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Basic Science

Abstract Title

Investigating the effects of in utero type 2 diabetes exposure and the HNF-1 α G319S variant on offspring kidney structure and function

Authors

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Background

Exposure to maternal type 2 diabetes (T2D) disrupts nephrogenesis and kidney development in offspring. The HNF-1 α G319S variant is linked to youth-onset T2D in the Anishinaabe First Nations of Northwestern Ontario and Northeastern Manitoba, but its effect on the proximal tubule in the kidney remains unclear.

Objective

Our objective is to establish how maternal T2D exposure impairs offspring proximal tubule maturation and function in a genotype-dependent manner and if postnatal metabolic exposures exacerbate these effects.

Methods

We utilized two mouse models: a diet-induced T2D model (8-10 weeks of high-fat/sucrose feeding and injection of 75 mg/kg streptozotocin) on a C57BL/6J and HNF-1 α G319S knock-in background. Control females received a standard chow diet and vehicle injections, and both groups were mated with C57BL/6J lean males or HNF-1 α G319S lean males. Kidney structure and function were assessed in offspring at 4 and 12 weeks of age.

Results

In offspring exposed to T2D, left kidney weight increased at 4 and 12 weeks. Urinary KIM-1 levels increased at 4 weeks. Proximal tubule mRNA expression analysis indicated a reduction in megalin at 4 weeks, which was later stabilized by 12 weeks, alongside an increase in HNF-1 α and a significant reduction in PPAR α , particularly in females. Among 12-week-old control offspring, GG mice had larger left kidneys than GS and SS mice, while males had larger kidneys than females irrespective of genotype. Data represented as mean $\pm$ SEM; $p > 0.05$.

Conclusion

Maternal T2D exposure alters offspring kidney growth and is associated with early changes in proximal tubule injury and maturation. Reduced PPAR α expression suggests altered regulation of proximal tubular fatty-acid metabolism, increasing susceptibility to tubular dysfunction. The HNF-1 α G319S variant's association with reduced kidney size suggests genotype independently influences renal development. Together, these findings support maternal T2D exposure and inherited HNF-1 α G319S genotype as interacting determinants of offspring kidney phenotype.