Nutritional Intervention to Modify Pro-atherogenic Effects of Persistent Organic Pollutants

Bernhard Hennig[1,2,3] Zuzana Majkova[3], Gudrun Reiterer[2], Lei Wang[2], Eun Jin Lim[1], Yuan Yuan Zheng[2], Beth Oesterling[3], Michal Toborek[3,4], and Lisa Cassis[2,3]

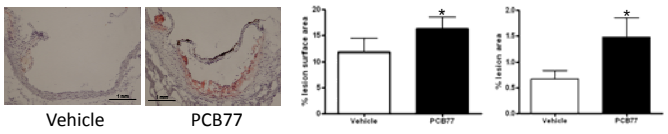
[1]Molecular and Cell Nutrition Laboratory, College of Agriculture, Graduate Centers for [2]Nutritional Sciences and [3]Toxicology, and [4]Department of Neurosurgery, University of Kentucky, Lexington, KY 40536

Abstract

Nutrition and lifestyle are well-defined modulators of chronic diseases, and evidence is accumulating that dietary components can modulate toxic insults mediated by environmental pollutants. Results from epidemiological studies support the hypothesis that cardiovascular diseases such as atherosclerosis are linked to environmental pollution. There is also evidence linking the arylhydrocarbon receptor (AhR) with mechanisms associated with cardiovascular diseases and that AhR ligands such as coplanar PCBs may be atherogenic by disrupting the functions of endothelial cells in blood vessels. Because PCBs are in general very persistent and proinflammatory, life-long exposure to these pollutants may fuel vascular inflammation and the pathology of atherosclerosis. We are exploring the paradigm that nutrition can modulate environmental insults in the vasculature and thus modulate endothelial dysfunction induced by exposure to PCBs. Nutrition can dictate the lipid milieu, oxidative stress, and antioxidant status within cells. The modulation of these parameters through diets may influence the effects of environmental pollutants to cause disease such as vascular dysfunction. For example, certain dietary fats may increase the risk to environmental insults induced by PCBs, while fruits and vegetables, rich in antioxidant and anti-inflammatory nutrients or bioactive compounds, may provide protection. Our studies indicate that an increase in cellular oxidative stress and an imbalance in antioxidant status are critical events in PCB-mediated induction of inflammatory genes and endothelial cell dysfunction. We have demonstrated that diet-derived lipids and bioactive compounds can alter the cellular lipid milieu, oxidative stress and antioxidant status, and thus modulate mechanisms of cytotoxicity mediated by PCBs. We also have evidence that the plasma membrane microdomains called caveolae play an important role in endothelial activation and toxicity mediated by coplanar PCBs. Caveolae are particularly abundant in endothelial cells and play a major role in endothelial trafficking and the regulation of signaling pathways associated with the pathology of vascular diseases. There is a great need to further explore this nutritional paradigm in environmental toxicology and to improve our understanding of the relationship between nutrition and lifestyle, exposure to environmental toxicants and disease

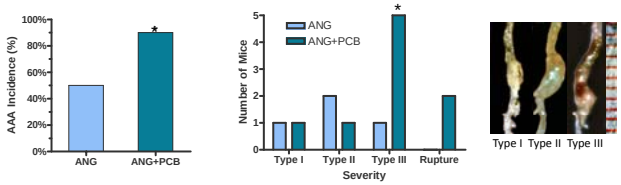
Results

PCB77 increases extent of atherosclerosis



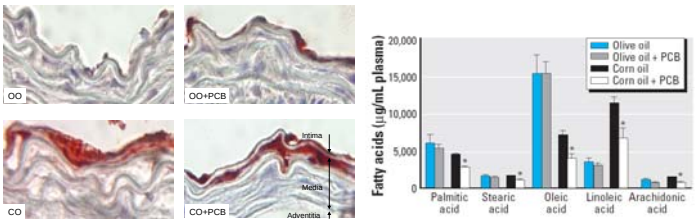
LDLr-/- mice were injected (i.p.) with PCB77 or vehicle (safflower oil). Cross-sections were stained with Oil Red-O. En face method for quantification of atherosclerosis was used. Aorta are removed, cleaned of adhering tissue, cut and pinned to illustrate the intimal surface. The percentage of the total surface area covered by a grossly discernible lesion is imaged using software to quantify lesions (opaque white areas). Data are mean ± SEM from n = 8-10 mice/group. * A significant difference compared with vehicle (p<0.05).

PCB77 increases abdominal aortic aneurysms (AAA)



ApoE-/- mice were injected (i.p.) with PCB77 or vehicle (corn oil). Saline or Angiotensin II (1,000 ng/kg/min) were infused for 28 days using osmotic minipumps implanted subcutaneously in the interscapular region of anesthetized mice. AAA incidence was defined as an increase in aortic diameter >100%. Severity of the lesion was defined using the illustrated classification scheme and was increased by PCB77. * A significant difference compared with vehicle (p<0.05).

High omega-6 oil (corn oil) increases PCB77 induced vascular cell adhesion molecule-1 and decreases major serum fatty acids



LDLr-/- mice were injected (i.p.) with PCB77 or vehicle (olive oil or corn oil). Immunoreactivity of VCAM-1 antiserum against sections of mouse aortic arches. Red staining reflects positive chromogen development for VCAM-1 immunostaining on the endothelial surface and in subendothelial tissue. Magnification, 400×. Total plasma lipids were extracted and fatty acid methyl esters were injected into gas chromatograph analyzed by mass-selective detector. Palmitic acid, 16:0; stearic acid, 18:0; oleic acid, 18:1; linoleic acid, 18:2; arachidonic acid, 20:4. *Significantly different from respective diet treatment without PCBs.

References

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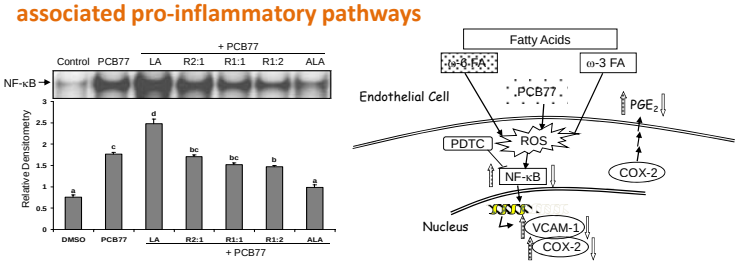
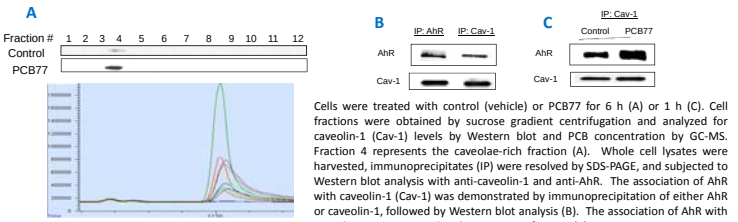
Omega-3 and omega-6 fatty acids differentially regulate NF-KB and associated pro-inflammatory pathways



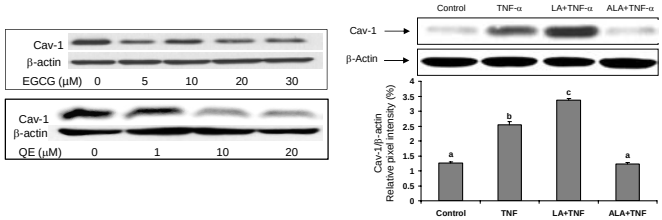
Endothelial cells were treated with of linoleic acid (LA), α-linolenic acid (ALA), or different ratios of LA to ALA (R2:1, R1:1, R1:2) prior to exposure to PCB77. Experiments were repeated three times, and the blots shown are a representative of one of the experiments. The bar graph shows the corresponding densitometric analysis of the blots. Values are means ± SEM. Different letters represent significant differences among treatment groups. Omega-6 or omega-3 fatty acids can either enhance or reduce PCB77-induced up-regulation of oxidative stress and activation of NF-κB. Relative activation of NF-κB will further regulate VCAM-1, as well as cyclooxygenase-2 (COX-2) enzyme activity and subsequent prostaglandin (PGE2) release from endothelial cells.

PCB77 and AhR are localized to caveolae-rich cellular fractions



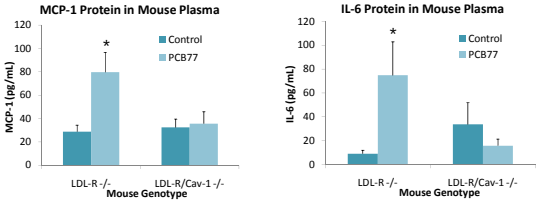
Cells were treated with control (vehicle) or PCB77 for 6 h (A) or 1 h (C). Cell fractions were obtained by sucrose gradient centrifugation and analyzed for caveolin-1 (Cav-1) levels by Western blot and PCB concentration by GC-MS. Fraction 4 represents the caveolae-rich fraction (A). Whole cell lysates were harvested, immunoprecipitates (IP) were resolved by SDS-PAGE, and subjected to Western blot analysis with anti-caveolin-1 and anti-AhR. The association of AhR with caveolin-1 (Cav-1) was demonstrated by immunoprecipitation of either AhR or caveolin-1, followed by Western blot analysis (B). The association of AhR with caveolin-1 was increased in the presence of PCB77 (C).

Dietary compounds can modulate caveolin-1 expression



Endothelial cells were treated with epigallocatechin gallate (EGCG) or quercetin (QE). Caveolin-1 protein levels were detected by western blot. Cells were treated TNF-α alone, or pretreated with linoleic acid (LA) or α-linolenic acid (ALA) followed by exposure to TNF-α. Caveolin-1 protein levels were detected by western blot. β-Actin was used as a housekeeping gene in the measurement. The bar graph shows the corresponding densitometric analysis of the blots. Values are means ± SEM. Different letters represent significant differences among treatment groups.

Caveolae deficiency protects against PCB77-induced pro-inflammatory events



Plasma samples were analyzed for monocyte chemoattractant protein-1 (MCP-1) (A) and interleukin-6 (IL-6) (B) levels using mouse adipokine LINCOplex kit (Linco Research, St. Charles, MO) according to the manufacturer's instructions. Results represent mean ± SEM. * A significant difference compared with control (vehicle) mice (p<0.05).

Conclusions

- PCB77 increases the incidence and severity of atherosclerosis and AAA.
- High omega-6 fatty acids increase the pro-inflammatory properties of PCB77, whereas omega-3 fatty acids protect against these events.
- PCB77 and AhR are localized to caveolae domains.
- Dietary compounds can modulate expression of caveolin-1, the structural component of caveolae.
- Deletion of caveolin-1 protects against PCB77-induced pro-inflammatory events.
- These data suggest that caveolae are a critical signaling platform in the interactive regulation of environmentally-induced pro-inflammatory events.

Acknowledgements

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