Perinatal exposure to Bisphenol A induces sex-specific modifications in lipid profile of mouse liver

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Introduction

Bisphenol A (BPA) is a major concern to public health due to its properties as an endocrine disrupting chemical (EDC) and its important worldwide production. Extensively found in the environment, humans are exposed by many routes such as oral, inhalation and transdermal. BPA is metabolized in the liver to form BPA-glucuronide and excreted within urine. One main issue is the exposure during pregnancy. Indeed, the fetus can reactivate the inactive BPA-glucuronide and exacerbate the exposure to bioactive BPA [1]. It has been recently reviewed that estrogenic properties of EDC can be linked to the worldwide rise of metabolic diseases (obesity, insulinoresistance and Type 2 Diabetes) [2]. We assessed the effect of perinatal exposure to BPA on mouse liver metabolism by non-invasive *in vivo* ^{1}H Magnetic Resonance Spectroscopy (MRS).

Methods

Animals and Treatments

Fertilised Swiss female mice (n=6) are injected intraperitoneally during gestation and lactation (from Embryonary day 1 until 3 weeks) with 20 µg/kg of body weight/day of BPA diluted in sunflower oil or vehicle only (sunflower oil) (**Fig 1**). Male and female pups are separated in 4 experimental groups: Male Control (n=13); Female Control (n=16); Male BPA (n=19); Female BPA (n=16).

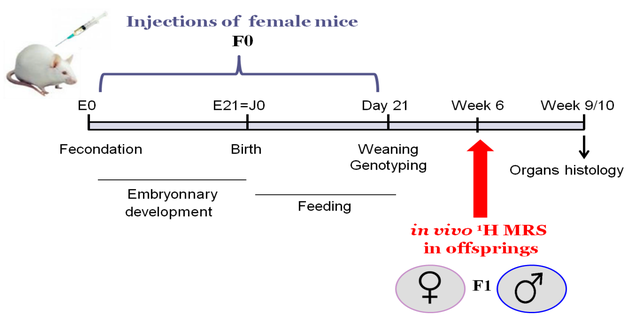

Figure 1: *Experimental protocol*

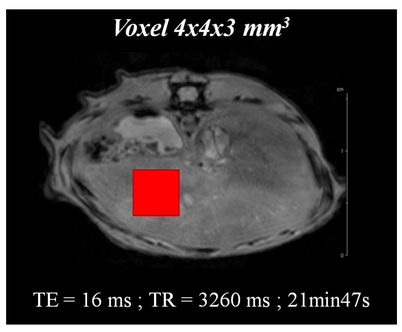

Figure 2: *Axial Image of mouse abdomen; the voxel is placed in the right liver lobe*

Magnetic Resonance Spectroscopy

At 6 weeks, Magnetic Resonance acquisition is performed on a 7T horizontal magnet (70/16 Bruker Pharmascan). PRESS (Point Resolved Spectroscopy) sequence (voxel 4x4x3 mm^3; TE=16ms; TR=3260 ms) is used to characterise the lipid profile in the right liver lobe (**Fig 2**).

Quantification

Area under each peak is measured in arbitrary unit by ERETIC method (a synthetic signal previously calibrated and then integrated to each spectrum in post-treatment). The rTUFA (Total Unsaturated Fatty Acids relative to total amount of fatty acids: 5.4/1.3 ppm) and rPUFA (Polyunsatured Fatty Acid relative to total amount of fatty acids: 2.8/1.3 ppm) are calculated based on [3]. Welch-corrected t test is realised and $p<0.05$ is significant.

Results

A significant increase in lipid peaks have been measured in Female BPA (**Fig 3 & 4**): methyl (+71.4%), methylene (+78.8%), allylic (+68.9%), α methylene to carbonyl (+80.9%) and methine (+51.2%) *vs* Female Control (mean±SEM) ($p<0.05$). A decrease of 33.4% of rPUFA is measured in Female BPA group (*vs* Female Control: $p=0.07$) (**Fig 5**). There is no difference in lipid profile in Male Control *vs* Male BPA (**Fig 4 & 5**).

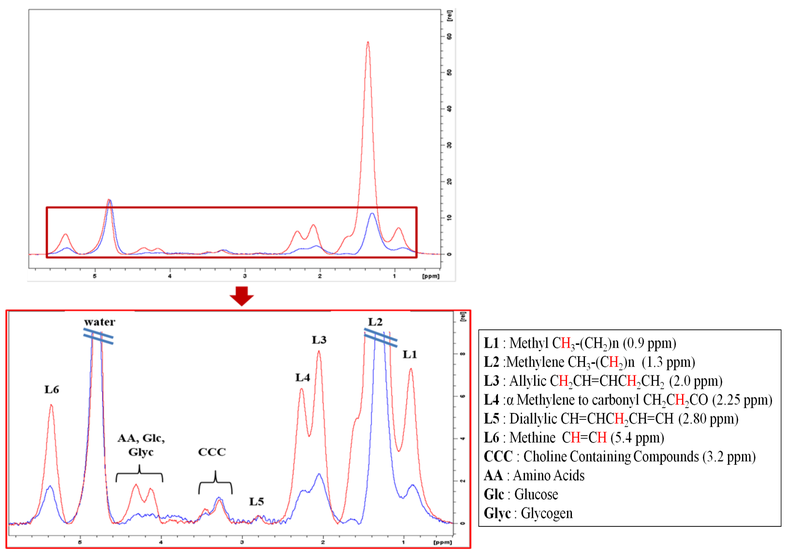

Figure 3 **(a)** *Superposition of female mice liver spectra and* **(b)** *shows insert in (a): female control (blue) and female BPA (red)*

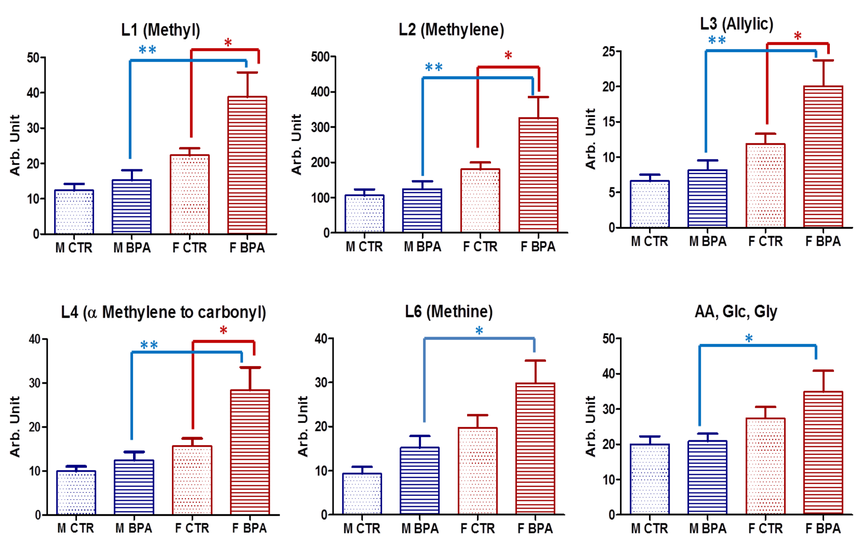

Figure 4: *Histograms representative of lipid metabolism (L1 to L6) and glucose metabolism (AA, Glc, Gly)*

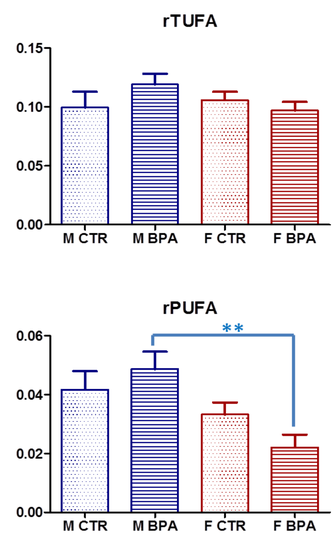

Figure 5: *Histograms of* ***rTUFA*** *(Total Unsaturated FA relative to total FA) &* ***rPUFA*** *(Polyunsaturated FA relative to total FA)*

Discussion

We have shown that a gestational and lactational exposure to BPA at a very low dose (20 µg/kg/day < Tolerable Daily Intake 50 µg/kg/day) induces a sex-specific alteration of the hepatic lipid composition in young female mice (6 weeks). It has been shown recently that the perinatal exposure to BPA (5 mg/kg/day in the diet) alters fetal liver biochemical maturation in female offspring only [4]. An increase in fatty acids (palmitic and oleic acids: major constituents of triglycerides) as well a decrease in the PUFA have been measured in mice directly treated with 50 µg/kg/day BPA [5]. A decrease in PUFA in mice (by its depletion in the diet) have been previously demonstrated to lead to hepatic steatosis [6]. BPA exposure during pregnancy and lactation alters fatty acids composition in female offspring at 6 weeks which might lead to hepatic steatosis later in adulthood. Histological studies (Oil Red O and Hematoxylin Eosin staining) will be realised to confirm the steatosis.

References

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