Study in mice of the transcriptional effects of PCB118 and PCB153 in liver, adipose tissue, muscle and colon: Highlighting of Glut4 and Lipin 1 as main targets for PCB induced metabolic disorders

MAY Phealy1, SAUZET Christophe1, LOUIS Laurence2, BENBRAHIM Karim3, ABRALDES Joelle1, PICCERELLE Philippe1, CHAMPION Serge1, VILLARD Pierre-Henri1
1. IMBE - UMR CNRS 7263 - IRD 237 Aix-Marseille Université Campus Timone - Faculté de Pharmacie, 27 Boulevard Jean Moulin, F-13385 Marseille cedex 05, France.
2. Medical Genetics and Functional Genomics, Inserm UMR_S910, Aix-Marseille Université Campus Timone - Faculté de Médecine, 27 Boulevard Jean Moulin, F-13385 Marseille cedex 05, France.

Introduction:
Today there is a worldwide pandemic of diabetes and obesity. The increasing prevalence of these pathologies cannot be only explained by the modification of the way of life (hypercaloric diet and sedentary lifestyle) and genetic susceptibilities. Environmental pollutant exposure seems to be also involved.

PCB are polyhalogenated organic compounds which are widespread disseminated, notably in water. Recent epidemiological studies suggested that PCB are potent endocrine disruptors and environmental exposure (notably through fish consumption) is associated to an increase of metabolic diseases such as metabolic syndrome and type 2 diabetes. However, molecular mechanisms involved in the etiology of these diseases are poorly understood.

However, molecular mechanisms involved in PCB-induced metabolic disorders remain poorly understood. The aim of our study performed in mice, was to evaluate in various tissues (liver, visceral adipose tissue, muscle, and colon) the genomic effects of a subchronic exposure to PCB118 (dioxin-like PCB), or to PCB153 (non-dioxin-like PCB), or to an equimolar mixture of PCB118 and PCB153.

Methods:
Animals: male C57Bl/6 mice were exposed at 10 or 100 μmol/kg bw for 30 days (P at Day0 and Day15) to a PCB-DL (PCB118), or to PCB-non DL (PCB153), or to a mixture of PCB118 and 153. There were 9 mice per group.

Blood biochemical parameters: Blood levels of glucose, cholesterol (total and HDL), triglycerides, phospholipids, and hepatic function markers (AST, ALT, ALK) were evaluated at D30. Genomic analyses in liver, brown adipose tissue, muscle and colon: Total RNA was extracted using Triozol Reagent®. Genomic analyses were performed using Whole Mouse Genome Microarray Kit (4x44k) from Agilent® (France). Data were analysed using Genespring® and public data bases. Only changes greater than two fold were considered and further verified by qRT-PCR.

Results:

Conclusion:
In summary, our results showed that short term exposure to PCB118, or PCB153, or a mixture of PCB118 and PCB153 enhances triglyceride circulating levels, but glycemia remains unaffected. Interestingly, some observed effects are higher with the lowest studied doses of PCB, as it has already been described for numerous endocrine disruption processes.

Among the studied tissues, we did not observed any modification of the expression of genes involved in inflammation, such as cytokines or chemokines.

The main transcriptional effects were observed in visceral adipose tissue and in liver. We demonstrated a downregulation of lipin1 and Glut4 expression in these two target organs. In adipose tissue, we also showed a downregulation of Agpat2, Ss25as1, and Fasn. These genes are involved in lipid metabolism and are associated to insulin resistance. In muscles, we observed an induction of Cnfl and Fads3 expression which could also be involved at least in part in the reduction of insulin sensitivity. The induction of Fads3, suggested that PCB could induce mitochondrial dysfunction in muscles. Metabolic side-effects of PCB could also implicated the modulation of Cnfl in the hypothalamus which controls appetite and regulates AMPK activity. Moreover, we are exposed through our alimentation to various exogenous compounds including procarogens such as PAH and arylamines. Their bioactivation catalyzed by CytoP can induce inflammatory responses, which could enhance metabolic effects of PCB since type 2 diabetes is linked to low grade inflammation of visceral adipose tissue.

Even if our results suggested that adipocytes are the main target in metabolic disorders induced by PCB, further studies are required to fully elucidate the involved mechanisms, notably the link between Sirt1 and Glut4 expression and the redistribution of Glut4 from intracellular storage sites to the plasma membrane. Moreover, it would be of interest to better characterize cocktail effects and evaluate the implication of epigenetic regulations.