. Acquaintances mean that these participants are personal friends of our group member. The sample sizes and ages of participants are as follows. Male ($n = 20$, age; 61.5 ± 8.8) acquaintances older than 50 years.

We recruited patients of T2DM ($n = 20$, age; $65.7 + 10.4$).

We obtained an informed consent prior to conducting the protocol which had been approved by the Ethical Committee of Showa Women's University and Saiseikai Main Hospital.

Plasma specimens were collected for assays of blood parameters. We obtained an informed consent prior to conducting the protocol which had been approved by the Ethical Committee of Showa Women's University and Saiseikai Shibuya Satellite Clinic.

Healthy participants were given self-administered diet history questionnaires and described answers on each item by recollection of diets they took (7 days dietary recall). We used a brief-type self-administered diet history questionnaire (BDHQ) by using which the Japanese Ministry of Health, Labor, and Welfare reports National Nutrition Surveys. From these questionnaires, we calculated the intakes of energy, carbohydrate, fat, and protein.

Plasma factors were measured after plasma was separated from blood. Ethylenediamine tetra acetic acid (EDTA) was used as an anticoagulant. Blood glucose levels were

measured by a hexokinase UV method. Insulin was measured by the chemiluminescent immunoassay (CLEIA) method. We also measured glycemic indexes after giving glucose and sucrose to participants, so that we did not use HbA1c as a marker of glycemia.

Lipid and lipoprotein concentrations such as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) were determined using a Polychem Chemistry Analyzer (Polymedco Inc.). Free fatty acid (FFA) and the concentrations of ω fatty acids such as arachidonic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) were measured by a gas chromatography.

The thawed samples were deproteinized with acetonitrile followed by the amino acid analysis. Precolumn 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-pressure liquid chromatography (UHPLC) condition and determined by the liquid chromatograph mass spectrometer.

Remnant lipoproteins (RLPs) were isolated from the serum to an immunoaffinity mixed gel containing antiapolipoprotein A1 and antiapolipoprotein B100 monoclonal antibodies (Japan Immunoresearch Laboratories, Takasaki, Japan), and the cholesterol and TG concentrations of the unbound fraction were measured as RLP cholesterol and RLP-TG, respectively.

Measurements of TRP metabolites were performed by using a reversed-phase ultrahigh-pressure liquid chromatography (UHPLC). Metatabolites are shown in Fig.1.

4.1 Assays of TRP Metabolites

4.1.1 Reagents

The standard materials of 15 major TRP metabolites such as TRP, 5-hydroxytryptophan (5-HTRP), serotonin, KN, 3-hydroxykynurenine (3-HKN), 5-hydroxytryptophol (5-HTOL), tryptophol (TOL), kynurenic acid (KNA), xanthurenic acid (XA), 5-hydroyindole-3-cetic acid (HIAA), indole-3-acetic acid (IAA), 3-hydroxyanthranilic acid (HAA), anthranilic acid (AA), quinolinic acid, and indole-3-lactic acid (ILA) are special grade or biochemical grade regents purchased from the Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Formic acid and acetonitrile are liquid chromatography-mass spectrometry (LC/MS) grade regents and other major chemicals such as methanol are special grade purchased from the Wako Chemical as well. Water was obtained as occasion demands from the installed Milli-Q water purification system (Merck-Millipore, MA, USA).

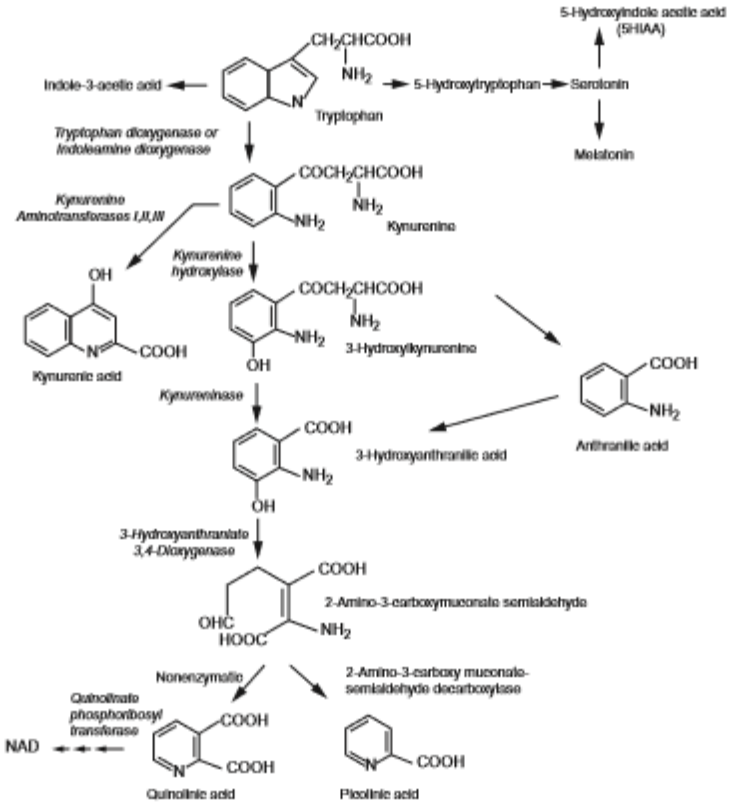

Fig.1 Tryptophan degradation pathway.

Each standard mother solution was prepared as 1000 mg/L from each regent above in water and/or 0.1 mol/L sodium hydroxide aqueous solution. Standard mixture solution for each concentration level of a calibration curve was prepared by dilution of the mother solution with water.

4.1.2 Instrumentation and Analytical Conditions

TRP metabolites were analyzed. Shimadzu LCMS-8060 or 8050 system consists of Nexera UHPLC system such as solvent delivery units, an autosampler and column oven, and liquid chromatograph mass spectrometer LCMS-8060 or 8050 with its electro spray

interface (Shimadzu Corporation, Kyoto, Japan). The high-performance liquid chromatography (HPLC) column used was L-column 2 ODS [2.1 mm × 150 mm, 3 μm, Chemical Evaluation and Research Institute (CERI), Tokyo, Japan] with a gradient elution of 0.1% formic acid/acetonitrile system. Before analyses, the condition of multi reaction monitoring (MRM) was optimized using each standard solution, respectively.

Gradient elution was performed by the high-pressure binary gradient program, 5% of 0.1 formic acid aqueous solution fold in 3 min with acetonitrile, 5%–95% of 0.1% formic acid aqueous solution in the next 6 min followed by 95% hold in another 3 min at flow rate 0.4 mL/min under 40°C. Ionization was executed by an electrospray (ESI) positive mode at 150°C (the desolvation line) and 400°C (the interface) with 3 L/min nebulizing and 5 L/min drying gas. Chromatographic data were obtained by MRM mode under optimized transition.

4.1.3 Sample Pretreatment

The samples were stored at −80°C.

In all, 50 μL aliquot of the blood plasma sample was took in 1.5 mL test tube, and then 25 μL 0.1% formic acid aqueous solution, 150 μL of acetonitrile, and an additional 75 μL of 0.1% formic acid aqueous solution were added, respectively. The solution was vortexed in 30 s followed by standing in 5 min under cooling temperature. After this, each sample was centrifuged at 3000 rpm under 4°C in 10 min. After the centrifugation, 120 μL aliquot of supernatant for each sample solution in the 1.5-mL test tube was transferred into other 1.5-mL test tube and additional 80 μL of 0.1% formic acid aqueous solution was added followed by being vortexed in 30 s, respectively. The final solution was 10-fold dilution from its original blood plasma sample. In all, 1 μL of each final solution was injected into the LC/MS system by an autosampler.

5. RESULTS

Table 1 shows the backgrounds of healthy old men and patients of T2DM. Plasma levels of HDL cholesterol, TG, and arachidonic acid were higher in healthy old men than patients of T2DM.

Table 2 shows amino acids profiles of healthy old men and patients of T2DM. Amino acids which were different between healthy old men and T2DM patients were shown. Also, plasma levels of total amino acids, nonessential amino acids, essential amino acids, and branched chain amino acids were shown.

Plasma levels of some nonessential amino acids such as glutamic acid and aspartic acid were higher in T2DM patients. On the other hand, glutamine levels were higher in healthy old men.

Table 1 The background of healthy old men and patients of T2DM

Subject	Healthy old men ($n=20$)	DM ($n=20$)	Significance
Age (years)	61.5±8.8	65.7±10.4	
Height (m)	1.68±0.07	1.70±0.06	
Weight (kg)	67.2±12.9	68.2±11.5	
BMI (kg/m^2)	23.7±3.9	23.7±3.7	
Energy intake (kcal/day)	2155±416	–	
Protein intake (g/day)	69.8±25.2	–	
Lipid intake (g/day)	49.8±20.3	–	
Carbohydrate intake (g/day)	209.6±86.8	–	
blood glucose (mg/dL)	92.5±16.4	–	
HbA1C (%)	–	6.8±0.6	
Insulin (μIU/mL)	6.23±4.08	–	
HDL-Chol. (mg/dL)	64.1±16.9	50.7±11.4	**
LDL-Chol. (mg/dL)	121.3±26.5	113.6±25.9	
TG (mg/dL)	127.1±70.0	157.8±88.8	
T-Chol. (mg/dL)	210.4±34.1	189.5±28.4	*
Dihomo-gamma-linolenic acid (μg/mL)	37.6±12.7	35.0±8.6	
Arachidonic acid (μg/mL)	215.0±60.1	180.4±36.3	**
EPA (μg/mL)	91.5±51.2	82.1±59.7	
DHA (μg/mL)	163.3±53.4	139.4±48.9	
EPA/AA	0.440±0.229	0.482±0.432	
RLP-Chol. (mg/dL)	6.97±6.25	6.03±5.21	
RLP-TG (mg/dL)	30.0±24.7	23.8±25.3	

Chol, cholesterol; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *RLP*, remnant-like particles; *TG*, triglyceride.
One-way ANOVA was used for evaluating statistical significance.
$P<.05$ was considered significant.

Of interest, TRP levels were lower in T2DM patients, and the levels of branched chain amino acids such as leucine, isoleucine, and valine were higher in T2DM patients.

Table 3 shows that the plasma levels of 5-HTRP, 5-hydroxyindoleacetic acid (5-HIAA), kynurenic acid (KNA), 3-HKN, and 3-HAA were higher in patients of T2DM than healthy old men. Since 5-HTRP and 5-HIAA belong to the serotonin pathway, and KNA, 3-HKN, and 3-HAA belong to the KN pathway of Try metabolism, these pathways were activated more in the patients of T2DM. Since plasma levels of IAA was not elevated in T2DM, that pathway was not activated more in T2DM.

Table 2 Main amino acids profiles of healthy old men and T2DM patients

Amino acid	Healthy old men ($n = 20$)	T2DM ($n = 20$)	Significance			
Tryptophan	59.0 ± 9.2	53.4 ± 13.1	*	Aspartic acid	3.59 ± 0.65	6.01 ± 2.99
Isoleucine	63.1 ± 8.9	75.1 ± 7.9	**			
Leucine	126.5 ± 14.1	141.1 ± 14.2	**			
Arginine	86.1 ± 20.8	72.6 ± 16.7	*			
Asparagine	46.5 ± 5.5	41.4 ± 7.8	*			
Aspartic acid	3.72 ± 0.59	6.05 ± 3.30	**			
Cystine	21.0 ± 5.3	8.7 ± 5.4	**			
Glutamic acid	52.2 ± 17.1	154.5 ± 113.4	**			
Glutamine	550.7 ± 66.1	449.0 ± 138.6	**			
Taurine	80.6 ± 16.2	48.6 ± 8.8	**			
Total AA	2825 ± 225	2843 ± 187				
EAA	961.4 ± 64.3	995.8 ± 93.0				
NEAA	1864 ± 188	1848 ± 142				
EAA/NEAA	0.520 ± 0.050	0.542 ± 0.057				
BCAA	413.6 ± 39.7	452.5 ± 45.1	**			
BCAA/AAA	3.24 ± 0.30	3.76 ± 0.65	**			
BCAA/Total AA	0.146 ± 0.013	0.160 ± 0.016	**			

*$P < 0.05$, **$P < 0.01$, adult vs DM; *AAA*, aromatic amino acid; *BCAA*, branched chain amino acid; *EAA*, essential amino acid.

Table 3 Plasma levels of tryptophan metabolites

Subject		Healthy old men ($n=20$)	DM ($n=20$)	Significance
Tryptophan	μM	68.89±13.32	67.79±15.49	
5-Hydroxytryptophan	nM	0.62±0.00	2.19±1.72	**
Serotonin	nM	30.87±0.07	101.22±213.67	
Kynurenine	nM	1696.82±1.07	1625.47±539.78	
5-Hydroxy-tryptophol	nM	Tr	Tr	
Tryptophol	nM	Tr	Tr	
5-Hydroxyindole acetic acid	nM	33.15±0.01	48.87±21.18	**
Indole-3-acetic acid	nM	2433.30±854.69	3089.91±1642.17	
Anthranilic acid	nM	16.03±12.06	21.74±8.01	
Kynurenic acid	nM	64.03±21.65	94.80±34.86	**
Quinolinic acid	nM	8.82±7.76	9.04±10.41	
3-Indolebutyric acid	nM	5.94±4.78	4.88±7.84	
3-Hydroxykynurenine	nM	2.60±2.25	4.68±2.35	**
3-Hydroxyanthranilic acid	nM	8.67±9.74	20.24±13.99	**
Xanthurenic acid	nM	12.37±5.29	14.87±5.22	

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

Table 4 Relationship between body mass index (BMI) and plasma levels of various tryptophan metabolites

	Correlation coefficients	
BMI vs	T2DM ($n=20$)	Healthy old men ($n=20$)
Tryptophan	−0.171	0.153
5-Hydroxytryptophan	−0.154	0.291
Serotonin	0.164	−0.263
Kynurenine	−0.266	−0.146
5-Hydroxyindoleacetic acid	−0.005	−0.289
Indole-3-acetic acid	−0.044	0.278
Anthranilic acid	0.041	−0.054
Kynurenic acid	0.076	−0.147
Quinolinic acid	0.263	−0.398
3-Indolebutyric acid	0.238	−0.111
3-Hydroxykynurenine	−0.123	−0.044
3-Hydroxyanthranilic acid	−0.020	−0.122
Xanthurenic acid	0.123	0.041

Not significant between BMI and any tryptophan metabolite.

Although the serotonin pathway was activated more in the patients of T2DM, the serotonin levels were not increased, which may mean that serotonin was quickly metabolized to 5-HIAA in the patients of T2DM.

Table 4 indicates that there was no relationship between BMI and plasma levels of any TRP metabolite. This means that obesity may not influence TRP metabolism in T2DM patients.

6. DISCUSSION

TRP has been paid attention by scientists due to its role in the production of serotonin in the brain, which is an important transmitter regulating mood, anxiety, cognition, or memory.[12] Serotonin is further converted to 5-HIAA, or *N*-acetyserotonin or melatonin, which controls circadian rhythmicity. However, as stated in Introduction, the majority of free TRP is degraded through KP. The final product is nicotinamide adenine dinucleotide (NAD^+), which is now under investigation for therapeutic target of several diseases.[13] KN and its metabolites are also known for their actions in the CNS. There stimulate or suppress the functions of glia cells. Defects in KN signaling are shown in mouse model of Alzheimer's disease or Huntington's disease.

TRP is an essential amino acid which must be taken from the food. Eggs, fish, dairy products, meat, and legumes contain higher levels of TRP compared with other foods of vegetable origin.

We first measured plasma levels of various amino acids in healthy old men and T2DM patients (Table 2).

Plasma levels of some nonessential amino acids such as glutamic acid and aspartic acid were higher in T2DM patients. On the other hand, glutamine levels were higher in healthy old men.

Of interest, TRP levels were lower in T2DM patients, and the levels of branched chain amino acids such as leucine, isoleucine, and valine were higher in T2DM patients.

There are some papers indicating that insulin regulates the metabolism of carbohydrate, lipid, protein, and amino acid.[14] Proteolysis and associated release of amino acids are inhibited by insulin and insulin stimulates amino acid uptake and protein synthesis in skeletal muscle.[15,16] High insulin levels were shown to stimulate skeletal muscle protein synthesis.[17] As to individual amino acids, the plasma levels of alanine, phenylalanine, valine, leucine, isoleucine, and tyrosine were shown to increase and the plasma levels of histidine and glutamine were shown to decrease in hyperglycemia.[18]

Our results shown in Table 2 partly support these results because the plasma levels of branched chain amino acids were higher in T2DM patients.

The majority of TRP is metabolized along the serotonin, KN, or indole pathways. After the absorption of amino acids from the intestine, TRP is transported by large neutral amino acid transporters.

The majority of TRP is imported into the gut, where only a fraction is used. The remaining TRP is imported to the liver and then transported to tissues such as the brain, heart, and skeletal muscle.

Although TRP metabolites play important roles in the intestine, pancreas, skeletal muscle, liver, or immune system, we here discuss their roles in pathogenesis of diabetes mellitus.

As stated above, TRP metabolism is linked through inflammation and immune suppression. The increased production of serotonin is reported to be related to pathogenesis of diabetes.[19] Our results, however, show that plasma levels of serotonin were not significantly increased in T2DM patients (Table 3). TRP hydroxylase which converts TRP to 5-HTRP is known to be a rate-limiting factor[20] The increased plasma levels of 5-HRPP and 5-HIAA may mean that serotonin was rapidly formed from TRP and also rapidly metabolized to 5-HIAA in patients of T2DM.

Chronic stress and low-grade inflammation are major risk factors in prediabetes to diabetes transition. They can change the balance of TRP metabolism toward KN, 3-HK, and KNA, both by activating tryptophan 2,3 dioxygenase (TDO)/indoleamine 2,3 dioxygenase (IDO) and by reducing the availability of pyridoxal-5-phosphate, a necessary cofactor for many KP enzymes.

Diabetic patients show increased levels of XA and KNA in urine, which have been consequently suggested as biomarkers for T2DM.[21,22] Our results, however, show that although plasma levels of KNA were increased, those of XA were not elevated in patients of T2DM. Moreover, TRP metabolites inhibit both proinsulin synthesis and glucose- and leucine-induced insulin release from rat pancreatic islets, and XA in particular binds to circulating insulin and prevents its action on target cells.[23] Recently, KN-aryl hydrocarbon receptor (AhR) signaling in mice has been suggested to play a role in the etiology of obesity.

In the present research, we report that the degradation of TRP into the serotonin and KP was increased in T2DM patients, but that plasma levels of not all the metabolites increased in patients of T2DM.

These results, however, support the idea that there are increased immune and stress activities in diabetes. Quinolinic acid is an agonist of N-methyl-D-aspartate receptor and kynurenic acid is an antagonist.[7,8] Our results show that the plasma levels of KNA was increased in patients of T2DM. So, it is possible that the balance of nerve agonist and antagonist is impaired in diabetes.

In fact, TRP metabolites were shown to be increased in patients of acute coronary diseases, of which the etiology acute or chronic stress is implicated. In patients with suspected stable angina pectoris, elevated levels of plasma KNs predicted increased risk of acute myocardial infarction, and risk estimates were generally stronger in subgroups of impaired glucose homeostasis.[24] IDO activation was shown to be associated with depressive symptoms of coronary artery disease.[25] These results may suggest that stress may activate TRP degradation and cause thrombosis in the artery.

As indicated before, we applied electric foot shock to rats and measured TRP metabolites in the plasma, the CNS, and peripheral tissues. Plasma levels of TRP increased significantly immediately after the foot shock and returned to normal values within 24 h. TRP levels also increased in all the brain areas immediately after stress application.

Foot shock elevated the levels of KN in the plasma, liver, kidney, and every part of the brain. 3-HKN and KNA levels increased in the brain. These results indicate that stress activates not only serotonergic pathway but also KN pathway in the CNS and periphery. Some metabolites of KN pathway, such as 3-HKN are neurotoxic while other metabolite such as KNA is neuroprotective. Increase in serotonin levels in the hypothalamus and midbrain stabilizes emotion and prevents mood disorders. Therefore, some brain dysfunction resulting from stress may be prevented by the metabolites of TRP. The balance of these functions may be important in the maintenance of nerve integrity and peripheral homeostasis under stress.

We think that such stress may contribute to the etiology of T2DM.

We also examined relationship between BMI and various TRP metabolites. We have already shown that intake of various foods (carbohydrate, lipid, and protein) or BMI had little to do with various plasma factors such as amino acids, lipids, glucose, or insulin),[21] we wanted to know if BMI has anything to do with plasma levels of TRP metabolites. As shown in Table 4, changes in BMI had nothing to do with plasma levels of any TRP metabolite, which suggest that increase in body weight do not cause change in TRP metabolism.

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Experiments were designed and carried out by all the authors. AT wrote a manuscript. Statistical analyses were done by FS. All authors read the manuscript and approved the final version. All the authors had responsibilities for the final content. No conflicts of interest for any author.

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