Study of Prostaglandin E2 Role in the Pathogenesis of Primary Mono-Symptmatic Nocturnal Enuresis

Thesis

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in **Pediatrics**

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Introduction

The word enuresis is derived from a Greek word that means to make water. Urinary incontinence is a common problem in children. At five years of age, 15% of children remain incompletly continent of urine, most of these children have isolated nocturnal enuresis (Monosymptomatic Nocturnal Enuresis).

Nocturnal enuresis can be defined as the involuntary or voluntary repeated discharge of urine into clothes or bed after a developmental age when bladder control should be established (most children with a mental age of 5 years obtain bladder control during the day and night).

Enuresis may be primary (75-90% of enuretic children are primary, nocturnal urinary control never achieved) or secondary (10-25% of enuretic children are secondary, the child is dry at night for at least six months and then enuresis develop).

An increase in diuresis and solute excretion is of essential significance in pathogenesis of some forms of nocturnal enuresis. Studies of both the mechanisms of increased diuresis and decreased ion and fluid reabsorption in the nephron have lead to the suggestion that nocturnal enuresis is a result of a decrease in ion reabsorption, including that of sodium and magnesium ions in the thick ascending limp ***(Kuznetzova et al., 1996, 1998).*** It is in this part of the nephron that the sodium ion reabsorption is

increased by vasopressin and decreased by prostaglandins. Since vasopressin and prostaglandins are antagonists in the regulation of water transport ***(Breyer et al., 1990).***

The foregoing data suggest that either disturbances of the local prostaglandin synthesis or a change in response of renal tubular cells to prostaglandins may have some role in the pathogenesis of nocturnal enuresis.

Aim of the study

The present study was designed to assess the excretion of Na, K, and prostaglandin E2 in the urine of children with primary mono-symptomatic nocturnal enuresis (PMNE) aiming at investigating its potential role in the pathogenesis of the disease.

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Functional Anatomy and Physiology of the Kidney

Functional Anatomy of the kidney:

The Nephron:

Each individual renal tubule and its glomerulus is a unit **(nephron).** The size of the kidneys between species varies, as does the number of nephrons they contain. Each human kidney has approximately 1.3 million nephrons.

The glomerulus:

Is formed by the invagination of a tuft of capillaries into the dilated, blind end of the nephron **(Bowman's capsule).** The capillaries are supplied by an **afferent arteriole** and drained by a slightly smaller **efferent arteriole**, and it is from the glomerulus that the filtrate is formed. Two cellular layers separate the blood from the glomerular filtrate in Bowman's capsule: the capillary endothelium and the specialized epithelium of the capsule. The endothelium of the glomerular capillaries is fenestrated, with pores that are 70 to 90 nm in diameter. The endothelium of the glomerular capillaries is completely surrounded by the glomerular basement membrane along with specialized cells called podocytes. **Podocytes** have numerous pseudopodia that interdigitate to form **filtration slits** along the capillary wall. The slits are approximately 25 nm wide, and each is closed by a thin membrane. The glomerular basement membrane, the basal lamina, does not contain visible gaps or pores. Stellate cells

called **mesangial cells** are located between the basal lamina and the endothelium. They are similar to cells called **pericytes,** which are found in the walls of capillaries elsewhere in the body. Mesangial cells are especially common between two neighboring capillaries, and in these locations the basal membrane forms a sheath shared by both capillaries. The mesangial cells are contractile and play a role in the regulation of glomerular filtration. Mesangial cells secrete the extracellular matrix, take up immune complexes, and are involved in the progression of glomerular disease ***(Beeuwkes, 1980).***

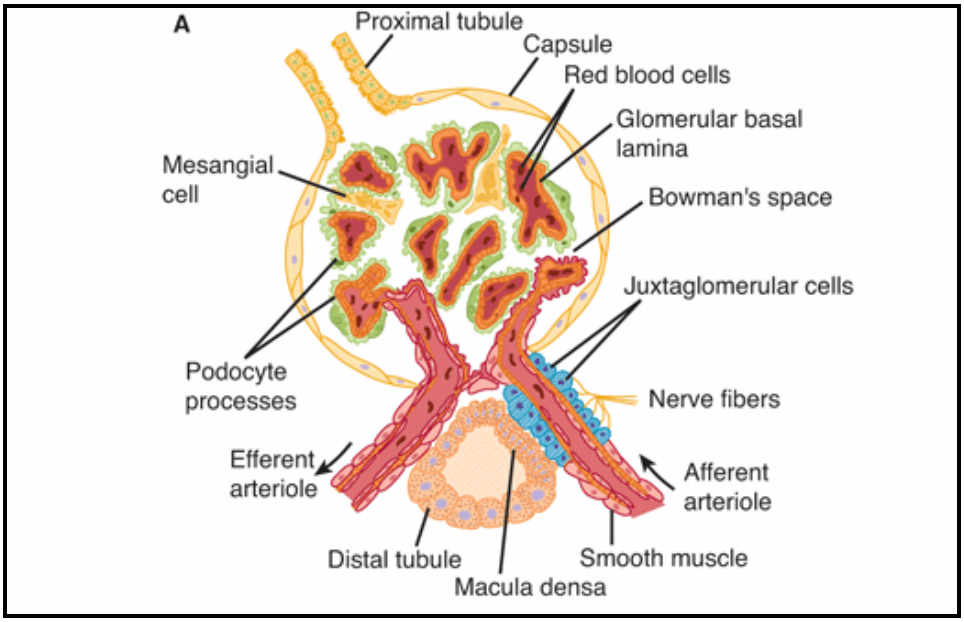

Figure (1): The glomerulus

Functionally, the glomerular membrane permits the free passage of neutral substances up to 4 nm in diameter and almost totally excludes those with diameters greater than 8 nm. However, the charges on molecules as well as their diameters affect their

passage into Bowman's capsule. The total area of glomerular capillary endothelium across which filtration occurs in humans is about 0.8 m^2 ***(Deen et al., 2001& Haraldsson et al., 2004).***

The human **proximal convoluted tubule** is about 15 mm long and 55 um in diameters. Its wall is made up of a single layer of cells that interdigitate with one another and is united by apical tight junctions. Between the bases of the cells are extensions of the extracellular space called the **lateral intercellular spaces.** The luminal edges of the cells have a striate **brush border** due to the presence of many microvilli.

The convoluted proximal tubule straightens and the next portion of each nephron is the **loop of Henle.** The descending portion of the loop and the proximal portion of the ascending limb are made up of thin, permeable cells. On the other hand, the thick portion of the ascending limb is made up of thick cells containing many mitochondria. The nephrons with glomeruli in the outer portions of the renal cortex have short loops of Henle **(cortical nephrons),** whereas those with glomeruli in the juxtamedullary region of the cortex **(juxtamedullary nephrons)** have long loops extending down into the medullary pyramids. In humans, only 15% of the nephrons have long loops.

The thick end of the ascending limb of the loop of Henle reaches the glomerulus of the nephron from which the tubule arose and nestles between its afferent and efferent arterioles. Specialized cells at the end form the **macula densa,** which is close to the efferent and particularly the afferent arteriole. The

macula, the neighboring **lacis cells,** and the renin-secreting **juxtaglomerular cells** in the afferent arteriole form the **juxtaglomerular apparatus**.

The **distal convoluted tubule,** which starts at the macula densa, is about 5 mm long. Its epithelium is lower than that of the proximal tubule, and although a few microvilli are present, there is no distinct brush border. The distal tubules coalesce to form **collecting ducts** that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The epithelium of the collecting ducts is made up of **principal cells (P cells)** and **intercalated cells (I cells).** The P cells, which predominate, are relatively tall and have few organelles. They are involved in Na^+ reabsorption and vasopressin-stimulated water reabsorption. The I cells, which are present in smaller numbers and are also found in the distal tubules, have more microvilli, cytoplasmic vesicles, and mitochondria. They are concerned with acid secretion and HCO_3^- transport. The total length of the nephrons, including the collecting ducts, ranges from 45 to 65 mm.

Cells in the kidneys that appear to have a secretory function include not only the juxtaglomerular cells but also some of the cells in the interstitial tissue of the medulla. These cells are called **type I medullary interstitial cells.** They contain lipid droplets and probably secrete prostaglandins, predominantly PGE2. PGE_2 is also secreted by the cells in the collecting ducts; prostacyclin (PGI2) and other prostaglandins are secreted by the arterioles and glomeruli.

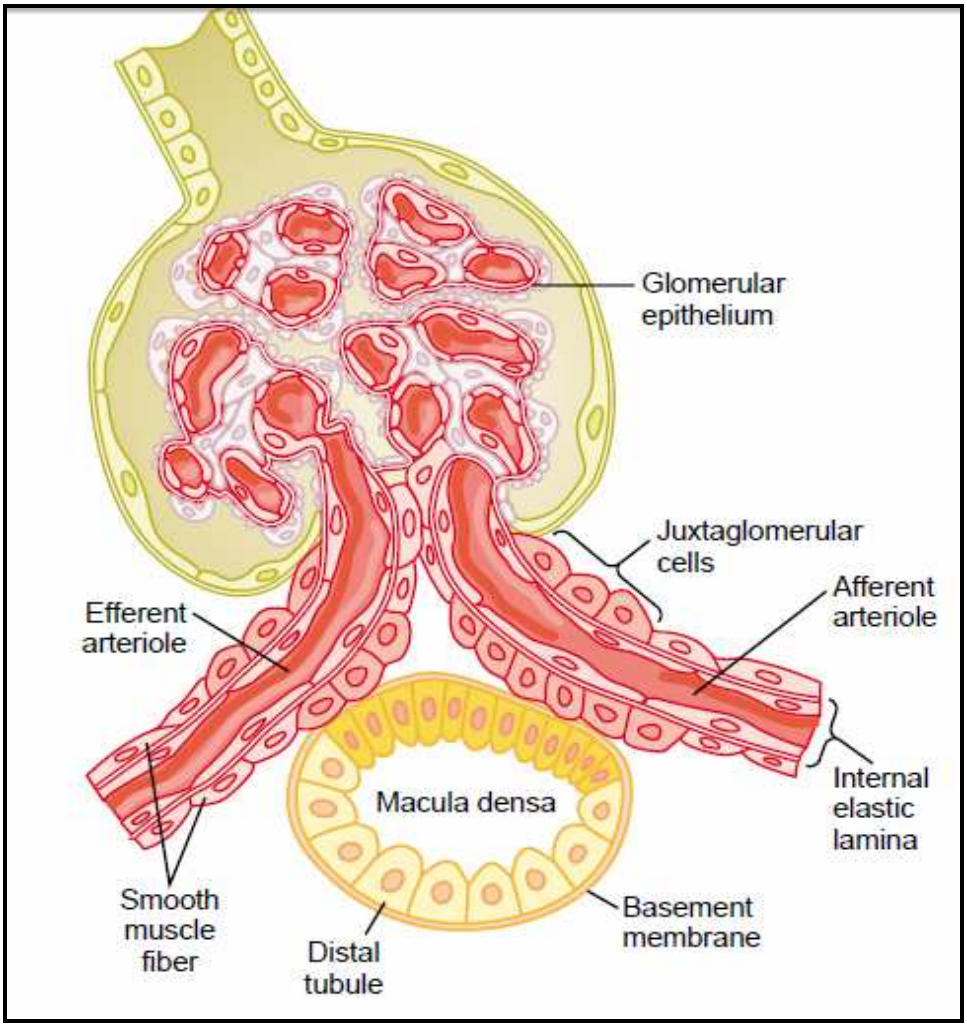

Figure (2): Structure of juxtaglomerular apparatus

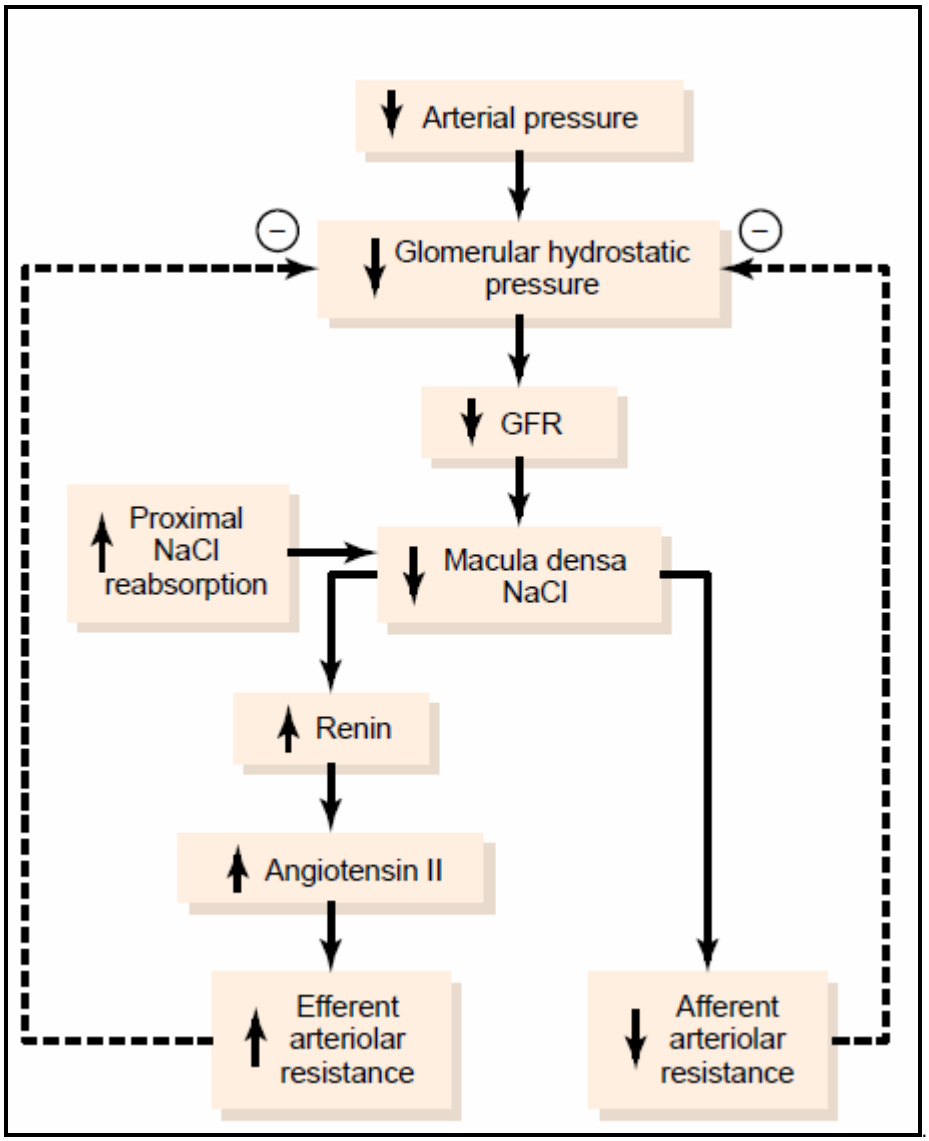

Figure (3): Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure ***(Bell et al., 2003& Navar et al., 2003).***

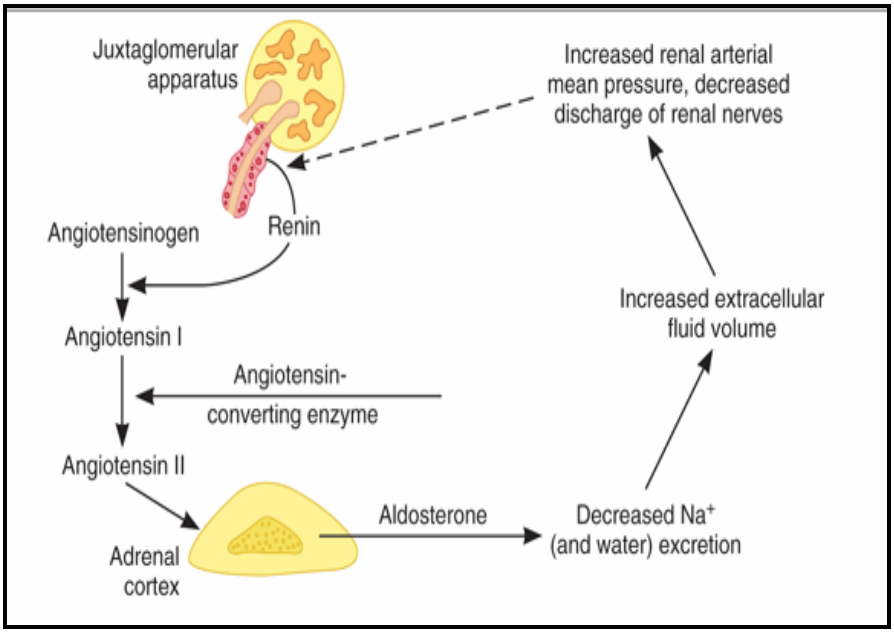

Figure (4): Feedback mechanism regulating aldosterone secretion ***(Hall et al., 1999, 2000).***

Normal GFR:

The GFR in a healthy person of average size is approximately 125 mL/min. Its magnitude correlates fairly well with surface area, but values in women are 10% lower than those in men even after correction for surface area. A rate of 125 mL/min is 7.5 L/h, or 180 L/d, whereas the normal urine volume is about 1 L/d. Thus, 99% or more of the filtrate is normally reabsorbed. At the rate of 125 mL/min, in 1 day the kidneys filter an amount of fluid equal to 4 times the total body water, 15 times the ECF volume, and 60 times the plasma volume.

Control of GFR:

The factors governing filtration across the glomerular capillaries are the same as those governing filtration across all

other capillaries, that is, the size of the capillary bed, the permeability of the capillaries, and the hydrostatic and osmotic pressure gradients across the capillary wall.

Size of the Capillary Bed:

The glomerular ultrafiltration coefficient can be altered by the mesangial cells, with contraction of these cells producing a decrease in glomerular ultrafiltration coefficient that is largely due to a reduction in the area available for filtration. Contraction of points where the capillary loops bifurcate probably shifts flow away from some of the loops, and elsewhere, contracted mesangial cells distort and encroach on the capillary lumen. Angiotensin II is an important regulator of mesangial contraction, and there are Angiotensin II receptors in the glomeruli. In addition, some evidence suggests that mesangial cells make renin.

Table (1): Agents Causing Contraction or Relaxation of Mesangial Cells

Contraction	**Relaxation**
Endothelins	ANP
Angiotensin II	Dopamine
Vasopressin	PGE2
Norepinephrine	cAMP
Platelet-activating factor	
Platelet-derived growth factor	
Thromboxane A_2	
PGF_2	
Leukotrienes C_4 and D_4	
Histamine	

Changes in GFR:

These factors have predictable effects on the GFR. Changes in renal vascular resistance as a result of autoregulation tend to stabilize filtration pressure, but when the mean systemic arterial pressure drops below the autoregulatory range, GFR drops sharply. The GFR tends to be maintained when efferent arteriolar constriction is greater than afferent constriction, but either type of constriction decreases blood flow to the tubules.

Table (2): Factors Affecting the GFR

Changes in renal blood flow
Changes in glomerular capillary hydrostatic pressure
Changes in systemic blood pressure
Afferent or efferent arteriolar constriction
Changes in hydrostatic pressure in Bowman's capsule
Ureteral obstruction
Edema of kidney inside tight renal capsule
Changes in concentration of plasma proteins:dehydration, hypoproteinemia, etc (minor factors)
Changes in K_f
Changes in glomerular capillary permeability
Changes in effective filtration surface area

Na^+ Reabsorption:

The reabsorption of Na^+ and Cl^- plays a major role in body electrolyte and water homeostasis. In addition, Na^+ transport is coupled to the movement of H^+, glucose, amino acids, organic acids, phosphate, and other electrolytes and substances across the tubule walls. In the proximal tubules, the thick portion of the ascending limb of the loop of Henle, the distal tubules, and the collecting ducts, Na^+ moves by cotransport or exchange from the tubular lumen into the tubular epithelial cells down its concentration and electrical gradients, and is then actively pumped from these cells into the interstitial space. Na^+ is pumped into the interstitium by Na, K ATPase in the basolateral membrane. Thus, Na^+ is actively transported out of all parts of the renal tubule except the thin portions of the loop of Henle. It extrudes three Na^+ in exchange for two K^+ that are pumped into the cell.

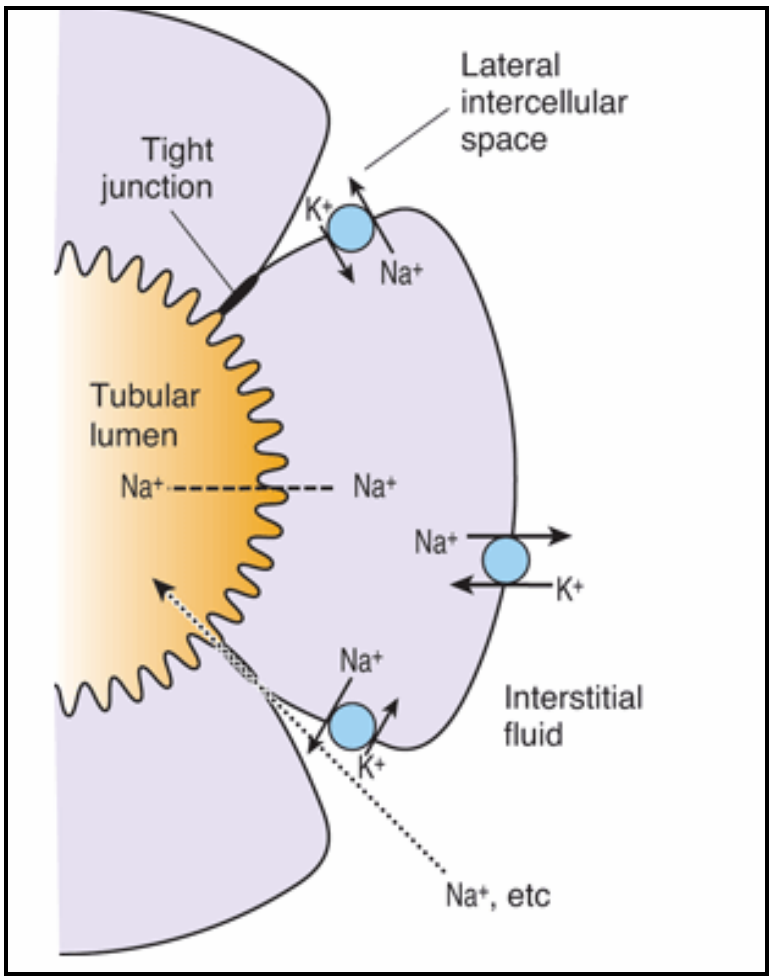

Figure (5): Mechanism of Na^+ reabsorption in the proximal tubule

Na^+ moves out of the tubular lumen by cotransport and exchange mechanism through the apical membrane of the tubule (dashed line). The Na^+ is then actively transported into the interstitial fluid by Na, K ATPase in the basolateral membrane (solid lines). K^+ enters the interstitial fluid via K^+ channels. A small amount of Na^+, other solutes, and H_2O re-enter the tubular lumen by passive transport through the tight junctions (dotted lines).