THE ROLE OF HUMAN AND MICROBIAL METABOLITES OF TRIPTOPHANE IN SEVERE DISEASES AND CRITICAL ILL (REVIEW)

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The growing interest to metabolites circulating in the blood is associated with the accumulation of factual material on the involvement of low-molecular compounds in the development of a number of serious diseases. This review reveals the effect of a whole class of chemical compounds — tryptophan metabolites — on various pathological processes. The following keywords were used to find the publications in the PubMed database for the last 10 years: names of natural indole compounds, methods for their detection, nosology of diseases and critical illness . The data are presented in sections, with the studies of tryptophan metabolites in a variety of disease groups, such as cancer, cardiovascular disease, kidney disease, bowel, mental disorders, atherosclerosis, etc. A particular attention is paid to the role of indole compounds that enter the systemic circulation as a result of microbial biotransformation of tryptophan, serotonin and other indole metabolites, which can be attributed to the "common metabolites" of humans and microbiota. The most interesting clinical studies are summarized in the tables and figures. A number of indole metabolites are considered as potential biomarkers. The authors of the review substantiate the metabolomic approach to the study of a number of oncological, septic, mental and other intractable diseases, which opens up new possibilities of influence on the pathological process by targeted regulation in the metabolome/microbiome system.

Keywords: *review, tryptophan, indole metabolites, uremia, colorectal cancer, atherosclerosis, intestinal inflammation, schizophrenia, depressive disorders, metabolic approach, biomarkers, critical ill.*

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INTRODUCTION

Low molecular weight metabolites are intermediate and final products of the main metabolic pathways, indicate the degree of gene expression, the functional activity of cellular enzymes, and other aspects, which enables to consider them as probable participants in pathological processes and often as candidate biomarkers of various conditions. Modern laboratory technologies have made it possible to establish that a number of classes of low molecular weight compounds in human blood are exclusively of microbial origin, that is, they are products of microbiota metabolism [1], and a number of other compounds have a common structure in both humans and bacteria, that is, they are common metabolites [2]. In a healthy organism, low molecular weight compounds represented by metabolites of normal intestinal microflora, are determined in the blood at relatively stable concentrations, which indicates the adequacy of biochemical processes aimed at maintaining homeostasis. Moreover, many metabolites are directly involved in the mechanisms of human vital activity. With an excessive intake of microbial metabolites from the intestine into the internal environment of the human body, they are neutralized in the liver with the formation of sulfates, conjugates, and other water-soluble components for excretion in the urine. In various diseases, the natural interactions of bacterial metabolites with the human body become distorted, and the normally harmonious integration of the endogenous metabolic pathways of an individual and microbiota is destroyed, which can acquire a pathological pattern in different organs and systems. Much attention in the literature is paid to such microbiota metabolites as short certain fatty acids (SCFA). It has been proven that they are an important energy substrate for enterocytes, ensure the functioning of the local immunological barrier, prevent the development of inflammation of the intestinal wall, etc. [3]. Microbial metabolites of aromatic structure, products of microbial biodegradation of the amino acid tyrosine are significant in the development of septic shock and multiple organ failure [4].

In a number of diseases, special attention should be paid to serotonin and other indole metabolites that have their own biological activity and enter the

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systemic circulation, including as a result of microbial biotransformation of tryptophan and other indole compounds. Tryptophan is one of the essential amino acids; the indole ring of tryptophan is synthesized in nature by microorganisms and plants, and cannot be synthesized by the human body. Tryptophan enters the human body with food, therefore it is believed that the tryptophan content can be regulated by diet [5]. However, it turned out that it is much more difficult to control the metabolism of tryptophan and its derivatives.

GENERAL INFORMATION ON TRYPTOPHAN METABOLISM

Tryptophan plays an important role in human metabolism. Tryptophan derivatives are formed in two main ways, which can be called indole and kynurenine (Fig. 1) [6]. The indole pathway of tryptophan conversion (conditionally divided into serotonin and microbial) leads to the formation of the neurotransmitter serotonin, the "sleep hormone" melatonin, as well as a number of other metabolites containing the indole ring, such as tryptamine, which undergoes further biotransformation with the formation of indoleacetic, indole propionic acid, indole, and indoxyl. The kynurenine pathway is accompanied by destruction of the indole ring of tryptophan and leads to the formation of L-kynurenine, kynurenine and quinolinic acids or the coenzyme nicotinamide adenine dinucleotide (NAD+). The formation of kynurenine consumes most of the incoming tryptophan, and only 5–10% is used for the formation of serotonin and melatonin [5]. Part of the tryptophan absorbed with food goes to bacterial degradation (4–6%), resulting in the formation of indole acids (for example, 3-indole propionic acid) and indole. As a result of serotonin metabolism, in particular, 5-hydroxyindoleacetic acid is formed [7].

Despite the growing interest in the clinical significance of indole compounds, in the international database of the human metabolome [8], the information on changes in blood concentrations of certain tryptophan metabolites in various diseases is rather scarce. The information is given mainly about schizophrenia and uremia, which are summarized in Table 1.

The ratio of kynurenine to tryptophan serum levels enables to assess the production and activity of the key enzyme indolamine 2,3-dioxygenase. This non-secreted intracellular enzyme is capable of inducing tryptophan catabolism with the formation of a number of products that have a significant effect on the immune system functions. Changes in the activity of indolamine-2,3-dioxygenase can be considered as an informative biomarker that has prognostic value in assessing the course and outcome for a number of diseases and conditions, such as sepsis, community-acquired

Fig. 1. Scheme of tryptophan metabolism: (1) tryptophan 5-hydroxylase; (2) tryptophan 2,3-dioxygenase; (3) aromatic-L-amino acid decarboxylase; (4) indolethylamine N-methyltransferase; (5) kynurenine formamidase; (6) kynurenine 3-monoxidase; (7) mitochondrial aldehyde dehydroxylase; (8) mitochondrial aldehyde dehydroxylase or aldehyde oxidase; (9) serotonin N-acetyltransferase; (10) acetylserotonin O-methyltransferase (Cited from [6]).

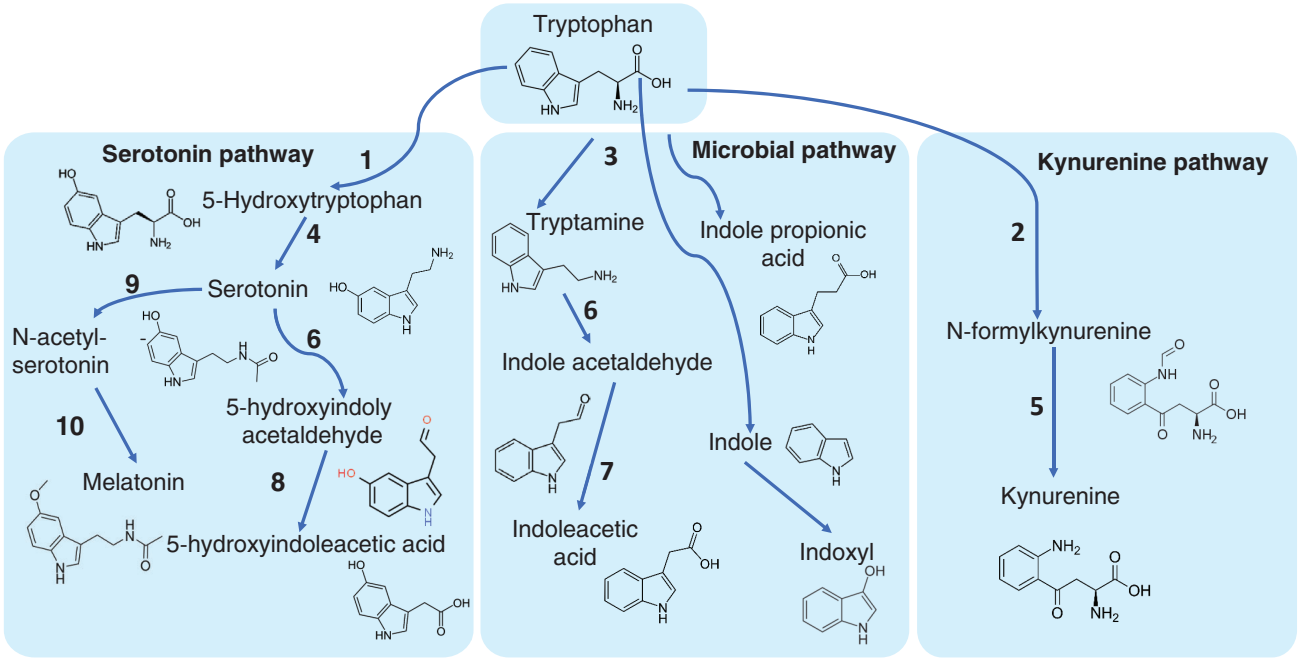

Table 1

Concentrations of indole compounds (tryptophan metabolites) in normal conditions and in various diseases according to the Humane Metabolom Data Base (HMDB) [8]

Indole compounds / tryptophan metabolites	Norm, blood, μM	Source	Disease	Abnormalities in diseases, blood, μM	Source
Tryptophan	54.5±9.7 81.3±3.36	[9] [10]	Schizophrenia Epilepsy	101±4.48 37.2 (34.3–40.1)	[10] [11]
Serotonin	0.85±0.077	[10]	Schizophrenia	0.61±0.096	[10]
Kynurenine	1.6±0.1 1.74±0.121	[12] [10]	Schizophrenia	2.35±0.162	[10]
Indoleacetic acid	2.85 0.05	[13] [14]	Uremia	13.7	[13]
Indole-3 propionic acid	0.481	[15]	No data	-	-
5-hydroxyindoleacetic acid	0.0516	[16]	Schizophrenia	0.0475	[16]
Indoxyl sulfate	2.49±1.36	[13]	Uremia	21.11±12.20	[13]

pneumonia, angina pectoris, acute myocardial infarction, etc. [17].

Impairment of tryptophan metabolism leads to the formation of immunoactive kynurenines, which affects the function of T cells and is associated with the development of autoimmune reactions [18]. Not only a decrease in the tryptophan level can be considered as the consequences, but also the production of immunoactive kynurenines which can act as ligands of the aryl hydrocarbon receptor [19]. Changes in the levels of metabolites of the kynurenine pathway are associated with mental disorders and dysfunctions of the gastrointestinal tract [20]. Thus, the regulation of the bioavailability of circulating tryptophan and its metabolites may depend on the composition of the intestinal microbiota, which in turn affects the state of immunoreactivity and influences the functioning of various organs and systems.

Cardiovascular diseases

The effects of serotonin in the body are determined by its interaction with various types of central and peripheral 5-hydroxytryptamine receptors (5-HT receptors). Currently, 7 main types of serotonin receptors and many subtypes have been identified, and the activation of these receptor structures can cause both a decrease and an increase in vascular tone, i.e. serotonin is a smooth muscle tone modulator. The serotonergic signaling system is involved in the regulation of some vital functions of the body and is the target of many pharmacologically active substances such as antidepressants, anxiolytics, nootropics, antiemetics, prokinetics, antimigraine and other groups of drugs. The possibilities of correcting vascular insufficiency using an analogue of endogenous serotonin, a Russian pharmacopoeial drug serotonin adipate ester, are being studied; and its stable normalizing effect on vascular tone has been demonstrated [21].

The negative effects of serotonin include tachycardia with preceding brief reflex bradycardia, increased atrial contractility, development of atrial arrhythmias [22] and pulmonary arterial hypertension through effects on smooth muscle contractility and vascular remodeling [23]. In addition, increased plasma serotonin levels have been identified in sudden infant death syndrome. In serum samples taken from children who died due to this syndrome (n = 61), serotonin levels were significantly higher than in other children (n = 15) who died from other causes (177 and 91 ng/ml, respectively, p = 0.014). When comparing the same groups of children, differences were also revealed in serum concentrations of 5-hydroxyindoleacetic acid (70 and 36 ng/ml, respectively, p = 0.09). The data obtained may have potential clinical significance, allowing an early assessment of the risk of sudden infant death syndrome [24].

But not only serotonin can be used as a marker indicating the cardiovascular system condition. The researchers used potentially temperature-related key inflammatory pathways measured by the levels of tryptophan, tryptophan catabolites (including kynurenines), and indolamine-2,3-dioxygenase activity in patients survived after cardiac arrest. It is known that controlled hypothermia in such patients improves significantly the neurological prognosis, but increases the risk of infectious complications. It was noted that a decrease in serum tryptophan levels and an increase in the activity of indolamine-2,3-dioxygenase in hypothermia are associated with an unfavorable outcome, probably due

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to an increase in sensitivity to infectious complications and sepsis under the influence of low temperatures, while in patients with a favorable outcome, a tendency towards higher values of tryptophan and low activity of indolamine-2,3-dioxygenase persisted [25].

The levels of tryptophan and indole derivatives also decrease significantly in cases of complicated atherosclerosis, correlating with the ankle-brachial index which is an indicator reflecting the state of blood circulation in the lower extremities. An inverse correlation was revealed with progressive atherosclerosis for indole, indole-3-propionic acid, and indole-3-aldehyde concentration, while a positive correlation was found for the ratio of kynurenine to tryptophan. In multivariate analysis, the kynurenine to tryptophan ratio was significantly associated with postoperative cardiac complications [26].

Bowel diseases

A distinctive aspect of metabolomic studies in gastroenterology is their focus on microbial metabolites. It has been revealed that the tryptophan metabolites 3-indoleacetic and indole propionic acids are predominantly of bacterial origin and are present in small concentrations not only in the serum, but also in the urine of healthy people. In patients with ulcerative colitis and celiac disease, a significant increase in 3-indoleacetic acid was found in the blood, which may be due to an increase in the metabolic activity of clostridia in relation to aromatic amino acids. The authors explain the revealed increase in 3-indole propionic acid in patients with celiac disease, compared with patients with ulcerative colitis and healthy volunteers, by a possible difference in the amount and metabolic activity of *Clostridium sporogenes* in patients of these two groups [27].

Another metabolite of the intestinal microbiota is 5-hydroxyindoleacetic acid (5-HIAA). Elevated (> 20 μM) urinary 5-HIAA levels are noted in appendicitis and gastroenteritis [28]. In these situations, the source of 5-HIAA is the vasospastic mediator 5-hydroxytryptamine which is released from enterochromaffin cells during inflammatory processes and is metabolized to the final product [29]. Some authors believe that if the 5-HIAA level is not increased, appendicitis can be ruled out with a high degree of probability [30]. The level of 5-HIAA has been shown to decrease in gangrenous appendicitis and in the case of the appendix perforation [31], while a number of authors note that a decrease in the concentration of 5-HIAA may be a warning sign of perforation [32]. However, other authors do not support this idea and believe that the diagnostic value in acute appendicitis is not so great, and cite comparison of 5-HIAA with other blood indicators of inflammation (the level of leukocytes/neutrophils and C-reactive protein) [33].

Colorectal and other cancers

In the pathogenesis of oncological diseases, there are disorders of various metabolic pathways, namely glycolysis, tricarboxylic acid cycle, urea, arginine, proline, fatty acid metabolism, as well as metabolic disorders associated with intestinal microbiota. When studying the diagnostic significance and correlation with the diagnosis, blood serum is more often the object of research. For example, in patients diagnosed with a colorectal cancer, 249 serum metabolites were analyzed, and only 72 of them differed significantly when compared with those of healthy volunteers, and 5 of them were tryptophan metabolites, namely 5-hydroxytryptamine, tryptophan, indoxyl sulfate, indoxyl, N-acetyl-5-hydroxytryptamine, and tended to decrease in concentration compared to healthy subjects [34]. The subject of research can also be metabolites of other biological substrates, for example, intestinal contents, however the authors note that these data are more difficult to interpret, since the quantitative and qualitative composition of fecal metabolites is more variable [35]. In urine, the tryptophan metabolite 5-hydroxyindoleacetic acid is regarded as a good biomarker for early diagnostics of small intestine tumors [36]. In colorectal cancer, the decrease in indole propionic acid in the intestinal contents is in a strong correlation with the growth of actinobacteria in the intestinal microbiota [37].

Metabolomics analysis can be informative not only for early diagnostics, but also for monitoring the oncological process. Depending on the colorectal cancer stage, the blood serum levels of metabolites change. Thus, for benzoic acid, the strongest statistically significant inverse correlation with the stage of the disease was revealed. It was revealed that the level of 3-indoleacetic acid also decreased with the disease progression [38].

In patients diagnosed with leukoplakia and oral cancer, saliva was used as the test material, from which five prognostically significant metabolites were isolated, namely c-aminobutyric acid, phenylalanine, valine, n-eicosanoic and lactic acids. Among the metabolites, a significant increase in the concentration of 3-indole propionic acid was noted [39]. Table 2 presents the changes over time of tryptophan metabolites in cancerous diseases.

Table 2

Changes in tryptophan metabolites in gastrointestinal cancerous diseases.

Substance	Diagnosis	Change	Source
Indoxyl sulfate	Colorectal cancer	↓	[34]
Tryptophan	Colorectal cancer	↓	
3-Indole propionic acid	Leukoplakia and oral cancer	↑	[39]
3-Indoleacetic acid	Colorectal cancer	↓	[38]
Tyrosine			
Tryptophan			
3-Indoxyl sulfate			

Note. ↓/↑ — decrease/increase in the indicator.

Critical conditions, trauma, sepsis

The need to develop an individual approach to the correction of metabolism leading to more effective treatment of critically ill patients is being discussed [40]. In patients with community-acquired pneumonia with an adverse clinical outcome, the ratios of the concentrations of tryptophan to serotonin and tryptophan to kynurenine were studied in correlation with C-reactive protein, procalcitonin, a simplified scale for assessing multiple organ failure qSOFA (quick Sequential (Sepsis-related) Organ Failure Assessment) and the scale for assessing the severity of pneumonia, but came to the conclusion that the data on significance of changes in indolamine-2,3-dioxygenase is still insufficient for predicting the outcome [41].

The study of the serum metabolomic profile in traumatic brain injury revealed a decrease in the concentration of indole-3-propanoic acid in the blood serum [42], while the level of another indole derivative of serotonin, namely melatonin, increased in the blood after traumatic brain injury in children, which is possibly related to the response to oxidative stress or inflammation caused by trauma [43]. Blood levels of melatonin in subsequently deceased patients with severe traumatic brain injury were higher than in survivors and correlated with levels of malondialdehyde (an indicator of lipid peroxidation) and total antioxidant activity indicating the severity of brain damage [44]. The correlation of increased concentrations of melatonin in the blood with the mortality rate in septic patients was also previously established [45]. However, experimental work on mice has shown that melatonin promotes the removal of damaged mitochondria using autophagy, which suppresses traumatic brain injury-induced inflammation and weakens the secretion of inflammatory cytokines [46]. The intake of exogenous melatonin after traumatic brain injury improved sleep parameters and had no side effects [47]; in patients in the resuscitation and intensive care unit, it increased the total antioxidant activity of the blood due to its immunomodulatory and antioxidant properties [48].

Renal dysfunction, uremia

Colonic microorganisms produce compounds that are normally excreted by the kidneys. Dysfunction of the kidneys leads to the accumulation of certain compounds in the patient's body, which have a toxic effect on vital organs; therefore, they are often called potential uremic toxins [49]. Uremic toxins include phenylacetyl-1-glutamine, 5-hydroxyindole, indoxyl glucuronide, p-cresol sulfate, and indoxyl sulfate. Some of them, such as indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide, are involved in the destruction of the intestinal epithelial barrier, thereby facilitating the entry of toxins into the bloodstream. Part of tryptophan under the action of tryptophanase, an enzyme of the intestinal microbiota, in particular *Escherichia coli*, is converted into indole. Further, part of the indole is removed along with the feces, and part is absorbed and enters the liver through the blood flow, where, after oxidation and sulfatation, converts into indoxyl sulfate. In chronic kidney disease, the concentration of indoxyl sulfate in the blood gradually increases [50]. The entry of uremic toxins into the bloodstream affects the state of the cardiovascular system. Thus, in cardiovascular diseases, an increase in the blood concentration of 3-indoleacetic acid above 3.73 μM/l correlates with a higher mortality rate [51]. In an experiment on rats, it was revealed that indole and indoxyl cause significant hemodynamic changes, the effect of which is leveled through the central and peripheral mechanisms with the participation of serotonin receptors [52].

One of the main methods of combating chronic renal failure is hemodialysis to reduce the amount of

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toxins in the blood. To assess the efficiency, a metabolomic analysis of serum is performed before and after the hemodialysis procedure, with assessment of the content of such uremic toxins as indoxyl sulfate, 3-indoleacetic acid, and hippuric acid [53].

Diseases of the central nervous system and depressive disorders

The metabolic activity of the intestinal microbiome can influence the development of depressive disorder [54]. The effect of tryptophan metabolites on human mental health can be assessed by laboratory methods by their level in the urine of patients. For example, severe depressive disorder is characterized by decreased levels of trimethylamine oxide, indoxyl sulfate, m-hydroxyphenyl acetate, 3-hydroxyphenylacetic acid, as well as increased levels of p-hydroxyphenyl acetate, isobutyrate, palmitic acid, lactate, and glycine. In moderate depressive disorder, only two compounds have been found, isobutyrate and trimethylamine oxide. In schizophrenia, a kynurenine pathway disorder of tryptophan metabolism is registered. namely a decrease in the concentration of kynurenine acid is noted in the blood plasma, and after therapy, its level is normalized [55]. To assess the probability of acute cerebral dysfunction, the evaluation of prognostic potential of plasma serotonin concentration or acetylcholinesterase activity upon admission to the intensive care unit is indicated [56]. A decrease in the concentration of platelet serotonin is a differential sign of schizophrenia with symptoms of depression [57]. In women with postpartum depression, a decrease in the level of neurotransmitters (serotonin, dopamine, norepinephrine) is noted, but, according to the authors, the development of depression in these patients may be due to other causes not associated with childbirth [58].

In patients with multiple sclerosis, molecular mechanisms have been identified, through which the microbiota regulates the immune response, namely, tryptophan is metabolized by the intestinal microbiota into agonists of the aromatic hydrocarbon receptor, which influence astrocytes and limit inflammation in the central nervous system [59].

INFLUENCE OF MICROBIOTA ON INTESTINAL PERMEABILITY

It is noteworthy that the biodegradation products of the aromatic amino acids tyrosine, phenylalanine, and tryptophan regulate directly the degree of intestinal permeability. In particular, indole propionic acid, a metabolic product of *Clostridium sporogenes*, increases the permeability of the intestinal barrier in case of a decrease in concentration in the systemic circulation, with subsequent disorders in the human immune system [1, 60]. However, even an acute shortage of tryptophan itself does not impair intestinal permeability and does not affect significantly the levels of metabolites in the blood [61].

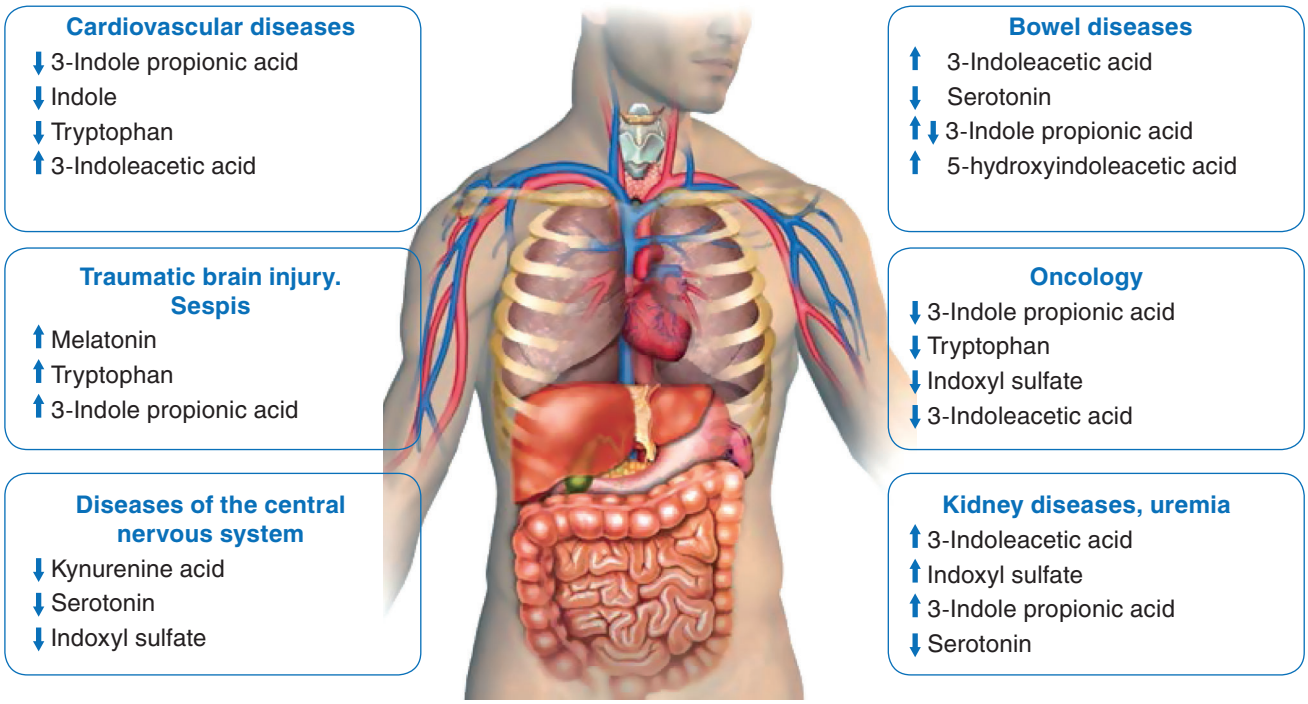
Correction of the metabolic activity of the intestinal microbiota is proposed to be used to restore mental health. The term “psychobiotics” appeared not so long ago, and distinguishes a group of probiotics that have the ability to correct mental state [62]. A number of experimental studies demonstrate the efficiency of taking various strains of microorganisms (*Lactobacillus helveticus*, *Lactobacillus casei*, *Bifidobacterium longum*, etc.) to reduce stress, anxiety, and improve the emotional state [63]. Major placebo-controlled studies are required to assess the psychobiotic potential of various strains, as well as their efficacy and safety in humans.

The aryl hydrocarbon receptor (AHR) is a major regulator of immune function in the gastrointestinal tract. The resident microbiota is able to influence the AHR-dependent signaling pathways through the production of a variety of biologically active molecules that act as agonists of the aryl hydrocarbon receptor, such as indole or indole-3-aldehyde [64]. Indole-pyroracemic acid is considered a precursor of indole-3-acetaldehyde, indole-3-aldehyde, and indole-3-acetic acid, agonists of the aryl hydrocarbon receptor. The ability of this acid to reduce inflammation by activating the work of the AHR receptor has been demonstrated in a mouse model of colitis [65]. In chronic kidney disease, uremic toxins indoxyl sulfate (IS) and indole-3-acetic acid of microbial origin may be involved in the inflammatory signaling pathway [66]. Thus, indoleacetic acid affects the function of the aryl carbon receptor, which leads to the expression of tissue factor in endothelial cells and increases the risk of thrombosis [67].

METHODS FOR DETERMINING INDOLE COMPOUNDS

The main methods of metabolic screening analysis are gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry [68, 69]; nuclear magnetic resonance spectroscopy and other analytical methods are also used [70]. Methods of sample preparation for analysis play an important role in the interpretation of the results [71–74]. The components analyzed are extracted by the method of liquid-liquid extraction using diethyl ether or by the method of solid-phase extraction [75, 76].

Fig. 2. The main changes characteristic of tryptophan and its metabolites in severe diseases and critical conditions.



Mass spectrometry techniques are not widely used in clinical laboratory practice. A number of indole compounds (serotonin, melatonin, 5-hydroxyindoleacetic acid, trimethylamine oxide) can be determined by enzyme-linked immunosorbent assay, however, to date, the test systems are generally validated only for scientific research.

CONCLUSION

Thus, a number of indole compounds are found in the systemic circulation, which are significant in the pathogenesis and diagnostics of a number of diseases. The main regularities of changes in the blood levels of indole compounds presented in the review are summarized in Fig. 2. It is important that most of them are metabolites of the microbiota. Purposeful regulation in the metabolome/microbiome system opens up new perspectives for therapeutic effects on the pathological process through the human microbiota. Until now, the evidence base is not so great, and research in this field continues and opens up a huge space for further scientific research.

ADDITIONAL INFORMATION

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AUTHOR CONTRIBUTIONS

M.L. Getsina, E.A. Chernevskaya processed the material and wrote the text; M.L. Getsina collected and processed the material; E.A. Chernevskaya, N.V. Beloborodova edited the text; N.V. Beloborodova was responsible for the integrity of all parts of the article. All authors made a significant contribution to the preparation of the article, read and approved the final version before its publication.

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