

Introduction

Acute kidney injury (AKI) is an independent risk factor for the development and progression of chronic kidney disease (CKD)¹.

Aristolochic acid (AA)-induced nephropathy is a form of AKI that can transition to CKD. AA-induced nephropathy can be caused by ingestion of Chinese herbal remedies containing AA. In addition, AA ingestion was found to be the cause of "Balkan endemic nephropathy", due to contamination of flour seeds with aristolochia clematitis².

Proximal tubular uptake of AA forms aristolactam (AL)-DNA adducts, which cause a p53/p21-mediated DNA damage response and acute tubular injury. Recurrent exposure to AA causes kidney function loss and fibrosis in humans and mice³.

Western diet (WD) is rich in saturated fats, sugars, and salt and facilitates metabolic disorders (e.g., obesity and diabetes), but also CKD progression.

The aim of this study is to elucidate the impact of WD on AA-induced nephropathy.

Methods and Materials

Mice: 5-week-old of male C57BL/6J mice (n=4/group for vehicle; n=7-8/group for AA)

1st set - groups:

1. Normal chow + vehicle
2. Western diet + vehicle
3. Normal chow + AA (3 mg/kg i.p., total 0.6 mg)
4. Western diet + AA (3 mg/kg i.p., total 0.73 mg)

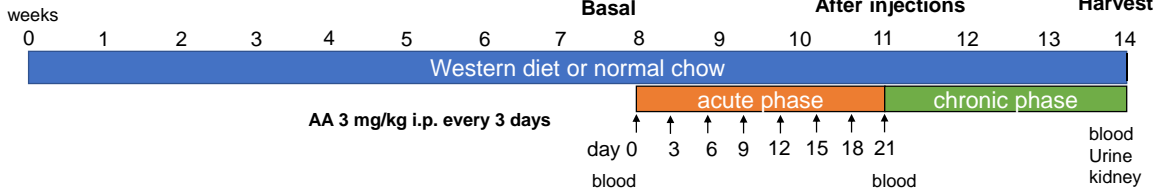
For the 1st set, AA was dosed based on body wt. Since mice on WD were heavier, total injected AA (for 8 injections) was somewhat greater (0.73 vs 0.6 mg).

2nd set - groups:

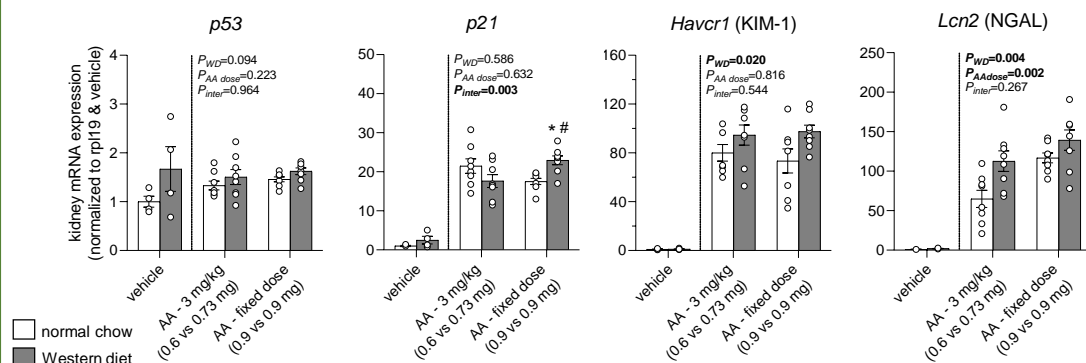
5. Normal chow + AA-fixed dose (Total 0.9 mg)
6. Western diet + AA-fixed dose (Total 0.9 mg)

For the 2nd set, total injected AA was set at a "fixed dose" of 0.9 mg (for 8 injections) for every mouse.

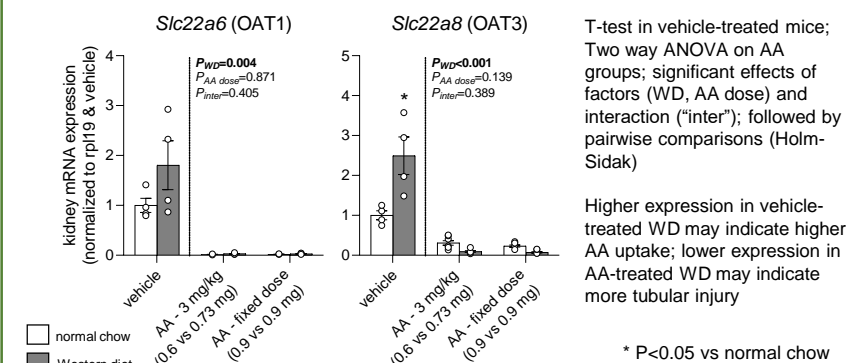
Protocol:



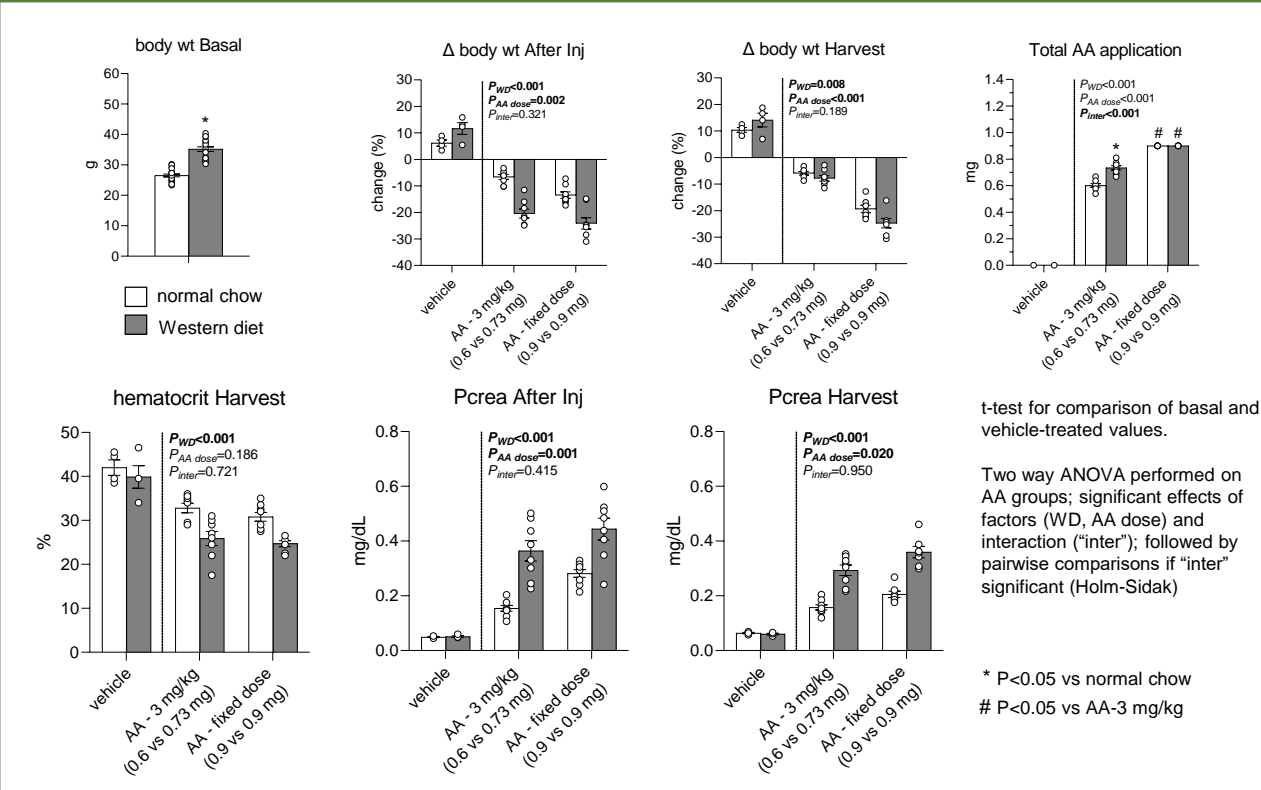
1. WD modestly enhanced AA-induced markers of tubular injury & inflammation



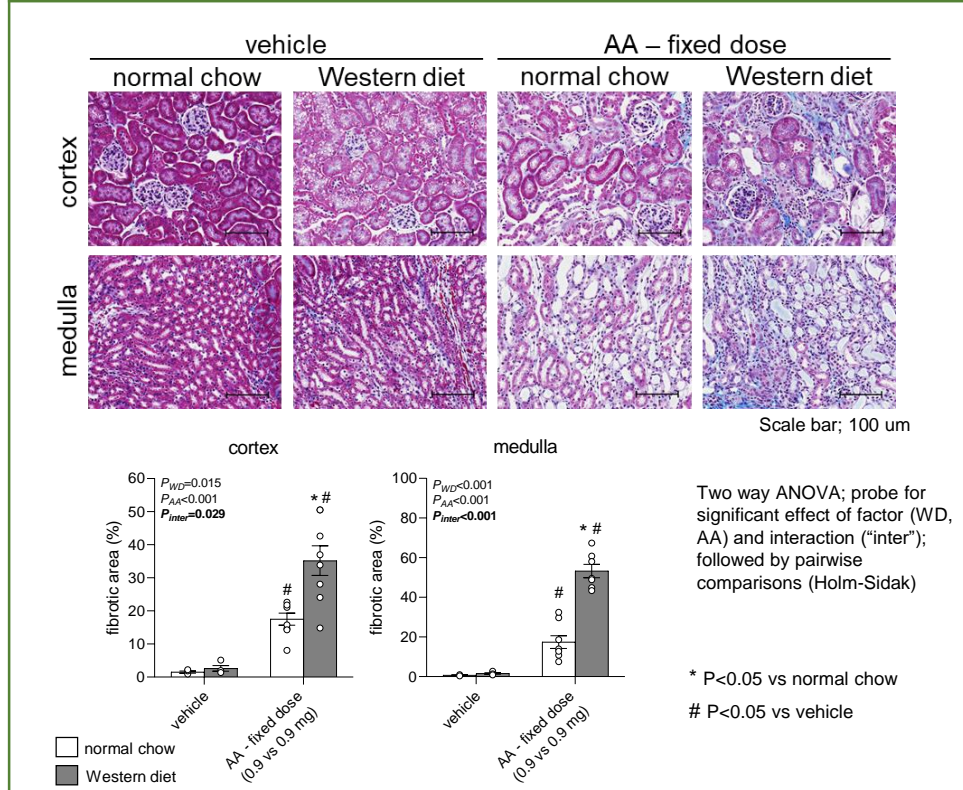
4. WD increased renal OAT3 expression in vehicle-treated mice



2. WD aggravated the AA-induced fall in hematocrit and rise in plasma creatinine

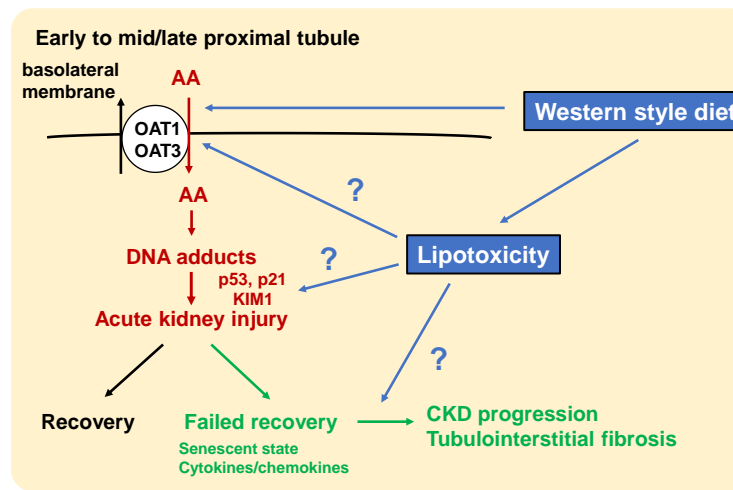


3. WD exacerbated AA-induced renal fibrosis



Summary and discussion

- WD modestly enhanced renal markers of injury (*p53*(trend), *p21*, *Kim1* and *Ngal* mRNA).
- WD robustly attenuated the AA-induced increase in plasma creatinine and the decrease in hematocrit in the acute and chronic phase, as well as the renal fibrotic response.
- The mechanism involved in the deleterious impact of WD on AA-nephropathy remains unclear.
- High fat diet causes lipotoxicity in tubular cells, which is associated with mitochondria dysfunction and oxidative stress⁴. The latter has been implicated in promoting the AA-induced p53 DNA damage response⁵.
- WD increased expression of organic anion transporter OAT3, which takes up AA into proximal tubular cells. WD may worsen AA-induced renal injury, in part, by enhancing tubular AA uptake.



References

- 1) Coca SG, et al. *Kidney Int* 2012.
- 2) DeBelle FD, et al. *Kidney Int*. 2008 J
- 3) Baudoux T, et al. *Front Med* 2022.
- 4) Szeto HH, et al. *Kidney Int*. 2016.
- 5) Romanov V, et al. *Arch Toxicol* 2015.

Acknowledgements

Supported by NIH grants RF1AG061296, R01DK132690, UAB-UCSD O'Brien Center for Acute Kidney Injury Research NIH P30DK079337, and a fellowship of the Manpei Suzuki Diabetes Foundation.