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Chronic exposure to low concentrations of lead induces metabolic disorder and dysbiosis of the gut microbiota in mice

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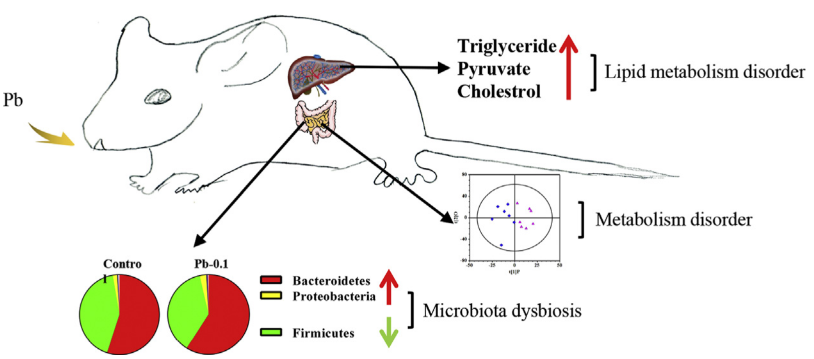
HIGHLIGHTS

- Chronic Pb exposure induced the dysbiosis of gut microbiota in mice.
- Chronic Pb exposure changed the composition of metabolites in the cecum contents.
- Chronic Pb exposure disturbed hepatic lipid metabolism in mice.

GRAPHICAL ABSTRACT



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ABSTRACT

Lead (Pb) is one of the most prevalent toxic, nonessential heavy metals that can contaminate food and water. In this study, effects of chronic exposure to low concentrations of Pb on metabolism and gut microbiota were evaluated in mice. It was observed that exposure of mice to 0.1 mg/L Pb, supplied *via* drinking water, for 15 weeks increased hepatic TG and TCH levels. The levels of some key genes related to lipid metabolism in the liver increased significantly in Pb-treated mice. For the gut microbiota, at the phylum level, the relative abundance of *Firmicutes* and *Bacteroidetes* changed obviously in the feces and the cecal contents of mice exposed to 0.1 mg/L Pb for 15 weeks. In addition, 16 s rRNA gene sequencing further discovered that Pb exposure affected the structure and richness of the gut microbiota. Moreover, a ^{1}H NMR metabolic analysis unambiguously identified 31 metabolites, and 15 metabolites were noticeably altered in 0.1 mg/L Pb-treated mice. Taken together, the data indicate that chronic Pb exposure induces dysbiosis of the gut microbiota and metabolic disorder in mice.
Capsule: Chronic Pb exposure induces metabolic disorder, dysbiosis of the gut microbiota and hepatic lipid metabolism disorder in mice.

1. Introduction

Environmental pollutants, including various chemical, biological, and physical agents, are increasingly being recognized as having considerably harmful effects on living organisms (Greven et al., 2016; Liu et al., 2016; Liu et al., 2017; Kais et al., 2018). Lead (Pb) is the most represented toxic, non-essential heavy metal that can affect humans through

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food and water. Consumption of food with high concentrations of Pb can result in some serious health problems, including liver damage (Zhang et al., 2015a, 2015b), central nervous system disorder, inflammatory response, and gut microbiota dysbiosis (Breton et al., 2013a, 2013b). The gut microbiota has been considered as a complex “hidden” organ. The gut microbiota protects the host from infection and disease and maintains the normal physiological functions of host. The presence or absence of specific species is essential for maintaining homeostasis both inside and outside the intestinal tract (O'Hara and Shanahan, 2006; Sekirov et al., 2010). Hence, evaluation of the co-metabolic interactions of the host-gut microbiota can provide new insight into the important role of the gut microbiota in host health. Although the composition of the gut microbiota is relatively stable in animals, this composition can be influenced by different environmental factors, food, drugs and even stress (Nicholson et al., 2003; Zhang et al., 2015a, 2015b). Non-absorbed heavy metals (HMs) remain at high concentrations in the gut microenvironment, where they may have a direct impact on the gut ecosystem and on the overall physiology of the gut (James et al., 1985; O'Hara and Shanahan, 2006). Biological systems are exposed to complex environmental ecosystems where the chemical element species may have synergistic or antagonistic effects and have to be considered in relation to the metabolic processes involved (Liu et al., 2015). Since microbiome play a major role in host homeostasis, the effects of heavy metals on the gut microbiota has received much attention in recent years (Zhang et al., 2015a, 2015b; O'Hara and Shanahan, 2006; Sekirov et al., 2010).

Pb is a major heavy-metal pollutant in environmental systems and is the cause of numerous environmental issues (Mortada et al., 2015). More importantly, Pb can cause adverse effects even at very low concentrations (Gupta et al., 2013). The European Union has set the maximum acceptable level of Pb in fresh fish as 0.3 mg/kg (Garcia-Barrera et al., 2012). Given the wide range of potential targets of Pb, it is possible that Pb can change the composition of the gut microbiota and cause subsequent adverse effects in animals (Li et al., 2015a, 2015b; Jin et al., 2017b). However, it is still unclear whether and how chronic exposure with Pb impacts the gut microbiota or metabolism in detail. Here, we investigated the effects of Pb on hepatic energy metabolism and on the gut microbiota and examined the toxicological mechanisms involved. The results obtained in this study provide new insight into the potential health risks of Pb in animals.

2. Materials and methods

2.1. Chemicals, animals and experimental protocol

Lead acetate trihydrate ($C_4H_6O_4Pb \cdot 3H_2O$) was purchased from Sangon Biotech (Shanghai, China). A total of 28 of five-week-old ICR male mice were purchased from the China National Laboratory Animal Resource Center. The mice were reared in an animal facility (illuminated with strip lights; 200 lx at cage level with a photoperiod of 12 h light and 12 h dark; 22 ± 1 °C) for 1 week prior to the experiments, and each mouse had a separate cage. Water and food were available *ad libitum* during the entire experimental period. Mice were randomly divided into 4 groups containing 7 animals each. One group, serving as a control, was provided with lead-free water, and the other three groups were provided with drinking water containing 0.01, 0.03, or 0.1 mg/L Pb for 15 weeks. In this study, the doses of Pb were selected were lower than some reported environmental concentrations and even equal to the permitted concentration of Pb in tap water (0.05 mg/L, GHZB1-1999).

After exposure, all mice were sacrificed after anesthetization with ether. Sera were collected and stored at −40 °C before use. Liver and cecal content were quickly collected and immediately frozen by liquid

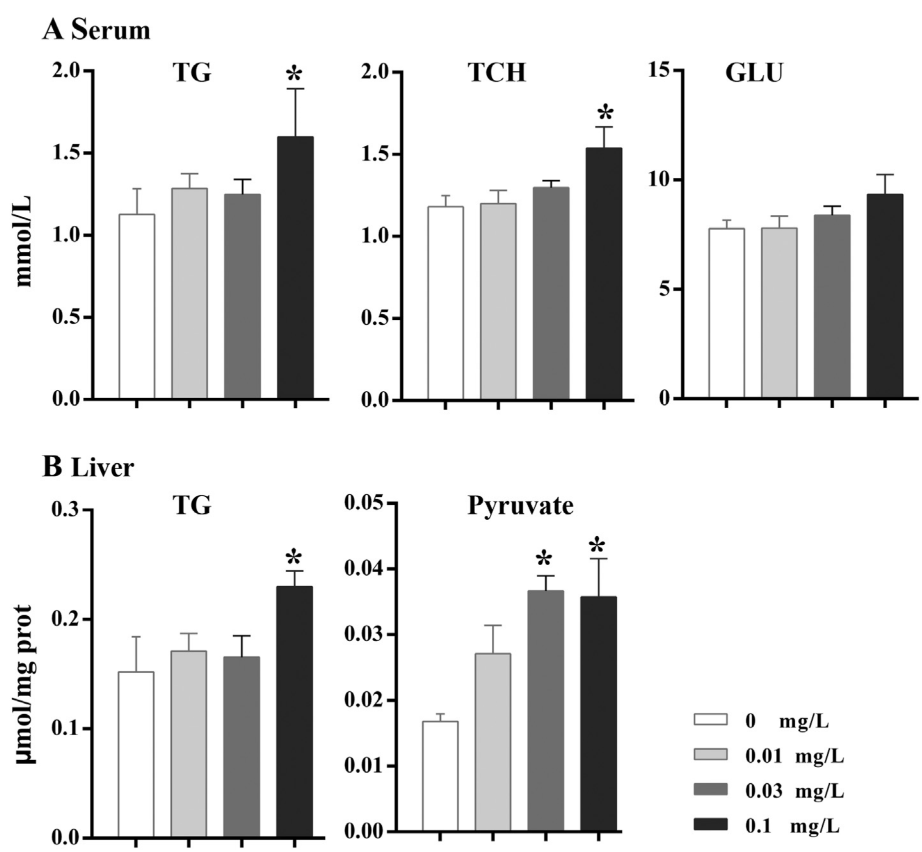

Fig. 1. Effects of chronic Pb exposure on liver and serum parameters in mice. Male mice were exposed to 0.01, 0.03, and 0.1 mg/L Pb-supplemented drinking water for 15 weeks. A. Effects of chronic Pb exposure on the levels of TG, TCH, and GLU in the serum; B. Effects of chronic Pb exposure on the levels of TG and pyruvate in the liver. The presented values are the means±SEM ($n = 7$). An asterisk indicates a significant difference (*$p < 0.05$) between control and Pb treated groups.