Chronic nasal inflammation during the lactation period induces transient and long-term effects of gut microbiota in mice

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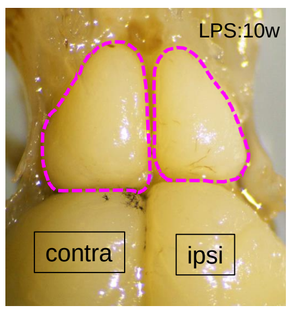
Introduction

1. Impact of early life events on health and disease
   - Maternal and neonatal immune activation leads to psychiatric disorders.
   - Gut microbiota begins to reside the host body after birth and develops during the lactation period. The use of antibiotics in this period leads to a variety of diseases, such as obesity, allergy, asthma, diabetes, and neuropsychiatric disorders.
   - Inflammation- and/or antibiotics-induced dysbiosis in early life may cause neuropsychiatry diseases. But it is not clear whether dysbiosis is retained whole life long.

2. Chronic nasal inflammation perturbs gut microbiota in adult mice
   - Repeated unilateral intranasal LPS administration (3 times/ week) for 10 weeks (wks) causes ipsilateral olfactory bulb atrophy.
   - Bilateral chronic nasal inflammation leads to dysbiosis of gut microbiota particularly in male mice.
   - They show the common dysbiosis patterns with human and animals under stress and depression.



Hasegawa-Ishii S. et al. *eNeuro* (2020)

Male	Genus	
Up	*Bacteroides*	1.9
	Oscillospira	1.7
	Parabacteroides	2.1
	Prevotella	2.2
Down	*Allobaculum*	0.3
	Lactobacillus	0.3

Mishima Y. et al. *Sci Rep* (2021)

Hypothesis

Perturbation of gut microbiota during the lactation period may induce persistent dysbiosis throughout the life, which may lead to neuropsychiatric disorders.

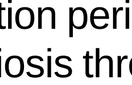
Specific Questions

(1) Does chronic nasal inflammation during the lactation period cause dysbiosis?

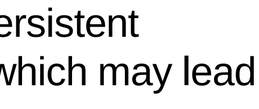
(2) If so, does the dysbiosis of gut microbiota during the lactation period is retained whole life long?

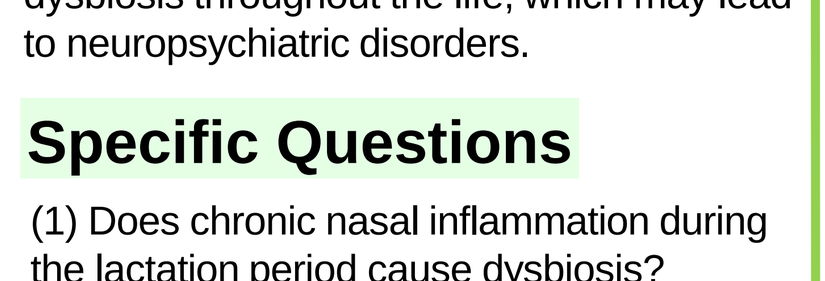
Methods

Male and female mice were co-housed with mom.



Saline- and LPS-treated mice were co-housed. Male and female mice were in different cages.





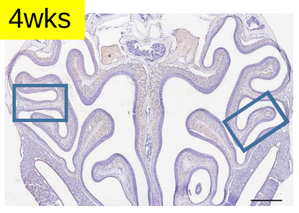
- Body weight
- Histological analysis
- 16SrRNA analysis of gut microbiota using cecal contents

I have no COI with regard to the presentation.

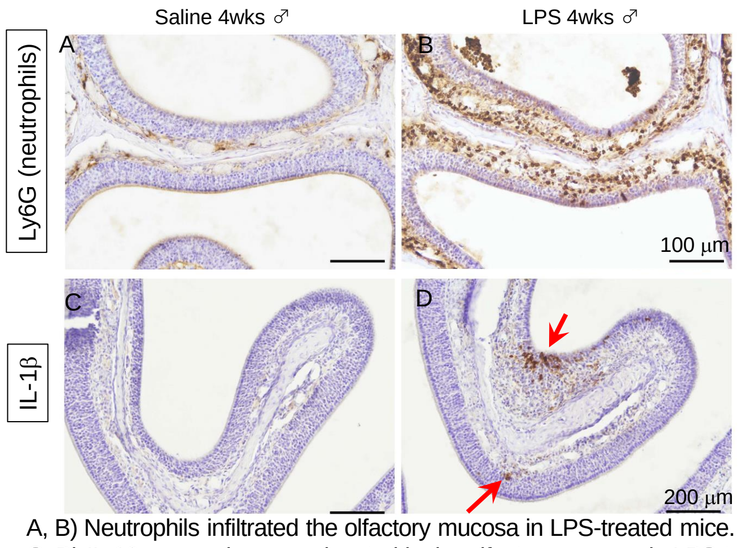
Results

① Nasal inflammation

4wks



In LPS-treated male and female mice, nasal inflammation occurred similarly at 4wks.

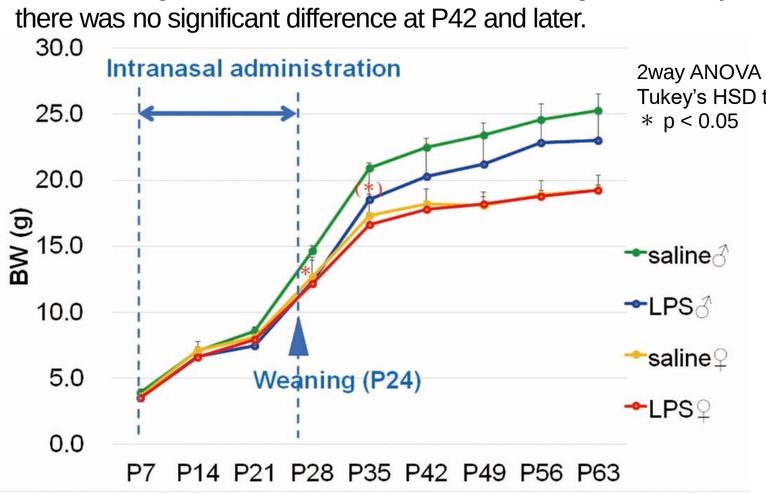


A, B) Neutrophils infiltrated the olfactory mucosa in LPS-treated mice.
C, D) IL-1β expression was elevated in the olfactory mucosa in LPS-treated mice.

② Growth curve of the body weight

Body weight did not change in saline- and LPS-treated male or female mice during the lactation period, indicating that baby mice sucked similar amount of mothers' milk.

After weaning, LPS-treated male mice lost the weight transiently, but there was no significant difference at P42 and later.



2way ANOVA
Tukey's HSD test
* $p < 0.05$

Saline♂ n = 13 (P7-P21), 12 (P28), 6 (P35,P63), 7 (P42-P56)
LPS♂ n = 14 (P7-P21), 12 (P28), 7 (P35-P63)
Saline♀ n = 19 (P7-P21), 18 (P28), 13 (P35-P56), 12 (P63)
LPS♀ n = 21 (P7-P21), 20 (P28), 14 (P35-P63)

③ Comparison in the gut microbiota

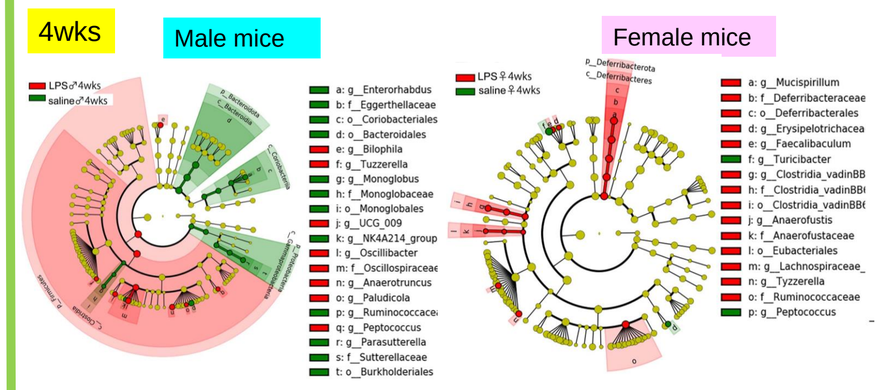
(1) Diversity and phylum analysis

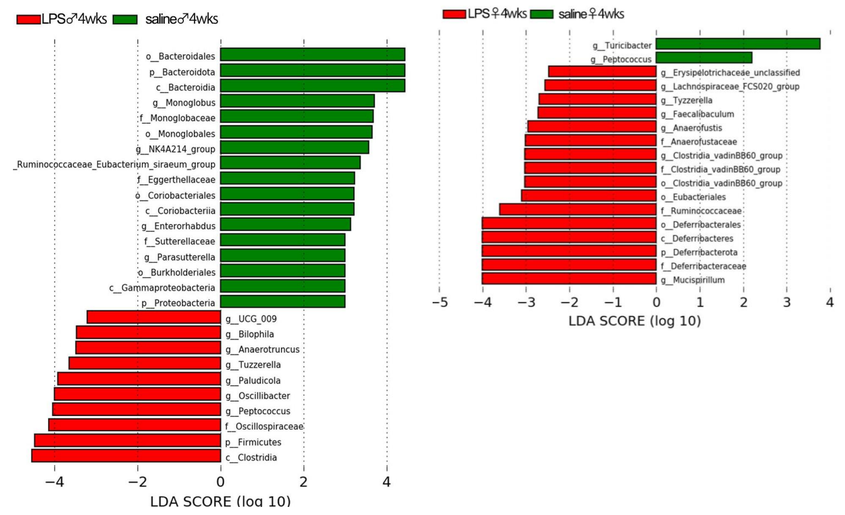
The composition of the gut microbiota changed in LPS-treated mice compared to saline-treated mice at 4wks, but it became similar at 10wks.

A, B) Gut microbiota in LPS-treated mice was significantly different from that of saline-treated mice in male and female at 4 wks, but not at 10 wks by jaccard distance (Perm ANOVA).. C, D) The abundance of Bacteroidota tended to be lower and that of Firmicutes was significantly higher in LPS-treated male mice, while the abundance of Deferribacterota was significantly higher in LPS-treated female mice at 4wks. At 10wks, only Desulfobacterota increased in LPS-treated female mice.

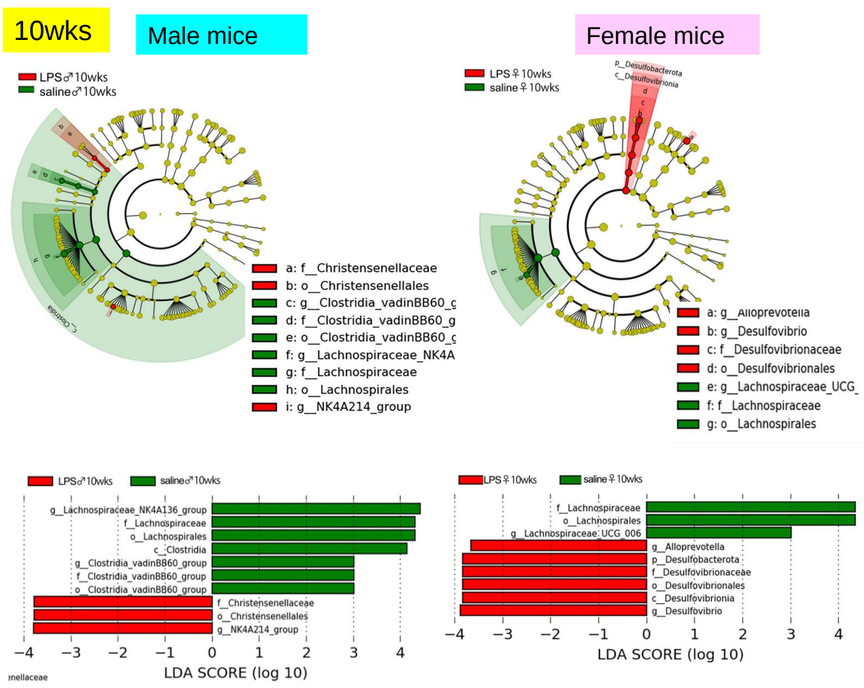
(2) Lefse analysis

The composition of gut microbiota changed differently in male and female mice by intranasal LPS administration at 4wks.





The composition of gut microbiota became similar in 10wks compared to 4wks, but there were still some differences in the ratio of bacteria. Particularly, the abundance of family Lachnospiraceae was lower in LPS-treated male and female mice at 10wks.



Summary & Discussion

- Chronic nasal inflammation during the lactation period caused dysbiosis after weaning, which was no longer detected when they grew up to the adult.
- At 4wks, the ratio of harmful bacteria increased and useful bacteria decreased in LPS-treated male mice, suggesting that mild systemic inflammation may occur by intranasal LPS administration.
- At 10wks, the component of gut microbiota became similar, but the ratio of family Lachnospiraceae decreased in LPS-treated male and female mice.
- Family Lachnospiraceae is butyric acid producing bacteria. Thus, the decrease in the useful bacteria may affect the host physiology.

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