Dopamine D$_2$ Receptor is Associated with Inverse Salt Sensitivity

**Peng Xu**, John J Gildea, Univ of Virginia, Charlottesville, VA; Pedro A Jose, George Washington Univ Sch of Med, Washington DC, DC; Robert M Carey, Robin A Felder, Univ of Virginia, Charlottesville, VA

Our previous studies of salt sensitivity of blood pressure have demonstrated that approximately 11% of study participants have a paradoxical increase in blood pressure (> or = to 7-mm Hg) on a low NaCl diet (defined as inverse salt sensitivity (ISS)). However the mechanisms responsible for this effect are not known. We demonstrated that single nucleotide polymorphisms (SNPs) in the dopamine type 2 receptor (D$_2$R) (RS6276 and 6267) are highly associated with ISS (P values of 1.0×10$^{-2}$ and 3.8×10$^{-2}$ with odds ratios of 0.32 and 0.48 in unadjusted regression models, respectively). The C allele at both sites confers protection. The D$_2$R is strongly expressed throughout the cytoplasm of proximal tubule cells in human kidney tissue slices. We also cultured RPTC from the urine from 4 salt resistant (SR) and 3 ISS participants enrolled in our clinical salt sensitivity studies. We hypothesize that D$_2$R containing SNPs have altered receptor expression, and altered signaling compared to wild type controls. ISS participants were homozygous variant for the two D$_2$R alleles and showed more D$_2$R expression than SR RPTC heterozygous variant (HV) for the two alleles (ISS: 1.166±0.059 n=3 vs SR: 0.969±0.024 n=4, P<0.05, t-test). D$_2$R expression was increased when the ISS cells were stimulated by a non-selective D$_2$R agonist bromocriptine to a greater extent in the D$_2$R SNP cell lines (ISS: VEH 1.166±0.059, vs bromocriptine 1.474 ± 0.040, n=3, P<0.05, t-test). Using the ROS reagent assay, dihydroethidium, there was found to be more ROS products in ISS cells than SR cells when stimulated under low salt (ISS: 1.145 ± 0.053, n=3 vs SR: 0.722 ± 0.101, n=4, P<0.05, t-test). We used a highly selective D$_2$R agonist (sumanirole) to stimulate wild-type and SNPed cells, and the results demonstrated no effect in the cells with wild type D$_2$R but an increase in ROS in cells heterozygous for the D$_2$R SNPs (SNP: VEH 38,364±1,266, sumanirole 50,926 ± 3,310, VS WT: VEH 34,562±1,831 sumanirole 34,435 ± 1,614 RFU n=12, P<0.05, t-test) consistent with the higher expression of D$_2$R found in ISS urine cells. We hypothesize that SNPs in the D$_2$R lead to increased reactive oxygen species which has previously been associated with renal fibrosis and hypertension.

Disclosure Block:

**P. Xu**: None. **J.J. Gildea**: None. **P.A. Jose**: B. Research Grant (includes principal investigator, collaborator, or consultant and pending grants as well as grants already received); Significant; 5P01HL074940-12. **R.M. Carey**: B. Research Grant (includes principal investigator, collaborator, or consultant and pending grants as well as grants already received); Significant; 5P01HL074940-12. **R.A. Felder**: B. Research Grant (includes principal investigator, collaborator, or consultant and pending grants as well as grants already received); Significant; 5P01HL074940-12.