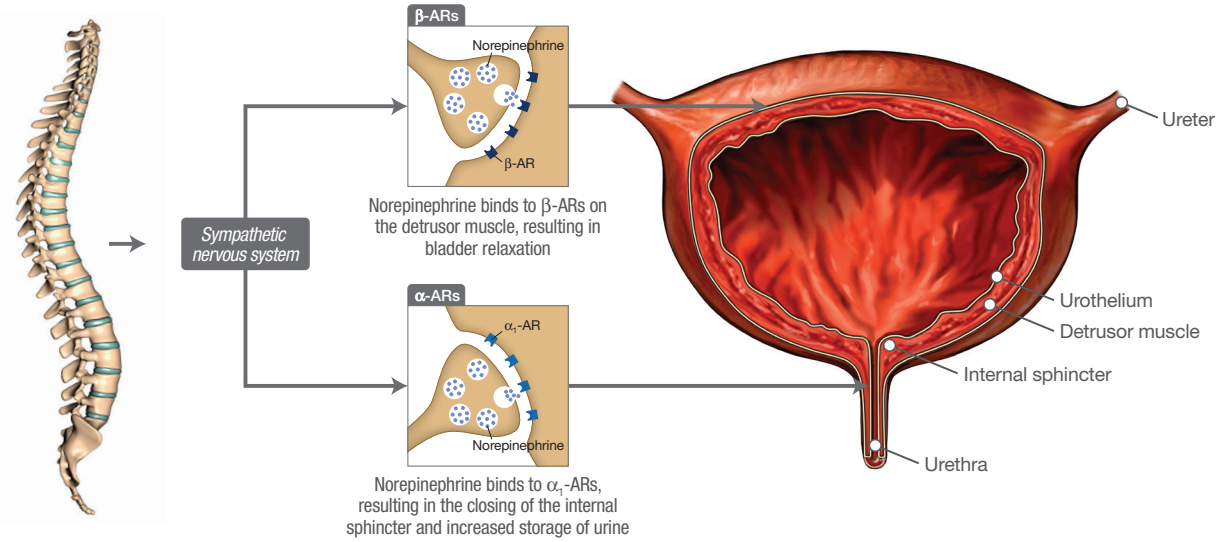
Center for Advanced Gyn
5530 Wisconsin Ave Suite 914
Chevy Chase, MD 20815
301-652-1231
www.centerforadvancedgyn.com

Regulation of bladder storage and voiding involves both sympathetic and parasympathetic control[1]

BLADDER STORAGE

Storage, which makes up the majority of the micturition cycle, is primarily regulated by the sympathetic nervous system via the neurotransmitter, norepinephrine.[2]

- Norepinephrine, released from the sympathetic nerves, activates the adrenergic receptors (ARs), beta-ARs, and alpha-ARs in the bladder to relax the detrusor muscle and close the internal sphincter, respectively[2]



Three different types of β-ARs are expressed in the human bladder: β_1-AR, β_2-AR, and β_3-AR. The β_3-AR made up 97% of the total β-AR messenger RNA (mRNA) in bladder tissue samples in an experiment to determine β-AR subtype expression, making it predominantly responsible for detrusor muscle relaxation. The β_1-AR and β_2-AR subtypes made up 1.5% and 1.4% of the total β-AR mRNA, respectively.[3]

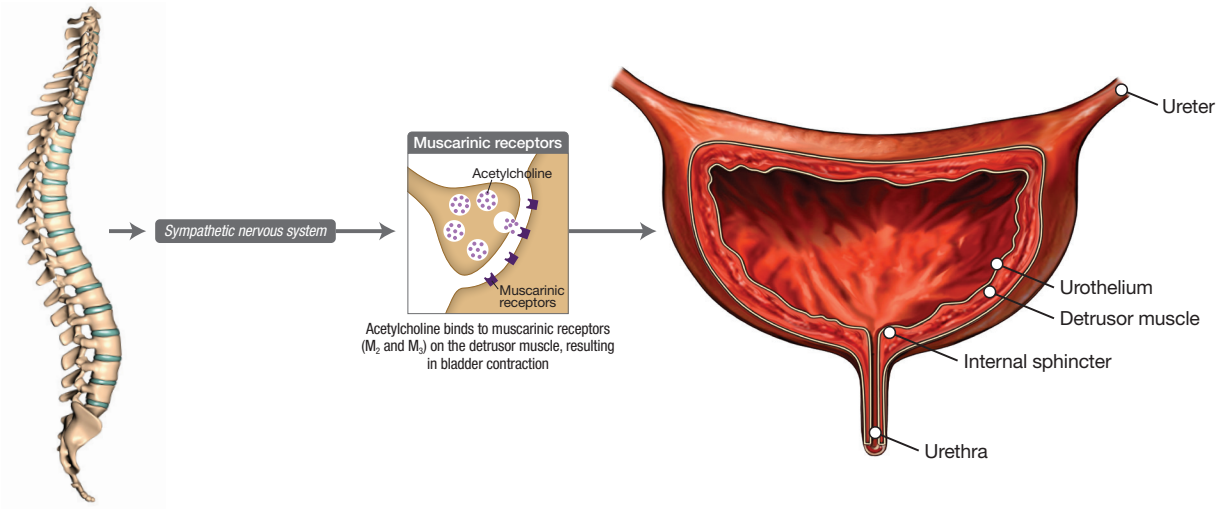
While β-ARs are expressed on the detrusor muscle, they are also found on the urothelium. These receptors contribute to the regulation of bladder function. During the storage phase, the urothelium stretches in tandem with the bladder wall when the bladder starts filling with urine.[4,5]

Both α_1-ARs and α_2-ARs are expressed in the lower urinary tract in humans.[6] Activation of noradrenergic pathways contracts the urethra to maintain continence at the onset of the storage phase of micturition.[7] Although expressed in the bladder to a lesser degree than β receptors, α1 predominates in the bladder neck.[6]

Norepinephrine binds to α_1-ARs, which are expressed in the urethra, resulting in the closing of the internal sphincter and an increase in urine volume. Contraction of the internal sphincter is mediated by both the sympathetic and pudendal nerves.[2]

BLADDER VOIDING

- Voiding is primarily regulated by the parasympathetic nervous system via the neurotransmitter, acetylcholine[1,7]
- The muscarinic receptors (M1 to M5) are mediated by acetylcholine and control the contraction of the detrusor muscle and relaxation of the internal sphincter muscle to facilitate voiding[2,8,9,10]
- Purinergic receptors ($P2X_3$) are mediated by ATP and function to sense bladder fullness for voiding[5]



- The muscarinic receptors can be found in urothelial cells[4,11]
- M2 and M3 are the predominant muscarinic receptors found in the bladder[12]
- M3 receptors are important for normal bladder contraction, while M2 receptors may play a more prominent role in certain disease states (demonstrated *in vitro*)[13]
- Binding of acetylcholine to M2 and M3 receptors on the detrusor muscle signals the bladder to contract so voiding can occur[7]

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