EXPERIMENTAL STUDIES

THE EFFECT OF FECAL MICROBIOTA TRANSPLANTATION ON LEVELS OF TRYPTOPHAN METABOLITES IN THE INTESTINE AND SERUM OF GNOTOBIOTIC MICE

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Gut microbiota is one of the key suppliers of tryptophan metabolites, which perform various functions in the host organism, including their role as signaling molecules. Fecal microbiota transplantation (FMT) is widely used as a method for determining the contribution of microorganisms to the content of various metabolites in the holoorganism. In this regard, the aim of our study was to investigate the effect of FMT on the level of tryptophan metabolites in feces and blood in gnotobiotic mice. It was found that both before and after FMT, indole-3-lactate and quinolinic acid were the dominant tryptophan metabolites in the intestine. FMT increased the content of both indoles (indole-3-acetate, indole-3-acrylate, indole-3-butyrate, indole-3-lactate) and kynurenines (anthranilic and xanthurenic acids) in the intestine. In serum of mice after FMT, indole metabolites (indole-3-butyrate, indole-3-carboxaldehyde, indole-3-lactate, indole-3-propionate) predominantly increased; however, tryptamine and xanthurenic acid also demonstrated a clear increase. The use of FMT demonstrates that the intestinal microbiota is a source of not only indole derivatives of tryptophan, but also metabolites of the kynurenine pathway.

Keywords: intestinal microbiota; tryptophan catabolites; fecal microbiota transplantation; indoles; kynurenines

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INTRODUCTION

Epithelial tissues (skin, reproductive, respiratory, and gastrointestinal tracts) play a major role in creation of barriers for the formation of a dynamic external environment required for maintenance of homeostasis of the body as a whole [1]. During the last decade, sufficient knowledge has been accumulated that the colonization of various epithelial tissues of the host organism by microbiota is important both for its physiology and for the development of various diseases of the holoorganism [2]. Such influence is mediated to a large extent by various microbial metabolites and factors, rather than microbiota itself [3]. These microbial substances are commonly referred to as “postbiotics” [4]. The metabolism of postbiotics makes a significant contribution to the immune training of the host and the provocation of its autoaggression [5], as well as to the regulation of eating behavior [6] and the formation of orosensory preferences. In addition, these substances are involved in the development of metabolic diseases such as obesity [7], insulin resistance, and diabetes mellitus [8]. A number of studies have shown the leading role of microbiotic metabolites in the development of cancer or, conversely, in the prevention of tumor growth [9, 10].

Microbial metabolism of food components provides the host organism with nutrients, vitamins, short-chain fatty acids, secondary and tertiary bile acids, essential amino acids, and their derivatives [1]. Among the amino acids, tryptophan and its metabolites play an important role in the homeostasis of the holoorganism [11]. Tryptophan is an essential amino acid. It is believed that only a small portion of exogenous tryptophan serves as a substrate for protein synthesis, and the remaining tryptophan is metabolized by the cells of the macroorganism (kynurenine and serotonin pathways) or intestinal microorganisms (indole pathway) [12]. Deviations in the metabolism of this amino acid characterize the dysbiotic phenotype of the microbiota, and this is often accompanied by the development of inflammatory bowel diseases [13], metabolic disorders [7], tumor development [14], progression of atherosclerosis [15–17], etc. Tryptophan metabolism in the intestine includes its direct conversion by intestinal microorganisms to indole and its derivatives, which may act as ligands for aryl hydrocarbon receptors (AhR) [18]. These receptors are directly activated by food molecules and xenobiotics. AhR signaling is considered as a key component of the immune response at epithelial barrier sites, which is important for intestinal homeostasis, epithelial

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renewal, barrier integrity, and many types of immune cells, such as intraepithelial lymphocytes, Th17 cells, innate lymphoid cells, macrophages, etc. [19].

It has been previously shown that although kynurenine production in the intestine of gnotobiotic mice was reduced, indole-3-acetate production was normal; at the same time sterile animals were deficient in AhR tryptophan ligands [20]. In this context, it is not entirely clear, why indole-3-acetate is not reduced in sterile animals if the microbiota is the main supplier of indole metabolites. It is assumed that intestinal inflammation and impaired intestinal permeability develop due to deficiency of the AhR tryptophan ligands [17]. Potentially, fecal microbiota transplantation (FMT) can provide normal levels of tryptophan metabolites in the intestine, and this may be promising in the treatment of intestinal inflammatory diseases. FMT is a method of transporting fecal microbiota from a healthy donor to a recipient through a nasogastric tube, colonoscope, enema, capsule, or their combinations to restore the normal general condition of the body. FMT has been widely recognized as an approach to determining the causal role of the microbiome in disease models associated with intestinal dysbiosis, as well as a new therapeutic method that positively affects the course of various diseases [21]. FMT has a significant impact on the metabolic activity of the intestinal microbiota and the synthesis of alkylresorcinols [22].

However, it remains unclear how FMT affects the content of tryptophan and its metabolites in the intestine and in the blood serum of recipients under normal conditions. Therefore, the aim of our study was to investigate the effect of FMT on the content of tryptophan metabolism metabolites in gnotobiotic mice in the intestine and serum.

MATERIALS AND METHODS

The study was conducted at the National Medical Research Centre for Oncology (NMRCO).

Animals

Balb/c germ-free mice with germ-free status were obtained from Taconic Biosciences (USA). The animals weighed 18–28 g and were 8–10 weeks old. The acclimatization period of the mice was at least 4 days. The animals were kept in the SPF zone of the vivarium in Iso cages for mice in groups of 5 animals per cage at 20–23°C, humidity of 35–75%, with purified air circulation of 10–15 l/h. Rehofix MK 2000 bedding for laboratory animals (JRS, Germany) was used. The animals received complete granulated extruded feed (Laboratorkorm, Russia) and clean drinking water *ad libitum*. The bedding, chow, and water bottles were autoclaved using a DGM AND 300 autoclave (DGM Global Trading AG, Switzerland). Before the experiment, the animals were clinically examined and weighed. Each animal was assigned an individual identification number by attaching an ear tag.

Two groups of gnotobiotic mice were studied. Mice of the control group (n=10) received 0.9% NaCl solution intragastrically. Mice of the experimental group (n=10) were intragastrically administered fecal microbiota from a conditionally healthy 48-year-old female donor who had not taken antibiotics, pro-, pre- or symbiotic drugs in the last 3 months.

Euthanasia was performed by decapitation on 14 day after the last FMT procedure.

Preparation of Fecal Microbiota for Transplantation to Experimental Animals

Donor fecal samples (1 g) were frozen at -70°C. To prepare fecal samples for FMT a frozen donor fecal sample was chipped and homogenized using an ultrasonic homogenizer in saline (0.1 g feces to 1000 μl saline). The homogenate was filtered through an ashless paper filter with medium filtration speed, and the filtrate was used for subsequent administration to mice.

Routes and Modes of Fecal Microbiota Administration

The fecal microbiota was administered intragastrically. Animals of the experimental group were intragastrically administered 100 μl of filtered donor fecal microbiota suspension three times (100 μl/day). Mice in the control group were administered 100 μl of 0.9% saline three times (100 μl/day).

Determination of Tryptophan and its Metabolites in the Intestine and Serum

Standard solutions for tryptophan metabolites profiling, as well as formic acid, bovine serum albumin (BSA), sodium chloride, 6-hydroxynicotinic acid, 3-indoleacrylic acid, and ascorbic acid were obtained from Sigma-Aldrich (USA). Acetonitrile was obtained from Chromasolv®, Sigma-Aldrich Chemie GmbH (Switzerland).

Quantitative analysis of tryptophan metabolites in the blood serum and intestine was performed by high-performance liquid chromatography with mass spectrometric (MS) detection (HPLC-MS/MS). The analysis was performed using an Agilent 1200 liquid chromatograph (Agilent Inc., USA) with an automatic sample injection system, column thermostat, and degasser. Chromatographic separation was performed using a Discovery PFP HS F5 analytical column (2.1×150 mm; 3 μm, Supelco Inc., USA). The gradient was formed by mobile phase A (0.1% formic acid solution in deionized water) and mobile phase B (100% acetonitrile for chromatography). The gradient was formed as follows: from 1% B to 10% in 4 min, then to 90% B by the 9th min of analysis. The flow rate of the mobile phase was 0.40 ml/min.

For detection, an Agilent 6460 triple quadrupole MS detector (Agilent Inc.), MRM and electrospray ionization were used. The parent and daughter ions specific for each compound for the MRM mode, as well as the ionization and dissociation parameters, were optimized using the standards of the studied metabolites. The resulting signal was processed using the Masshunter software (Agilent Inc.).

Metabolite concentrations were calculated using an internal standard (2-hydroxynicotinic acid (Sigma-Aldrich)). Standard solutions of the studied compounds were prepared using an artificial matrix containing 2% bovine serum albumin and 0.9% sodium chloride. The studied metabolites were added to the matrix and processed according to the analytical procedure [23].

To prepare the serum samples, an internal standard (2-hydroxynicotinic acid) was added to 100 μl of blood. Proteins were precipitated with acetonitrile, the supernatant was evaporated and redissolved in 10% methanol in water with the addition of ascorbic acid to prevent oxidation of the analytes.

To prepare the stool sample, it was lyophilized to a dry residue; then a sample of about 5 mg was extracted with 50% methanol in water with the addition of an internal standard and ascorbic acid. After centrifugation, the sample was analyzed by HPLC-MS/MS.

The method was validated for selectivity, linearity, accuracy, reproducibility, matrix effect, and analyte stability. Validation was carried out in accordance with the FDA bioanalytical method validation guide [24].

Statistical Analysis Methods

The accumulation, adjustment, and systematization of the initial information of were carried out in Microsoft Office Excel 2021 spreadsheets. Statistical processing of the data obtained was carried out using MedCalc® Statistical Software v. 22.013 (MedCalc Software Ltd., Belgium). All obtained data sets were tested for normal distribution using the Shapiro-Wilk test. Due to the prevalence of abnormal distribution, nonparametric analysis methods were used. Comparative analysis was performed using the Kruskal-Wallis test. When rejecting the null hypothesis ($p<0.05$), a post-hoc test was automatically performed using the Conover method for pairwise comparison of groups. The median (Me) and the interquartile range ([Q1; Q3]) were used to describe the obtained data.

RESULTS

The tryptophan content in the feces of the control gnotobiotic animals was slightly and statistically insignificantly (11%) higher than in the group of animals treated with FMT. In the intestinal contents of control mice, minor catabolites of tryptophan metabolism (up to 1 nmol/g) were represented by both derivatives of the kynurenine pathway and indole metabolites. These included: anthranilic acid, indole-3-carboxaldehyde, indole-3-butyrate, indole-3-propionate, xanthurenic acid, hydroxyindole acetate, indole-3-acetate, and kynurenine. Among indole metabolites, indole-3-lactate and indole dominated in the control gnotobiotic control group mice, while among kynurenines quinolinic acid prevailed (Fig. 1).

It should be noted that after FMT in mice, indole-3-lactate also remained the dominant metabolite of indole metabolism in the intestine, and quinolinic acid prevailed among kynurenines. The concentrations of both metabolites demonstrated a statistically significant increase. For example, the intestinal quinolinic acid concentration increased by 47%, and the content of indole-3-lactate increased much higher (by 6.5 times). At the same time, after FMT indole-3-acetate and xanthurenic acid were no longer minor metabolites. The content of indole-3-acetate after FMT increased by 7.1 times, while for xanthurenic acid demonstrated almost a 10-fold increase. Also, the following metabolites demonstrated a statistically significant increase in comparison with control mice: anthranilic acid (2.4-fold increase), indole-3-acrylate (1.45-fold increase) and indole-3-butyrate (2.2-fold increase) (Fig. 1).

After FMT, changes in the content of tryptophan metabolites occurred not only in the intestinal contents, but also in serum of animals (Fig. 2). The blood levels of indole-3-butyrate, indole-3-carboxaldehyde, indole-3-lactate, indole-3-propionate, tryptamine, and xanthurenic acid demonstrated a statistically significant increase.

Since after FMT, a statistically significant increase in the content of indole-3-butyrate, indole-3-lactate, and xanthurenic acid has been detected in the intestine (Fig. 1) this suggests that the intestinal microbiota may be considered as the main source of these tryptophan metabolites in serum.

DISCUSSION

The presence of indole tryptophan metabolites in the intestine of gnotobiotic mice may be due to food intake, production by microbiota of other localizations, as well as partial contamination of the intestine and production by host cells [20]. An increase in the content of metabolites of both the kynurenine and indole tryptophan catabolism pathways in feces reflects the stimulation of tryptophan catabolism after FMT. At the same time, the predominance of indole-3-lactate and quinolinic acid remains. For the human body, the dominant indole derivatives in feces are indole, indole-3-acetate, and indole-3-propionate [25]. The high content of indole-3-lactate in both the control

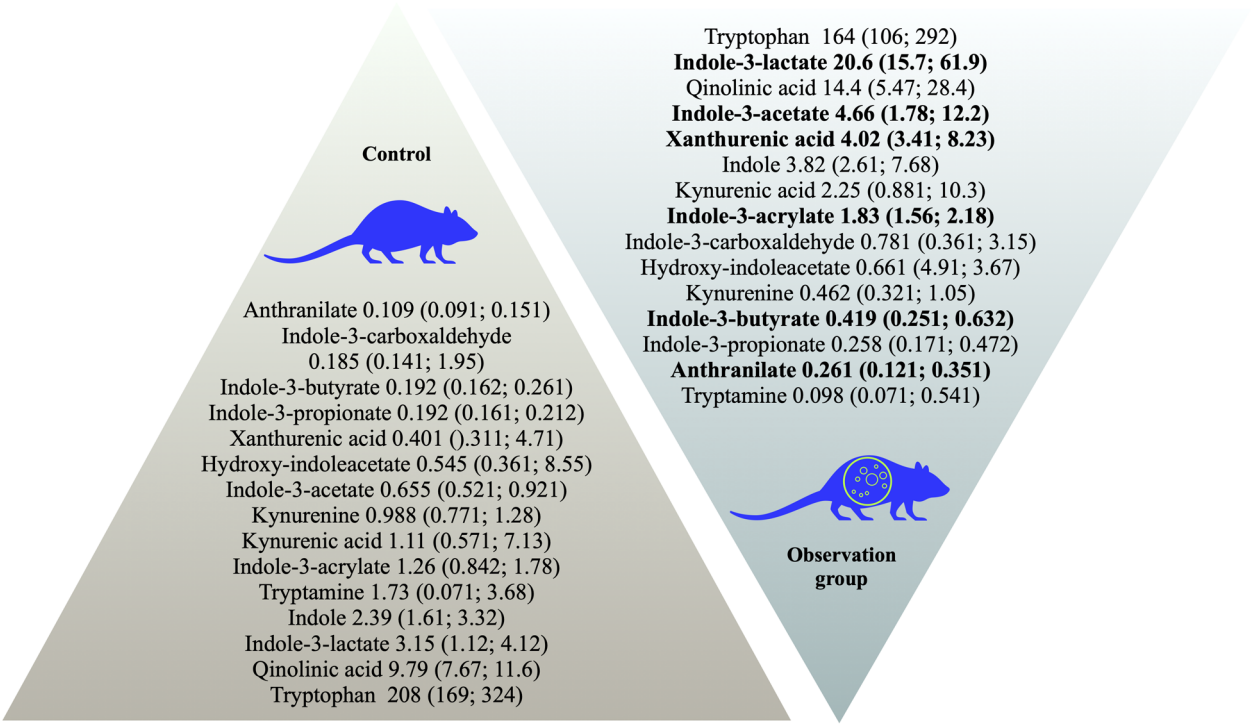

Figure 1. Fecal tryptophan metabolite levels (nmol/g). Data are expressed as median (Me) and interquartile range (Q1; Q3). Statistically significant differences ($p<0.05$) in tryptophan metabolite levels in animals of the control and experimental groups are shown in bold.

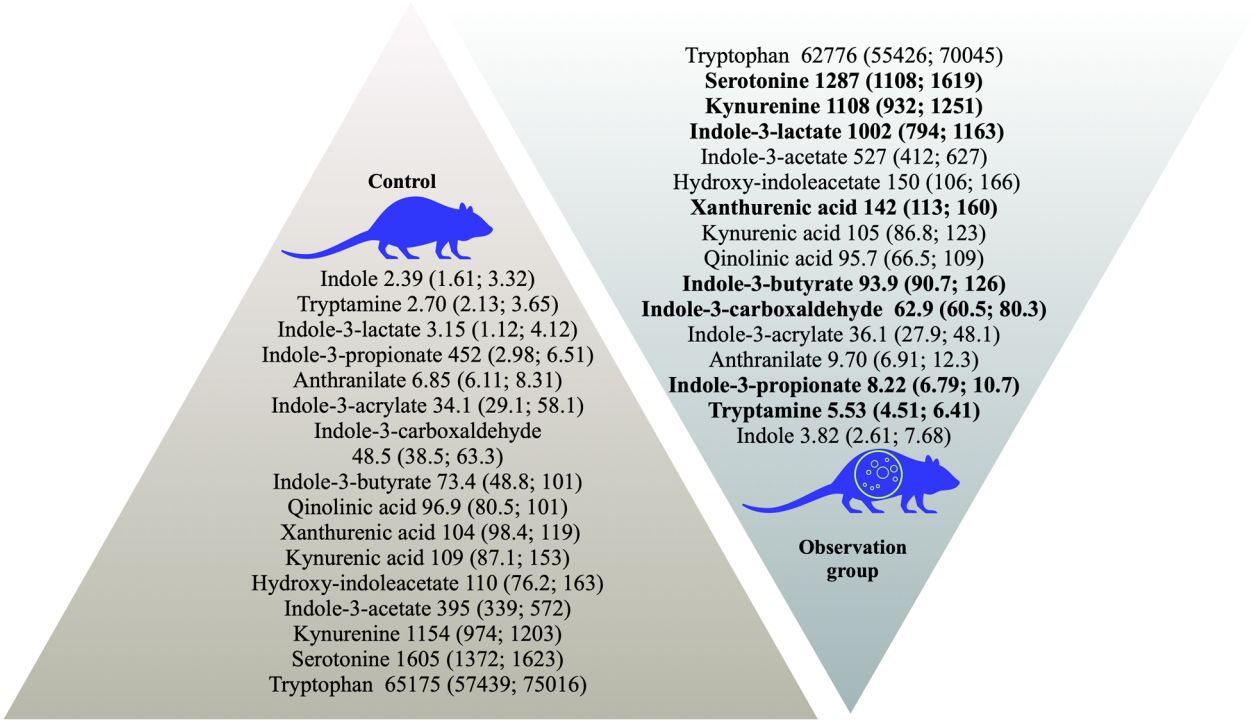

Figure 2. Blood tryptophan metabolite levels (nmol/l). Data are expressed as median (Me) and interquartile range (Q1; Q3). Statistically significant differences ($p<0.05$) in tryptophan metabolite levels in animals of the control and experimental groups are shown in bold.

and the experimental mice exposed to FMT may reflect the activation of the metabolism of mouse species-specific microbiota. We have shown that FMT stimulates tryptophan conversion via both catabolic pathways. After FMT, not only the indole pathway of tryptophan catabolism specific to microorganisms was stimulated, but also the kynurenine pathway of tryptophan metabolism characteristic of the cells of the host organism. Previously, it was shown in laboratory animals (chickens) that FMT led to an increase in the content of tryptophan, serotonin, and indole in the small intestine [26]. At the same time, there was an increase in Lactobacillus and a decrease in the number of some opportunistic bacteria, such as *Enterococcus* and *Streptococcus*. In the same study, it was found that FMT increased AhR expression, which, in turn, could maintain the balance of Th17/Treg cells [26] and could contribute to the anti-inflammatory effect of FMT. It can be assumed that FMT changes microbial diversity and at the same time significantly affects both production of tryptophan and all three its key catabolic pathways. There is evidence for a significant increase in tryptamine (more than 200 times) after human FMT to mice [12]. However, our study did not reveal any statistically significant differences in tryptamine levels in the feces or blood of mice after FMT.

Taking into consideration that in the human body the indole pathway consumes only 1% of exogenous tryptophan, while the kynurenine pathway uses 95% [27], we have calculated the amount of exogenous tryptophan that could be metabolized in the intestine in control mice and mice exposed to the FMT procedure. We defined the tryptophan content in the intestine as 100% and calculated the total content of metabolites of the indole pathway of tryptophan catabolism separately (the sum of all indole metabolites ×100 / tryptophan content) and metabolites of kynurenine metabolism separately (the sum of all metabolites of the kynurenine pathway ×100 / tryptophan content). As our work has shown, in control animals, potentially about 6% of tryptophan may be utilized via the kynurenine pathway, while only 4.1% of tryptophan may be catabolized via the indole pathway. After FMT, the level of tryptophan utilization via the kynurenine pathway reached 13%, while via the indole pathway, tryptophan conversion exceeded 20%. This confirms the significant role of the intestinal microbiota in both the formation of kynurenine metabolites and the formation of indole metabolites of tryptophan. In addition, the amount of tryptophan converted via the indole pathway significantly exceeds the existing viewpoints about utilization of 1% tryptophan to indoles.

It should be noted that the serum levels of indole metabolites of tryptophan increased predominantly. Indoles are generally considered as metabolites of exclusive microbial origin [28]. Serum serotonin, kynurenine, and quinolinic acid did not differ between animals of control and experimental groups. At the same time, certain evidence exists that FMT increases the level of blood serotonin [26]. It is important to note the statistically significant increase in xanthurenic acid in the blood of animals after FMT. Xanthurenic acid is a kynurenine metabolite formed during 3-hydroxykynurenine transamination. Recent data indicate that xanthurenic acid can affect brain function and neurotransmission, and it can interact with metabotropic glutamate receptors (mGlu) [29]. The *in vitro* and *in vivo* effects of xanthurenic acid appear to be mediated via activation of mGlu2 and mGlu3 receptors. However, xanthurenic acid may act beyond the regulation of mGlu receptors and affect various molecular targets (e.g. such as vesicular glutamate transporters) [29]. Xanthurenic acid is considered as a species-specific metabolite, which is produced exclusively by host cells and not by the microbiota [3]. Our results suggest that xanthurenic acid may also have a microbiotic origin. Serum levels of indole-3-butyrate, indole-3-lactate, and xanthurenic acid may potentially reflect abiosis or dysbiosis, highlighting the key role of the gut microbiota in their production. Indole and its derivatives promote intestinal immune homeostasis by activating AhR to protect the intestinal barrier. Activation of the AhR pathway in intestinal epithelial cells is vitally important for protection of stem cell niches and maintaining the integrity of the intestinal barrier [30]. It should be noted that in our study we have used the principle of a “single random donor”, while there are works showing the selection of a “super donor” or the combination of multiple donors [31].

CONCLUSIONS

The FMT procedure has a significant impact on tryptophan metabolism in the body and the content of its metabolites both in the intestine and in the blood serum. FMT increases the production of not only indole metabolites, which are considered as metabolites of exclusive microbial origin, but also metabolites of the kynurenine pathway. The dominant metabolites of tryptophan in the intestine both in the control and after FMT are indole-3-lactate and quinolinic acid. At the same time, for serum, statistical significance in the difference neither for indole-3-lactate, nor for quinolinic acid in animals of the examined groups was established. It is specific that after FMT, the content of indole-3-butyrate, indole-3-lactate, and xanthurenic acid increases both in the intestinal contents and in the blood serum.

FUNDING

The study was carried out at the expense of State Budget.

COMPLIANCE WITH ETHICAL STANDARDS

The study was conducted in accordance with the Declaration of Helsinki and the Federal Law of November 21, 2011 No. 323-FZ "On the Fundamentals of Health Protection of Citizens in the Russian Federation" and approved by the Ethics Council of the National Medical Research Center of Oncology (protocol code No. 44, approval date December 20, 2019). The donor of the metabolites signed an informed consent to participate in the study. The animal study protocol was approved by the Ethics Council of the National Medical Research Center of Oncology (protocol code No. 44, approval date December 20, 2019).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ВЛИЯНИЕ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ НА УРОВЕНЬ МЕТАБОЛИТОВ ТРИПТОФАНА В КИШЕЧНИКЕ И СЫВОРОТКЕ КРОВИ ГНОТОБИОНТНЫХ МЫШЕЙ

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Микробиота кишечника — один из ключевых поставщиков метаболитов триптофана — катаболитов, которые выполняют различные функции в организме хозяина, в том числе являются сигнальными молекулами. Трансплантация фекальной микробиоты (ТФМ) получила достаточно sширокое применение как метод, позволяющий определить вклад микроорганизмов в содержание различных метаболитов в холоорганизме. В связи с этим целью нашего исследования было изучение влияния ТФМ на уровень метаболитов триптофана в кале и крови у гнотобионтных мышей. Установлено, что как до, так и после ТФМ доминантными метаболитами триптофана в кишечнике являются индол-3-лактат и хинолиновая кислота. ТФМ повышает содержание как индолов (индол-3-ацетата, индол-3-акрилата, индол-3-бутирата, индол-3-лактата), так и кинуренинов (антраниловой и ксантуреновой кислот) в кишечнике. В сыворотке крови после проведения ТФМ повышаются преимущественно индольные метаболиты (индол-3-бутират, индол-3-карбоксальдегид, индол-3-лактат, индол-3-пропионат), однако также повышаются триптамин и ксантуреновая кислота. Применение ТФМ демонстрирует, что микробиота кишечника — источник не только индольных производных триптофана, а и метаболитов кинуренинового пути.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: микробиота кишечника; триптофановые катаболиты; трансплантация фекальной микробиоты; индолы; кинуренины

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