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Renal Proximal Tubule Centric View of Health and Homeostasis in Mammals

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Introduction

Renal proximal tubules are generally accepted to be a central player in the slow progression toward one of the most costly and deadly chronic diseases of aging, called chronic kidney disease. Maintenance of the healthy differentiated state of the proximal tubule should be the goal of every pet owner striving to increase their pet's health span.

The renal proximal tubule is the part of the kidney that processes the blood after being filtered by the glomerulus. The filtered blood excludes red blood cells, extracellular vesicles, and proteins larger than 40 kDa before passing into the lumen of the proximal tubule that is composed of proximal tubule cells, an essential cell type that maintains homeostasis for all cells of the body. This segment of the nephron, the proximal tubule, reabsorbs numerous molecules from the lumen and returns them back into circulation while removing waste products from the body after a short stint in the bladder.

In all types of mammals, the proximal tubule is necessary to reclaim vital nutrients such as sodium, chloride, calcium, phosphate, glucose, amino acids, bicarbonate, citrate, triglycerides, and water. The tubules also regulate the pH homeostasis of the body by exchanging hydrogen ions for bicarbonate ions. They are also a central player in oxygen homeostasis, by sensing oxygen saturation and upon sensing lowered oxygen levels, generate erythropoietin and send it back into the circulation, which in turn stimulates red blood cell production. Waste products like urea are also removed by the proximal tubule by directing it into the urine for elimination. A correctly formed barrier in the kidneys comes from the proximal tubules functioning well and is essential for both electrical and concentration gradients. These gradients allow for active and passive pumping across this barrier which is required to accomplish the essential kidney functions described. In this paper, we measure the electrical gradients across these barriers and discuss the effects of ION* Gut Support For Pets, a dietary supplement, on these critical barriers.

Materials and Methods

Cell Culture

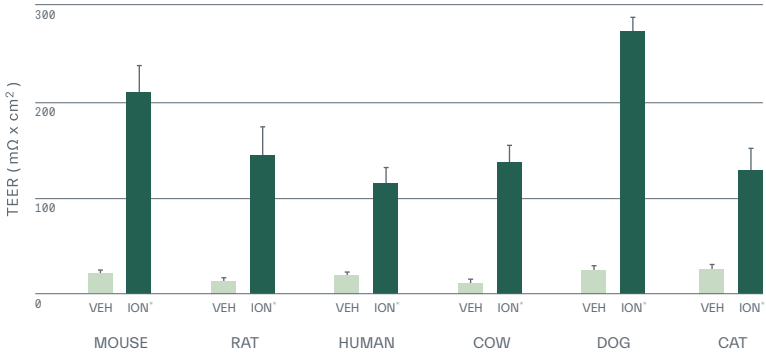
Primary renal proximal tubule cells were isolated and grown from approximately one gram fresh renal cortex of mouse, rat, cow, dog, and cat as starting material, identically to previous protocols. Primary human renal proximal tubule cells were purchased and grown according to manufacturer's instructions (Lifeline Cell Technology).

Trans-Epithelial Electrical Resistance (TEER)

Cells were plated in the apical compartment of 24 well collagen coated Transwell Inserts (Corning, Sigma Aldritch) at 90% confluence and incubated for three days when the TEER values stabilized. TEER values were measured with an EVOM2 (World Precision Instruments). Briefly, electrodes were sterilized by soaking in 70% ethanol for 10 minutes then conditioned by soaking in cell culture media for 1 hour. A background reading of an empty Transwell Insert without cells was subtracted from all values and recorded as Ohms x CM^2. Six Transwell Inserts were used for either vehicle treatment, phosphate buffered saline (VEH), or ION* Gut Support For Pets treatment added to 20% ION* by adding to both apical and basolateral media for four hours.

Results

Impact of ION* on the Barrier Integrity Across Renal Proximal Tubules for Multiple Species



A proximal tubule cells is known to be a leaky epithelium, meaning that they are characterized ashaving a relatively low TEER value compared to other epithelial layers. In growth media, the TEER value was found to be barely over background for all 6 species tested (VEH in graph). However, in all 6 species, a dramatic and significant increase in TEER was observed when treated for only four hours with ION* Gut Support For Pets (*p<0.01 ION vs VEH, n=6 per group).

Discussion

The integrity of epithelial barriers is now considered a major component of a long health span and is actually one of the pillars in the recent publication on the Hallmarks of Health. This essential feature of health is now gaining much more wide acceptance, especially in the field of gut health. One of the features of a disrupted epithelium is the concept of epithelial to mesenchymal transition, where the confluent cell layer cells loses its close association with its neighbors. This disruption of its barrier function causes the cells to progressively become more like mesenchymal cells (which are cells that develop into connective tissue, blood vessels, and lymphatic tissue). These cells are then responsible for the fibronic conversion of a tissue toward a less resilient condition. Tight junctions are among the structures within the cells that are disrupted as cells lose their identity, and are the feature of an epithelial layer that mediates the TEER measured in this paper. The ability of ION* Gut Support For Pets to increase TEER and inhibit the reduced differentiation observed in these proximal tubule cell cultures may be an important component supporting overall kidney health, whole body homeostasis, and overall health.

References

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