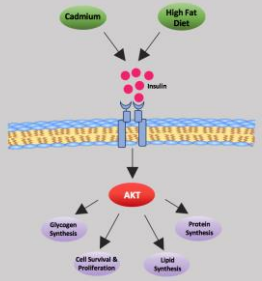
The Effects of Cadmium on Kidney Tissue

Brittani D'Angelo, Yong Guang Tong, PhD, Jamie Young, Jonathan Freedman, PhD
University of Louisville School of Medicine, Department of Pharmacology and Toxicology, R25 Cancer Education Program

Introduction

AKT signaling pathways can respond to extracellular signals and promote growth and cell survival. AKT pathways can have varying affects on different downstream pathways within the cell. It has been shown that dysregulation in the activity of AKT can lead to cancer. The transition metal cadmium is a know human carcinogen that mainly affects the kidneys. Cadmium has been proven to cause a dysregulation in the activity of AKT. Kidney cancer is among the top 10 most common cancers and it usually develops later in life, around the age of 65, and is more prevalent in men than in women. For this project, we looked at lower, environmentally relevant levels of cadmium exposure and the affects on both the function of the kidney (determined levels of damage in the tissue samples), as well as the AKT activity. We also wanted to see if there was a difference in groups that were exposed to a high-fat vs a low-fat diet in combination with cadmium. For this project, we had differing groups to determine the effects of diet, gender, and exposure time on kidney damage and levels of AKT to see if there were correlations. Clinical implications include looking at people being exposed to cadmium through normal living conditions and determining their chances of developing kidney disease that can ultimately lead to kidney cancer.

The AKT signaling pathway of interest:



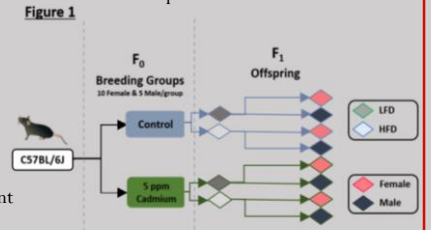
Objective and Hypothesis

The main objective of this project was to determine how cadmium affects the tissue of the kidney and how that can ultimately lead to kidney damage/the onset or growth of cancer. Our hypothesis is that cadmium exposure as well as a high-fat diet can increase kidney damage which can ultimately lead to the onset of cancer in the kidney\s.

Methods

Before I joined the lab, mice had been exposed to cadmium through drinking water both prenatally and after birth. Mice then were sacrificed at either 10 weeks or 24 weeks. Kidneys were then harvested to be used for analysis in this projects. Figure 1 below outlines the different treatment groups of mice used for this project. Every sample of tissue was analyzed a couple different ways. The main analysis used for my research and project was to stain tissue samples with sirius red to determine the percentage of collagen accumulation on those stained samples. This determines the amount of damage on the tissue due to either their diet or cadmium exposure. We also looked at the differences in their gender and if that had an affect on the collagen accumulation in theie kidney tissue.

Figure 1



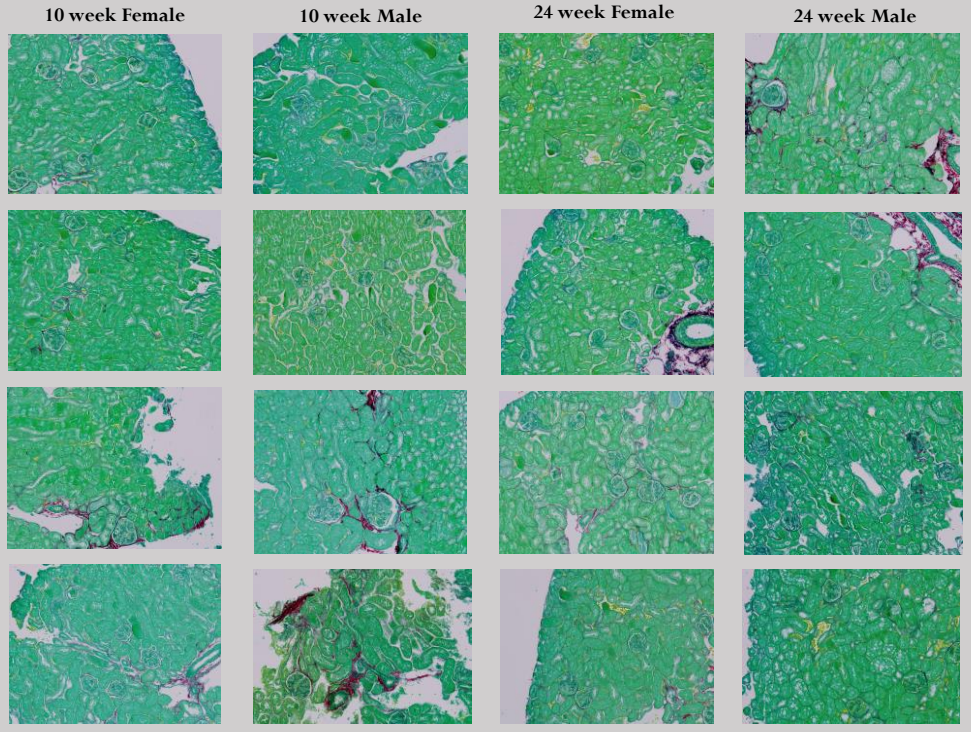
Future Directions

The next step to take after this project concludes would be to look at a much smaller amount of cadmium exposure to see if the same patterns and results found in this project are also present and significant.

Conclusions

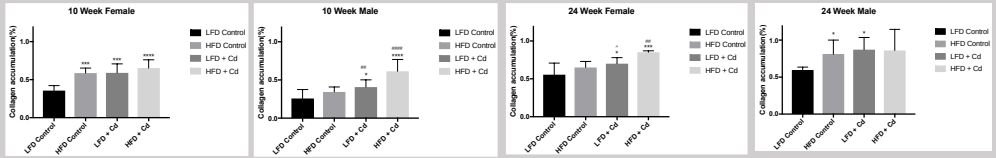
From the research done, it can be concluded that cadmium does contribute to tissue damage in the kidneys that can lead to kidney disease and cancer. It can also be seen that there is a difference between low-fat and high-fat diets. Additionally, longer exposure to cadmium contributes to a higher percentage of collagen and therefore increased tissue damage.

Results



10 week female samples: 704-LFD control; 709-HFD control; 127-LFD + Cd; 108-HFD + Cd
10 week male samples: 707-LFD control; 32-HFD control; 135-LFD + Cd; 210-HFD + Cd
24 week female samples: 36-LFD control; 224-HFD control; 138-LFD + Cd; 133-HFD + Cd
24 week male samples: 31-LFD control; 226-HFD control; 109-LFD + Cd; 1004-HFD + Cd

In both male and female groups, it is clear that the high-fat diet with cadmium had the most percentage collagen in the tissue indicating that those samples had the most tissue damage as a residual effect. All the graphs below share the same trend, which is that cadmium and the high fat diet both contribute to the percentage of collagen present. This can be determined by comparing these groups to the control groups.



Symbols on graphs: significantly different ($p<0.05$)
* = compared to LFD no metal
# = compared to HFD no metal
^ = LFD + Cd compared to HFD + Cd

Acknowledgements

Research funded by NCI R25 University of Louisville Cancer Education Program (R25-CA134283). I would also like to acknowledge Dr. Lu Cai and Yixian Zhang for their assistance.

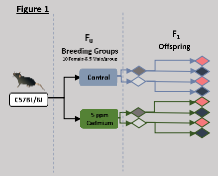
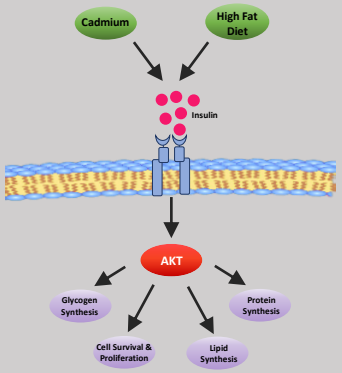


Figure 1
F0
Breeding Groups
F1
Offspring
Control
C57BL/6J


Cadmium
High Fat Diet
Insulin
AKT
Glycogen Synthesis
Protein Synthesis
Cell Survival & Proliferation
Lipid Synthesis

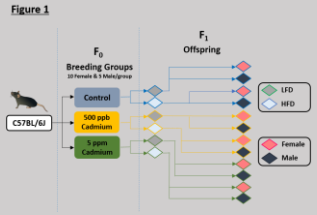


Figure 1
F0
Breeding Groups
F1
Offspring
Control
500 ppb Cadmium
5 ppm Cadmium
C57BL/6J
LFD
HFD
Female
Male