STRONG CHILDREN'S RESEARCH CENTER

Summer 2016 Research Scholar

Name: Amanda Jimcosky

School: Dickinson College

Mentor: George Schwartz, MD; Jeffrey Purkerson, PhD

ABSTRACT

Title: Maternal Acidosis Transiently Shifts Differentiation of Collecting Duct Intercalated Cells

Background: Intercalated cells (ICs) of the renal collecting ducts (CDs) maintain acid-base homeostasis. α-ICs acidify the urine by secreting protons into the lumen of the CD via an apical H^+ATPase and basolateral Cl^-/HCO_3^- exchanger (AE1) whereas β-ICs have opposite pH effects due to expression of an apical Cl^-/HCO_3^- exchanger (Pendrin) and basolateral H^+ATPase. Metabolic acidosis is known to negatively affect overall fetal and neonatal development and thus maternal acidosis may predispose progeny to health complications in respect to renal function. Rabbits are an excellent model for studying the effects of maternal acidosis on IC maturation since rabbit physiology is adapted to an alkaline-rich diet, reflected by a predominance of β-ICs and net HCO_3 secretion in the cortical collecting ducts (CCDs).

Objective: To determine how maternal acidosis influences the distribution of IC subtypes in CCDs of progeny, using a rabbit model.

Results: Previous studies have shown that the IC subtype distribution in the normal adult rabbit is α:β = 23.3:76.7. In the present study, we found this proportion to be fairly consistent throughout normal maturation (1 week – 26.2:73.8; 3 week – 25.3:74.6; 6 week – 22.9:77.1); the proportion of α:β ICs in the acidotic rabbit shifts toward the α subtype during early maturation then returns to normal by six weeks: 1 week – 38.9:61.1; 3 week – 33.8:66.2; 6 week – 23.7:76.3. The number of α-ICs is stable throughout all conditions while the number of β-ICs varies between conditions (see Table 1). Compared to normal 1-week CCDs, qRT-PCR shows a 1.6-fold increase in AE1 expression in acidotic 1-week CCDs, a 7.0-fold increase in AE1 expression in acidotic 3-week CCDs, and a 9.2-fold increase in AE1 expression in acidotic 6-week CCDs. The normal condition shows a 1.9-fold increase in AE1 expression between weeks 1 and 3 and a 1.5-fold increase in AE1 expression between weeks 1 and 6. Compared to normal 1-week CCDs, PND expression increases at 3 weeks in both conditions (3.9-fold in normal, 8.3-fold in acidotic) and then stabilizes or decreases at 6 weeks (3.6-fold in normal, 5.6-fold in acidotic).

Table 1. Average number of α, β, and total ICs per 100 um throughout maturation in both conditions.

Average per 100 um	1 week		3 week		6 week		Adult
	Normal	Acid	Normal	Acid	Normal	Acid	Normal
AE1	**2.6** ± 0.17	**2.9** ± 0.24	**3.0** ± 0.34	**3.3** ± 0.32	**2.9** ± 0.15	**3.3** ± 0.25	**2.6** ± 0.06
Pendrin	**7.4** ± 0.52	**4.6** ± 0.49	**8.7** ± 0.69	**6.4** ± 0.41	**9.8** ± 3.20	**10.4** ± 1.92	**8.5** ± 0.20
Total IC	**10.1** ± 0.59	**7.6** ± 0.61	**11.7** ± 0.83	**9.7** ± 0.66	**12.7** ± 3.11	**13.7** ± 1.92	**11.1** ± 0.25

Conclusion: Maternal acidosis downregulates β-IC differentiation during early development; however, this decrease in proportion of pendrin-positive cells reverted to normal by the 6-week time point. This implies that the effects of maternal acidosis are reversible over time as offspring are weaned and placed on the normal, alkaline rabbit diet. Additionally, elevated AE1 gene expression through the 6-week time point could indicate a change in epigenetic regulation of AE1 genes that could allow for more effective adaptation and urine acidification in response to an acid-load. . Further experiments to study how offspring of maternal acidosis react to an acidic diet would be necessary to investigate this phenomenon.