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EXPLORING THE IMPACT OF GUT MICROBIOTA ON EPILEPSY PATHOGENESIS IN KRUSHINSKY-MOLODKINA RATS

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ИЗУЧЕНИЕ ВЛИЯНИЯ МИКРОБИОТЫ КИШЕЧНИКА НА ПАТОГЕНЕЗ ЭПИЛЕПСИИ У КРЫС КРУШИНСКОГО-МОЛОДКИНОЙ

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Abstract

The gut–brain axis represents a bidirectional communication network that integrates neural, endocrine, and immune pathways with intestinal microbiota-derived signals. Disruption of this system, often resulting from gut microbiota dysbiosis, has been increasingly associated with neurological and psychiatric disorders, including depression, Alzheimer's disease, and Parkinson's disease. Understanding a crosstalk between host genetics, microbiota composition, and neuroinflammatory processes is therefore crucial for elucidating the mechanisms underlying brain health and disease. In the present study, we investigated gut microbiota composition in two genetically distinct rat Wistar and Krushinsky-Molodkina (KM) strains, and further assessed the effects of kindling-induced epileptogenesis and associated neuroinflammation on the KM microbiota. Our analyses revealed notable inter-group alterations in microbial composition. In particular, *Enterococcus hirae* abundance differed significantly between Wistar and KM control rats, while *Streptococcus hyointestinalis* exhibited changes between the KM control and KM kindling groups. Furthermore, we observed a reduced relative abundance of *Lactobacillus murinus* and *Lactobacillus reuteri* in KM control rats compared with both Wistar and KM kindling animals. In parallel, we observed altered expression of NF-κB p65 in the temporal lobe white matter. Specifically, Wistar vs. KM control rats displayed lower NF-κB p65 expression, whereas KM kindling rats showed reduced expression compared to the KM control group. Such alterations in NF-kB p65 expression correlate with observed shifts in abundance of *Lactobacillus murinus* and *Lactobacillus reuteri*, suggesting a link between microbiota composition and neuroinflammatory processes. These findings provide deeper insight into the multifaceted interplay between host genetic background, neuroinflammation, and gut microbial composition. The results suggest that differences in bacterial taxa, particularly within Lactobacillus species, may be linked to NF-κB–mediated processes in the brain, thereby shaping the pathophysiological landscape of neurological disorders. Further investigations are required to better understand the

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complex crosstalk between host genetics, brain and gut microbiota, and their implication for health and disease.

Keywords: Epilepsy, gut microbiota, gut-brain axis, *Lactobacillus murinus*, *Lactobacillus reuteri*, NF-kB p65.

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Резюме

Ось кишечник-мозг - это двунаправленная коммуникационная система, которая включает в себя сложные взаимодействия между кишечником и мозгом. Дисбактериоз кишечной микробиоты, характеризующийся дисбалансом в ее составе, был связан с несколькими неврологическими расстройствами - депрессией, болезнью Альцгеймера, болезнью Паркинсона и другими. В этой статье мы ставим своей целью проанализировать микробиоту кишечника двух генетически различных линий крыс Wistar и Крушинского-Молодкиной (КМ) и оценить влияние киндлинга и связанного с ним нейровоспаления на микробиоту кишечника крыс КМ. Методы исследования включали в себя классические бактериологические, биологические на моделях крыс двух линий Wistar и КМ, масс-спектрометрический метод идентификации бактерий, вестерн-блоттинг для исследования срезов коры височной доли и белого вещества мозга крыс, статистические методы анализа данных. Результаты. Наши результаты свидетельствуют об изменениях в составе микробиоты у крыс разных линий: *Enterococcus hirae* преобладали у линии КМ, *Streptococcus hyointestinalis* - у крыс линии КМ (киндлинг). Низкая численность *Lactobacillus murinus* и *Lactobacillus reuteri* отмечена в контрольной группе по сравнению с крысами линии Вистар и крысами линии КМ, подвергнутых киндлингу. В белом веществе височной доли у крыс линии Вистар был обнаружен более низкий уровень экспрессии NF-κB p65 по сравнению с контрольной группой КМ, и экспрессия этого белка в группе КМ, подвергнутых киндлингу, была ниже по сравнению с контрольной группой КМ. Эти изменения в экспрессии NF-κB p65 коррелируют с наблюдаемыми изменениями в численности *Lactobacillus murinus* и *Lactobacillus reuteri*, которые, будучи гетероферментирующими бактериями, могут продуцировать метаболиты, которые способствуют изменениям в биохимической среде организма. Обнаруженное размножение этих видов бактерий в ответ на аудиогенные стимулы может потенциально повлиять на уровень экспрессии

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NF-κB p65 в организме хозяина. Эти результаты подчеркивают потенциальную важность микробиоты кишечника как терапевтической мишени для лечения эпилепсии. Манипулирование кишечной микробиотой с помощью пробиотиков или диетических вмешательств потенциально может служить терапевтическим подходом в контексте эпилепсии. Выводы: Результаты этого исследования могут способствовать лучшему пониманию сложных взаимодействий между генетикой хозяина, мозгом и микробиотой кишечника, а также их последствий для возникновения патологических состояний и сохранением или восстановлением здоровья.

Ключевые слова: Эпилепсия, кишечная микрофлора, ось кишечник-мозг, *Lactobacillus murinus, Lactobacillus reuteri,* NF-kB.

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1 Introduction

The gut microbiome, which refers to the complex community of microorganisms residing in the gastrointestinal tract, has been increasingly recognized for its potential role in neurological disorders (1, 2).

Emerging evidence suggests that alterations in the gut microbiome may lead to increased inflammation (2, 3), which has been implicated in epilepsy. The gut and brain are closely connected via a bidirectional communication pathway known as the gut-brain axis (4, 5, 6). The gut microbiota can influence brain function through various mechanisms, including the production of neurotransmitters, metabolic byproducts, and immune signaling molecules (2, 5, 7) that can impact the excitability of brain cells. Dysbiosis, or an imbalance in the gut microbial community, can modulate adaptive and innate immunity (8) and result in the production of pro-inflammatory molecules that may trigger inflammation in the brain (9), potentially leading to seizures.

Studies using animal models and clinical patients have shown that manipulation of the gut microbiota through probiotics, prebiotics or fecal microbiota transplantation can influence CNS functions, implicated in neurodegenerative processes (10, 11, 12, 13, 14) and seizure activity (15, 16). For example, administration of certain probiotic strains has been found to reduce seizure frequency and severity of epilepsy (15, 16).

Certain species of gut bacteria, such as those belonging to the *Clostridioides* and *Bacteroides* genera, have been shown to possess anti-inflammatory and neuroprotective properties, while others, such a *Prevotella copri, Escherichia and Shigella* have been associated with pro-inflammatory effects (17, 18, 19, 20, 21, 22). Imbalances in the relative abundance of these microbial species in the gut may contribute to chronic inflammation (20). Inflammation can increase the excitability of brain cells and promote the development of seizures or exacerbation of epilepsy.

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Krushinsky-Molodkina (KM) rats are a widely used experimental model for studying epilepsy pathophysiology, characterized by genetically determined alterations (23, 24).

The aim of this study was to analyze the gut microbiota in two distinct rat models – Wistar and KM rat model, in order to provide insights into the impact of genetic alteration on the gut microbiota. In addition, we studied the potential implications of audiogenic kindling on the gut microbiota in KM rats. Next, we study the NF-kB p65 expression level in white matter and cortex of brain temporal lobe in all experimental groups.

2 **Materials and Methods**

1 Animal Model

We used 15 adult male and female Krushinsky-Molodkina rats (KM naive n = 5, KM kindling = 10) (IEPhB RAS, Russia), the control group was Wistar rats (n = 5). At the beginning of the experiment, the rats were 10-12 months old. All rats were housed in groups of 5 in separate cages (light and dark 12:12, free access to food and water).

All procedures were carried out in compliance with the recommendations and ethical principles set out in the EC Directive 86/609/EEC for animal experiments and approved by the Institutional Animal Care and Use Committee at the Sechenov Institute of Evolutionary Physiology and Biochemistry.

2. Audiogenic kindling

The experimental protocol involved subjecting rats to repeated audiogenic seizures. Briefly, rats were housed individually in a transparent Plexiglas chamber (50 × 30 × 20 cm) equipped with a loudspeaker located above the chamber. Audiogenic seizures were induced for 21 days (9 kHz, 50 dB) before seizure onset or for 1 minute if seizures did not occur, and seizure activity was monitored and recorded during each session. After 7 days of rest, an autopsy was performed.

3 Fecal samples collection and Bacterial Cultivation

Fresh fecal samples were collected from KM naive and KM kindling rats 21 days after the start of the experiment. For Wistar rats, samples were collected after 7 days. Each collected sample was utilized for cultivating both anaerobic and aerobic bacteria. Sample collection was carried out using appropriate aseptic techniques to minimize contamination. All samples were immediately transferred to the laboratory and processed without delay. For anaerobic bacteria cultivation, samples were streaked onto sterile thioglycolate broth, transferred to anaerobic chamber (anaerostat) and incubated at 37ºC for 24 hours. For aerobic bacteria cultivation, samples were streaked onto sterile meat broth and incubated at 37ºC for 24 hours. Subsequently, the specimens were inoculated onto blood agar sterile plates at 37ºC for 24 hours to facilitate sub-culturing and obtain pure bacterial colonies on the next step. Pure bacterial isolates were inoculated onto blood agar sterile plates at 37ºC for 24. All broth and solid nutrient media were obtained from «Biovitrum», Russain Federation.

4 MALDI-TOF analysis

Bacterial isolates were cultured for 18-24 hours at 37°C on blood agar plates. For mass spectrometer analysis, a single colony from each pure culture was picked using a sterile toothpick and directly spotted onto an MSP chip (MSP 96, Bruker Daltonics, Germany). Each spot was overlaid with 1μl of matrix solution (α-cyano-4-hydroxycinnamic acid, dissolved in 50% acetonitrile and 2.5% trifluoroacetic acid) and allowed to co-crystallize at room temperature. As the calibrating standard, protein extract from E. coli DH5α (ref. № 255343, Bruker Daltonics) was used. The target plate was loaded into a Microflex™ LT MALDI-TOF mass spectrometer (Bruker Daltonics, Germany) using the application FlexControl, and mass spectra were acquired in the automated linear positive mode with all necessary parameters detailed in the device instruction. Each spectrum represented an accumulation of 240 laser shots. The acquired mass spectra were analyzed using the software MALDI Biotyper 3.0 (Bruker Daltonics). Bacterial identification was achieved by comparing the obtained spectra against a reference database included with the MALDI-TOF

system. Scores SV > 2.3 were considered as reliable identification at the species level; scores between 2.299 and 2.00 indicated genus identification; SV between 1.99 and 1.7 as probable genus-level identification; scores lower than 1.7 were considered unreliable identification.

5 Western-blotting

For the Western blot analysis, sections of the temporal lobe cortex and white matter were first homogenized in lysate buffer containing added phosphatase and protease inhibitors (10 μl/ml, Sigma-Aldrich). The homogenates were then cooled at 4ºC for one hour, followed by centrifugation at 12,000 g. After centrifugation, the clear supernatant liquid was collected and mixed with Laemmli buffer, which includes mercaptoethanol. This mixture was heated at 95ºC for 10 minutes. The samples were then run on a vertical electrophoresis gel, followed by the transfer of the separated proteins onto a nitrocellulose membrane. The membranes were immersed in a 3% BSA solution (Biolot, Russia) prepared in Tris buffer (0.1% Tween 20, 0.2 mM Tris, 137 mM NaCl) for one hour. Subsequently, the membranes were incubated at 4ºC overnight with primary antibodies to NF-kB p65 (pAb, ab86299, Abcam, 1:1000) while undergoing continuous stirring. This step was followed by incubation with secondary antibodies (pAb, 1:5000, Anti-Rabbit IgG, Sigma), and the protein bands were visualized using enhanced chemiluminescence. The bands were analyzed with the ChemiDoc gel detection system (BioRad), with subsequent densitometry (ImageJ).

6 Statistical analysis

Comparisons between two groups of bacterial genera were conducted using the chi-square Pearson test or exact Fisher test. Comparisons between two groups of bacterial species were performed using the exact Fisher test. Protein expression levels between two groups were assessed using the Mann-Whitney U test. To compare differences among multiple groups concerning protein expression levels, one-way ANOVA with Tukey’s post hoc analysis was applied. Significance was

established at a threshold of $p < 0.05$. The construction of the heatmap was accomplished through the implementation of a Python script.

7. Artificial Intelligence

In the preparation of this manuscript, we utilized the Large Language Model (LLM), ChatGPT, developed by OpenAI, for grammatical corrections and to improve the clarity and understandability of the text. This tool assisted in refining the language and structure of the manuscript without contributing to the conceptual framework, experimental design, data collection, or analysis.

3 **Results and Discussions**

The gut microbiome is a complex ecosystem that influences a wide range of physiological processes in the host. In this article, we analyze the relationship between the gut microbiota, and its potential implications for epilepsy pathogenesis and treatment. Our findings (Fig. 1) reveal noteworthy differences in the abundance of specific bacterial genera between the KM control and Wistar groups. Specifically, we observed a notable reduction in the prevalence of *Lactobacillus murinus* and *Enterococcus* genera in KM control rats when compared to the Wistar rats. Interestingly, discernable variations in the abundance of *Lactobacillus murinus* and *Lactobacillus reuteri* were observed between the KM control and KM kindling groups. Whereas the population of these bacterial strains were decreased in KM control compared to the Wistar group, a contrasting trend was identified in the KM kindling group, where the abundance of these bacteria were increased in comparison to the KM control group. According to other studies it is apparent that patients exhibiting lower seizure frequency tend to possess higher level of *Bifidobacteria* and *Lactobacillus* (25). This finding implies that *Lactobacilli* may potentially serve a protective function in the management of epilepsy, given the association between gut microbiota alterations and lowered seizure threshold. Same as in KM control, the abundance of Enterococcus was found to be decreased in KM rats after 21 days of audiogenic kindling compared to Wistar group, which speak in favor of relation between development of epilepsy and alterations in gut microbiota composition.

Another notable shifts observed in the abundance of bacterial strains between KM naive and KM kindling groups was an increase in the *Streptococcus hyointestinalis* after 21 days of kindling. This may underlie the involvement of these bacteria into epilepsy pathogenesis.

One possible explanation for the decreased abundance of *Lactobacillus* and *Enterococcus* genera, and the increased abundance of *Streptococcus hyointestinalis* could be due to genetic differences between Wistar and KM rats , which subsequently leading to impairment of the barrier function within the intestinal lumen. These changes may be attributed to altered host-microbiota interactions or changes in the intestinal metabolism. It is known, that the microorganisms inhabiting the gastrointestinal tract and their metabolites have the potential to modulate various physiological processes in the host, including neuroinflammation, BBB permeability and subsequent chronic inflammation (26, 27). Increased prevalence of opportunistic pathogens, such as *Streptococcus*, in the gut may be associated with inflammatory processes and could potentially contribute to the development or exacerbation of epilepsy.

NF-kB is a key regulator of inflammation and plays a crucial role in the activation of inflammatory responses. It has been shown that gut microbiota disturbances can activate NF-kB p65 expression and promote apoptosis and inflammation (31). In our study, we analyzed the expression level of NF-kB p65 in the cortex and the white matter of the temporal lobe region of the Wistar, KM control and KM kindling groups.

An elevated level of NF-kB p65 expression was observed in the white matter of the temporal lobe region of the KM control group compared to the Wistar rats (Fig. 2A).. While the expression level of this protein in KM kindling group was still higher than in Wistar rats, the comparison between KM control and KM kindling rats demonstrate the descend of its expression in KM kindling group (Fig. 2B).. The observed increased level of NF-kB p65 in KM control rats compared to Wistar rats, with subsequent decreased of its level after audiogenic kindling is notably consistent

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with the observed shifts in abundance of Lactobacillus in these experimental groups. Previous research has demonstrated that *Lactobacillus* and their metabolites possess anti-inflammatory properties by inhibiting the overexpression of NF-kB signaling pathway (28, 29, 30). In the context of KM rats, which exhibit audiogenic epilepsy and altered level of NF-kB p65, it is plausible that the decreased abundance of *Lactobacillus murinus* may contribute to the dysregulation of the NF-kB signaling pathway and altered seizure threshold, while the increased populations of *Lactobacillus murinus* and *Lactobacillus reuteri* in KM rats after audiogenic kindling may demonstrate some compensatory mechanism triggering by audiogenic kindling. A distinctive feature of these two Lactobacillus species is that they belong to the group of heterofermentative bacteria (32). It is possible that the production of certain metabolites by these bacteria contributes to changes in the biochemical environment of the host organism. Therefore, the detected reproduction of these bacterial species in response to audiogenic stimuli can potentially affect the expression level of NF-kB p65 in the host body. The level of this protein in KM kindling group was still significantly higher in comparison to Wistar rats (Fig. 2C).. These results emphasize the potential importance of the gut microbiota as a therapeutic target for therapy of epilepsy. Manipulating the gut microbiota through probiotics or dietary interventions could potentially serve as a therapeutic approach in the context of epilepsy.

In the temporal cortex, our study revealed no statistically significant differences in the level of studied protein between the Wistar and KM control groups as well as between the KM control and KM kindling groups (Fig. 3). The observed changes between the Wistar and KM kindling groups should not be interpreted in isolation from the outcomes of the two previous comparisons.

4 **Conclusion**

In summary, the gut microbiota appears to play role in the epilepsy pathogenesis through the influence of specific microbial compositions on the modulation of seizure activity.

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We observed the compatible changes in the level of NF-kB p65 in the white matter and the changes of populations of *Lactobacillus murinus* and *Lactobacillus reuteri* in all three compared groups of experimental animals. Specifically, the elevated level of this protein in KM control compare to Wistar group and decline of this protein in KM kindling compare to KM control inversely correlated with the abundance of *Lactobacillus murinus* and *Lactobacillus reuteri* species in this groups. Next, we noticed the decreased level of *Enterococcus* bacteria in KM control and KM kindling groups compared to Wistar rats and increased level of *Streptococcus hyointestinalis* in KM kindling rats.

The results of this study may contribute to a better understanding of the complex interactions between host genetics, brain and microbiota of gut, and their implications for health and disease. Continued research in this area is critical to expanding knowledge of the gut microbiota and its impact on host health.

List of abbreviations

KM – Krushinsky-Molodkina rats

NF-kB p65 – nuclear factor kappa-light-chain-enhancer of activated B cells

CNS – central nervous system

BBB – blood brain barrier

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РИСУНКИ

Figure 1. Heatmap of rat groups and bacterial species. WC – Wistar control group; KMC– Krushinsky-Molodkina rats, control group; KM21+7– Krushinsky-Molodkina rats, kindling group.

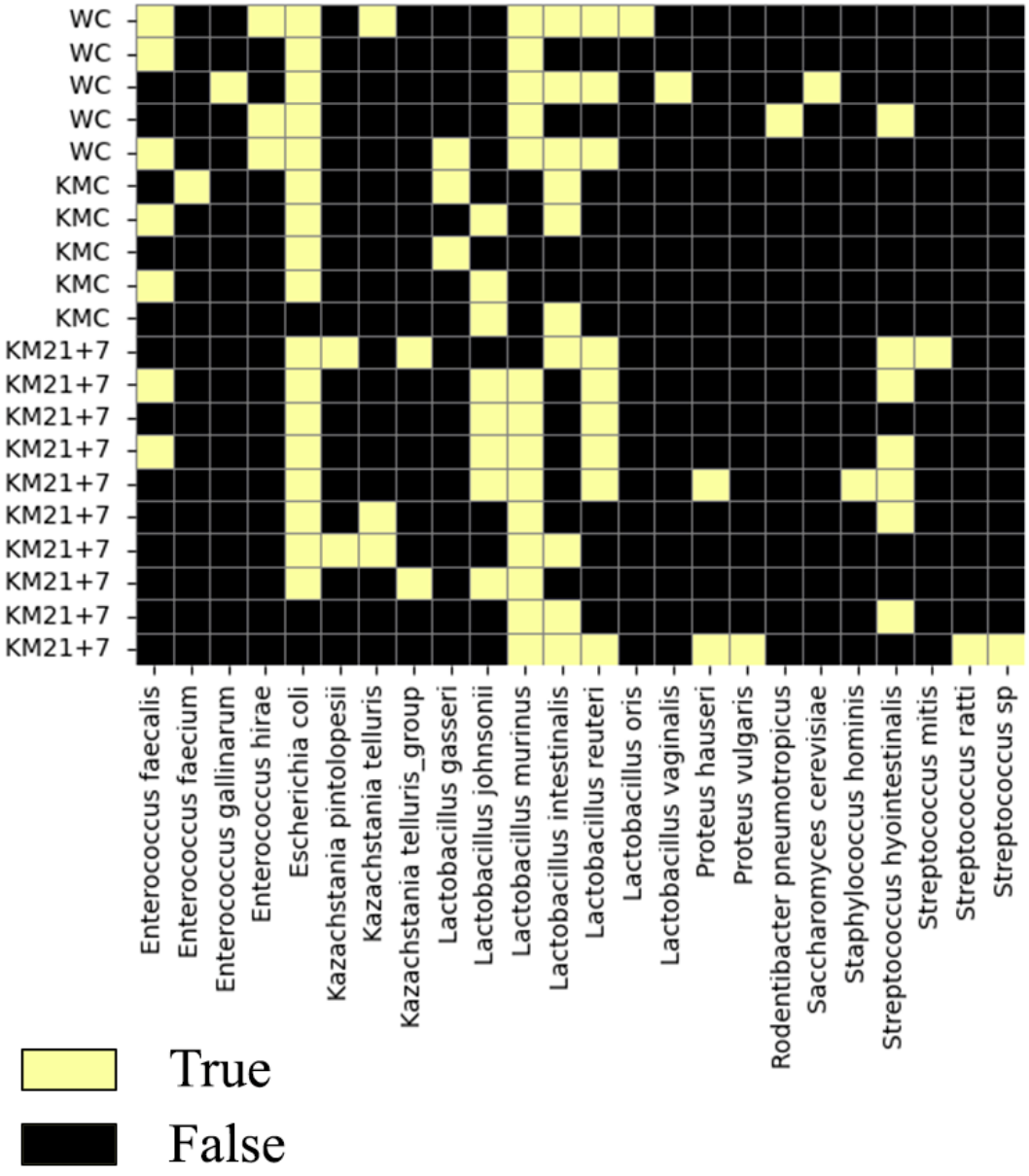

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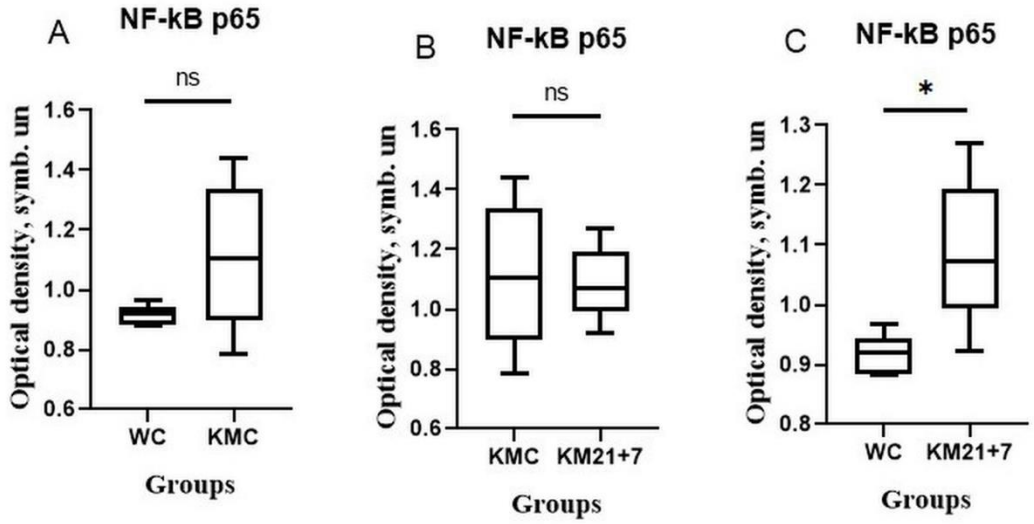
Figure 2. NF-kB p65 expression in white matter of temporal lobe. WC – Wistar rat control group, KMC – Krushinsky-Molodkina rat control group, KM21+7 – Krushinsky-Molodkina rat kindling group (21 days of audiogenic kindling); * - significant changes ($p<0.05$).



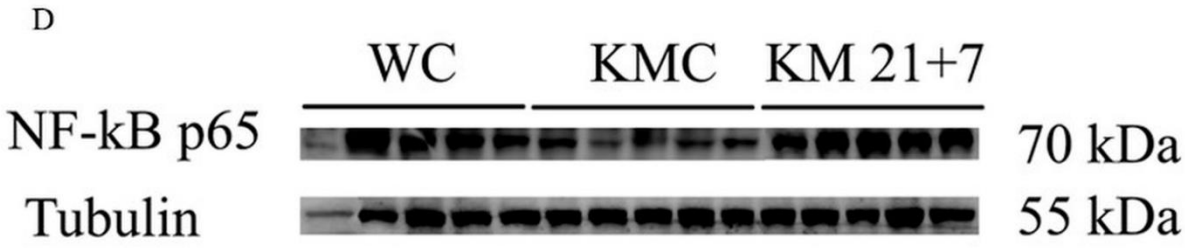


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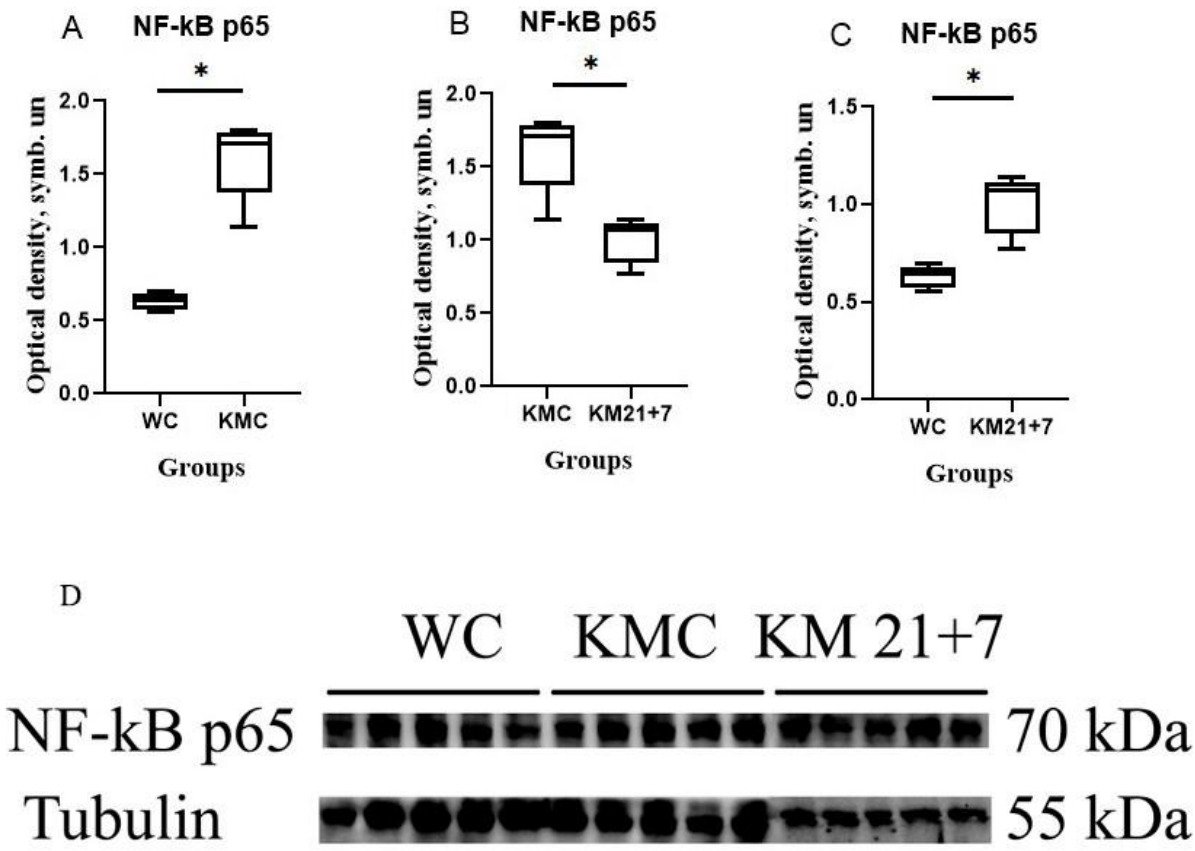
Figure 3. NF-kB p65 expression in cortex of temporal lobe. WC – Wistar rat control group, KMC – Krushinsky-Molodkina rat control group, KM21+7 – Krushinsky-Molodkina rat kindling group (21 days of audiogenic kindling); * - significant changes ($p<0.05$), ns – no significance ($p>0.05$).



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

EXPLORING THE IMPACT OF GUT MICROBIOTA ON EPILEPSY PATHOGENESIS IN KRUSHINSKY-MOLODKINA RATS

ИЗУЧЕНИЕ ВЛИЯНИЯ МИКРОБИОТЫ КИШЕЧНИКА НА ПАТОГЕНЕЗ ЭПИЛЕПСИИ У КРЫС КРУШИНСКОГО-МОЛОДКИНОЙ

Сокращенное название статьи для верхнего колонтитула:

RAT INTESTINAL MICROBIOTA AND EPILEPSY

МИКРОБИОТА КИШЕЧНИКА КРЫС И ЭПИЛЕПСИЯ

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Ключевые слова: Эпилепсия, кишечная микрофлора, ось кишечник-мозг, *Lactobacillus murinus*, *Lactobacillus reuteri*, NF-kB.

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