

## **A Fructose-enriched Diet Stimulates Superoxide Production in Juxtaglomerular Cells and Prevents High-salt Induced Inhibition of Plasma Renin Activity (PRA)**

**Mariela Mendez**, Kevin L Gordish, Emily Henson, Pablo A. Ortiz, William H Beierwaltes, Henry Ford Hosp, Detroit, MI

A fructose-enriched diet has been associated with hypertension. Western diets are rich in fructose and salt. We found that a fructose enriched diet plus high-salt induced salt sensitive hypertension. Plasma renin activity (PRA) is essential for blood pressure (BP) control. A high-salt diet decreases PRA by inhibiting renin release from juxtaglomerular (JG) cells. However it is not known if dietary fructose might impair the inhibition of renin release by high salt to promote salt sensitivity. Salt sensitive rats have enhanced levels of superoxide in the renal cortex, and we found that superoxide stimulates renin release from JG cells. Thus, we hypothesized that a fructose-enriched diet (20%) promotes salt sensitive hypertension in part by preventing high salt-induced inhibition of renin release from JG cells by enhancing superoxide production. To test this, Sprague Dawley rats were given 20% fructose in their drinking water, with normal or high salt diet (4% NaCl) for up to 4 weeks. Feeding normal rats a fructose+High-salt diet increased systolic BP by 30 mmHg whereas fructose or high-salt alone did not change BP (High-salt =  $125 \pm 4$ , Fruct =  $131 \pm 4$ , Fruct+High-salt =  $147 \pm 7$ ;  $n=6$ ,  $p<0.05$ ). A high-salt diet alone for 4 weeks decreased PRA by 85%. However, in rats fed fructose+High-salt did not decrease PRA (in ng All/ml/hr: Ctrl =  $2.51 \pm 0.72$ , High-salt =  $0.43 \pm 0.07$ , Fruct =  $2.71 \pm 0.9$ , Fruct+High-salt =  $1.89 \pm 0.43$ ;  $n=10$ ,  $p<0.05$ ). We next examined the role of the fructose or fructose+High-salt diet on NADPH oxidase expression in isolated JG cells. NOX4 expression was enhanced in JG cells from rats fed fructose+High-salt diet ( $n=4$ ;  $p<0.05$ ). Next, we measured superoxide production with Dihydroethidium and found it was higher in JG cells from rats fed fructose+high-salt diet compared to high-salt alone (% of Ctrl: High-salt =  $90.7 \pm 37$ ; fruct+High-salt =  $289 \pm 85$ ;  $n=4$ ;  $p<0.05$ ). We conclude that a 20% fructose-diet promotes salt sensitivity of BP. The mechanism may involve enhanced NOX4 expression and elevated superoxide levels within JG cells stimulating renin release. 15 million Americans consume 20% of their calories from fructose, and most, 4-8 times the recommended salt intake. Decreasing fructose intake could have a beneficial BP effect in hypertensive patients.

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