Signal transduction underlying the control of urinary bladder smooth muscle tone
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a. Background
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Bladder functions

The bladder has several functions including: collecting urine produced continuously by the kidneys, storing urine for extended periods of time and expelling it by urination (Andersson and Arner, 2004). Urine enters the bladder via the ureters in an area called trigone, and it exits the bladder through the urethra at the lowest point of the trigone (Figure 1). A healthy human bladder can hold at least 500 ml of urine; however, the first desire to void can already be sensed when it contains about 150-200 ml of urine. The biggest functional challenge of the bladder as an organ is to accommodate urine storage for an extensive period since the continuous production of urine by kidneys is not usually accompanied by continuous voiding; instead voiding is a non-continuous process and relatively a rare event in humans (occurs less than 8 times per day).

Figure 1. Anatomy of urinary bladder
Anatomy of bladder

The lower urinary tract includes bladder and urethra. The bladder contains two main parts: the bladder body (located above the ureteral openings) and the bladder base (consisting of trigone, urethrovesical junction, and anterior bladder wall). The urinary bladder is a very elastic and muscular hollow organ with its inner surface lined by a specialized urothelium. The bladder wall consists of three layers which are mucosa (transitional epithelium/urothelium and lamina propia), detrusor and fibrous adventitia and visceral peritoneum (Figure 2). The detrusor is the muscular part of the bladder and comprised of smooth muscle cells. The smooth muscle cell thickness varies during distension or contraction. Three layers of detrusor smooth muscle have been described (except in the trigone) and are arranged as follows: both inner and outer layers are oriented longitudinally, and the middle layer has a circular orientation. The human detrusor contains interlacing smooth muscle cell bundles of varying sizes that makes it difficult to differentiate between layers (Christ and Hodges, 2006; Silva and Karram, 2004).

Figure 2. Schematic drawing of the bladder.
Bladder relaxation and contraction directly depend on the detrusor smooth muscle tone, i.e., are the result of detrusor smooth muscle relaxation and contraction, respectively. This involves a rather intricate interaction between the structural/anatomical parts of the urinary tracts and between nervous control systems.

Urine storage during the filling phase of the micturition cycles occurs at a low pressure and this requires bladder distension. In order to accomplish storing urine, the bladder is entailed to be compliant to accommodate relatively large volume of urine storage (~ 500 ml). This process requires the bladder to relax/distend with concomitant contraction of the bladder neck, urethra and pelvic floor to prevent leakage. Voiding, in contrast, is a rapid event and requires a vigorous and synchronized contraction to generate a sufficient pressure that allows the bladder to be emptied completely. A synchronized bladder contraction and urethral relaxation are essential for a complete voiding.

Central Nervous System and Neuronal Innervation

Bladder function is controlled by central nervous system (CNS). The bladder functions in the CNS are controlled in the following areas: the sacral micturition centre, pontine micturition centre, pontine storage centre and cerebral cortex. The sacral micturition centre is located in the spinal cord at sacral (S2-S4) levels and is responsible for bladder contraction. The pontine micturition centre is located in the brainstem (pons) and appears to play a role in detrusor contraction and sphincter relaxation; via the spinal cord it leads to stimulation of the autonomic centres of thoracolumbar sympathetic nervous system, somatic pudendal nerves and parasympathetic pelvic nerves from sacral spinal cord. The pontine storage centre is also located in the pons and regulates bladder relaxation and external sphincter contraction. The cerebral cortex plays an inhibitory role in relation to the sacral micturition centre. A perfect organization of micturition cycles requires a complex neural control that innervates with various anatomical structures (Michel and Peters, 2004).

The bladder distends during the filling phase of the micturition cycle and elicits a low-frequency stimulation of the afferent nerve fibres. These are communicated via spinal cord to the pontine storage centre and lead to the activation of the descending nerve fibres which stimulate the thoracolumbar (T11-L2) sympathetic and the somatic nervous systems to initiate relaxation of the detrusor and contraction of the urethral muscle and pelvic floor to prevent leakage. When bladder distension reaches a critical level, the afferent nerve fibres fire at the high frequency, pending release by cerebral cortex (when the subject reaches the toilet and knows that it is acceptable to void), then this will promote a switch from the pontine storage to pontine micturition centre, cease the firing of sympathetic nerve and starts firing the parasympathetic nerve to elicit contraction if detrusor
and relaxation of the bladder neck, urethra and pelvic floor (Figure 3) (Michel and Peters, 2004).

**Figure 3. Neuronal innervation**

The main stimulus for physiological voiding and urine storage is provided by parasympathetic and sympathetic systems, respectively. Parasympathetic pelvic nerves release acetylcholine that activates post-junctional muscarinic acetylcholine receptors to cause contraction. Sympathetic hypogastric nerves
release noradrenaline which activates both β-adrenoceptors to relax the bladder and α₁-adrenoceptors to contract bladder neck and urethra. Pudendal somatic nerves release acetylcholine which activates the striated muscle of the external sphincter (Figure 4) (Andersson and Arner, 2004; Michel and Peters, 2004).

**Figure 4. Neurotransmitters**

![Diagram showing neurotransmitters](image)

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During the initial step of filling phase, the detrusor smooth muscle relaxes while urethra and pelvic floor contract to accommodate the urine without major rises in intravesical pressure. As the volume further increases, one starts to feel the first sensation to void, but this desire can be postponed because the detrusor continues to relax and the urethra and pelvic floor to contract to prevent the leakage. At the initiation of the voiding phase the urethra and pelvic floor relax which the detrusor muscle contracts to increase intravesical pressure and expel the urine (Figure 5).
Receptors involved in bladder contraction and relaxation

In humans and most mammals, the M₃ muscarinic receptors are the main muscarinic receptor subtype mediating bladder contraction. The prototypical signalling pathway of M₃ receptors is activation of a phospholipase C to generate inositol phosphates and diacylglycerol to release Ca^{2+} from the intracellular stores and to activate a protein kinase C, respectively (Figure 6)(Caulfield, 1993; Caulfield and Birdsall, 1998).

Bladder relaxation, however, is mediated by β₃-adrenoceptors subtype in humans and many other mammalian species. The prototypical signalling pathway of β-adrenoceptors is the activation of an adenylyl cyclase to form cyclic AMP with the subsequent activation of protein kinase A (Figure 6)(Bylund, et al., 1994).

Signalling mechanisms at these receptors in mediating bladder relaxation and contraction are extensively discussed in the section b (Review) (Figure 6).
Figure 6. Bladder signal transduction. Classical concepts.
References


