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TRANSLOCATION OF MICROORGANISMS OF INTESTINAL BIOTOPE OF RATS UNDER THE CONDITIONS OF MOTOR ACTIVITY LIMITATION OF DIFFERENT DURATION

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Normal microbiocenosis of intestinal biotope of the body is a sophisticated phylogenetically established dynamic complex that performs vital functions, the constancy and balance of which significantly affects the homeostasis of the body and its functional state [2, 13, 16, 17, 24].

The impact on the body of different factors of exogenous and endogenous origin, among which an important role belongs to the stressors of various nature and duration (limitation of motor activity, Crush-syndrome, immobilization and social stress), is expressed by a change in the quantitative and qualitative composition of dominant and associative microbes of the luminal (fecal) and parietal (mucosal) microflora of the intestinal tract [1, 10, 18, 19, 21, 22].

Such violations in the composition of the normal intestinal microflora contribute to the formation and development of the process of translocation of intestinal microbes and their toxins into the internal environment of the body due to disruption of the functioning of the epithelial and immune intestinal barrier and increasing its permeability.

In experiments on mice, it was established [10] that the limitation of motor activity lasting 6 hours contributes to the translocation of *E. coli* from the large intestine into the parenchymal organs (liver, spleenand lungs), mesenteric lymph nodes and blood. At the same time, it was shown that the infection of the organs was maximal immediately after the immobilization, and after 24 hours the number of *E.coli* in organs reduced 3-50 times. This is indicative of the elimination of the macroorganism that, according to the authors, could be due to removing bacteria with bile and urine, as well as due to the elimination of the effectors of antibacterial protection.

Short-term restriction of motor activity of rats lasting from 30 minutes to 4 hours in combination with elements of physical stress (immersion in water at 20°C, keeping animals at 8°C) causes an increase in the permeability of the intestinal wall for both the micromolecules (bacterial chemotactic peptides) and the macromolecules, and contributes to their penetration into the mucous membrane and the development of inflammatory process in the intestinal wall [12].

Under conditions of 7-day immobilization stress lasting one hour daily, in combination with occlusion of the middle cerebral artery, translocation of aerobic and anaerobic gram positive (*Enterococcus faecalis, Staphylococcus aureus, Peptostreptococcus spp., Propionobacterium acnes*) and anaerobic gram negative (*Bacteroidesfragilis*) bacteria is observed in the lymph nodes, spleen and lungs of rats. The isolated effect of these factors under similar experimental conditions does not cause translocation of bacteria [3].

The exposure of social disruption stress (SDR) on mice (a social stressor, which involves repeated social defeat in subordinate mice for six consecutive nights, 2 hours per day) causes translocation of intestinal commensal *Lactobacillus spp.*to the spleen [15].

In conditions of short-term (1 hour) Crush syndrome, after decompression of 1, 24 hours, 7, and 14 days, an increase in the dissemination of the lungs, liver, pancreas, and mesenteric lymph nodes by *E. coli* is observed in the early stages of decompression (1 and 24 hours), whereas in subsequent periods of observation only single colonies were found in biopsy specimens [19].

In the mechanisms of disturbance origination in population profile of intestinal microbiocenosis in the conditions of stress (including hypokinetic), one of the leading roles has changes in the functioning of the immune sys-

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tem, which has a negative effect on the factors of innate (phagocytosis, activity of complement and lysozyme), humoral and local immunity (sIgA), on the functional activity of macrophages, T-lymphocytes and the level of IL-1,2,6,10, TNF- , IF- [4, 9, 14, 20, 23], which play an extremely important role in ensuring antimicrobial resistance, stability and permeability of the intestinal barrier.

The results of experiments in this aspect differ in the ambiguity and inconsistency of the data obtained, which depend on the type of used animals and various experimental models of stress applied, its depth and duration. During studying the effect of hypokinetic stress on the translocation of representatives of intestinal microbiocenosis experimental models were used, the duration of which varied from 30 minutes to 6 hours, while there is practically no data on the study of the longer effects of limiting motor activity, despite the fact, that hypokinesia may be experienced by disabled people, by the scientists in a pressure chamber during various studies, by submariners and other groups of people, which served as the basis for the implementation of this work.

The aim of this research is to study the translocation of representatives of the normal microflora of the intestinal biotope of rats into parenchymal organs, mesenteric lymph nodes and blood under conditions of 22-hour hypokinesia.

Material and Methods

Experiments were carried out on 75 non-linear white male rats weighing 150-170g. Animals were subdivided into 5 groups (15 rats in each group): control (intact) and experimental animals exposed to 3-, 7-, 14- and 30-day hypokinesia, which were kept on a normal diet under the usual conditions of vivarium.

The experimental model of hypokinesia was obtained by placing the animals into the special ventilated Plexiglas individual cages limiting their mobility in all directions without interfering with respiratory movements and availability of food and water. The animals were kept under the limitation of motor activity for 22 hours a day and were transferred to usual cages only for 2 hours.

The experiments were carried out in accordance with the criteria of evidence-based medicine and in compliance with the ethical standards that received a positive conclusion of the Committee on Bioethics of the YSMU after M. Heratsi.

For the study, biopsy specimens from the pancreas, liver, spleen, lungs, mesenteric lymph nodes and blood were taken under Nembutal anesthesia (40mg/kg, i.p.).

The study of the quantitative and qualitative composition of microflora was carried out by the bacteriological method [8], and identification was carried out based on the tinctorial, cultural and biochemical properties and using the API 50 Test System (bioMerieux, France).

The investigating material was weighed under the aseptic conditions and placed into the sterile physiological solution at the ratio of 1 mg of tissue to 100 l solution for up to 2 hours. Then, biopsy dilutions were prepared to a concentration of 10^{-2}-10^{-6}, and 0.1 ml of each dilution was transferred to the surface of the corresponding medium: Endo agar, SS agar (Himedia, India), MRS agar (Biomark, India), MSA, Schaedler agar (Biolab, Hungary), Saburo, TSI agar, Bismuth-sulfite agar (SRI, Obolensk, Russia). The media were incubated at 37°C under aerobic and anaerobic conditions.

The most common microbes of human intestine have been isolated: *Bifidobacterium spp., Lactobacillus spp., E.coli, Enterococcus spp., Clostridium spp., Proteus spp., Staphylococcus spp. and Candida spp*.

The frequency of detection of microorganisms in % and average concentration of them expressed in lgCFU/g was determined. The concentration of microbes in less than 10^2CFU/g was not taken into account.

Distribution of variables was tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For the intergroup comparison of outcomes, the Non-Parametric Mann–Whitney U test was used. All analyses were performed using the SPSS statistical software, version 16 (SPSS Inc., Chicago, IL, USA). The level of statistical significance for all tests was $P \leq 0.05$.

Results and Discussion

The experiments have shown that hypokinetic stress promotes translocation of some representatives of the intestinal microbiota into the internal environment of the body and its effect is ambiguous and depends mainly on the duration of the stress exposure.

It has been shown, that none of the studied microorganisms were detected in the lungs, liver, pancreas, spleen, mesenteric lymph nodes and blood of the rats exposed to a 3-day hypokinesia for 22 hours a day like in the animals control group.

At the same time, thementioned literature data show that a single stressor effect (immobilization for 6 hours or compression of the inner surface of mice hip for an hour) immediately after the influence and within an hour after it is accompanied by a notable increase in the number of *E.coli* in all the above-mentioned biopsy specimens. In

Table 1. *Frequency of detection (%) and concentration (in lgCFU/g (Mean±SE)) of E. coli in biotopes of organs during hypokinetic stress*

Group of animals / Organs	Control n=15	3 days n=15	7 days n=15	14 days n=15	30 days n=15
Mesenteric lymph nodes	0	0	1.6 ± 0.38^{ab} 60%	1.07 ± 0.32^{ab} 33.3%	0^{cd}
Liver	0	0	1.33 ± 0.41^{ab} 46.7%	0.87 ± 0.29^{ab} 40%	0^{cd}
Spleen	0	0	1.6 ± 0.42^{ab} 53.3%	1.07 ± 0.32^{ab} 33.3%	0^{cd}
Pancreas	0	0	1.33 ± 0.41^{db} 46.7%	1.2 ± 0.31^{ab} 46.6%	0^{cd}
Lung	0	0	1.8 ± 0.37^{ab} 66.7%	0.6 ± 0.27^{abc} 26.6%	0^{cd}

Note:
*a Significant difference between control group and 7, 14 days of hypokinesia**
*b Significant difference between 3 and 7, 14 days of hypokinesia**
*c Significant difference between 7 and 14, 30 days of hypokinesia**
*d Significant difference between 14 and 30 days of hypokinesia**
$*=P<0.05$

Table 2. *Frequency of detection (%) and concentration (in lgCFU/g (Mean±SE)) of Staphylococcus spp. in biotopes of organs during hypokinetic stress*

Group of animals / Organs	Control n=15	3 days n=15	7 days n=15	14 days n=15	30 days n=15
Mesenteric lymph nodes	0	0	0.47 ± 0.26 20%	0.80 ± 0.31^{abc} 33.3%	0^{d}
Liver	0	0	0.73 ± 0.33^{ab} 26.6%	0.93 ± 0.32^{ab} 40%	0^{cd}
Spleen	0	0	0.47 ± 0.26 20%	0.80 ± 0.31^{ab} 33.3%	0^{d}
Pancreas	0	0	0	1.27 ± 0.40^{abc} 46.6%	0^{d}
Lung	0	0	1.00 ± 0.41^{ab} 33.3%	1.00 ± 0.34^{ab} 40%	0^{cd}

Note:
*a Significant difference between control group and 7, 14 days of hypokinesia**
*b Significant difference between 3 and 7, 14 days of hypokinesia**
*c Significant difference between 7 and 14, 30 days of hypokinesia**
*d Significant difference between 14 and 30 days of hypokinesia**
$*=P<0.05$

more prolonged periods after stress exposure (24 hours, 7 and 14 days), the frequency of *E.coli* detection in the studied biopsy specimens was manifested either as single colonies, or was completely absent.

A completely different picture was observed in our experiments with an increase in the duration of restriction of the motor activity of animals for consecutive 7 and 14 days, under the conditions of which the translocation of *E. coli* and *Staphylococcus spp.* occurs from the intestinal biotope into the internal environment of the macro-organism, but the remaining micro-organisms in the studied material were not found, as well as in the control group of rats (Table 1, 2).

As it is shown in Table 1, immediately after completion of a 7-day hypokinesia, there is a marked increase in the detection rate of *E. coli* in the studied parenchymal organs and mesenteric lymph nodes, as compared with the control and groups of animals that are under conditions of limitation of motor activity for the consecutive three and 30 days.

The most pronounced changes were observed in the lungs, spleen, and lymph nodes, in which the frequency of detection of *E. coli* varies in the range of 53.3–66.7%, while in the liver and pancreas it was 46.7%. A significant increase in the average concentrations of *Escherichia* was observed in all studied biopsy specimens in comparison with other groups of animals, with the most pronounced increase of it in the lungs, and it varied within 1.33 - 1.8 lgCFU/g of tissue.

An increase in the duration of hypokinesia up to 14 days caused a significant decrease in the detection rate of *E. coli* in the studied biopsies of animals compared with the previous experimental group, it was most pronounced in the lungs (by 40.1%), mesenteric lymph nodes (by 26.7%) and in the spleen (by 20%), remaining almost unchanged in the liver and pancreas.

At the same time, a significant decrease in the average concentration of the microbe (3 times) is detected only in the lungs compared with the group with a restricted motor activity for 7 days.

Under the conditions of 7- and 14-day hypokinesia, migration of *Staphylococcus spp*. was also detected. It was less pronounced as compared with the *E. coli* translocation (Table 2).

Immediately after completion of the 7-day hypokinesia, *Stphylococcus spp.* was excreted from the lungs of 33.3% of rats, without being found in the pancreas, and in the remaining biopsy specimens the detection rate was quite low. Significantly high average concentration of the microbe was detected in the lungs and to a certain extent in the liver (0.73 lgCFU/g of tissue) with a complete absence in the pancreas.

A completely different picture was observed with the prolongation of the hypokinesia duration to 14 days, when a significant increase in the frequency of detection of bacteria excreted in all studied bioptates was revealed, as compared with the control animals and those exposed to the 3-day hypokinesia, which was most pronounced in the pancreas (46.6%). Detection rate of *Staphylococcus spp.*, compared with the previous experimental group, had a tendency to increase by 13% in parenchymal organs and mesenteric lymph nodes.

Under these experimental conditions, the highest reliable concentration of bacteria was observed in the pancreas, remaining high in the lungs and liver, compared with other groups of animals.

With an increase of the duration of hypokinesia up to 30 days in all experimental groups of animals, the microorganisms were not found in the studied biopsy specimens of parenchymal organs and mesenteric lymph nodes. It should also be noted that transient bacteremia was not detected in either the control rats or the experimental animals that were under the conditions of limitation of their motor activity for 3-30 days. Although, according to the published data, *E. coli* was isolated from the blood of animals immediately after stressor exposure and within 24 hours [10]. It is also considered that the migration of bacteria from the intestine occurs mainly in the mesenteric lymph nodes; therefore, blood cultures are often negative.

It has now been established that bacterial translocation through the intestinal wall epithelium into the internal environment of the body occurs due to an increase in the permeability of the intestinal barrier, which can be developed under various pathological processes and stress conditions and may be accompanied by pronounced dysbiotic changes in the composition of the intestinal microbiocenosis, which plays an important role in ensuring colonization resistance of the organism [1, 3, 5, 11, 12, 18].

It is believed that a decrease in the effectiveness of the intestinal barrier arising from dysfunction or defects of epithelial cells, tight intercellular compounds and other morpho-functional components of the barrier leads to the penetration of microbes into mesenteric lymph nodes and blood stream.

At the same time, bacteria and their products (endotoxins, lipoteichoic acids and peptidoglycan of gram-positive bacteria) enter mainly the liverfrom the intestinal lumen through the portal vein system [17].

In the lymphogenous pathway of translocation from the intestine, bacteria, bypassing the liver through the thoracic duct and subclavian vein, enter the lungs first, in which pathological processes develop [6, 7].

Summarizing the data of this study, which indicate the activation of translocation of intestinal microbiota representatives into the internal environment of the body under the conditions of prolonged hypokinesia, we can conclude that, perhaps, bacterial migration is one of the leading pathogenic mechanisms for the appearance and development of diseases with extra-intestinal localization, especially in groups of people under the influence of prolonged restriction of motor activity.

Conclusion

Thus, the results of the study indicate that hypokinesia lasting 22 hours daily for consecutive 7 and 14 days promotes translocation of *E. coli* and *Staphylococcus spp.* from the intestinal biotope to parenchymal organs and mesenteric lymph nodes, which may be accompanied by the appearance and development of pathological processes in them. There is the need for further study of the problem in order to develop the methods to correct the negative effects of a hypokinetic stress.

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ԱՄՓՈՓՈՒՄ

ԱՌՆԵՏՆԵՐԻ ԱՂԻՔԱՅԻՆ ԲԻՈՏՈՊԻ ԲԱԿՏԵՐԻԱՆԵՐԻ ՏՐԱՆՍԼՈԿԱՑԻԱՆ ՇԱՐԺՈՂԱԿԱՆ ԱԿՏԻՎՈՒԹՅԱՆ ՍԱՀՄԱՆԱՓԱԿՄԱՆ ՏԱՐԲԵՐ ՏԵՎՈՂՈՒԹՅԱՆ ՊԱՅՄԱՆՆԵՐՈՒՄ

Պողոսյան Գ.Մ., Գևորգյան Զ.Հ., Աբգարյան Ք.Հ., Հովհաննիսյան Մ.Ս., Մանուկյան Կ.Ղ., Մուրադյան Դ.Մ., Էլբակյան Ա.Վ., Ղալաչյան Ժ.Է., Սարգսյան Լ.Հ., Շեկոյան Վ.Ա.*

ԵՊԲՀ, բժշկական մանրէաբանության ամբիոն

Բանալի բառեր՝ *սթրես, սակավաշարժություն, աղիքային միկրոֆլորա, բակտերիաների տրանսլոկացիա:*

Սթրեսը, այդ թվում հիպոկինետիկ, խանգարումներ է առաջացնում հոմեոստազի հաստատունության պահպանման գործում կարևոր նշանակություն ունեցող աղիքների նորմալ միկրոֆլորայի դոմինանտ և ասոցիատիվ մանրէների կազմում, որը կարող է նպաստել դրանց տրանսլոկացիային պարենքիմատոզ օրգաններ՝ դրսևորվելով տարբեր ախտաբանական պրոցեսներով:

Սույն հետազոտության նպատակն է ուսումնասիրել աղիքային մանրէների տրանսլոկացիան օրգանիզմի ներքին միջավայր սակավաշարժության պայմաններում:

Հետազոտություններն իրականացվել են 75 սպիտականցեղ 150-170գ քաշով արուառնետների վրա, որոնք բաժանվել են 5 խմբի (յուրաքանչյուր խմբում 15 առնետ)՝ ինտակտ (ստուգիչ) և 3, 7, 14 ու 30 օր սակավաշարժության ենթարկված:

Սթրեսի մոդելավորումը իրականացվել է կենդանիներին

տեղավորելով պլեքսիգլասային անհատական վանդակխցիկների մեջ՝ օրական 22 ժամով, և միայն 2 ժամով նրանք տեղափոխվել են սովորական վանդակներ:

Բակտերաբանական եղանակով ենթաստամոքսային գեղձից, լյարդից, փայծաղից, թոքերից, միջընդերային ավշային հանգույցներից ու արյունից անջատվել են *Bifidobacterium spp., Lactobacillus spp., E.coli, Enterococcus spp., Clostridium spp., Proteus spp., Staphylococcus spp.* և *Candida spp.* մանրէները: Ցեղային պատկանելությունը որոշվել է ստանդարտ մեթոդով և API 50 թեստ համակարգի միջոցով (bioMerieux, France):

Որոշվել է մանրէների հայտնաբերման հաճախականությունը (%) և անջատված մանրէների միջին կոնցենտրացիան (lg ԳԱՄ/գ):

Ցույց է տրվել, որ ստուգիչ և 3 ու 30 օր տևողությամբ սակավաշարժության ենթարկված կենդանիների խմբերում հետազոտվող բիոպտատներում մանրէներ չեն հայտնաբերվել, այն դեպքում, երբ 7 և 14 օր տևողության սակավաշարժությունը նպաստել է *E.coli*-ի և *Staphylococcus spp.*-ի տրանսլոկացիային:

E.coli-ի հայտնաբերման հաճախականությունը սակավաշարժության 7-րդ օրը էականորեն բարձրացել է թոքերում, ավշային հանգույցներում և փայծաղում (համապատասխանաբար 66,7%, 60% և 53,3%), և դրա ամենաբարձր կոնցենտրացիան հայտնաբերվել է թոքերում (1,8 lg ԳԱՄ/գ, p<0,05), իսկ հետազոտության 14-րդ օրը թոքերում նշանակալիորեն (p<0,05) նվազել է մանրէի և՛ հայտնաբերման հաճախականությունը (2,5 անգամ), և՛ միջին կոնցենտրացիան (3 անգամ)՝ հավաստիորեն չփոփոխվելով մնացած բիոպտատներում:

Փորձի նույն պայմաններում հայտնաբերվել է ստաֆիլոկոկերի՝ *E.coli*-ի համեմատ ավելի մեղմ արտահայտված տրանսլոկացիա, որն առավել դրսևորվել է սակավաշարժության 14-րդ օրը: Մանրէի հայտնաբերման հաճախականությունը (46,6%) և միջին կոնցենտրացիան (1,27 lg ԳԱՄ/գ, p<0,05) բարձր էին ենթաստամոքսային գեղձում՝ մյուս բիոպտատներում տատանվելով 0,8-1,0 lg ԳԱՄ/գ սահմաններում:

Այսպիսով, սակավաշարժությունը նպաստում է աղիքային բակտերիաների տրանսլոկացիային պարենքիմատոզ օրգաններ և կարող է ուղեկցվել նրանցում ծանր ախտաբանական գործընթացների զարգացումով, որն էլ պայմանավորում է սթրեսի ազդեցության բացասական հետևանքների համուղղման մեթոդների հայտնաբերման անհրաժեշտությունը:

РЕЗЮМЕ

ТРАНСЛОКАЦИЯ МИКРООРГАНИЗМОВ КИШЕЧНОЙ МИКРОБИОТЫ КРЫС ПРИ ОГРАНИЧЕНИИ ДВИГАТЕЛЬНОЙ АКТИВНОСТИ РАЗЛИЧНОЙ ДЛИТЕЛЬНОСТИ

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Ключевые слова: *стресс, гипокинезия, кишечная микрофлора, транслокация бактерий.*

Стресс, в том числе и гипокинетический, вызывает нарушения в составе доминантных и ассоциативных бактерий нормальной микрофлоры кишечника, играющей важную роль в сохранении постоянства гомеостаза, что может способствовать транслокации бактерий в паренхиматозные органы с развитием в них различных патологических процессов.

Целью исследования явилось изучение транслокации кишечных бактерий во внутреннюю среду организма в условиях гипокинезии.

Исследования проводились на 75 белых беспородных крысах самцах массой 150-170 г., разделенных на 5 групп (по n=15). Интактные животные составили контрольную группу, а подопытные группы были подвергнуты стрессу различной длительности действия (3-, 7-, 14- и 30-дней). Стресс моделировали, ежедневно помещая животных в индивидуальные плексигласовые клетки-камеры в течение 22 часов, и только на 2 часа они переносились в обычные условия вивария.

Бактериологическим методом из поджелудочной железы, печени, селезенки, легких, мезентериальных лимфоузлов, крови выделяли *Bifidobacterium spp., Lactobacillus spp., E.coli, Enterococcus spp., Clostridium spp., Proteus spp., Staphylococcus spp.* и *Candida spp*.

Родовую идентификацию проводили по стандартной методике и с помощью тест-системы API 50 (bioMerieux, Франция). Определяли частоту выделения (%) и их среднюю концентрацию (lg КОЕ/г).

Показано, что при 3- и 30-дневной гипокинезии и в группе контроля в изученных биоптатах бактерии не выделялись, тогда как 7- и 14-дневная гипокинезия способствовала транслокации *E. coli* и *Staphylococcus spp.* Частота выделения *E. coli* на 7-ой день гипокинезии значительно повышалась в легких, лимфоузлах и селезенке (66,7%, 60% и 53,3% соответственно), при этом наиболее высокие концентрации определялись в легких (1,8 lg КОЕ/г, p<0,05), а на 14-ый день исследования в легких происходило значительное уменьшение высеваемости микроба - в 2,5 раза и средней концентрации в 3 раза (p<0,05), достоверно не изменяясь в остальных биоптатах.

В аналогичных условиях эксперимента выявлена менее выраженная по сравнению с *E. coli* транслокация стафилококка, наиболее проявляющаяся на 14-ый день гипокинезии. Процент высеваемости (46,6%) и средняя концентрация (1,27 lg КОЕ/г, p<0,05) были высоки в поджелудочной железе, в остальных же биоптатах варьировали в пределах 0,8-1,0 lg КОЕ/г.

Таким образом, гипокинезия способствует транслокации кишечных бактерий в паренхиматозные органы и может сопровождаться развитием в них тяжелых патологических процессов, что обусловливает необходимость изыскания методов коррекции отрицательных последствий влияния стресса.