The physiology and pharmacology of the lower urinary tract

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Abstract

The lower urinary tract consists of the bladder and urethra in both sexes, and the prostate additionally in men and is concerned with the storage of urine and its voluntary and controlled expulsion from the body when socially convenient. These mutually exclusive states are mediated by complex neural networks that when dysfunctional may generate bothersome and prevalent lower urinary tract symptoms (LUTS). These symptoms are often idiopathic and not pathology specific. Most may be caused by bladder outflow obstruction, disorders of bladder contractility or conditions which increase bladder sensitivity and a combination of any of these states. Despite the precise mechanisms of symptom generation remaining unclear, the receptor mechanisms involved in controlling lower urinary tract function can be pharmacologically manipulated to achieve useful clinical outcomes.

Keywords Bladder dysfunction; lower urinary tract symptoms; overactive bladder

The urinary bladder

The urinary bladder lies in an extraperitoneal position in the pelvis and becomes oval when full. It comprises predominantly of smooth muscle, and has an apex that connects the urachus to the anterior abdominal wall, a body that lies above the ureteric orifices and a base comprising the trigone and bladder neck (Figure 1). In males, the seminal vesicles, ampullae of the vas deferens and terminal ureter are closely related to the bladder base, whilst in the female, the bladder base rests on the anterior vaginal wall and cervix. In both sexes the bladder is supported by the pelvic floor musculature which, particularly in the female, plays an important role in maintaining continence.

The ureters enter the bladder base posteriorly and travel obliquely in the wall for 1–2 cm before terminating at the ureteric orifices. This arrangement, together with the fibromuscular sheath (of Waldeyer) that covers the distal ends of the ureters, ensures they are compressed as the bladder fills, providing a valve-like mechanism which prevents the retrograde flow of urine under pressure. The trigone is triangular in shape and stabilizes the attachment of the ureters to the bladder, and the otherwise mobile bladder to the pelvic fascia. It has three distinct layers; a superficial layer from the longitudinal smooth muscle of the ureters which terminates at the verumontanum, an intermediate detrusor layer that is continuous with the bladder wall, and a deep layer formed from the sheath of Waldeyer that terminates at the bladder neck.

Transitional cell epithelium lines the lumen of the bladder and is usually 5–6 cells thick, except at the trigone where it is thinner. It also consists of three distinct layers namely, basal cells resting on a lamina propria, a multilayer of intermediate cells and a layer of multinucleated umbrella cells joined together by tight junctions at the luminal surface. Each umbrella cell covers several underlying smaller intermediate cells with a stem that extends to the lamina propria, and can alter their surface area significantly to accommodate bladder distention. Covering the umbrella cells is a layer of glycosaminoglycans, which protects the urothelium from damage by urinary constituents and bacterial adherence. Despite this multilayer barrier, the urothelium remains permeable to solutes and water through processes of active transport, osmotic and passive diffusion. Sodium ions enter umbrella cells through the luminal membrane and leave by the basolateral route both by active transport mechanisms. The role of sodium movement is unknown but may be important in generating the sensation of bladder fullness.

Lying deep to the urothelium is a richly innervated and vascularized suburothelial layer containing interstitial cells. Bladder afferent nerves originate here, and it is believed they are activated by ATP release from urothelial stretch during bladder filling. The permeability of the urothelium may increase when there is a defect in the glycosaminoglycan layer and up-regulation of the sensory mechanism associated with this may be responsible for generating bladder pain syndromes.

The bladder wall contains detrusor smooth muscle, the fibres of which are randomly arranged and separated by variable amounts of connective tissue stroma. Quantitative changes in connective tissue may contribute to the loss of bladder compliance and contractility disorders that characterize bladder outflow obstruction. At the bladder neck and trigone, the fibres become finer and more organized into layers. In males, the inner layer becomes continuous with that of the urethra, whilst the middle layer forms a pre-prostatic ring around the bladder neck that can function as an internal urinary sphincter. The outer layer forms the backing of the ureters and a loop around the anterior bladder neck. In females, only the inner longitudinal layer definitively exists at the bladder neck whilst the presence of the middle and outer layers is doubtful. The detrusor muscle is innervated by both parasympathetic (pelvic nerves) and parasympathetic (hypogastric) nerves.

The bladder neck and prostate

The bladder neck is a circular continuation of detrusor muscle, that is under adrenergic control and involuntary. In men, it actively contracts as part of the ejaculatory reflex preventing retrograde ejaculation, and during bladder filling the bladder neck remains closed although generally not sufficiently enough to provide absolute continence. The prostate gland merges with the bladder neck and contributes resistance to urine flow during

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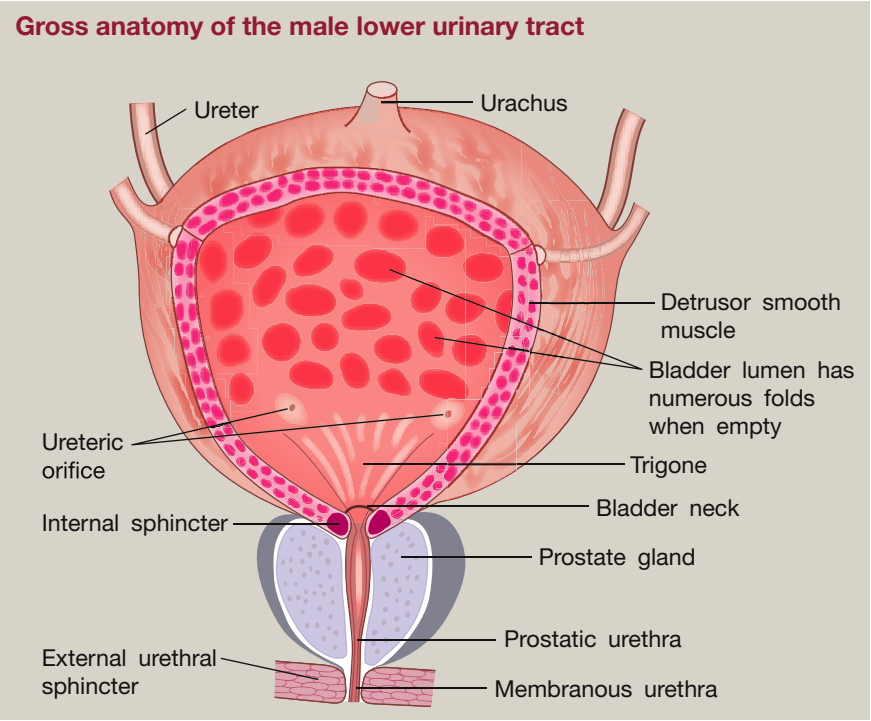

Figure 1

voiding. It consists of secretory tubular-acinar glands lined by epithelium and supporting fibromuscular stroma consisting of fibroblasts, connective tissue and a considerable amount of adrenergically innervated smooth muscle. This, like the bladder neck, generates an adrenergically mediated contractile tone sufficient to mediate a variable dynamic increase in bladder outflow tract resistance. In addition to this dynamic obstruction, growth factor-mediated enlargement of the stromal and epithelial cells in the transitional zone and periurethral areas of the prostate gives rise to benign prostatic enlargement (BPE) and static obstruction to the outflow tract.

Urethra and sphincter mechanism

The external urinary sphincter consists of three elements. The membranous urethra itself has viscoelastic properties that endow sphincteric function and also contains a thin smooth muscle layer extending along its length that is under sympathetic neuromuscular control. Situated around this is the horseshoe shaped rhabdosphincter that consists of slow-twitch skeletal muscle, and is under voluntary control. The rhabdosphincter is situated just distal to the prostate apex encircling the membranous urethra in men and at the mid-urethra in women, and is deficient posteriorly. It provides the primary continence mechanism by maintaining a constant tone. The periurethral striated muscles of the pelvic floor lie external to the rhabdosphincter, and sphincteric activity can be increased by voluntary contraction of the pelvic floor muscles in both sexes. In females, a hammock-like sling of endo pelvic fascia within the pelvic floor supports the mid urethra and plays a crucial additional role in maintaining continence by compressing and kinking the urethra during rises in intra-abdominal pressure.

The cellular mechanism of detrusor muscle contraction

Detrusor smooth muscle consists of spindle shaped cells up to 200 μm in length and 5 μm in diameter, each containing thin actin and thick myosin myofilaments that repeat along its length in a lattice pattern. The cells are electrically and mechanically connected and contain intermediate filaments binding the contractile proteins to dense bodies which distribute contractile forces to neighbouring cells (Figure 2). Smooth muscle contraction occurs by a different mechanism from that of skeletal and cardiac counterparts. The arrival of a nerve impulse at the parasympathetic nerve terminal leads to the release of acetylcholine (ACh) that activates muscarinic M3 detrusor receptors. This hydrolyses phospholipase-C to inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) (Figure 3). IP3 triggers the release of intracellular calcium from the sarcoplasmic reticulum whilst DAG acts on the L-gated channels in the plasma membrane to allow an influx of extracellular calcium. The calcium then binds to the protein calmodulin and activates myosin light chain kinase. This enzyme acts as a catalyst in the transfer of phosphate from ATP to myosin, causing ATPase enzyme activation on the myosin heads that allow contractile proteins to interact and generate force. The contraction of smooth muscle is characteristically slow and sustained because ATP is hydrolysed at a slower rate that allows tension to be generated and maintained without much energy expenditure and confers resistance to fatigue. Although M3 receptors mediate contraction, M2 receptors are more abundant and are thought to enhance the action of M3 receptors by suppressing sympathetic activity through the inhibition of adenylate cyclase. In obstructed or denervated bladders, M2 receptors may become functionally more important.