

TOXICOLOGY AND APPLIED PHARMACOLOGY

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4-OH-PCB11 alters fatty acid and glucose metabolism in the absence of functional sirtuin3

Sirtuin3 (*SIRT3*) is the major deacetylase in mitochondria. It has been determined that *SIRT3* null mice have deficiencies in ATP production and demonstrate a susceptibility to develop metabolic syndrome. Polychlorinated biphenyls (PCBs) are organic pollutants that accumulate in adipose tissue and have been shown to disrupt metabolism. They have been proposed to contribute to metabolic diseases including diabetes and obesity. Our goal is to examine the effects of 4-hydroxy-3,3'-dichlorobiphenyl (4OH-PCB11), a major PCB 11 metabolite, on fatty acid and glucose metabolism using embryonic fibroblasts (MEF) isolated from *SIRT3* wild type and *SIRT3* null mice. RT² Profiler™ PCR array for fatty acid metabolism demonstrated a dose dependent up-regulation of *ACOT12*, *ACSBG2*, *ACSM2*, *FABP1*, *OXCT2A*, *GK2*, *HMGS2*, *LPI*, *SLC27A5* and *ACSL1* genes in *SIRT3*^{-/-} MEFs compared to *SIRT3*^{+/+} MEFs following 24 hours treatment with 0.1, 1 and 3 μM 4OH-PCB11. PCR array for glucose metabolism also demonstrated up-regulation of *G6PC*, *PDK4* and *PRPS1L1* in both *SIRT3*^{-/-} and *SIRT3*^{+/+} MEFs upon 3 μM 4OH-PCB11 exposure, however fold increases in the expression of these genes were more pronounced in the knockout background. On the other hand, the expression of *PYGL* gene was down-regulated in both *SIRT3*^{-/-} and *SIRT3*^{+/+} MEFs at comparable levels. Our future studies will investigate the enzymatic activities of proteins encoded by these genes as well as utilize proteomics and metabolomics approaches to determine if they are specific *SIRT3* targets during PCB induced cellular stress.

Biography

Nukhet Aykin-Burns has received her PhD degree from the University of Missouri-Rolla focusing on antioxidant-based therapies in lead poisoning and completed her Post-doctoral training in the Free Radical and Radiation Biology Program at the University of Iowa. She is an Assistant Professor of Pharmaceutical Sciences at University of Arkansas for Medical Sciences, Member of the College of Pharmacy Division of Radiation Health. Her research focuses on reactive oxygen species (ROS), radiation induced (IR and UV) normal tissue damage and wound healing as well as polychlorinated biphenyl (PCB) induced oxidative stress.

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