Targeted deletion of Fatty Acid Binding Protein (FABP) does not influence perfluorooctanesulfonic acid (PFOS) tissue distribution or elimination

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THE UNIVERSITY OF RHODE ISLAND COLLEGE OF PHARMACY

STEEP Sources, Transport, Exposure & Effects of PFASs
UNIVERSITY OF RHODE ISLAND SUPERFUND RESEARCH PROGRAM

Introduction

- Per- and polyfluoroalkyl substances (PFAS), such as perfluorooctane sulfonic acid (PFOS) are persistent environmental organic pollutants (1).
- Liver is an important target for PFAS but the mechanisms that the PFAS interact with hepatocytes proteins and how these interactions can affect their absorption and distribution remain to be understood.
- Liver-type Fatty acid binding protein (LFABP) is a highly expressed liver protein, which represents 2%-5% of the total cytosolic proteins and is important in lipid-mediated biological processes (2, 3).

Hypothesis

- PFAS structurally resemble fatty acids and it has been shown that they bind to FABP using only *in vitro* techniques.
- We hypothesized that PFOS binding and distribution to liver would be decreased in mice lacking Fabp in either liver or intestine.

Materials and Methods

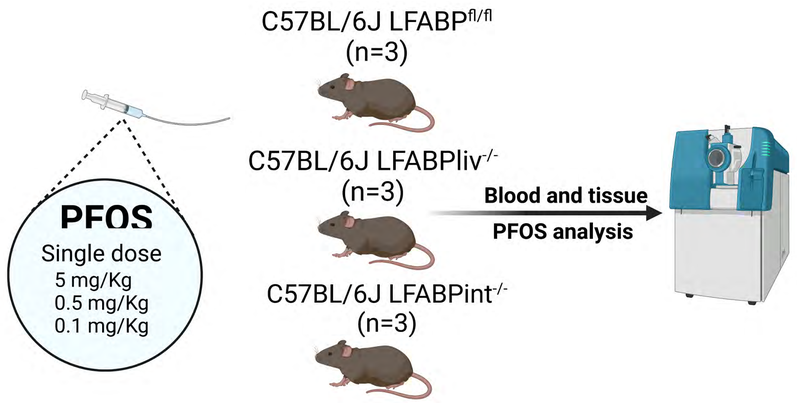


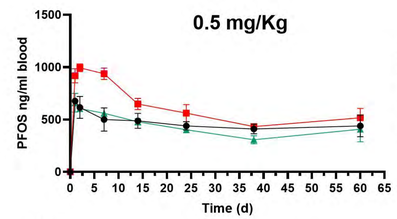
Figure. 1. Treatment Paradigm. Serial blood, urine and fecal samples collected before sacrificing the mice at day 65.

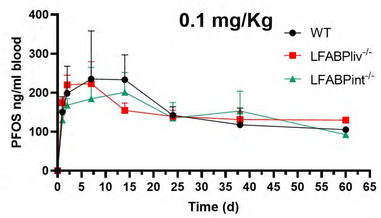
PFOS Extraction

Figure. 2. PFOS extraction. Sample preparation was accom-plished using roQ QuECh-ERS kit (Phenomenex)

- ***In vitro* FABP binding** data was evaluated using an equilibrium dialysis with an HTDialysis apparatus. Test compounds (PFOS, PFOA, and PFHxs) spiked in different liver homogenate models was run against blank buffer to calculate for fraction unbound (fu).

Results





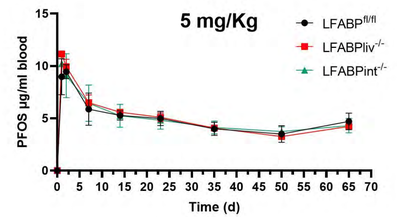


Figure 3. Time course of PFOS in blood of Control, LFABP$^{-/-}$, and IFABP$^{-/-}$ following oral gavage at 5, 0.5, and 0.1 mg/kg body weight (Mean ± SEM). Blood samples were processed and no significant difference with the concentration of 0.1 or 5 mg/kg and no significant difference was observed at time points after 15 days with the concentration of 0.5 mg/kg.

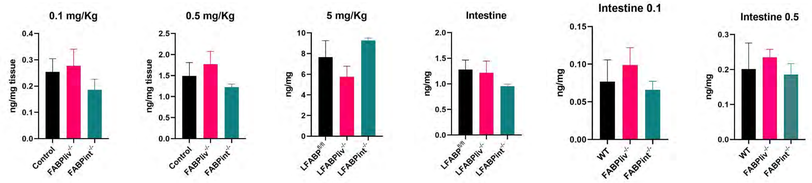
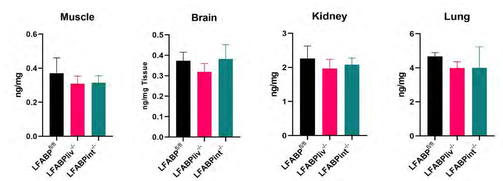


Figure 4. Concentration of PFOS in liver of B6 mice following oral gavage dosing at 5, 0.5, and 0.1 mg/kg body weight (Mean ± SEM). No significant difference of PFOS concentration in liver, intestine or other tissues was observed (p>0.05, n=3-5).

Figure 5. Concentration of PFOS in tissues following oral gavage dosing at 5 mg/kg body weight (Mean ± SEM). No significant difference of PFOS concentration was observed (p>0.05, n=3)



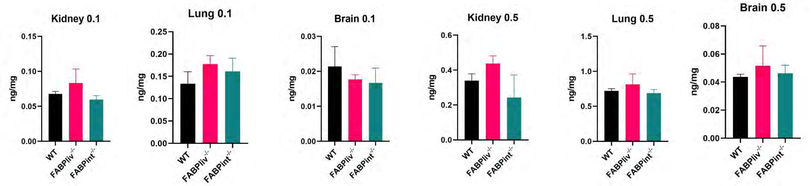


Figure 6. Concentration of PFOS in kidney, lung, and brain of B6 mice following oral gavage single dosing at concentrations of 0.5, and 0.1 mg/kg body weight (Mean ± SEM). No significant difference of PFOS concentration was observed in kidney, and brain at either 0.5 or 0.1 mg/kg between Control, LFABP-/-, and IFABP-/-. Moreover, no significant difference in PFOS concentration was observed in lung with the concentration of 0.5 mg/kg. (p>0.05, n=3-5).

Results Cont'd

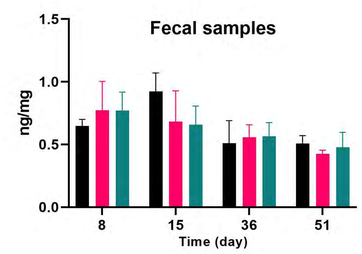


Figure 7. PFOS concentration in urine and feces (Mean ± SEM). No significant difference was observed among three groups (p>0.05). The PFOS is mostly eliminated through renal clearance.

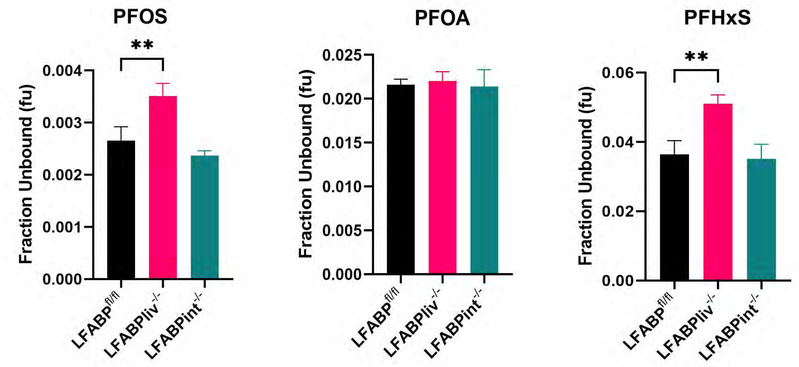


Figure 8. *In vitro* binding assay. For PFOA, the fraction unbound was similar in control, LFABPliv$^{-/-}$, and LFABPint$^{-/-}$ mice, which shows FABP is not critical for determining PFOA tissue binding. Regarding PFOS, and PFHxS, the fraction unbound in LFABPliv$^{-/-}$ mice are higher than LFABP$^{fl/fl}$ controls. The hypothesis of these results was confirmed in *in vivo* study with liver knock out FABP mice.

Summary and Conclusions

Studies have shown that the different binding affinities of various PFAS to LFABP contribute to their tissue distribution (4), Bioaccumulation and bioconcentration potential (5) and placental transfer (6). Other studies (7-8) have calculated the dissociation constants for PFAS binding with serum albumin, serum proteins, and LFABP which the findings show a very large range of Kd for the PFAS. Given these information, this is the first study focusing on the contribution of liver FABP on toxicokinetic aspects of PFOS and the current findings didn't show the LFABP as a significant protein.

References

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