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Tryptophan Metabolism and Gut Microbiota

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Abstract

Background: Tryptophan metabolites such as serotonin, kynurenine, or kynurenic acids are considered to be the most important metabolites of gut microbiota. We wanted to know about changes in tryptophan metabolites in various diseases in which the etiology gut microbiota are considered to participate. **Methods:** Ultra-high speed liquid chromatography/mass spectroscopy (LC/MS) has been used to analyze simultaneously all the tryptophan metabolites, which we have explored for the first time in the world. **Results:** We analyzed plasma levels of tryptophan metabolites in patients with depression, autism, diabetes mellitus 'DM'), and acute coronary syndrome (ACS). Of all the metabolites serotonin and kynurenine levels of these patients were higher than those of controls. **Conclusion:** Measurements of tryptophan metabolites in plasma of various diseases are important to know roles of gut microbiota in etiology, further therapeutic measures.

Keywords

Tryptophan, Serotonin, Microbiota, Depression, Obesity, Kynurenine, Blood Brain Barrier, Kynurenine, Permeability, Autism, Depression, Diabetes

1. Introduction

The human microbiota or microbiota live symbiotically in our body. In our gastrointestinal tract approximately $10^{13\text{-}14}$ microorganisms (mainly bacteria) live This number is said to be equal to human cells [1]. The amount of genomic content is over 100 times as compared to the whole human genome. Since the gut microbiota is involved in many different metabolic activities the gut microbiota is also known as the second brain since an enteric nervous system communicates with the brain via the nervous system [2].

Each compartment of the digestive tract has a diverse microbial population and functions since environmental conditions change in each compartment. The major environmental conditions are such as acidic nature of gastric juices, the

presence of bile salts, pancreatic enzymes, presence of mucous layer of pathogenic microorganisms.

There are significant differences in concentration and diversity of microbial communities ranging 10^2 per gram in the stomach to 10^{14} per gram in the colon [3] [4]

2. Microbiota and Diseases

Tremendous amounts of data indicate that variations and changes in the composition of the gut microbiota contribute to diseases such as Alzheimer's disease, Parkinson's disease, autism, depression to obesity and diabetes mellitus [5]. It has been experimentally validated that the gut microbiota influences distant organs such as lung, heart, liver, kidney and the central nervous system.

In order to tackle this subject, Long Li *et al.* [6] developed Amadis, a manually curated database that microbiota disease associations experimentally supported.

Here, I discuss diseases of which we have been working these days.

2.1. Depression

We all suffer and grieve at some point in our life. It is an unescapable response and such response may be needed for us to overcome such unhappiness in the future. Anxiety may prepare us to deal with stress by sharpening your senses.

In life we often lose beloved persons or cannot achieve our objectives successfully. In such cases we grieve. This is called situational depression. But when your depression last long you feel sad or do not intend to work more.

This is not caused by affairs in the world outside but by the brain chemistry.

The disease affects up to 15% of the general population and accounts for 12.3% global disease burden [7].

Weight fluctuation and insomnia accompany depression. Gut problems such as diarrhea or constipation are often involved either as cause or effects.

Sometimes depressive symptoms are experienced as a comorbidity of other diseases. When we are sick we feel depressed and lose hope for the present or future life. Almost every disease increases our chance of having either depression or anxiety.

Tryptophan metabolites, especially serotonin (5-hydroxytryptamine; 5-HT), are considered to be very important for etiology and treatment of depression. Serotonergic neurons in the central nervous system (CNS) are involved in regular behavioral states and physiological processes including arousal, sleep, appetite, pain, release of hormones and mood [8] [9]. Dysfunction of serotonin neurons may lead to depression and other neural disorders [10] [11] [12]. Pharmacological manipulation can successfully increase 5-HT availability in 5-HT neurotransmission in the CNS.

Several biochemical processes intrinsic to the 5-HT neurons were considered to be effectively manipulated by actions of chemical substances including the loading of a precursor amino acid, tryptophan or 5-hydroxytryptophan (5-HTP)

inhibiting degradative enzymes, the monoamine oxydases; inducing release of 5-HT; inhibiting 5-HT transport or uptake; blocking autoreceptors at the terminals or cell bodies as well as agonists activating post synaptic receptors.

Recently, however, the serotonin theory of depression has been questioned as reviewed by Moncrief J. *et al.* [13]

For example, two meta-analyses indicated that 5-HIAA levels in the cerebrospinal fluid showed no association with depression. Plasma levels of serotonin were also shown to have no relationship with depression. Two meta-analyses showed the 5-HT1A receptor and SERT (serotonin reuptake transporter) binding showed weak and inconsistent evidence of reduced binding in some areas. One meta-analysis of tryptophan depletion studies found no effect in most healthy volunteers. The SERT genes such as (5-HTTLPR) revealed no evidence of an association with depression or of an interaction between genotype, stress and depression. The main areas of serotonin research provided no consistent evidence of there being an association between serotonin and depression. Furthermore, it was shown that 5-HT synthesis in suicides in the brainstem is higher than healthy people [14].

We recently showed that there are no significant differences between plasma levels of TRP between HC and MMD (major monopolar depression). Plasma levels of TRP of HC (healthy controls) are higher in young men, young women, old men, and old women in this order. Serotonin (5-HT) levels are higher in MMD than HC. Plasma levels of 5-HIAA of HC are also higher than those of patients of MMD. Plasma levels of kynurenine (KYN) of healthy old men and old women are higher than those of young men and old women. Plasma levels of KYN are higher in old women and young men of MMD than those of HC [15] [16] [17].

We also studied about tryptophan metabolites levels in bipolar depression (BD). Plasma levels of TRP are not different between HC and patients of BDII (type II BD). Serotonin (5-HT) levels are higher in BDII than HC. Plasma levels of 5-HIAA of HC are higher than those of old women of BDII, but lower in young women of BDII. Plasma levels of kynurenine (KYN) of HC are not different from those of patients of BDII [18].

These results suggest that tryptophan metabolites such as serotonin or kynurenine may be produced by gut microbiota and may have nothing to do with biochemical changes in the brain in patients of depression.

2.2. Transport of Amino Acids from the Blood to the Brain

Amino acids are important substances that must be transported to tissues such as the brain and muscles. The process is considered insulin dependent. We want to know whether some important amino acids are transported differently from other amino acids. Especially tryptophan is important because it is converted to serotonin, melatonin or kynurenine. Results showed that Amino acids levels in the plasma were measured after the intakes of 50 grams of glucose or sucrose to young (18 - 22 years old) and old (≥ 50 years old) men. Total amino acids in the plasma decreased after the intakes of glucose. Total and non-essential amino ac-

ids in the plasma decreased significantly at 120 min after the intakes of glucose in young and old men, but only sucrose caused their decreases in both aged and young men. Both glucose and sucrose intakes decreased significantly the plasma levels of the total essential and branched amino acids in young and old men. Surprisingly, plasma levels of tryptophan did not decrease upon the administration of glucose but only slightly decreased upon the administration of sucrose in young men. It is shown that not all the amino acids were transported well into tissues upon the administration of glucose or sucrose. Tryptophan seems to be relatively resistant for insulin to facilitate the transportation into tissues [19] [20].

As to the trans port of tryptophan to the brain, Fernstrome, J.D. and Wurtman R.J. indicated that intakes of tryptophan in foods or injection of insulin increased levels of serotonin and tryptophan in the brain [21] [22]. 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 [22]. As indicated by them [21] [22], tryptophan is one of the most important substrates for such transmitters as serotonin and melatonin. Since serotonin is known to decrease depression, it is important to know about transport of tryptophan to the brain and tissues. Tryptophan is transported to the brain competitively with other amino acids [21] [22]. **Figure 1** shows the transport of tryptophan and other amino acids to the brain and tissues.

2.3. Transport of Tryptophan or Serotonin in Diseased Brain

The endothelial cells of blood vessels in the brain have the blood brain barrier (BBB) which prevents the movement or infusion of substances toxic or hazardous substances. The brain protects from damages caused by such substances. BBB prevents the entrance of useful or important substances for the activity such

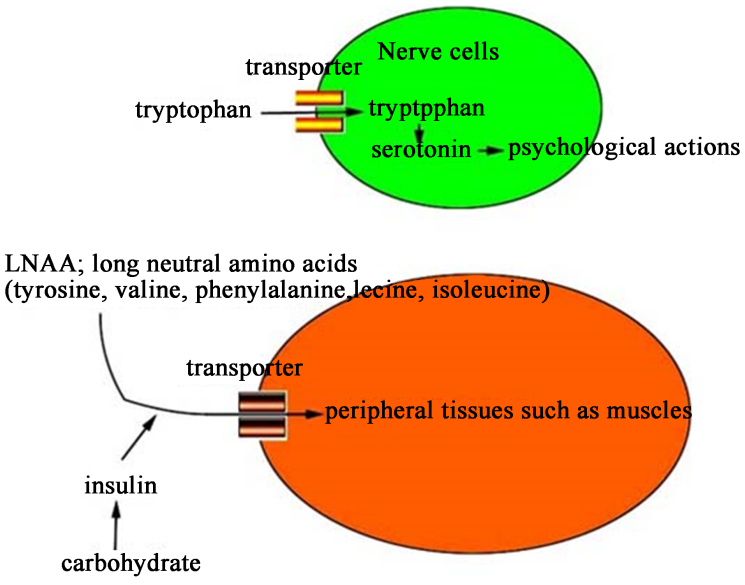


Figure 1. Transport of tryptophan or serotonin in deseased brain.

as drugs needed for mental health.

Recently, it was shown that the BBB was not functional and substances pass through the endothelial cells to the brain stroma.

Complex tight junctions (TJs) between brain ECs constituted by proteins of the claudin (Cldn) family and occludin (Ocln) block the paracellular pathway [23]. Whereas Cldn5 is also found in nonbarrier endothelium, Cldn3 is predominantly present in brain ECs with specific role in the establishment and maintenance of BBB TJ morphology [24] [25]. ECs rapidly lose their barrier and selective transport properties under pathological conditions in vivo and upon cultivation in vitro, indicating that the healthy brain provides inductive and maintenance signals for the BBB.

Blood-brain barrier and intestinal barrier leak in stress and mood disorders. The blood-brain barrier (BBB) is formed by endothelial cells, pericytes and astrocyte end-feet linking to the capillary wall (**Figure 2**). The restricted permeability between endothelial cells of the BBB is maintained by substances, such as TJ (tight junction) molecules and JAM (junction adhesion molecules). Depression, stress disorders, anxiety have all been associated with increased levels of circulating pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β. This caused breakdown of BBB.

As to tryptophan metabolites, especially tryptophan and serotonin, these molecules are produced by gut microbiota and pass through intestinal epithelia and

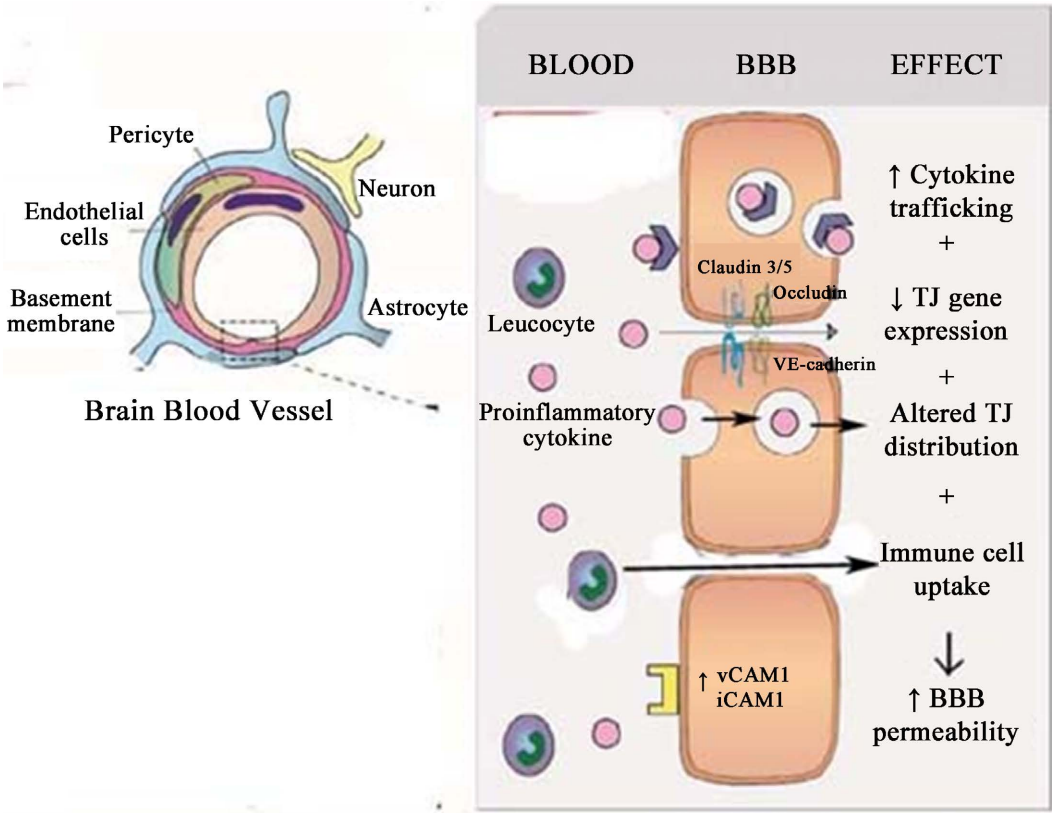


Figure 2. Permeability an its changes in many diseases.

enter the blood. In the brain, under disease conditions, they migrate into the brain.

Serotonin is transported by serotonin reuptake transporter [26], 5 HT4 receptor [27], and damaged BBB.

Taking the information into account, **Figure 3** is presented.

These data indicate that serotonin migrates into diseased brain so that the levels of serotonin in various mental diseases may be higher than in normal brain.

3. Importance of Tryptophan Metabolites in Health and Diseases

Dietary tryptophan is degraded by enzymes of digestive juice or microbiota.

There are three pathways in tryptophan metabolism (**Figure 4**).

Not much has been known about substances in indole pathway. Serotonin pathway is by far the most known pathway because serotonin (important for mental health or other physiological functions) and melatonin (important for a circadian rhythm) are involved.

Table 1 shows effects of tryptophan metabolites in diseases.

Many tryptophan metabolites play important roles in health and diseases which will be elucidated in details in the future.

Recently much attention has been paid to kynurenine because kynurenine inhibits T cell functions, thus causes tumor growth.

IDO, which converts tryptophan to kynurenine, was found to be broadly expressed in human tumors [28] [29] [30] and thought to bring about cancer development primarily by tumor immune escape [31] [32] [33] [34]. T cells are very sensitive to low tryptophan levels and cell death under tryptophan deprivation conditions [35]. Low tryptophan and kynurenine metabolites cause effector

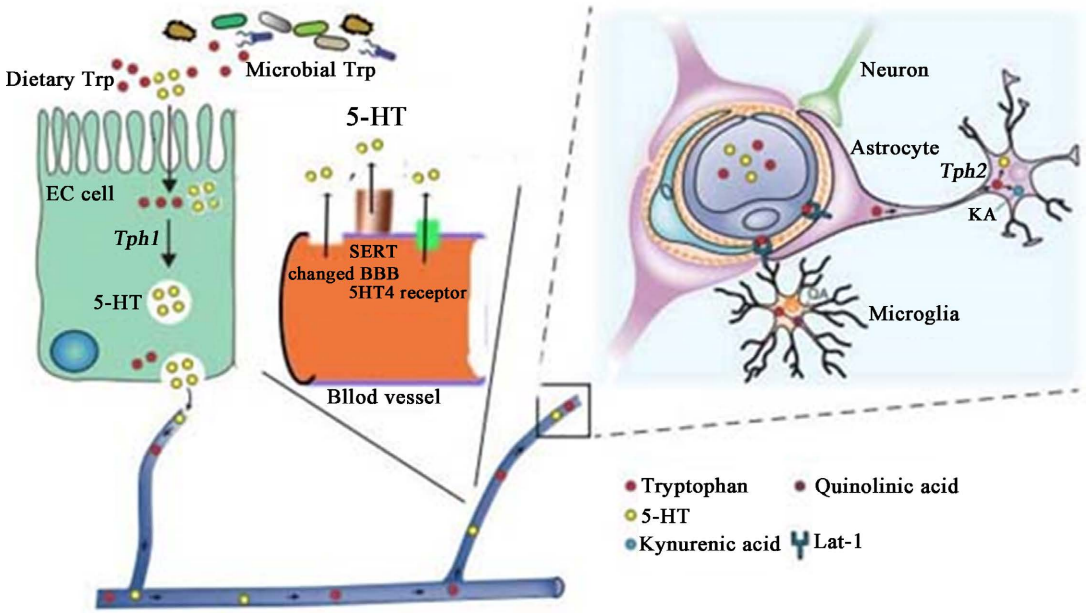


Figure 3. Transport of tryptophan and serotonin from the intestinal cavity to the brain.

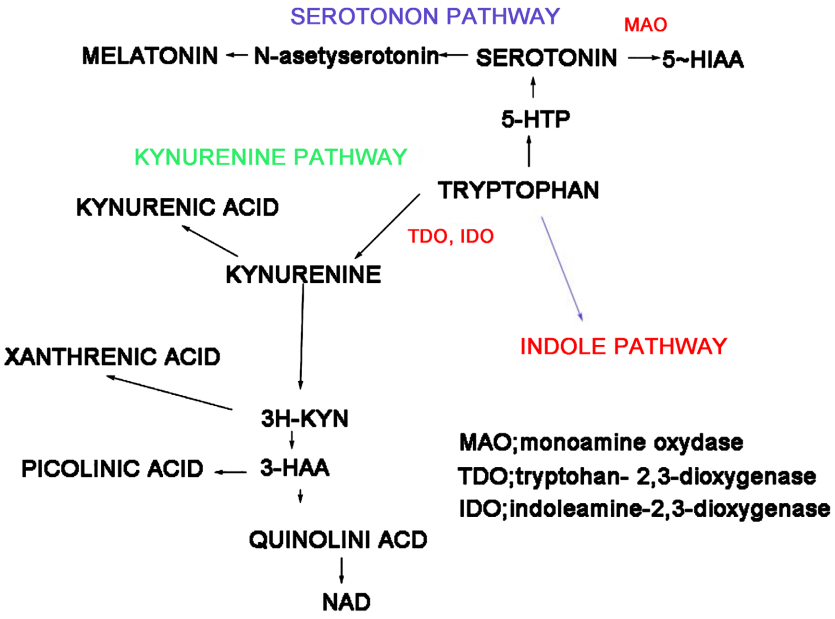


Figure 4. Pathways of tryptophan metabolism

Table 1. Effects of tryptophan metabolites.

Effects of tryptophan metabolites in diseases
Hypertention
Vascular disturbances
Impaired BBB integrity
Neuroinflamation
Neurotoxicity
Immunosuppression
Circadian disturbances
Impaired lymphatic flow

T cell anergy, decrease tumor immune cell infiltration and increase regulatory to effector T cell ratio [36] [37].

In the field of immunotherapy of cancer, roles of KYN pathway have been studied extensively. Some tumors express high levels of the PD-1 (programmed cell death-1)-biding ligand (PD-L1), and initial trials of anti-PD-1 therapy found that PD-L1 expression correlated well with response to therapy [38]. In order for checkpoint therapy more effective, IDO has been used. The rationale for the use of IDOI is that kynurenine is immunosuppressive, thus preventing effective T-cell attacks to tumors

To discuss more about functions of other metabolites may be beyond the scope of this review.

4. Autism

Autism is very controversial among many psychological disorders. Some people

affected by autism are completely disabled, while other people can enjoy high quality of life. Since autism has a wide range of symptoms, it is called autism spectrum disorder, or ASD. As many other psychiatric diseases, the number of people affected by ASD is increasing 10 fold increase in the past 40 years. Generally recognized symptoms of autism are difficulty socializing and repetitive behaviors. However some people ASD show excellent ability in math, music or art. Since some symptoms are not bothering daily lives, people do not recognize that they have symptoms of autism.

As to genetic components of autism, many genes have been identified to be involved in autism, but most of them are weak in detection of autism. Only 15% of genetic autism cases can be directly attributed to changes in genes [39].

40% to 50% of people with autism suffer from depression and anxiety, which rate is two to four times greater than that of general population [40]. Some 50% - 80% of people with ASD suffer from gut dysbiosis [41]. It has been shown that not only people with autism, but their close relatives have a high level of gastrointestinal symptoms.

Hereditary factors may be related to gut permeability.

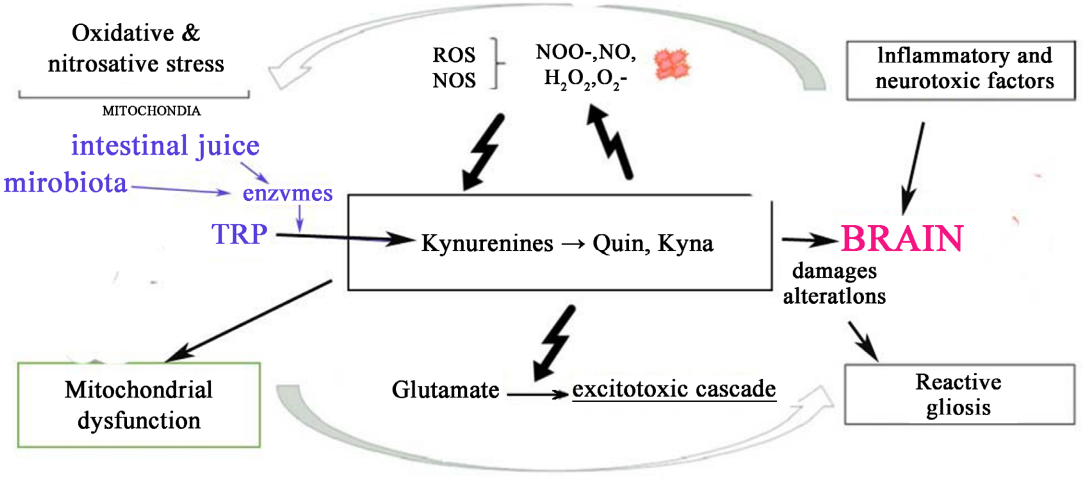
Numerous studies have demonstrated the relation between gut microbiota and ASD [40], I want discuss relationship between tryptophan metabolites, such as tryptophan or serotonin, in ASD.

Serotonin has existed as a signaling molecule across phylogeny [42]. More than 50 years ago whole blood serotonin levels have been shown in a subset of children with autism have been shown. Serotonin has been found to be important for social function, repetitive behavior and sensory development. Genetic linkage studies of whole blood serotonin levels and ASD risk indicate chromosomal region having the serotonin transporter (SERT) gen in males but not in females [43]. A knock-in mouse model of one of SERT genes variants show s increased serotonin clearance, increased serotonin receptor sensitivity, and repetitive behaviors. These results indicate importance of serotonin in many behaviors such as repetitive behavior in ASD.

What roles kynurenine pathways play in the brain of autistic patients?

Relationship between neuroinflammation and kynurenine pathway has attracted attention of researchers because increased frequency of autoimmune disease, allergies, infections have been shown in both autism patients and their parents [44] [45]. The persistence of immune inflammatory deregulation may result in mitochondrial dysfunction and oxidative stress. Chronic inflammation activate the kynurenine pathway which increase in neurotoxic metabolites and cytotoxicity, causing changes in the glutamate system.

As shown in **Figure 5** activated gut microbiota may degrades tryptophan leading to generation of kynurenine, further Quinolinic acid (Quin) or kynurenic acid (Kyna). Together with materials in oxidative and nitorosative stress ROS and NOS damages the functions of nerve cells and glia in the brain. The activation of kynurenine pathways may result the activation of glutamic nerves which may cause aberrant behaviors [45].



ROS; reactive oxygen species, NOS; nitric acid species.

Figure 5. Kynurenine pathway and effects on mitochondria and brain.

5. Diabetes Mellitus (DM)

There are two types diabetes, type 1 and 2. Compared to type 1 DM, where insulin deficiency is seen, type two shows a combination of insulin deficiency and insulin resistance. Various factors such as sedentary life work, visceral obesity, lack of exercise, poor dietary habits, and genetic factors contribute toward increasing incidences of type2 (T2) DM [46]. Obesity has been shown to increase T2DM by decreasing insulin sensitivity in adipose tissues, liver, skeletal muscle resulting in impaired β cell function [47].

Data from World Health Organization (WHO) shows that the number of people with diabetes increased from 108 million in 1980 to 422 million in 2014. The global prevalence among adults over 18 years of age increased from 4.7% in 1980 to 8.5% in 2014. It was noticed that between 2000 and 2016 there was a 5% increase in premature mortality from diabetes [48].

Depression occurs two to three times higher in people with diabetes mellitus, the majority of the cases remaining under-diagnosed. It is important to identify depression in diabetic patients and identify the possible ways to address both diseases. Possible common pathophysiological mechanisms are stress and inflammation, while emphasis was made on screening for depression in diabetic patients [49].

The microbiota of persons with obesity is highyly efficient in absorbing fats and sugars. This is seen in patients of DM.

We measured tryptophan metabolites of patients of T2DM [50].

Tryptophan metabolites in plasma samples from 20 male subjects with type 2 diabetes mellitus (T2DM) and 20 nondiabetic reference males were analyzed by ultra high performance liquid chromatography. Tryptophan levels in the diabetic subjects were significantly lower than those in nondiabetic subjects. The concentrations of 5-hydroxytryptophan, 5-hydroxyindoleacetic acid, kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and xanthurenic acid were

found to be higher in the diabetic patients. These results suggest that tryptophan was metabolized more in T2DM patients than in nondiabetic subjects. In the kynurenine pathway, the degradation of tryptophan seems to be accelerated in patients with higher plasma levels of tryptophan than in patients with lower levels of tryptophan. In the serotonin pathway, when the level of tryptophan is low, the conversion of serotonin to 5-hydroxyindoleacetic acid appears to be accelerated. In conclusion, our results suggest that T2DM patients may be exposed to stress constantly.

6. Heart Disease

Heart disease is closely linked depression. People with heart disease experience depression more than others. People who survive heart attacks feel depressed 6 times more than the general population. To have heart disease and depression increase the mortality rate more than twice.

Patients with affective disorder may have a higher rate of mortality from heart disease compared with normal controls; recent data on heart rate variability abnormalities in depressed patients may be a clue to the mechanism of the increased risk [51].

Gut microbiota seems to play a role in the health of heart. Methylamine N-oxide (TMAO) is known to cause atherosclerosis. When gut microbiomes digest meat, TMAO is produced. This may be caused increasing dangers of heart attacks

7. Conclusions

Tremendous amounts of research are going on about roles of microbiota in health and diseases. Microbiota seems t be causes of almost all of human diseases.

I am sure that more research will elucidate mechanisms of disease and therapeutic uses of microbiota and their metabolites.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Sender, R., Fuchs, S. and Milo, R. (2016) Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. *Cell*, **164**, 337-340. https://doi.org/10.1016/j.cell.2016.01.013

[2] Yoo, B.B. and Mazmanian, S.K. (2017) The Enteric Network: Interactions between the Immune and Nervous Systems of the Gut. *Immunity*, **46**, 910-926. https://doi.org/10.1016/j.immuni.2017.05.011

[3] Ruan, W., Engevik, M.A., Spinler, J.K. and Versalovic, J. (2020) Healthy Human Gastrointestinal Microbiome: Composition and Function after a Decade of Exploration. *Digestive Diseases and Sciences*, **65**, 695-705. https://doi.org/10.1007/s10620-020-06118-4

[4] Thursby, E. and Juge, N. (2017) Introduction to the Human Gut Microbiota. *Biochemical Journal*, **474**, 1823-1836. https://doi.org/10.1042/BCJ20160510

[5] Lloyd-Price, J., Arze, C., Ananthakrishnan, A.N., Schirmer, M., Avila-Pacheco, J., Poon, T.W., *et al.* (2019) Multi-Omics of the Gut Microbial Ecosystem in Inflammatory Bowel Diseases. *Nature*, **569**, 655-662. https://doi.org/10.1038/s41586-019-1237-9

[6] Li, L., Jing, Q., Yan, S., Liu, X., Sun, Y., Zhu, D., Wang, D., Hao, C. and Xue, D. (2021) Amadis: A Comprehensive Database for Association between Microbiota and Disease. *Frontiers in Physiology*, **12**, Article ID: 697059.

[7] Mitchell, A.J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C. and Meader, N. (2011) Prevalence of Depression, Anxiety, and Adjustment Disorder in Oncological, Haematological, and Palliative-Care Settings: A Meta-Analysis of 94 Interview-Based Studies. *The Lancet Oncology*, **12**, 160-174. https://doi.org/10.1016/S1470-2045(11)70002-X

[8] Jacobs, B.L., Fornal, C.A. and Wilkinson, L.O. (1990) Neurophysiological and Neurochemical Studies of Brain Serotonergic Neurons in Behaving Animals. *Annals of the New York Academy of Sciences*, **600**, 260-268. https://doi.org/10.1111/j.1749-6632.1990.tb16888.x

[9] Jacobs, B.L. and Fornal, C.A. (1991) Activity of Brain Serotonergic Neurons in the Behaving Animal. *Pharmacological Reviews*, **43**, 563-578.

[10] Delgado, P.L., Charney, D.S., Price, L.H., Aghajanian, G.K., Landis, H. and Heninger, G.R. (1990) Serotonin Function and the Mechanism of Antidepressant Action. Reversal of Antidepressant-Induced Remission by Rapid Depletion of Plasma Tryptophan. *Archives of General Psychiatry*, **47**, 411-418. https://doi.org/10.1001/archpsyc.1990.01810170011002

[11] Delgado, P.L., Price, L.H., Miller, H.L., Salomon, R.M., Aghajanian, G.K., Heninger, G.R. and Charney, D.S. (1994) Serotonin and the Neurobiology of Depression. Effects of Tryptophan Depletion in Drug-Free Depressed Patients. *Archives of General Psychiatry*, **51**, 865-784. https://doi.org/10.1001/archpsyc.1994.03950110025005

[12] Benkert, O., Szegedi, A. and Wetzel, H. (1996) Minimum Effective Dose for Antidepressants—An Obligatory Requirement for Antidepressant Drug Evaluation? *International Clinical Psychopharmacology*, **11**, 177-185. https://doi.org/10.1097/00004850-199609000-00004

[13] Moncrieff, J., Cooper, R.E., Stockmann, T., Amendola, S., Hengartner, M.P. and Horowitz, M.A. (2022) The Serotonin Theory of Depression: A Systematic Umbrella Review of the Evidence. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-022-01661-0

[14] Bach, H., Huang, Y.Y., Underwood, M.D., Dwork, A.J., Mann, J.J. and Arango, V. (2014) Elevated Serotonin and 5-HIAA in the Brainstem and Lower Serotonin Turnover in the Prefrontal Cortex of Suicides. *Synapse*, **68**, 127-130. https://doi.org/10.1002/syn.21695

[15] Tomioka, H., Masuda, J., Takada, A. and Iwanami, A. (2020) Differences of Plasma Levels of Tryptophan, Serotonin, 5-Hydroxyindole Acetic Acid, and Kynurenine between Healthy People and Patients of Major Monopolar Depression at Various Age and Gender. *Food and Nutrition Sciences*, **11**, 431-441. https://doi.org/10.4236/fns.2020.116031

[16] Tomioka, H., Masuda, J., Takada, A. and Iwanami, A. (2020) Comparison of Age and Gender Differences of Tryptophan Metabolites in Patients of Major Monopolar and Bipolar Depression. *Food and Nutrition Sciences*, **11**, 172-185.

https://doi.org/10.4236/fns.2020.113013

[17] Tomioka, H., Masuda, J., Takada, A. and Iwanami, A. (2020) Studies on Tryptophan Metabolites in Patients of Major Monopolar Depression. In: Vlachou, M., Ed., *Melatonin*, IntechOpen, London, 133-141. https://doi.org/10.5772/intechopen.91967

[18] Tomioka, H., Masuda, J., Takada, A. and Iwanami, A. (2020) Comparison of Plasma Levels of Tryptophan Metabolites between Healthy People and Patients of Bipolar Depression at Various Age and Gender. *Journal of Biomedical Science and Engineering*, **13**, 120-129. https://www.scirp.org/journal/jbise https://doi.org/10.4236/jbise.2020.136012

[19] Takada, A., Shimizu, F., Ishii, Y., Ogawa, M. and Takao, T. (2019) Plasma Levels of Amino Acids in Japanese Men and Their Changes after the Administration of Glucose and Sucrose. *Food and Nutrition Sciences*, **10**, 51-63. https://doi.org/10.4236/fns.2019.101005

[20] Ogawa, M., Shimizu, F., Ishii, Y., Takao, T. and Takada, A. (2023) Uniqueness of Tryptophan in the Transport System in the Brain and Peripheral Tissues. *Food and Nutrition Sciences*, **14**, 401-414. https://doi.org/10.4236/fns.2023.145026

[21] Fernstrom, J.D. and Wurtman, R.J. (1971) Brain Serotonin Content: Increase Following Ingestion of Carbohydrate Diet. *Science*, **174**, 1023-1025. https://doi.org/10.1126/science.174.4013.1023

[22] Fernstrom, J.D. and Wurtman, R.J. (1972) Brain Serotonin Content: Physiological Regulation by Plasma Neutral Amino Acids. *Science*, **178**, 414-416. https://doi.org/10.1126/science.178.4059.414

[23] Furuse, M. and Tsukita, S. (2006) Claudins in Occluding Junctions of Humans and Flies. *Trends in Cell Biology*, **16**, 181-188. https://doi.org/10.1016/j.tcb.2006.02.006

[24] Wolburg, H., Wolburg-Buchholz, K., Kraus, J., Rascher-Eggstein, G., Liebner, S., Hamm, F., Duffner, E.H., Grote, E.H., Risau, W. and Engelhardt, B. (2003) Localization of Claudin-3 in Tight Junctions of the Blood-Brain Barrier Is Selectively Lost during Experimental Autoimmune Encephalomyelitis and Human Glioblastoma Multiforme. *Acta Neuropathologica*, **105**, 586-592. https://doi.org/10.1007/s00401-003-0688-z

[25] Nitta, T., Hata, M., Gotoh, S., Seo, Y., Sasaki, H., Hashimoto, N., Furuse, M. and Tsukita, S. (2003) Size-Selective Loosening of the Blood-Brain Barrier in Claudin-5-Deficient Mice. *Journal of Cell Biology*, **161**, 653-660. https://doi.org/10.1083/jcb.200302070

[26] Young, L.W., Darios, E.S. and Watts, S.W. (2015) An Immunohistochemical Analysis of SERT in the Blood-Brain Barrier of the Male Rat Brain. *Histochemistry and Cell Biology*, **144**, 321-329. https://doi.org/10.1007/s00418-015-1343-1

[27] Becker, G., Da Silva, S., Sabo, A.N., Antal, M.C., Kemmel, V. and Monassier, L. (2021) Blood-Brain Barrier Permeability: Is 5-Hydroxytryptamine Receptor Type 4 a Game Changer? *Pharmaceutics*, **13**, Article No. 1856. https://doi.org/10.3390/pharmaceutics13111856

[28] Uyttenhove, C., Pilotte, L., Théate, I., Stroobant, V., Colau, D., Parmentier, N., Boon, T. and Van den Eynde, B.J. (2003) Evidence for a Tumoral Immune Resistance Mechanism Based on Tryptophan Degradation by Indoleamine 2,3-Dioxygenase. *Nature Medicine*, **9**, 1269-1274. https://doi.org/10.1038/nm934

[29] Godin-Ethier, J., Hanafi, L.A., Piccirillo, C.A. and Lapointe, R. (2011) Indoleamine 2,3-Dioxygenase Expression in Human Cancers: Clinical and Immunologic Perspectives. *Clinical Cancer Research*, **17**, 6985-6991.

https://doi.org/10.1158/1078-0432.CCR-11-1331

[30] Théate, I., van Baren, N., Pilotte, L., Moulin, P., Larrieu, P., Renauld, J.C., *et al.* (2015) Extensive Profiling of the Expression of the Indoleamine 2,3-Dioxygenase 1 Protein in Normal and Tumoral Human Tissues. *Cancer Immunology Research*, **3**, 161-172. https://doi.org/10.1158/2326-6066.CIR-14-0137

[31] Moon, Y.W., Hajjar, J., Hwu, P. and Naing, A. (2015) Targeting the Indoleamine 2,3-Dioxygenase Pathway in Cancer. *The Journal for ImmunoTherapy of Cancer*, **3**, Article No. 51. https://doi.org/10.1186/s40425-015-0094-9

[32] Bilir, C. and Sarisozen, C. (2017) Indoleamine 2,3-Dioxygenase (IDO): Only an Enzyme or a Checkpoint Controller? *Journal of Oncological Sciences*, **3**, 52-56. https://doi.org/10.1016/j.jons.2017.04.001

[33] Munn, D.H. and Mellor, A.L. (2013) Indoleamine 2,3-Dioxygenase and Metabolic Control of Immune Responses. *Trends in Immunology*, **34**, 137-143. https://doi.org/10.1016/j.it.2012.10.001

[34] Van Baren, N. and Van den Eynde, B.J. (2015) Tryptophan-Degrading Enzymes in Tumoral Immune Resistance. *Frontiers in Immunology*, **6**, Article No. 34. https://doi.org/10.3389/fimmu.2015.00034

[35] Platten, M., Von Knebel Doeberitz, N., Oezen, I., Wick, W. and Ochs, K. (2015) Cancer Immunotherapy by Targeting IDO1/TDO and Their Downstream Effectors. *Frontiers in Immunology*, **5**, Article No. 673. https://doi.org/10.3389/fimmu.2014.00673

[36] Munn, D.H., Shafizadeh, E., Attwood, J.T., Bondarev, I., Pashine, A. and Mellor, A.L. (1999) Inhibition of T Cell Proliferation by Macrophage Tryptophan Catabolism. *Journal of Experimental Medicine*, **189**, 1363-1372. https://doi.org/10.1084/jem.189.9.1363

[37] Johnson, T.S. and Munn, D.H. (2012) Host Indoleamine 2,3-Dioxygenase: Contribution to Systemic Acquired Tumor Tolerance. *Immunological Investigations*, **41**, 765-797. https://doi.org/10.3109/08820139.2012.689405

[38] Keenan, T.E., Burke, K.P. and Van Allen, E.M. (2019) Genomic Correlates of Response to Immune Checkpoint Blockade. *Nature Medicine*, **25**, 389-402. https://doi.org/10.1038/s41591-019-0382-x

[39] Abrahams, B.S. and Geschwind, D.H. (2008) Advances in Autism Genetics: On the Threshold of a New Neurobiology. *Nature Reviews Genetics*, **9**, 341-355. https://doi.org/10.1038/nrg2346

[40] Labus, J.S., Hubbard, C.S., Bueller, J., Ebrat, B., Tillisch, K., Chen, M., *et al.* (2013) Impaired Emotional Learning and Involvement of the Corticotropin-Releasing Factor Signaling System in Patients with Irritable Bowel Syndrome. *Gastroenterology*, **145**, 1253-1261.e1-3. https://doi.org/10.1053/j.gastro.2013.08.016

[41] Pandey, K.B. and Rizvi, S.I. (2009) Plant Polyphenols as Dietary Antioxidants in Human Health and Disease. *Oxidative Medicine and Cellular Longevity*, **2**, 270-278. https://doi.org/10.4161/oxim.2.5.9498

[42] Hay-Schmidt, A. (2000) The Evolution of the Serotonergic Nervous System. *Proceedings Biological Sciences/ The Royal Society*, **267**, 1071-1079. https://doi.org/10.1098/rspb.2000.1111

[43] Pullikan, J., Mazumder, A. and Grace, T. (2019) Role of Gut Microbiome in Autism Spectrum Disorders. In: Guest, P.C., Ed., *Reviews of Biomarker Studies in Psychiatric and Neurodegenerative Disorders*, Springer, Berlin, 253-269. https://doi.org/10.1007/978-3-030-05542-4_13

[44] Muller, C.L., Anacker, A.M.J. and Veenstra-Vander, W. (2016) The Serotonin Sys-

tem in Autism Spectrum Disorder: From Biomarker to Animal Models. *Journal of Neuroscience*, **321**, 24-41. https://doi.org/10.1016/j.neuroscience.2015.11.010

[45] Savino, R., Carotenuto, M., Polito, A.N., Di Noia, S., Albenzio, M., Scarinci, A., Ambrosi, A., Sessa, F., Tartaglia, N. and Messina, G. (2020) Analyzing the Potential Biological Determinants of Autism Spectrum Disorder: From Neuroinflammation to the Kynurenine Pathway. *Brain Sciences*, **10**, Article No. 631. https://doi.org/10.3390/brainsci10090631

[46] Aw, W. and Fukuda, S. (2018) Understanding the Role of the Gut Ecosystem in Diabetes Mellitus. *Journal of Diabetes Investigation*, **9**, 5-12. https://doi.org/10.1111/jdi.12673

[47] Aydin, Ö., Nieuwdorp, M. and Gerdes, V. (2018) The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes. *Current Diabetes Reports*, **18**, Article No. 55. https://doi.org/10.1007/s11892-018-1020-6

[48] Zahiu, D.M., Zăgrean, A.M. and Zăgrean, L. (2016) The Association between Diabetes Mellitus and Depression. *Journal of medicine and life*, **9**, 120-125.

[49] Matsuoka, K., Kato, K., Takao, T., Ogawa, M., Ishii, Y., Shimizu, F., Masuda, J. and Takada, A. (2017) Concentrations of Various Tryptophan Metabolites Are Higher in Patients with Diabetes Mellitus than in Healthy Aged Male Adults. *Diabetology International*, **8**, 69-75. https://doi.org/10.1007/s13340-016-0282-y

[50] Roose, S.P., Glassman, A.H. and Dalack, G.W. (1989) Depression, Heart Disease, and Tricyclic Antidepressants. *Journal of Clinical Psychiatry*, **50**, 12-16.

[51] Anderson, S.C., Crya, J.F. and Dinan, T. (2017) The Psychobiotic Revolution. National Geographic, Washington DC.