A New Role for Exercise: Examining the Effects of Physical Activity on Polychlorinated Biphenyl-induced Cardiovascular Disease

Margaret Murphy[1], Katryn Eske[1], Sung Gu Han[1], Michael Petriello[1], Brad Newsome,[1] Karyn Esser[2], and Bernhard Hennig[1]

University of Kentucky Superfund Research Program[1], and Department of Physiology[2], University of Kentucky, Lexington, KY 40536-0200

Abstract

Cardiovascular disease is the leading cause of mortality in developed countries. Polychlorinated biphenyls (PCBs) are persistent environmental pollutants that contribute to the initiation of cardiovascular disease. Previous work in our laboratory has examined the potential role of nutrition in modulating the toxicity of PCBs in vascular endothelial cells. We hypothesize that, in addition to nutrition, exercise also can modulate the vulnerability to environmental insults. There is strong evidence that exercise can reduce the risk of cardiovascular disease; however, whether exercise can modulate PCB-induced cardiovascular inflammation and dysfunction is unknown. Results from our preliminary study suggest that exercise can antagonize the progression of atherosclerosis induced by exposure to PCB 77. Mice were allowed voluntary exercise prior to PCB exposure. In this study, exercise also prevented elevated cholesterol and insulin associated with PCB treatment. A follow-up study was initiated where male ApoE-/- mice were divided into sedentary and exercise groups and allowed to develop atherosclerosis over a 12 week period. Half of each group was exposed to PCB 77 at a dose of 170 µmoles/kg mouse during weeks 1, 2, 9 and 10. The dosing schedule is based on previous studies that have demonstrated glucose intolerance and increased levels of atherosclerosis in this mouse model. This study determined the effects of voluntary exercise on PCB77 exposure in relation to body weight, body composition, blood pressure, distribution of PCB in tissues, glucose tolerance, serum cholesterol, systemic inflammation, and atherosclerosis. Results from this study provide novel findings suggesting that regular physical activity could be utilized as a therapeutic approach for the prevention of adverse cardiovascular health effects induced by environmental pollutants such as PCBs.

Experimental Design

All mice at 2 months of age fed standard chow diet

- ApoE -/-, sedentary, vehicle
- ApoE -/-, sedentary, PCB77 gavaged (170 µM/kg)
- ApoE -/-, exercise, vehicle
- ApoE -/-, exercise, PCB77gavaged(170 µM/kg)

Week	1	2	3	4	5	6	7	8	9	10	11	12	Take-down
Weight													
Exercise													
Oral gavage													
Blood Pressure													
EchoMRI													
Metabolic Cages													

Exercise increases body weight & lean body mass

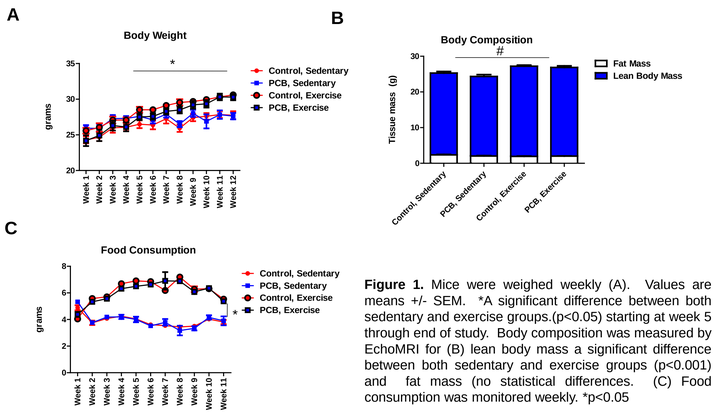

Figure 1. Mice were weighed weekly (A). Values are means +/- SEM. *A significant difference between both sedentary and exercise groups.(p<0.05) starting at week 5 through end of study. Body composition was measured by EchoMRI for (B) lean body mass a significant difference between both sedentary and exercise groups (p<0.001) and fat mass (no statistical differences. (C) Food consumption was monitored weekly. *p<0.05

Results

Exercise attenuates PCB-induced glucose intolerance

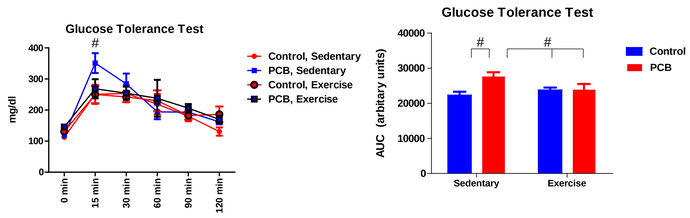

Figure 2. Blood glucose concentrations were examined in mice administered vehicle or PCB77. Mice were fasted for 6 hours and then given a bolus of glucose (20% D-glucose in saline). Blood collected from the tail vein was tested for glucose concentration using a handheld glucometer (Freedom Freestyle Lite; Abbott Laboratories, Abbott Park, IL.) and blood glucose was quantified at 0-120 min. Total area under the curve (AUC) calculates the area below the observed concentrations. Data are mean +/- SEM and represent 8 mice per treatment. #p<0.001

Exercise improves PCB-induced cardiovascular risk factors

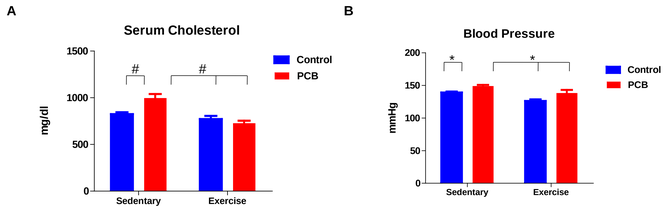

Figure 3 Plasma samples were tested for cholesterol using a serum cholesterol kit (Wako Chemicals USA, Inc, Richmond, VA) according to manufacturer's instructions. Results represent mean +/- SEM. # (p<0.001) Blood pressure was measured via the tail-cuff method (Coda). Values are mean +/- SEM. *(p<0.05)

Exercise decreases circulating inflammatory markers in the plasma

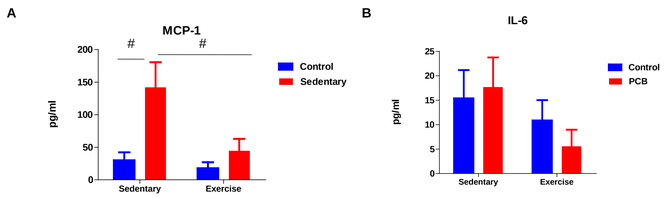

Figure 4 Plasma samples were tested for MCP-1 (A) and IL-6 (B) using mouse adipokine LINCOplex kit (Linco Research, St Charles, MO) according to manufacturer's instructions. Results represent mean +/- SEM. #A significant difference compared with PCB-treated sedentary mice (p<0.001)

Exercise attenuates PCB-induced atherosclerosis

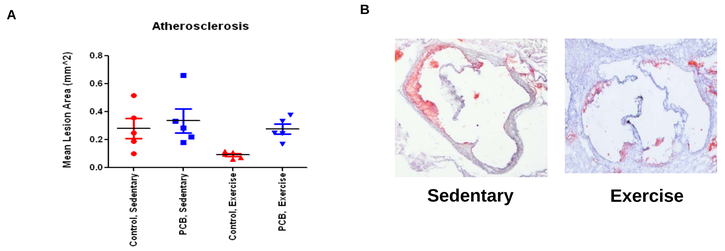

Figure 5. Lesion surface areas were quantified from the aortic root from sedentary or exercised mice administered PCB77. Exercise significantly attenuated lesion surface areas on the aortic arch in PCB-treated mice. **(A)** Lesion area of aortic sinus sections stained with oil Red O. **(B)** Oil Red O staining of representative aortic sinus for PCB-treated mice.

Exercised mice have less PCB Metabolite Concentration in Feces

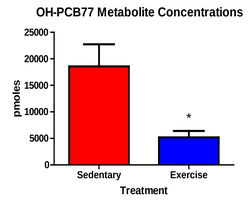

Figure 6. PCB77 and its hydroxylated metabolites were measured using a Shimadzu UFLC coupled with an AB Sciex 4000-Qtrap hybrid linear ion trap triple quadrupole mass spectrometer in multiple reaction monitoring (MRM) mode. 13C12 PCB126 and d6-PCB 77 were used as internal standards. The sample injection volume was 10 uL. Data are mean +/- SEM and represent 5 mice per treatment. *p<0.05

Conclusions

- Mice in the exercise groups weighed significantly more than their control counterparts regardless of PCB treatment. A significant increase in lean body mass and food consumption support this finding.
- Exercise attenuates PCB77-induced glucose intolerance, supporting a protective role for exercise against the development of diabetes.
- Exercise decreases serum blood cholesterol, blood pressure, and circulating proinflammatory cytokines in PCB-treated mice suggesting a potential role as an inexpensive therapeutic therapy against PCB exposure .
- Exercise shows a trend towards protection against PCB77-induced atherosclerosis. A repeated study with a larger sample size may demonstrate protection.
- PCB77 concentrations were not detected in tissues; however, the metabolites were detected in feces. Exercised mice have significantly less PCB metabolites than their sedentary counterparts, suggesting that exercise may increase clearance of PCBs from the body and this may. be one of the mechanisms of protection.

References

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Acknowledgments

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NIEHS National Institute of Environmental Health Sciences U.S. National Institutes of Health

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