BLADDER DYSFUNCTION IN NEUROLOGICAL DISEASES – A REVIEW AND COMMON TEATMENT OPTIONS

Abstract

- The process of micturition is controlled by neural circuits in the brain and spinal cord coordinating the activity of smooth muscle in the bladder and urethra. Because this process is complex, a variety of neurologic disorders and injuries can result in urge incontinence.
- The lower urinary tract is innervated by 3 sets of peripheral nerves: pelvic parasympathetic nerves, which arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra; lumbar sympathetic nerves, which inhibit the bladder body and excite the bladder base and urethra; and pudendal nerves, which excite the external urethral sphincter.
- Detrusor strips from healthy human bladders are contracted by cholinergic muscarinic receptor agonists and electrical stimulation of intrinsic cholinergic nerves. Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder by receptor binding assays

Introduction

Micturition can be visualized as a process in which neural circuits in the brain and spinal cord coordinate the activity of smooth muscle in the bladder and urethra.

These circuits act as on-off switches to alternate the lower urinary tract between 2 modes of operation: *storage and elimination*.

Injuries or diseases of the nervous system in adults can disrupt the voluntary control of micturition and cause the re-emergence of reflex micturition, resulting in bladder hyperactivity and urge incontinence.

Because central nervous control of the lower urinary tract is complex, urge incontinence can result from a variety of neurologic disorders and abnormal sensory activation.

In addition, urge incontinence may be caused by intrinsic detrusor myogenic abnormalities that result in motor detrusor instability.

Neural Control of the Lower Urinary Tract

The lower urinary tract is innervated by 3 sets of peripheral nerves involving the parasympathetic, sympathetic, and somatic nervous systems:

- Pelvic parasympathetic nerves: arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra
- Lumbar sympathetic nerves: inhibit the bladder body and excite the bladder base and urethra
- Pudendal nerves: excite the external urethral sphincter

These nerves contain afferent (sensory) as well as efferent motor axons

Common neurological disorders usually associated bladder dysfunctions.:
Multiple sclerosis, Parkinson's disease, stroke, a brain tumor or a spinal injury can interfere with nerve signals involved in **bladdercontrol**, **causing** urinary **incontinence**.

Non-neurogenic voiding dysfunction

People with **non-neurogenic voiding dysfunction** have difficulty fully emptying their **bladder** due to either

- A weak bladder (atonic) muscle. This is similar to the next point.
- 'Lazy bladder' is an underactive **bladder** (also known as detrusor underactivity) is defined as a **bladder** which has a contraction of reduced strength and/ or reduced duration, which results

in prolonged or slow **bladder** emptying or inability to completely empty the **bladder** within a normal time span.

- A blockage in the flow of urine,
- Behavioural problems or habits that develop over time.
- Behavioural problems or habits may lead to non-neurogenic voiding dysfunction

(*Hinman syndrome (HS)* or non-neurogenic bladder is a voiding dysfunction of the bladder of neuropsychological origin that is characterized by functional bladder outlet obstruction in the absence of neurologic deficits).

Female voiding dysfunction

Voiding dysfunction is a broad term, used to describe conditions where there is poor coordination between the bladder muscle and the urethra.

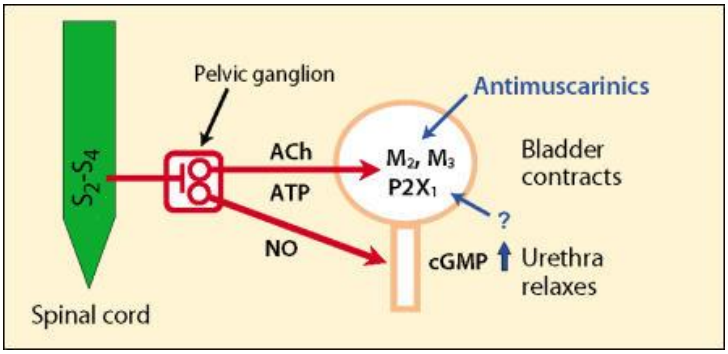
This results in incomplete relaxation or over activity of the pelvic floor muscles during voiding (commonly seen in old age or mutiparous women, with normal deliveries)

Parasympathetic Pathways

Parasympathetic preganglionic neurons innervating the lower urinary tract are located in the lateral part of the sacral intermediate gray matter in a region termed the sacral parasympathetic nucleus.

Parasympathetic preganglionic neurons send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter acetylcholine (ACh).

Parasympathetic postganglionic nerve terminals release ACh, which can excite various muscarinic receptors in bladder smooth muscles, leading to bladder contractions



In humans, parasympathetic postganglionic neurons are located in the detrusor wall layer, as well as in the pelvic plexus.

This is important in that patients with cauda equina or pelvic plexus injury, who are neurologically decentralized, may not be completely denervated.

Cauda equina injury allows possible interconnection between afferent and efferent nerves at the level of the intramural ganglia.

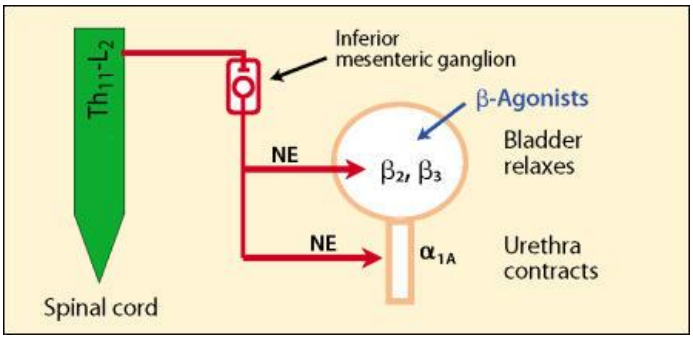
Sympathetic Pathways

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and urethra.

The peripheral sympathetic pathways follow a complex route that passes through the sympathetic chain ganglia to the inferior mesenteric ganglia and then, via the hypogastric nerves, to the pelvic ganglia.

Sympathetic preganglionic neurons synaptically connect with postganglionic neurons in the inferior mesenteric ganglion, as well as with postganglionic neurons in the paravertebral ganglia and pelvic ganglia.

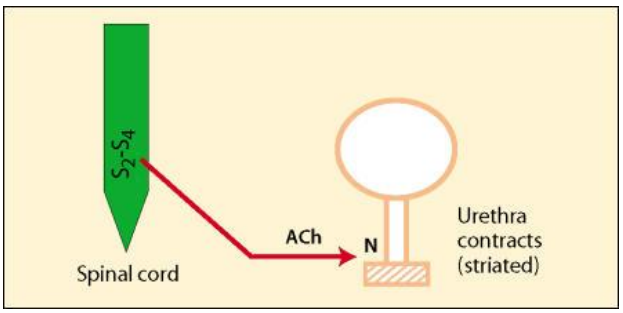
Ganglionic transmission in sympathetic pathways is also mediated by ACh acting on ganglionic-type nicotinic receptors. Sympathetic postganglionic terminals that release norepinephrine elicit contractions of bladder base and urethral smooth muscle and relaxation of the bladder body.



Somatic Pathways

Somatic efferent motor neurons that innervate the external striated urethral sphincter muscle and the pelvic floor musculature are located along the lateral border of the ventral horn in the sacral spinal cord, commonly referred to as Onuf's nucleus.

Sphincter motor neurons also exhibit transversely oriented dendritic bundles that project laterally into the lateral funiculus, dorsally into the intermediate gray matter, and dorsomedially toward the central canal. Somatic nerve terminals release ACh, which acts on skeletal muscle—type nicotinic receptors to induce a muscle contraction



Afferent Pathways

The pelvic, hypogastric, and pudendal nerves contain afferent axons that transmit information from the lower urinary tract to the lumbosacral spinal cord.

The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia, whereas afferent innervation in the hypogastric nerves arises in the rostral lumbar dorsal root ganglia.

The central axons of the dorsal root ganglion neurons carry sensory information from the lower urinary tract to second-order neurons in the spinal cord. Visceral afferent fibers of the pelvic and pudendal nerves enter the spinal cord and travel rostrocaudally within Lissauer's tract.

Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of bladder contractions, consist of small myelinated Aδ-fibers and unmyelinated C-fibers.

Although sensing bladder volume is of particular relevance during urine storage, afferent discharges that occur during a bladder contraction have an important reflex function and appear to reinforce the central drive that maintains bladder contractions.

Afferent nerves that respond to both distension and contraction, that is, "in-series tension receptors," have been identified in the pelvic and hypogastric nerves of cats and rats

NEUROPHARMACOLOGY

Cholinergic Mechanisms

Detrusor strips from healthy human bladders are contracted by cholinergic muscarinic receptor agonists and electrical stimulation of intrinsic cholinergic nerves. Contractile responses can be completely abolished by atropine.

There are at least 5 receptor subtypes based on molecular cloning and 4 different receptor subtypes based on pharmacology ($M_{1–5}$).

Pharmacologically, M_1, M_2, and M_3 receptor subtypes have been found in the human bladder by receptor binding assays.

Although ligand-receptor binding studies revealed that M_2 receptors predominate, M_3 receptors mediate cholinergic contractions.

Stimulation of M_3 receptors by ACh leads to phosphoinositol hydrolysis and, subsequently, to the release of intracellular Ca^{2+} and a smooth muscle contraction. It has been proposed that co-activation of M_2 receptors could enhance the response to M_3 stimulation through inhibition of adenylate cyclase and a subsequent suppression of sympathetically mediated depression of detrusor muscle, inactivation of K^+ channels, or activation of nonspecific cation channels.

It has also been documented that activation of M_1 prejunctional receptors facilitates Ach release, whereas activation of M_2/M_4 receptors inhibits ACh release.

It has been proposed that inhibitory M_2/M_4 receptors are preferentially activated by auto-feedback mechanisms during short periods of low-frequency nerve activity and, thereby, suppress cholinergic transmission during urine storage.

M_1 receptors are activated during more prolonged, high-frequency nerve firing that occurs during voiding and, thus, participate in an amplification mechanism to promote complete bladder emptying.

The muscarinic receptor antagonists tolterodine and oxybutynin (smooth muscle relaxant properties) are the most widely prescribed therapies for urinary incontinence.

These properties of smooth muscle relaxation may be clinically relevant only when the drug is administered as an intravesical instillation.

Purinergic Mechanisms

Pharmacologic and molecular studies have shown $P2X_1$ to be the predominant purinoceptor subtype in bladder smooth muscle to induce its contraction.

Although there is less evidence that purinergic neurotransmission exists in man, at least in regard to normal responses to stimulation, an increase in purinergic function may contribute to the unstable bladder under pathologic conditions such as bladder outlet obstruction.

Adrenergic Mechanisms

α-Adrenergic:

Although α-adrenergic stimulation is not prominent in the healthy bladder, recent evidence indicates that, under pathologic conditions, α-adrenergic receptor density can increase to such

an extent that the norepinephrine-induced response in the bladder is converted from relaxation to contraction.

It has been hypothesized that this shift in response may contribute to the bladder hyperactivity observed in a variety of pathologic conditions, including obstructive uropathy and incontinence.

Hyperreflexic human bladders and demonstrated significantly lower muscarinic receptor densities and higher α-adrenoceptor densities in the hyperreflexic bladders.

ß-Adrenergic:

The bladder smooth muscle contains 2 subtypes of ß-adrenoceptors ($ß_1$- and $ß_2$-receptors). Although $ß_2$-adrenoceptors have an important role in muscle relaxation via activation of adenylate cyclase, recent evidence indicates that the $ß_3$-receptor subtype mediates relaxation of human detrusor muscles, with predominant expression of $ß_3$-adrenoceptor messenger RNA in human bladder tissue.

ß-Adrenergic-stimulated relaxation is mediated through the stimulation of adenyl cyclase and the accumulation of c-AMP.

Thus, it is suggested that activation of bladder $ß_3$-adrenoceptors could be an effective treatment of bladder over activity.

Nitric Oxide

Nitric oxide (NO), which has been implicated as an important neurotransmitter in urethral relaxation and penile erection, is also involved in controlling bladder afferent nerve activity.

Intravesically administered capsaicin induces bladder hyperactivity that is not influenced by NOS inhibitors, although the behavioural effects of the irritation are reduced.

The inhibitory components of the somatovesical reflex elicited by electrical stimulation of the tibial nerve are reduced with NOS inhibition.

Intravesical application of NO can also suppress bladder hyperactivity caused by cyclophosphamide-induced bladder irritation in rats. These effects are mediated by suppression of Ca^{2+} channel activity in bladder afferent pathways.However role in humans is yet under research.

Tachykinins

The tachykinins are a family of small peptides, the main members of which are substance P, neurokinin A, and neurokinin B.

Tachykinins are found in both central and peripheral nervous systems.

In the peripheral nerves, substance P and neurokinin A are predominately located in the terminals of nonmyelinated, sensory C-fibres.

The diverse biologic effects of the tachykinins are mediated via 3 receptors—NK1, NK2, and NK3—belonging to a superfamily of 7 transmembrane-spanning G-protein-coupled receptors.

NK1- and NK2-specific antagonists were demonstrated to reduce the painful behavioural response in an experimental bladder inflammatory cystitis model.

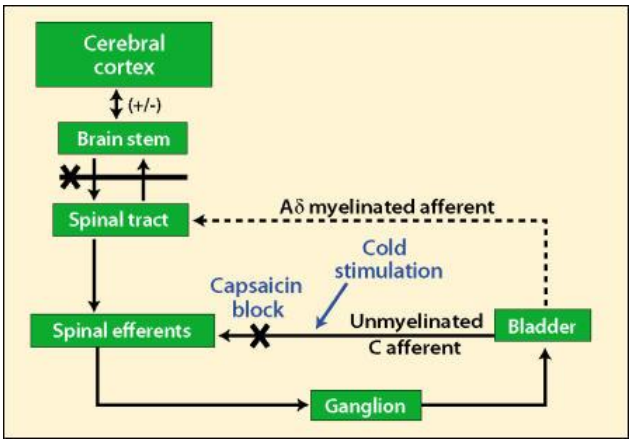
Study results suggest that tachykinin release from capsaicin-sensitive sensory C-fibers in response to irritation is mediated primarily by NK2 receptors and partially by NK1 receptors.

Capsaicin, Resiniferatoxin, Vanilloid Receptor, and C-Fiber Pharmacotherapy

Capsaicin and its ultra potent analogue resiniferatoxin are vanilloids that stimulate and desensitize a specific population of sensory nerves (predominantly unmyelinated C-fibres) that transmit pain signals and release neuropeptides.

Because of their unique property of C-fibre desensitization, the vanilloids are undergoing intensive study as a therapy for pain not only in the bladder but also in other systems.

The normal sensations of bladder filling appear to be mediated by small myelinated fibersIn the cat, Aδ-fibers have pressure thresholds in the range of those at which humans report the first sensation of bladder filling.



The vanilloids capsaicin and resiniferatoxin activate nociceptive sensory nerve fibres through a recently discovered ion channel known as vanilloid receptor subtype 1 (TRPV1).

This receptor, a nonselective cation channel, is activated by increases in temperature to within the noxious range and by protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity in vivo.

When TRPV1 is activated, the channel opens, allowing an influx of calcium and sodium ions that depolarizes the nociceptive afferent terminals, which initiates a nerve impulse that travels through the dorsal root ganglion into the central nervous system (CNS).

Serotonergic Mechanisms

In the CNS, serotonin-containing neurons in the raphe nucleus of the caudal brain stem send projections to the dorsal horn, as well as to the autonomic and sphincter motor nuclei in the lumbosacral spinal cord.

Activation of raphe neurons or serotonin receptors in the spinal cord inhibits reflex bladder contractions and firing of the sacral efferent pathways to the bladder, as well as firing of spinal dorsal horn neurons elicited by stimulation of pelvic nerve afferents.

DULOXTINE

In a bladder-irritation model, duloxetine, a combined noradrenaline and serotonin reuptake inhibitor, has been shown to increase neural activity of both the urethral sphincter and the bladder.

Duloxetine appears to have due effect on both the bladder and the sphincter and has been proposed as a treatment of both stress and urge incontinence.

It increases neural activity to the external urethral sphincter and decreases bladder activity through effects on the CNS.

It has been proved to be effective in the elderly with stress incontinence.

MECHANISMS OF BLADDER OVER ACTIVITY

A variety of models have been used to explore the pathogenesis of detrusor over activity and formulate therapies for urge incontinence.

Models for bladder over activity in several species have been developed relevant to spinal cord injury, obstruction, denervation, Parkinson disease, interstitial cystitis, diabetes, multiple sclerosis, and aging.

More recently, the spontaneously hypertensive rat has provided a useful genetic model for bladder over activity.

A common feature of many of these models is that changes in smooth muscle function can elicit long-term changes in nerves. Investigators are accustomed to examining short-term effects; however, there is now a greater appreciation that long-term events involving growth factors lead to plasticity in neural pathways, with implications for disorders of micturition.

Neurotransmitters, prostaglandins, and neurotrophic factors, such as nerve growth factor, provide mechanisms for communication between muscle and nerve. Disturbances in these mechanisms can cause bladder over activity due to alterations in autonomic reflex pathways. This bladder over activity can, in turn, lead to urge incontinence.

Cystometry and urinary frequency, which are commonly used to define bladder over activity, can be used to monitor response to drugs or other therapies.

A multidisciplinary approach to treatment, incorporating biochemical, molecular, pharmacologic, physiologic, and behavioural methods, can provide insight into the pathogenesis of bladder over activity.

TREATMENT

Drugs used for treating neurogenic bladder

- Medicines that relax the bladder (oxybutynin, tolterodine, or propantheline)
- Medicines that make certain nerves more active (bethanechol)
- *Botulinum toxin* – This is a novel procedure, though costly and lifetime use, can be a novel method to control neurogenic bladder.

An additional issue regarding the effects of antimuscarinic drugs is clinical relevancy. Antimuscarinic drugs are metabolized, and their metabolites have pharmacologic effects. For example, oxybutynin has less of a dry-mouth effect than does its metabolite N-desethyloxybutynin.

Therefore, the controlled-release formulation of oxybutynin maintains the efficacy of immediate-release oxybutynin but with significantly fewer side effects. Transdermal delivery of oxybutynin results in a lower concentration of metabolite and an improved side effect profile compared with the oral formulation.

Also to be noted is pharmacologically defined receptor subtype-selective drugs have been developed. Darifenacin and vamicamide have recently been demonstrated to be selective for the M_3 receptor subtype. A truly bladder-selective antimuscarinic drug that causes no dry mouth is the ultimate goal for overactive bladder drug therapy.

ß-Adrenergic blockers have also been advocated for urinary incontinence due to inappropriate reflex urethral relaxation, because propranolol prevents the reduction in urethral pressure following sacral root stimulation. However, $ß_2$-adrenergic antagonists are not particularly useful in treating bladder or urethral disorders.

New antimuscarinic drugs are a “hot topic” for pharmaceutical development, urologists should be aware of the muscarinic receptor subtypes and their distribution in the lower urinary tract and other organs.

It is to be remembered that in certain patients, eg, complete cord transection or severe atonic bladder due to other causes, self catherization (called C.I.C – clean intermittent catherization) is the only way to empty their bladder and can be done at 3-4 hrly interval.

(*Unlike to the common belief, this does not lead to infections as frequently as putting in a continuous indwelling catheter).*

CONCLUSION

Diseases of the nervous system in adults can disrupt the voluntary control of micturition and cause the re-emergence of reflex micturition, resulting in bladder hyperactivity and incontinence.

During the past several years, research in the field of neuro-urology has led to the emergence of new concepts regarding the neural control of the lower urinary tract and the aetiology of voiding dysfunction.

Thus, in addition to traditional drugs, which target the smooth muscle or post junctional muscarinic and adrenergic receptors, it is now clear that targets at other sites, such as afferent neurons, efferent nerve terminals, urothelial cells, and the CNS, are equally important for drug development.

Also other than medicines research is on several upcoming devices, controllable by patients to make their lives simpler and self-controllable.