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Melatonin protects *E.coli* neurons the intestinal microbiota influences meningitis

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SUMMARY

Avian meningitis Escherichia coli(E. coli) can beget acute bacterial meningitis which threatens flesh health, causes great profitable losses in the flesh assiduity, and has lately been suspected as a implicit zoonotic pathogen. Melatonin can offset bacterial meningitis- convinced dislocation of the blood – brain hedge(BBB), neuroinflammation, and reduce mortality. There are adding data showing that melatonin's salutary goods on bacterial meningitis are associated with intestinal microbiota. In this study, our data showed that melatonin soothed neurological symptoms, enhanced survival rate, defended the integrity of the BBB, reduced the bacterial cargo in colorful apkins and blood, and inhibited inflammation and neutrophil infiltration of brain towel in an APEC TW- XM- meningitis mice model. The results of 16S rRNA showed that melatonin pretreatment significantly maintained the composition of intestinal microbiota in APEC- meningitis mice. The cornucopia and diversity of intestinal microbiota were disturbed in APEC TW- XM- meningitis mice, with a dropped rate of Firmicutes to Bacteroides and an increased the cornucopia of Proteobacteria. Melatonin pretreatment could significantly ameliorate the composition and cornucopia of dangerous bacteria and palliate the dropped cornucopia of salutary bacteria. Importantly, melatonin failed to affect the meningitis neurologic symptoms caused by APEC TW- XM infection in antibiotic-pretreated mice. In conclusion, the results suggest that melatonin can effectively help meningitis convinced by APEC TW- XM infection in mice, depending on the intestinal microbiota. This finding is helpful to further explore the specific target medium of melatonin-intermediated intestinal microbiota in the forestallment of and protection against Escherichia coli meningitis.

Keywords: Intestinal microbiota; Bacterial meningitis; Inflammation; melatonin; Blood–brain barrier

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INTRODUCTION

Avian pathogenic Escherichia coli (APEC) are an important extraintestinal pathogenic Escherichia coli (ExPEC). Due to different serotypes, it can beget different conditions, similar as diarrhea, pneumonia, endocarditis, septicemia, and meningitis in flesh. In addition, experimenters have also set up that meningitis- causing APEC and neonatal meningitis Escherichia coli (NMEC) have analogous genome structures and the same beast model; there are also high parallels in inheritable elaboration and ecological distribution. These substantiation suggest that meningitis- causing APEC has a implicit threat of zoonosis, which not only causes huge profitable losses in the flesh assiduity, but also threatens mortal health. APEC TW- XM can infect Muscovy ducks, cravens, and mice and beget severe acute septicemia and meningitis, which show egregious meningitis neurological symptoms with a high probability of acute death. At the same time, it was also set up that the host produced severe systemic inflammation, systemic infection, and the destruction of the blood – brain hedge (BBB). In addition, the BBB is crucial to establishing and maintaining homeostasis in the brain. also, it was set up that, clinically, the symptoms of bacterial meningitis infection include anorexia, puking, and diarrhea, which reflect the changes in the intestinal homeostasis and affect the development of the complaint. For illustration, Listeria monocytogenes infection can change the intestinal microbiota of the host, which induces an increase in the cornucopia of Alloprevotella, Allobaculum, and Streptococcus in the intestinal tract, which destroys the integrity of the intestinal hedge and enters the abdominal blood rotation to promote severe septicemia or meningiti. At present, the use of antibiotics to treat Escherichia coli meningitis can reduce mortality, but it leads to the emergence of further medicine- resistant Escherichia coli and increases the difficulty of treatment [1].

CASE PRESENTATION

To determine the preventative goods of melatonin on TW- XM pathogenicity in ICR mice, three- week-old manly ICR mice were intraperitoneally fitted either with melatonin (10 mg/ kg/ day; 30 mg/ kg/ day; 60 mg/ kg/ day) or NS for seven successive days before TW- XM infection. As shown in Supplementary Figure S1 and Figure 1A, 8 h after infection, mice in the TW- XM and TW- XM MT10 mg/ kg groups began to develop neurological symptoms of meningitis, including internal malaise, anorexia, increased eye concealment, and unformed feces. After about 12 h,

the mice developed storms, neck stiffness, and, eventually, constantly failed of angular bow reversal. The mice in the TW- XM MT30 mg/ kg group and the TW- XM MT60 mg/ kg group still showed languor, lower food input, partial eye stashing to a certain extent, and a many marvels similar as unformed feces, storms, and neck stiffness, which were significantly lower than those in the TW- XM group($p<0.05$). As shown in Supplementary Figure S2 and Figure 1B, the survival rates of the TW- XM group and the TW- XM MT10 mg/ kg group were significantly lower than that of the TW- XM MT30mg/ kg group and the TW- XM MT60 mg/ kg group, that is, the mortality rates of the TW- XM group, TW- XM MT10 mg/ kg group, TW- XM MT30 mg/ kg group, and TW- XM MT60 mg/ kg group were 90, 90, 30, and 40, independently. The below results show that the pretreatment of melatonin at the boluses of 30 mg/ kg and 60 mg/ kg can significantly ameliorate the survival rates of mice and effectively help the circumstance of meningitis in mice infected with APEC TW- XM. thus, melatonin at the cure of 30 mg/ kg was chosen as the attention to help the circumstance and development of meningitis [2].

According to the results of PCoA, clusters of four groups can be set up, that is, the points of each group are concentrated in their separate regions. Compared with the NS group, the MT group is the closest, followed by the TW- XM MT group and the TW- XM group. It can be seen that APEC TW- XM infection can affect the species composition of intestinal microbiota, and melatonin can help the changes in intestinal microbiota species composition convinced by the APEC TW- XM infection.

In order to determine the specific bacterial taxa related to melatonin, the differences in intestinal microbiota of mice in the NS group, MT group, TW- XM group, and TW- XM MT group were compared using the direct discriminant analysis (LDA) effect size (LEfSe) system. The distribution histogram in each group was used to directly dissect the species with significant differences in cornucopia among the three groups. In addition, the length of the histogram represents the cornucopia of species with significant differences. As shown in Figure 4E, there were 9 species with significant differences in the NS group, 10 species with significant differences in the MT group, 8 species with significant differences in the TW- XM group, and 15 species with significant differences in the TW- XM MT group [3].

also, we further anatomized the relative cornucopia of species in Figure 4F. At the phylum position, Firmicute had the loftiest relative cornucopia of intestinal microbial structures in the NS group and the MT group. In discrepancy, the relative cornucopia of Firmicute dropped significantly and Proteobacteria had the loftiest cornucopia of intestinal microbial structures in the TW- XM group. Compared with the TW- XM group, melatonin pretreatment could elevate the relative cornucopia of Firmicute and reduce the relative cornucopia of Proteobacteria in the TW- XM MT group. At the order position, Lactobacillales, Clostridiales, and Bacterioidales are the dominant strains of NS and MT. Although the relative cornucopia of Xanthomonadales in the intestinal microbiota of the MT group was fairly high compared with the NS group, it was still lower than that of the TW- XM group. In the TW- XM group, Xanthomonadales, Enterobacteriales, and Bacterioidales were the dominant strains in the group. In the TW- XM MT group, melatonin pretreatment could significantly reduce the relative cornucopia of Xanthomonadales and Enterobacteriales and increase the relative cornucopia of Clostridiales and Lactobacillales compared with the TW- XM group. At the rubric position, Lactobacillus was the major dominant strain in the NS group, MT group, and TW- XM MT group, and Stenotrophomonas, Helicobacter, and Bacteroides were the major dominant strains in the TW- XM group. In the TW- XM MT group, melatonin pretreatment could significantly reduce the relative cornucopia of Stenotrophomonas, Helicobacter, and Bacteroides, and increase the relative cornucopia of Lactobacillus compared to the TW- XM group. These results suggest that APEC TW- XM infection can induce changes in the species composition and relative cornucopia of intestinal microbiota in mice, while melatonin can help and ameliorate changes in the species and relative cornucopia of intestinal microbiota convinced by bacteria [4].

RESULTS AND DISCUSSION

Intestinal microbiota is nearly identified with bacterial meningitis. The pathogenic medium of Escherichia coli meningitis is complex, and bacteremia caused by bacterial irruption of blood, destruction of the blood – brain hedge (BBB), and inordinate inflammation are the main factors of meningitis and brain injury. numerous studies have demonstrated the defensive goods of melatonin on whim-whams injury, the integrity of the BBB, andanti-inflammation in bacterial meningitis, but its goods on intestinal microbiota hadn't been explored. In this trial, we illustrated that melatonin intraperitoneal administration for one week could significantly help the circumstance of bacterial meningitis, cover the integrity of the BBB, reduce the bacterial loads in apkins and blood, and palliate systemic inflammation. Importantly, melatonin was set up to maintain the composition of intestinal microbiota, for which the changes convinced were nearly related to APEC TW- XM infection.

In this study, melatonin was set up to reduce the drop in the cornucopia of salutary bacteria and the increase in the cornucopia of dangerous bacteria in intestinal microbiota convinced by APEC TW- XM and play a defensive part in maintaining the balance of intestinal microbiota. still, when mice were pretreated with four kinds of antibiotics to exclude intestinal microbiota, melatonin pretreatment couldn't effectively palliate the clinical symptoms of meningitis, and the survival rate was only 10. It's suggested that intestinal microbiota are involved in the preventative effect of melatonin on APEC TW- XM- convinced meningitis. This result is harmonious with the fact that the destruction of microbiota by broad- diapason antibiotics weakens

the host's resistance to invasive pathogen colonization. Melatonin doesn't effectively reduce the colonization of enterotoxigenic Escherichia coli in the bowel of antibiotic-treated weaned mice, indicating that melatonin mediates intestinal microbiota to help host resistance to pathogen colonization. In addition, former experimental studies have shown that intestinal microbes and their metabolites play an important part in the conformation of the BBB in sterile mice. Compared with creatures fed routinely, the permeability of the BBB by macromolecules in aseptic mice increased significantly, indicating that intestinal microbiota are involved in the integrity of the BBB. The results show that the integrity of the BBB in mice in the MT Antibiotics group was destructed compared with the TW- XM MT group, indicating that melatonin defended the integrity of the blood – brain hedge of meningitis mice by maintain healthy intestinal microbiota. also, it was set up that melatonin reduced the expression of seditious factors IL- 1β, TNF- α, and IL- 6 in serum and brain towel and inhibited a large number of neutrophil infiltrations in brain towel, depending on healthy intestinal microbiota [5].

CONCLUSION

This study demonstrated that melatonin is a potent preventative agent against APEC TW- XM- convinced mice meningitis, dwindling the prevalence of bacterial meningitis. The preventative goods of melatonin on the integrity of the BBB, reduced bacterial cargo in colorful apkins and blood, and inhibited inflammation and neutrophil infiltration of brain towel may be dependent on intestinal microbiota. These findings are helpful to further explore the specific medium of melatonin- intermediated intestinal microbiota in the forestallment of and protection against Escherichia coli meningitis.

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CONFLICT OF INTEREST

None.

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