Chapter 7
Novel Drugs for Underactive Bladder

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Need for Novel Drugs

The International Continence Society (ICS) defines UAB as a detrusor contraction of inadequate strength and/or duration resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying in the absence of urethral obstruction (Abrams et al. 2002). A multifactorial etiology is implicated (Tyagi et al. 2014) including aging for idiopathic UAB, neurogenic UAB as a consequence of Parkinson disease, multiple sclerosis, spinal cord injury or cauda equina (e.g., herniated disc, pelvic fractures), infection (e.g., AIDS, herpes zoster infection), and myogenic UAB secondary to diabetes mellitus or bladder outlet obstruction.

Medical management of UAB does not always achieve satisfactory results and it remains an undertreated and underreported condition. Despite the enormous amount of new biologic insights, very few drugs with mechanism of action other than direct and indirect muscarinic agonists have passed as yet the proof-of-concept stage. Research and development of novel therapeutic options for UAB is therefore an area of active interest (Smith et al. 2014b). Although the exact etiology of UAB is unknown, pharmacological therapy has been targeted to both the central and peripheral nervous system. In order to understand the pharmacology guiding the enterprise of drug discovery for this ailment, it is important to describe the potential sites available for action by novel drugs. Complete bladder emptying during voluntarily initiated voiding relies on intact afferent transmission from the bladder to brain, which then activate the efferent outflow for coordinating the contraction and relaxation of the bladder and sphincter, respectively. During voiding, the pontine micturition reflex center stimulates the sacral parasympathetic nucleus to increase

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parasympathetic activity. This results in bladder contraction via activation of post-synaptic muscarinic receptors (M2/3) and relaxation of both urethral and prostatic smooth muscle by nitric oxide (NO) release (Tyagi et al. 2014). A defect at any link in the chain (from urothelium to nerve to detrusor smooth muscle) can ultimately lead to prolonged bladder emptying that characterizes UAB (Tyagi et al. 2014). Molecular pathways participating at each stage of micturition reflex can be potential drug targets for UAB.

Novel Drugs

A number of promising new drugs that target key molecular pathways (Fig. 7.1) (Table 7.1) involved in micturition control at the levels of the urothelium, detrusor muscle, peripheral and central nervous systems are being considered for treatment of UAB (Smith et al. 2014b). Preferred drug candidates either increase the afferent activity or the detrusor contractile force while decreasing the outflow resistance. Molecular targets in the periphery include muscarinic, prostaglandin receptors, neurotrophins, potassium, pannexin, and transient receptor potential (TRP) and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Potential targets in the CNS include dopamine, serotonin (5-HT), and opioid neurotransmission. In the standard pharmacotherapy for UAB, bethanechol mimics the acetylcholine action, which is the primary excitatory neurotransmitter involved in bladder (detrusor) contraction and emptying. Therefore, bethanechol can address the deficits in both afferent and efferent neurotransmission, but its clinical utility is limited by the lack of receptor selectivity and cholinergic side effects of sialorrhea, nausea, abdominal distension, and abdominal cramping (Manchana and Prasartsakulchai 2011), vision, and, potentially, cardiovascular and CNS effects. Further preclinical and clinical studies are therefore needed to meet the unmet medical need.

Drugs Targeting Urothelium Signaling

The sensory side of the micturition reflex (Smith et al. 2012) is a potential therapeutic target for UAB. Mechanoreceptive afferents residing in the bladder wall not only convey the state of bladder fullness during storage phase but also convey the magnitude of spontaneous (non-voiding) and voiding detrusor contractions (Meng et al. 2008). Several reports have suggested that reduced release of various substances, including adenosine triphosphate (ATP) (Munoz et al. 2011), prostaglandins, and acetylcholine (ACh), from bladder urothelium could contribute to decreased bladder sensation and cause a deficit in afferent input from the bladder(Smith et al. 2012). In addition, attenuated contractile stimulus (acetylcholine and ATP) can also lead to

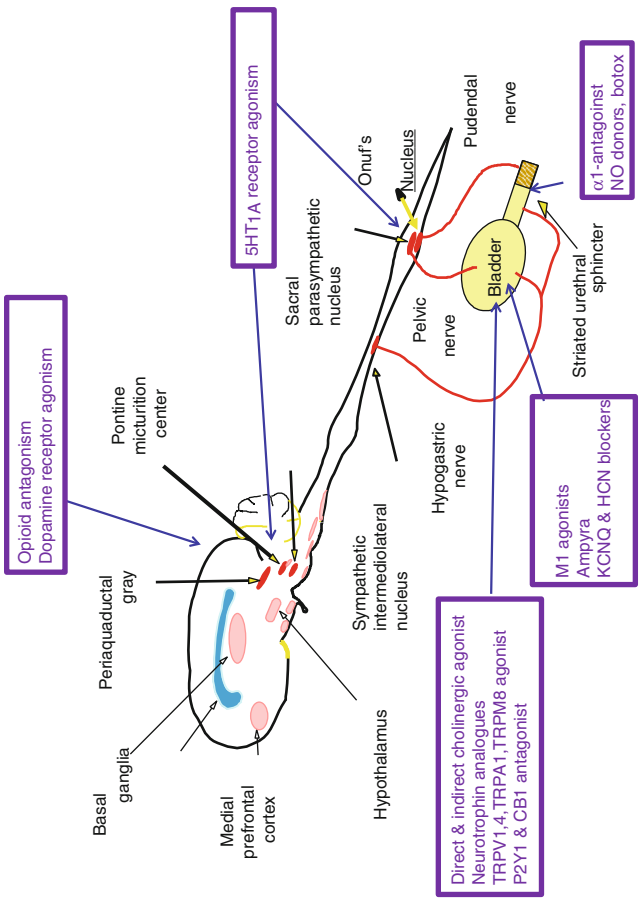

Fig. 7.1 Potential new drugs for UAB target key molecular pathways involved in micturition control at the levels of the urothelium, detrusor muscle autonomic and afferent pathways, spinal cord, and brain. Various drug classes are included in *purple boxes* with *arrows* indicating sites of action

Table 7.1 Novel drugs for underactive bladder

Drugs targeting urothelium signaling
Acetylcholine
Improve bladder emptying by indirect acting agonists
Neurotrophin mimetics
Neurite growth enhancer
Prostaglandins
Agents that activate pannexin channels
Agents that sensitize afferent nerve endings
TRPV1 and TRPV4 agonists
TRPA1 agonists
Transient receptor potential melastatin 8 (TRPM8) channel agonists
Cannabinoid receptor antagonists
Drugs improving muscle function for myogenic UAB
By facilitating nerve-evoked contraction
M_1 muscarinic agonists
N-Type high-voltage-activated Ca(2+) channels (HVACCs) agonists
By facilitating spontaneous contraction
Potassium channels
Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels
Centrally acting drugs for neurogenic UAB
Drugs acting on dopamine pathway
Drugs acting on serotonin pathway
Drugs acting on opioid pathway
Drugs that decrease urethral resistance

decreased detrusor contractility. Therefore, drugs that target urothelium can improve the defective initiation of afferent signals and enhance detrusor contractility.

Acetylcholine

Bladder urothelium possesses a nonneuronal cholinergic system and high density of muscarinic receptors. Impaired afferent signaling(Smith et al. 2014a) due to either reduced acetylcholine release from urothelium or due to changes in the sensitivity and coupling of the suburothelial interstitial cell network is offered as an explanation for UAB phenotype. Agents can either directly mimic the release of acetylcholine in the bladder or act indirectly by inhibiting the metabolism of acetylcholine. Acetylcholine released from parasympathetic nerves together with ATP (Burnstock 2013) at the detrusor neuromuscular synapse mediates detrusor contraction. ATP exerts activation of excitatory purinergic $P2X_1$ receptors on the detrusor smooth muscle, and inhibitory action on $P2Y_1$ receptors in cholinergic nerve endings controls the acetylcholine release.

Improve Bladder Emptying by Indirect Acting Agonists

Considering the adverse effect profile of direct acting agonists of acetylcholine, namely, bethanechol, there is a definite incentive for enhancing the action of acetylcholine through indirect means. Distigmine inhibits the enzyme, acetylcholinesterase, and thereby increases the pharmacodynamic half-life of endogenously released ACh. Three times daily treatment of distigmine 5 mg for 4 weeks was recently tested in 27 UAB patients (Bougas et al. 2004). In the phase II trial on UAB patients, distigmine was generally well tolerated by UAB patients. Pressure flow studies were conducted before the initiation of distigmine and at follow-up. Distigmine obviated the need for intermittent self-catheterization in 11 patients and PVR was significantly reduced. Treated patients also showed slight increase in maximum flow rate and detrusor pressure at maximum flow. Apart from cholinesterase inhibition for UAB, drugs that downregulate the expression of acetylcholinesterase can be another alternative option. Antagonists for P2Y1 receptor are known to block the ATP-mediated increase of cholinesterase activity with aging (Choi et al. 2003).

Neurotrophin Mimetics

A common trait shared by voiding dysfunctions such as UAB, irrespective of their origin, is dysregulation in synthesis and secretion of neurotrophins (Kim et al. 2005; Nirmal et al. 2014; Wang et al. 2015). Four neurotrophins have been identified in mammalian cells: most notably nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-4/5 (NT-4/5). These target tissue-derived neurotrophins exert their effects upon binding to their high-affinity receptors abundantly expressed in the bladder (Girard et al. 2011) and neuronal circuits regulating micturition function (Garraway et al. 2011). Studies have demonstrated that constitutive expression of NGF and BDNF from urothelium and detrusor smooth muscle cells can promote neuronal survival and maturation (Elmariah et al. 2004; Gonzalez et al. 1999). BDNF interacts with serotoninergic and cholinergic transmission as serotonin reuptake inhibitors increase BDNF levels (Song et al. 2014), and BDNF is known to increase the cholinergic transmission through a presynaptic mechanism (Slonimsky et al. 2003). In a recent study, exogenous expression of BDNF was shown to upregulate the expression of cholinergic genes in the bladder (Kashyap et al. 2014b, 2015).

It is known that NGF activates the cell-surface transmembrane glycoprotein TrkA receptor, whereas BDNF acts via high-affinity receptor tropomyosin-related kinase B (TrkB). TrkB receptor is co-expressed with acetylcholine receptors along the postsynaptic membrane of the neuromuscular junction, and expression is innervation dependent (Funakoshi et al. 1995; Pitts et al. 2006). TrkB signaling was demonstrated to be a key regulator of neuromuscular function as blockade of TrkB signaling (Kulakowski

et al. 2011) attenuated the neuromuscular transmission and fragmented postsynaptic acetylcholine receptors. Drugs mimicking BDNF action can therefore be potential drugs for increasing the cholinergic transmission in the bladder of UAB patients.

Neurite Growth Enhancer

Studies on animal models of neuropathy showed that TAC-302 a cyclohexenoic-long fatty alcohol derivative was able to enhance the outgrowth of neurites. Chronic oral administration of TAC-302 improved the voiding in diabetic bladder dysfunction with dose-dependent reduction in residual urine volume and increased voided volume in UAB secondary to streptozotocin (STZ)-induced diabetes (Takahisa et al. 2013; Yoshizawaa et al. 2012).

Prostaglandins

Prostaglandins, namely, PGE2, are synthesized by cyclooxygenase-1 (COX-1) and COX-2 in the bladder, which is released during bladder stretch and believed to be responsible for the spontaneous detrusor contractions (Fry et al. 2004). Instillation of PGE2 was able to reduce the voiding interval in UAB secondary to STZ-induced diabetes mellitus (Nirmal et al. 2014). In similar studies on UAB induced by lumbar canal stenosis (LCS), PGE2 infusion increased the frequency of small-amplitude phasic contractions during the filling phase of cystometry under urethane anesthesia performed 4 weeks after LCS (Fig. 7.2), whereas

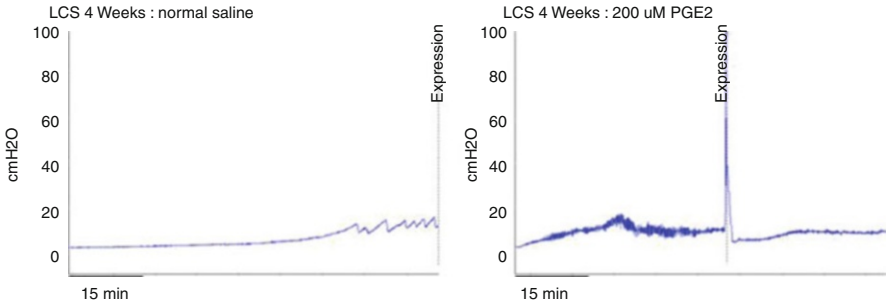

Fig. 7.2 The effect of PGE2 instillation on basal tone of the bladder in rat model of neurogenic UAB induced by lumbar canal stenosis. Bladder infusion of PGE2 in the concentration (200 uM) induced small-amplitude phasic contractions during the filling phase of cystometry under urethane anesthesia performed 4 weeks after LCS procedure (*right panel*). Saline-treated LCS rats at the same time point showed the acontractile phenotype with the absence of phasic contractions (*left panel*)

saline-treated group remained acontractile (Wang et al. 2015). Intravenous injection of sulprostone, a prostaglandin E receptor 3 (EP3) agonist at 2 weeks, reproduced the cystometric changes observed following intravesical PGE2 in 4-week old LCS rats under urethane anesthesia (Wang et al. 2015). In a clinical study, once-weekly intravesical PGE2 (1.5 mg in 20 mL 0.9 % saline) was combined with bethanechol 50 mg four times daily for a total of 6-week therapy of 17 male and 2 female UAB patients (Hindley et al. 2004). Combined therapy only showed limited therapeutic effect over placebo, where majority of the patients included in the trial were reliant on clean intermittent self-catheterization with PVR consistently >300 mL. Overall, studies support PGE2 analogues and EP1 receptor as potential drugs and drug target for UAB, respectively.

Agents That Activate Pannexin Channels

It is known that the bladder response to purinergic agents increases with age, whereas the response to cholinergic agents decreases with age (Yoshida et al. 2004). These age-dependent biochemical changes support the rationale of developing drugs acting on purinergic pathway for age-associated disorders such as UAB. A recent study showed that in response to distension, ATP is released through pannexin channels into the lumen (Beckel et al. 2015). Considering that aging is associated with loss of responsiveness to bladder filing (Smith et al. 2012), it is suggested that pannexin functionality is reduced with aging. Drugs that activate pannexin channels such as ATP diphosphohydrolase (apyrase) can be potential drugs for UAB.

Agents That Sensitize Afferent Nerve Endings

Bladder and urethral afferent dysfunction seen in UAB associated with diabetes (Lee et al. 2009) is associated with destruction of capsaicin-sensitive fibers in the bladder and urethra (Yang et al. 2010). Age-related decline in bladder sensation is also related to the sparse to moderate densities of TRPV1 immunoreactive nerves in the suburothelium and sparse fibers in the muscle layers. The capsaicin-sensitive afferents in the bladder are known to contain several peptides. These include tachykinins (such as substance P and neurokinin A and B), vasoactive intestinal polypeptide, and calcitonin gene-related peptide. Agents mimicking the action of these peptides can be potential drugs for UAB. Activation of transient receptor potential (TRP) channels on afferent nerves in the bladder induces the release of neurokinins, which increase detrusor contractility. Several partial or complete agonist of TRP channels TRPV1. TRPV4, TRPA1 and TRPM8 are potential drug candidates for UAB.

Transient Receptor Potential Vanilloid 1 (TRPV1) and TRPV4 Agonists

TRPV1 and TRPV4 are molecular transducers of hot temperature into neuronal signal. GSK 1016790A is a TRPV4 agonist and its intravesical instillation transiently decreased bladder capacity and voided volume (Aizawa et al. 2012). TRPV4 stimulation in the urothelium is considered to facilitate the micturition reflex by activation of the mechanosensitive, capsaicin-insensitive C-fibers of the primary bladder afferents. Extravesical application of piperine, a TRPV1 agonist to rat bladder, increased afferent input and detrusor contractility (Gevaert et al. 2007). Overall, studies support use of TRPV4 and TRPV1 agonists as a potential therapeutic approach for UAB.

Transient Receptor Potential Ankyrin 1 (TRPA1) Agonists

A recent study demonstrated that TRPV1 immunoreactivity in unmyelinated nerve fibers within the urothelium, suburothelial space, and muscle layer of the bladder is co-localized with TRPA1 immunoreactivity (Streng et al. 2008). Activation of TRPA1 by allyl isothiocyanate increased the micturition frequency and reduced the voided volume in rat. Findings support agonism of TRPA1 as a potential approach for improving afferent deficit in UAB.

Transient Receptor Potential Melastatin 8 (TRPM8) Channel Agonists

TRPM8 is a molecular thermal sensor for translating cold temperature into neuronal activity (Lei et al. 2013). It is recognized that cold temperature elicits urgency response in individuals with voiding dysfunction. Since sensory endings in the skin are responsible for perception of thermal cues, their stimulation can be harnessed to improve clinical outcomes. Spraying of menthol that activates TRPM8 decreased the voiding interval, micturition volume, and bladder capacity of rats (Lei et al. 2013), suggesting that topical activation of TRPM8 can be used to improve bladder emptying in UAB patients.

Cannabinoid Receptor Antagonists

In contrast to agonism of TRP channels, antagonism of cannabinoid receptors is a potential therapeutic approach for increasing afferent input from the bladder and reducing bladder capacity (Dmitrieva and Berkley 2002) in UAB patients.

Cannabinoid receptors were suggested to be responsible for the pathogenesis of UAB associated with diabetes (Li et al. 2013), and activity of bladder afferents was reduced following activation of CB1 receptors in mouse bladder (Walczak et al. 2009). Based on available research, we postulate that CB1 antagonist, rimonabant (Pataky et al. 2013), is a potential candidate for repositioning in UAB.

Drugs Improving Muscle Function for Myogenic UAB

The underlying pathobiology for myogenic UAB is considered to be either abnormal detrusor muscle contractility or secondary to bladder outlet obstruction. Decreased detrusor contractility can result from a lack of contractile stimulus from acetylcholine and ATP or a lack of tissue responsiveness to contractile stimuli due to irreversible changes in the bladder wall that are described as sarcopenia (loss of muscle tissue, increased collagen deposition) (Tyagi et al. 2014). The lack of tissue responsiveness to contractile stimuli may be due to altered excitation–contraction coupling mechanisms contributed by changes in the properties and density of calcium and potassium channels, gap junctions, and receptors in detrusor smooth muscles. It is considered that stimulus intensity of efferent nerve-evoked bladder contraction relies on afferent input (Zeng et al. 2012), which in turn is dependent on the strength of spontaneous detrusor contractions detected during storage phase. In fact, patients with mixed UAB (coexistence of both neurogenic and myogenic phenotype) are considered to have attenuated spontaneous detrusor contractions that reduce the afferent input (Andersson 2010), which ultimately causes insufficiency in nerve-evoked detrusor contractility. Therefore, drugs can address myogenic UAB by facilitating nerve-evoked contraction and/or by facilitating spontaneous contractions in UAB with acontractile bladder phenotype.

Drugs That Facilitate Nerve-Evoked Contraction

It is established that activation of muscarinic receptors in the bladder is responsible for normal voiding, and a subtype of muscarinic receptor can be pharmacologically manipulated for attenuating the prolonged bladder emptying of UAB. Presynaptic M1 muscarinic receptors on parasympathetic nerve terminals are involved in an auto-facilitatory mechanism that markedly enhances acetylcholine release (Somogyi and de Groat 1999). The facilitatory muscarinic mechanism is dependent upon a protein kinase A (Oliveira and Correia-de-Sa 2005)-mediated second messenger pathway and influx of extracellular Ca^{2+} into the parasympathetic nerve terminals via N-type Ca^{2+} channels. Both M1 receptors and N-type Ca^{2+} channels are suitable drug targets for UAB.

M_1 Muscarinic Agonists

Recent studies reported upregulation of M1 receptor subtype in an animal model of UAB induced by prolonged ischemia (Zhao et al. 2015), which suggests there is compensatory upregulation of receptors that can enhance the release of acetylcholine from nerves innervating the UAB. Presynaptic M1 receptors can facilitate the release of acetylcholine from nerves and thereby facilitate afferent signaling and voiding contraction (Witsell et al. 2012). Application of M1 agonist, cevimeline increased the spontaneous contractions of isolated guinea pig bladder strips (Arisawa et al. 2002). Intravenous administration of cevimeline (0.3 mg/kg or higher) in rats increased the non-voiding contractions, suggesting that the release of various substances, including acetylcholine (ACh) and ATP (Munoz et al. 2011), from bladder urothelium and efferent nerves in the bladder was increased. Oral dosing of cevimeline in rats at 30 mg/kg increased the urine volume, pH, and urinary excretion of Na^+ and Cl^- ions. Xanomeline [3(3-hexyloxy-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine] (Shannon et al. 1994) is another M1 agonist available as a drug candidate for UAB.

N-Type High-Voltage-Activated Ca(2+) Channels (HVACCs) Agonists

Since N-type HVACC are involved in facilitating the release of ACh from parasympathetic nerve terminals in the bladder, drugs that activate these channels can be potential agents for UAB. 4-Aminopyridine (4-AP) sold as Ampyra is known to directly stimulate presynaptic N-type VGCC at the concentration of 0.5 mM and blocks Kv1 family channels at 1 mM concentration (Wu et al. 2009). Ampyra and similar drug fampridine (Cardenas et al. 2014) can potentiate the release of neurotransmitters from both sensory and motor nerve terminals and improve neuromuscular function in patients with spinal cord injury, myasthenia gravis, or multiple sclerosis (Wu et al. 2009). The effect of Ampyra on improving bladder emptying was tested much earlier by Maggi et al., in urethane-anesthetized rats (Maggi et al. 1988). Ampyra potentiated nerve-evoked bladder contractions, and intravenous injection in the dose ranging from 0.15 to 2 mg/kg i.v. produced a dose-dependent potentiation of voiding frequency and activation of high-amplitude, hexamethonium-sensitive rhythmic bladder contractions.

Drugs That Facilitate Spontaneous Contraction

Spontaneous contractile activity of the urinary bladder (Turner and Brading 1997) is considered to underlie the basal tone that allows the bladder to maintain an optimum shape as it expands to accommodate increasing volumes of urine. In addition,

spontaneous contractions (Fry et al. 2004) are known to facilitate the generation of bladder sensation and afferent activity (Andersson 2010). Several tools have been used to investigate the origin of spontaneous activity in the bladder, which have noted that Ca^{2+} wave in the propagation of spontaneous activity arise in the suburothelial layer of interstitial cells and then spreads to the detrusor layer (Kanai et al. 2007). Interstitial cells are considered pacemaker cells that activate the periodic spontaneous inward currents (pacemaker currents) responsible for the origin of Ca^{2+} waves.

Several reports suggest that attenuated spontaneous activity of the bladder contributes to the UAB phenotype (Wang et al. 2015; Nirmal et al. 2014) by reducing the intensity of afferent input from the bladder. Incidentally, acontractile bladder that is devoid of spontaneous activity is frequently observed in iatrogenic UAB patients (Drossaerts et al. 2015; Mitchell et al. 2014). Therefore, drugs that can selectively augment the dormant spontaneous contractions in the bladder will be preferable agents for UAB as they can improve the afferent input from the bladder. Several channel isoforms selectively expressed in the bladder can be leveraged to increase spontaneous activity in UAB.

Potassium Channels

Several types of potassium currents have been characterized in the bladder, but the subtype of K_v is considered to play an important role in spontaneous activity by regulating the resting membrane potential of smooth muscles and for repolarizing the action potential (Petkov 2012). Other types include BK channels that control action potential duration and the resting membrane potential, whereas SK currents underlie after-hyperpolarizations (Thorneloe and Nelson 2003). KCNQ (K_v7) currents are outwardly rectifying, voltage-dependent K^+ currents that activate at potentials positive to −60 mV with little inactivation (Gribkoff 2008; Gu et al. 2005). Five genes encoding the KCNQ family of ion channel proteins have been identified, each encoding a different KCNQ α-subunit (1–5). KCNQ are considered important in the regulation of smooth muscle contractility and tone (Anderson et al. 2013). KCNQ subtypes 1–5 are functionally expressed in detrusor smooth muscle as KCNQ channel inhibitors XE991, linopirdine, or chromanol 293B increased the amplitude of tetrodotoxin TTX-insensitive myogenic spontaneous contractions (Anderson et al. 2013). KCNQ inhibition by XE991 depolarized the cell membrane and evoked transient depolarizations in quiescent cells. XE991 also increased the frequency of Ca^{2+}-oscillations in detrusor smooth muscles of guinea pig bladder (Anderson et al. 2013). On the other hand, spontaneous activity was inhibited by the KCNQ channel activators flupirtine or meclofenamic acid (Anderson et al. 2013), and, in a separate study, another KCNQ activator, retigabine, decreased the capsaicin-induced bladder overactivity in a freely moving, conscious rat (Streng et al. 2004). Taken together, blockade of KCNQ locally in the bladder is a potential approach for UAB.

Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channels

HCN channels (Cuttle et al. 2001; Greenwood and Prestwich 2002) belong to a family of nonselective cationic channels that conduct Na^+ and K^+ current and are activated by hyperpolarization in neurons and smooth muscles. HCN channels are comprised of four subtypes encoded by four genes (HCN1-4), which form the structural component of a voltage-gated inwardly rectifying I*h* current, which restores the resting membrane potential (Cuttle et al. 2001; Greenwood and Prestwich 2002). HCN channels are directly activated by direct binding of intracellular cyclic adenosine monophosphate (cAMP) inside the cells (Cuttle et al. 2001; Greenwood and Prestwich 2002). Expression of HCN channels has been recently reported in the rat and human bladder (He et al. 2012; Xue et al. 2012). Furthermore, the adenylate cyclase responsible for generating cAMP in the bladder smooth muscle, urothelium, and interstitial cells can be theoretically modulated by activation of M2 muscarinic receptor and β3 adrenoceptor, which raises the possibility of using bladder-selective M2 agonist or β3 adrenoceptor antagonists for modulating the kinetics of HCN channel.

Direct inhibition of HCN channels in the bladder with ZD7288 was shown to augment the spontaneous activity of the bladder (Green et al. 1996; Kashyap et al. 2015). Conversely, agents that activate HCN channels (Postea and Biel 2011; Albertson et al. 2011), such as lamotrigine and gabapentin, attenuate spontaneous activity of rat bladder (Kashyap et al. 2014a). We found that cumulative application of ZD7288 dose dependently increased the tetrodotoxin -insensitive phasic contractions of rat bladder (Fig. 7.3) as reported earlier by Green et al. (1996). In vitro studies suggested that a direct action of ZD7288 on HCN channels expressed by detrusor smooth muscles or interstitial cells is responsible for the increased spontaneous activity.

It is known that mechanosensitive Aδ bladder neurons play an important role in the control of normal voiding (de Groat and Yoshimura 2006), and localized blockade of HCN channels expressed in Aδ bladder neurons (Masuda et al. 2006) following intrathecal injection of ZD7288 (1 μg) blocked the voiding in normal rat. In a separate study, chronic administration of HCN channel activator, lamotrigine (20 mg/kg) (Loutochin et al. 2012), caused a urodynamic improvement in spinal cord-injured rat model. Apparently different subtypes of HCN channels are expressed in different tissue, such that expression of HCN 4 subtype (HCN4) is predominant in the bladder and HCN2 predominate in the heart (Kuwabara et al. 2013). There are also species differences in the bladder with predominant expression of HCN1 in rodents and HCN4 in human bladder (He et al. 2012; Xue et al. 2012). Based on available data, it is postulated that basal levels of intracellular cAMP constitutively activate the HCN channels, and therefore, agents that cannot penetrate the blood–brain barrier and are excreted unchanged in urine would be preferable to selectively block HCN4 channels in the bladder for augmenting spontaneous activity in the bladder of UAB patients without any cardiac effects. In contrast, selective activation of HCN channels expressed in bladder afferent neurons would be an alternative approach for increasing spontaneous activity in the bladder.

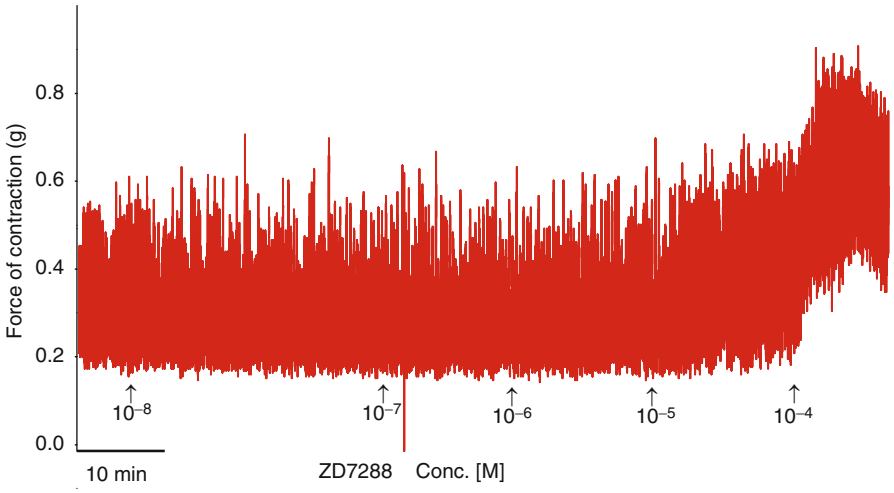

Fig. 7.3 The effect of HCN channel blocker ZD7288 on spontaneous activity of rat bladder. Cumulative application of ZD7288 dose dependently increased the tetrodotoxin-insensitive phasic contractions in bladder strips from healthy rats. Spontaneous contractility was measured in the presence of tetrodotoxin 1 μM

Centrally Acting Drugs for Neurogenic UAB

The potential targets for managing neurogenic UAB exist in the molecular pathways involved in spinal and supraspinal control of voiding reflex at the levels of autonomic and afferent pathways, spinal cord, and brain (Tyagi et al. 2014). Supraspinal control of the voiding reflex is dependent upon the normal relay of afferent input to the bladder as any deficit correlates with reduced activation in the insula and dorsal anterior cingulate cortex in the brain of older adults (Tadic et al. 2013). Therefore, efficient afferent signaling is integral for an efficient efferent outflow to the bladder, and neurogenic UAB can impact upon the key processes of perception and integration of afferent input from the bladder.

Drugs Acting on Dopamine Pathway

Age-related decline of dopamine binding has been reported in brain areas involved in cognition, and there is a tremendous overlap among regions involved in cognition and those involved in interpretation of afferent input from the bladder (MacDonald et al. 2012). Therefore, drugs that augment dopamine signaling can be potential drugs for neurogenic UAB. It is known that D1 receptors tonically inhibit and D2 facilitate micturition reflex, because D2-selective agonists and D1-selective antagonists produce a reduction of the bladder capacity in conscious

rat (Brusa et al. 2006). Studies on subcutaneous administration of apomorphine (a nonselective dopamine receptor agonist) 0.01–0.5 mg/kg in rodents found that it raises intravesical pressure through its biphasic action on the dopamine receptors, which is characterized by initial increase in afferent activity followed by a decrease (Uchiyama et al. 2009). Apomorphine increases the afferent activity and stimulates central micturition center. These pharmacodynamic characteristics of apomorphine suggest that D2-selective agonists can be potential agents for increasing afferent input and involuntary detrusor contraction threshold (reflex volume) (Brusa et al. 2006) in UAB patients. Apomorphine can be absorbed sublingually, which suggest that an on-demand therapy for bladder emptying is a possibility. Metoclopramide is another FDA-approved agent that can modulate dopaminergic pathways in UAB.

Drugs Acting on Serotonin Pathway

Drugs acting on serotonin pathway can increase the afferent input from bladder and urethra which in turn determines the force and duration of detrusor contraction. It is known that urethral afferents responding to urine flow in the urethra potentiate the detrusor contraction and bladder emptying (Torrens and Morrison 1987; de Groat et al. 1993; Jung et al. 1999). These reflexes require the integrative action of neuronal populations at multiple levels of the nervous system involving serotoninergic transmission (Song et al. 2014). In a recent study, supraspinal micturition reflex in rats with bilateral avulsion injury of the L5–S2 ventral roots was elicited by agonists for the $5HT_{1A}$ receptor, 8-hydroxy-2-(di-n-propylamino)-tetralin (8OH-DPAT) (Chang and Havton 2013). The voiding efficiency of rats exhibiting UAB phenotype was increased by 20 %, and there was an evidence of coordinated contraction of the bladder and activation of the external urethral sphincter.

Drugs Acting on Opioid Pathway

Pharmacologic experiments revealed that endorphins are inhibitory transmitters in the spinal and supraspinal control of micturition reflex. Agents inhibiting the opioid action have been used to reverse opioid-induced urinary retention. Blood–brain barrier non-permeant analogues of naloxone, namely, methylnaltrexone, are effective in reversing opioid-induced constipation in patients, but not effective in reversing urinary retention (Rosow et al. 2007). The effect of quaternary amine, methylnaltrexone, suggests that volitional control over micturition involve endogenous opioids as the neurotransmitter in polysynaptic pathways mediating the coordination between the urinary bladder and the urethra.

Drugs That Decrease Urethral Resistance

Bladder emptying is facilitated by non-cholinergic/non-adrenergic nitric oxide (NO) release onto the internal urethral sphincter resulting in a relaxation of the urethral outlet and by removal of excitatory inputs to the urethra (Takeda et al. 2010). Therefore, drugs that reduce the urethral resistance can improve bladder emptying with deficient detrusor contractility by reducing the back pressure from urethral resistance. Clinical use of α_1 adrenoceptor antagonists in UAB patients was able to improve the bladder emptying by reversing obstruction and increasing PVR (Yamanishi et al. 2004; Chang et al. 2008). A drug approved for angina, isosorbide dinitrate, has been reported to decrease urethral pressures in spinal cord injury (Mamas et al. 2001; Reitz et al. 2004) as urethral relaxation is mediated by NO. Chemodenervation of the urethra and rhabdosphincter with botulinum toxin has also been tried to reduce urethral resistance (Kuo 2003).

Conclusions

The future for the development of new modalities for the UAB treatment looks promising as several different therapeutic pathways are being explored in preclinical studies. Future prospective therapies are aimed at novel targets with novel mechanisms of action, including M1 receptor agonist, N-type HVACC agonist, KCNQ and HCN channel blockers, serotonin, and dopamine signaling modulators. Among other investigational therapies, purinergic receptor agonism, TRP channel agonism, cannabinoid receptor antagonism, neurotrophin mimetics, and neurokinin receptor agonists are of considerable interest. There is great hope that just as drugs for OAB and ED better define the disease condition in the general population, an effective drug capable of reducing PVR will also help in better definition and management of UAB.

References

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A, Standardisation Sub-committee of the International Continence S (2002) The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodyn 21:167–178

Aizawa N, Wyndaele JJ, Homma Y, Igawa Y (2012) Effects of TRPV4 cation channel activation on the primary bladder afferent activities of the rat. Neurourol Urodyn 31(1):148–55. doi:10.1002/nau.21212

Albertson AJ, Yang J, Hablitz JJ (2011) Decreased hyperpolarization-activated currents in layer 5 pyramidal neurons enhances excitability in focal cortical dysplasia. J Neurophys 106(5): 2189–2200. doi:10.1152/jn.00164.2011

Anderson UA, Carson C, Johnston L, Joshi S, Gurney AM, McCloskey KD (2013) Functional expression of KCNQ (Kv7) channels in guinea pig bladder smooth muscle and their contribution to spontaneous activity. Br J Pharmacol 169(6):1290–1304. doi:10.1111/bph.12210

Andersson KE (2010) Detrusor myocyte activity and afferent signaling. Neurourol Urodyn 29(1):97–106. 2009/12/22 edn. doi:10.1002/nau.20784.

Arisawa H, Fukui K, Imai E, Fujise N, Masunaga H (2002) General pharmacological profile of the novel muscarinic receptor agonist SNI-2011, a drug for xerostomia in Sjogren's syndrome. 4th communication: effects on gastrointestinal, urinary and reproductive systems and other effects. Arzneimittelforschung 52(4):225–232. doi:10.1055/s-0031-1299885

Beckel JM, Daugherty SL, Tyagi P, Wolf-Johnston AS, Birder LA, Mitchell CH, de Groat WC (2015) Pannexin 1 channels mediate the release of ATP into the lumen of the rat urinary bladder. J Physiol 593(8):1857–1871. doi:10.1113/jphysiol.2014.283119

Bougas DA, Mitsogiannis IC, Mitropoulos DN, Kollaitis GC, Serafetinides EN, Giannopoulos AM (2004) Clinical efficacy of distigmine bromide in the treatment of patients with underactive detrusor. Int Urol Nephrol 36(4):507–512

Brusa L, Petta F, Pisani A, Miano R, Stanzione P, Moschella V, Galati S, Finazzi Agro E (2006) Central acute D2 stimulation worsens bladder function in patients with mild Parkinson's disease. J Urol 175(1):202–206. doi:10.1016/S0022-5347(05)00058-3

Burnstock G (2013) Purinergic signalling in the lower urinary tract. Acta Physiol 207(1):40–52. doi:10.1111/apha.12012

Cardenas DD, Ditunno JF, Graziani V, McLain AB, Lammertse DP, Potter PJ, Alexander MS, Cohen R, Blight AR (2014) Two phase 3, multicenter, randomized, placebo-controlled clinical trials of fampridine-SR for treatment of spasticity in chronic spinal cord injury. Spinal Cord 52(1):70–76. doi:10.1038/sc.2013.137

Chang HH, Havton LA (2013) Serotonergic 5-HT(1A) receptor agonist (8-OH-DPAT) ameliorates impaired micturition reflexes in a chronic ventral root avulsion model of incomplete cauda equina/conus medullaris injury. Exp Neurol 239:210–217. doi:10.1016/j.expneurol.2012.10.015

Chang SJ, Chiang IN, Yu HJ (2008) The effectiveness of tamsulosin in treating women with voiding difficulty. Int J Urol Off J Jpn Urol Assoc 15(11):981–985. doi:10.1111/j.1442-2042.2008.02134.x

Choi RC, Siow NL, Cheng AW, Ling KK, Tung EK, Simon J, Barnard EA, Tsim KW (2003) ATP acts via P2Y1 receptors to stimulate acetylcholinesterase and acetylcholine receptor expression: transduction and transcription control. J Neurosc Off J Soc Neurosci 23(11):4445–4456

Cuttle MF, Rusznak Z, Wong AY, Owens S, Forsythe ID (2001) Modulation of a presynaptic hyperpolarization-activated cationic current (I(h)) at an excitatory synaptic terminal in the rat auditory brainstem. J Physiol 534(Pt 3):733–744, 2001/08/03 edn

de Groat WC, Booth AM, Yoshimura N (1993) Neurophysiology of micturition and its modification in animal models of human disease, vol 1. Harwood Academic Publishers, London 227–90

de Groat WC, Yoshimura N (2006) Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Prog Brain Res 152:59–84

Dmitrieva N, Berkley KJ (2002) Contrasting effects of WIN 55212–2 on motility of the rat bladder and uterus. J Neurosci Off J Soc Neurosci 22(16):7147–7153. doi: jneurosci.org/content/22/16/7147

Drossaerts J, Rademakers K, van Koeveringe G, Van Kerrebroeck P (2015) The value of urodynamic tools to guide patient selection in sacral neuromodulation. World J Urol. doi:10.1007/s00345-015-1479-6 epub

Elmariah SB, Crumling MA, Parsons TD, Balice-Gordon RJ (2004) Postsynaptic TrkB-mediated signaling modulates excitatory and inhibitory neurotransmitter receptor clustering at hippocampal synapses. J Neurosci Off J Soc Neurosci 24(10):2380–2393. doi:10.1523/JNEUROSCI.4112-03.2004

Fry CH, Sui GP, Severs NJ, Wu C (2004) Spontaneous activity and electrical coupling in human detrusor smooth muscle: implications for detrusor overactivity? Urology 63(3 Suppl 1):3–10. 2004/03/12 edn. doi:10.1016/j.urology.2003.11.005

Funakoshi H, Belluardo N, Arenas E, Yamamoto Y, Casabona A, Persson H, Ibanez CF (1995) Muscle-derived neurotrophin-4 as an activity-dependent trophic signal for adult motor neurons. Science 268(5216):1495–1499

Garraway SM, Turtle JD, Huie JR, Lee KH, Hook MA, Woller SA, Grau JW (2011) Intermittent noxious stimulation following spinal cord contusion injury impairs locomotor recovery and reduces spinal brain-derived neurotrophic factor-tropomyosin-receptor kinase signaling in adult rats. Neuroscience 199:86–102. 2011/10/27 edn. doi:10.1016/j.neuroscience.2011.10.007

Gevaert T, Vandepitte J, Hutchings G, Vriens J, Nilius B, De Ridder D (2007) TRPV1 is involved in stretch-evoked contractile changes in the rat autonomous bladder model: a study with piperine, a new TRPV1 agonist. Neurourol Urodyn 26(3):440–450. doi:10.1002/nau.20343

Girard BM, Malley SE, Vizzard MA (2011) Neurotrophin/receptor expression in urinary bladder of mice with overexpression of NGF in urothelium. Am J Physiol Renal Physiol 300(2): F345–355. 2010/11/05 edn. doi:10.1152/ajprenal.00515.2010

Gonzalez M, Ruggiero FP, Chang Q, Shi YJ, Rich MM, Kraner S, Balice-Gordon RJ (1999) Disruption of Trkb-mediated signaling induces disassembly of postsynaptic receptor clusters at neuromuscular junctions. Neuron 24(3):567–583

Green ME, Edwards G, Kirkup AJ, Miller M, Weston AH (1996) Pharmacological characterization of the inwardly-rectifying current in the smooth muscle cells of the rat bladder. Br J Pharmacol 119(8):1509–1518. 1996/12/01 edn

Greenwood IA, Prestwich SA (2002) Characteristics of hyperpolarization-activated cation currents in portal vein smooth muscle cells. Am J Physiol Cell Physiol 282(4):C744–753. 2002/03/07 edn. doi:10.1152/ajpcell.00393.2001

Gribkoff VK (2008) The therapeutic potential of neuronal K V 7 (KCNQ) channel modulators: an update. Exp Opin Ther Targets 12(5):565–581. doi:10.1517/14728222.12.5.565

Gu N, Vervaeke K, Hu H, Storm JF (2005) Kv7/KCNQ/M and HCN/h, but not KCa2/SK channels, contribute to the somatic medium after-hyperpolarization and excitability control in CA1 hippocampal pyramidal cells. J Physiol 566(Pt 3):689–715. 2005/05/14 edn. doi:10.1113/jphysiol.2005.086835

He P, Deng J, Zhong X, Zhou Z, Song B, Li L (2012) Identification of a hyperpolarization-activated cyclic nucleotide-gated channel and its subtypes in the urinary bladder of the rat. Urology 79(6):1411 e7–13. doi:10.1016/j.urology.2012.01.037

Hindley RG, Brierly RD, Thomas PJ (2004) Prostaglandin E2 and bethanechol in combination for treating detrusor underactivity. BJU Int 93(1):89–92

Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB (1999) Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. J Urol 162. S0022-5347(05)68742-3 [pii]. doi:10.1097/00005392-199907000-00069

Kanai A, Roppolo J, Ikeda Y, Zabbarova I, Tai C, Birder L, Griffiths D, de Groat W, Fry C (2007) Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists. Am J Physiol Renal Physiol 292(3):F1065–1072. doi:10.1152/ajprenal.00229.2006

Kashyap M, Yoshimura N, Smith P, Chancellor M, Tyagi P (2015) Characterization of the role of HCN channels in β3-adrenoceptor mediated rat bladder relaxation. Bladder 2(2):15–23. doi:10.14440/bladder.2015.44

Kashyap M, Yoshimura N, de Groat WC, Tyagi P (2014) Exogenous overexpression of Brain Derived Neurotrophic Factor (BDNF) in rat bladder evokes bladder overactivity. J Urol 191(4):4

Kashyap MP, Pore S, De Groat WC, Chermansky C, Yoshimura N, Tyagi P (2015) BDNF overexpression alters the phenotype of cholinergic neurons in rat bladder. J Urol 193(4):1108

Kim JC, Park EY, Hong SH, Seo SI, Park YH, Hwang TK (2005) Changes of urinary nerve growth factor and prostaglandins in male patients with overactive bladder symptom. Int J Urol Off J Jpn Urol Assoc 12(10):875–880. doi:10.1111/j.1442-2042.2005.01140.x

Kulakowski SA, Parker SD, Personius KE (2011) Reduced TrkB expression results in precocious age-like changes in neuromuscular structure, neurotransmission, and muscle function. J Appl Physiol 111(3):844–852. doi:10.1152/japplphysiol.00070.2011

Kuo HC (2003) Effect of botulinum a toxin in the treatment of voiding dysfunction due to detrusor underactivity. Urology 61(3):550–554. 2003/03/18 edn. doi:science/article/pii/S0090429502025414

Kuwabara Y, Kuwahara K, Takano M, Kinoshita H, Arai Y, Yasuno S, Nakagawa Y, Igata S, Usami S, Minami T, Yamada Y, Nakao K, Yamada C, Shibata J, Nishikimi T, Ueshima K, Nakao K (2013) Increased expression of HCN channels in the ventricular myocardium contributes to enhanced arrhythmicity in mouse failing hearts. J Am Heart Assoc 2(3):e000150. doi:10.1161/JAHA.113.000150

Lee WC, Wu HP, Tai TY, Yu HJ, Chiang PH (2009) Investigation of urodynamic characteristics and bladder sensory function in the early stages of diabetic bladder dysfunction in women with type 2 diabetes. J Urol 181(1):198–203. doi:10.1016/j.juro.2008.09.021

Lei Z, Ishizuka O, Imamura T, Noguchi W, Yamagishi T, Yokoyama H, Kurizaki Y, Sudha GS, Hosoda T, Nishizawa O, Andersson KE (2013) Functional roles of transient receptor potential melastatin 8 (TRPM8) channels in the cold stress-induced detrusor overactivity pathways in conscious rats. Neurourol Urodyn 32(5):500–504. doi:10.1002/nau.22325

Li Y, Sun Y, Zhang Z, Feng X, Meng H, Li S, Zhu Y, Chen S, Wang Y, Wang J, Zhang D, Jiang X, Li N, Shi B (2013) Cannabinoid receptors 1 and 2 are associated with bladder dysfunction in an experimental diabetic rat model. BJU Int 112(2):E143–150. doi:10.1111/bju.12172

Loutochin O, Afraa TA, Campeau L, Mahfouz W, Elzayat E, Corcos J (2012) Effect of the anticonvulsant medications Pregabalin and Lamotrigine on Urodynamic parameters in an animal model of neurogenic detrusor overactivity. Neurourol Urodyn 31(7):1197–1202. 2012/04/05 edn. doi:10.1002/nau.21214

MacDonald SW, Karlsson S, Rieckmann A, Nyberg L, Backman L (2012) Aging-related increases in behavioral variability: relations to losses of dopamine D1 receptors. J Neurosci Off J Soc Neurosci 32(24):8186–8191. doi:10.1523/JNEUROSCI.5474-11.2012

Maggi CA, Santicioli P, Borsini F, Giuliani S, Conte B, Lecci A, Meli A (1988) The effect of 4-aminopyridine on micturition reflex in normal or capsaicin-desensitized rats. Brain Res 449(1–2):61–70

Mamas MA, Reynard JM, Brading AF (2001) Augmentation of nitric oxide to treat detrusor-external sphincter dyssynergia in spinal cord injury. Lancet 357(9272):1964–1967

Manchana T, Prasartsakulchai C (2011) Bethanechol chloride for the prevention of bladder dysfunction after radical hysterectomy in gynecologic cancer patients: a randomized controlled trial study. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 21(4):730–736. doi:10.1111/IGC.0b013e3181f7d6de

Masuda N, Hayashi Y, Matsuyoshi H, Chancellor MB, de Groat WC, Yoshimura N (2006) Characterization of hyperpolarization-activated current (Ih) in dorsal root ganglion neurons innervating rat urinary bladder. Brain Res 1096(1):40–52. 2006/06/13 edn. doi:10.1016/j.brainres.2006.04.085

Meng E, Young JS, Brading AF (2008) Spontaneous activity of mouse detrusor smooth muscle and the effects of the urothelium. Neurourol Urodyn 27(1):79–87. 2007/05/10 edn. doi:10.1002/nau.20456

Mitchell CR, Mynderse LA, Lightner DJ, Husmann DA, Krambeck AE (2014) Efficacy of holmium laser enucleation of the prostate in patients with non-neurogenic impaired bladder contractility: results of a prospective trial. Urology 83(2):428–432. doi:10.1016/j.urology.2013.09.035

Munoz A, Smith CP, Boone TB, Somogyi GT (2011) Overactive and underactive bladder dysfunction is reflected by alterations in urothelial ATP and NO release. Neurochem Int 58(3):295–300. doi:10.1016/j.neuint.2010.12.002

Nirmal J, Tyagi P, Chuang YC, Lee WC, Yoshimura N, Huang CC, Rajaganapathy B, Chancellor MB (2014) Functional and molecular characterization of hyposensitive underactive bladder tissue and urine in streptozotocin-induced diabetic rat. PloS One 9(7):e102644. doi:10.1371/journal.pone.0102644

Oliveira L, Correia-de-Sa P (2005) Protein kinase A and Ca(v)1 (L-Type) channels are common targets to facilitatory adenosine A2A and muscarinic M1 receptors on rat motoneurons. Neurosignals 14(5):262–272. doi:10.1159/000088642

Pataky Z, Gasteyger C, Ziegler O, Rissanen A, Hanotin C, Golay A (2013) Efficacy of rimonabant in obese patients with binge eating disorder. Exp Clin Endocrinol Diabetes Off J German Soc Endocrinol German Diabetes Assoc 121(1):20–26. doi:10.1055/s-0032-1329957

Petkov GV (2012) Role of potassium ion channels in detrusor smooth muscle function and dysfunction. Nat Rev Urol 9(1):30–40. doi:10.1038/nrurol.2011.194

Pitts EV, Potluri S, Hess DM, Balice-Gordon RJ (2006) Neurotrophin and Trk-mediated signaling in the neuromuscular system. Int Anesthesiol Clin 44(2):21–76.

Postea O, Biel M (2011) Exploring HCN channels as novel drug targets. Nat Rev Drug Discov 10(12):903–914. 2011/11/19 edn. doi:10.1038/nrd3576

Reitz A, Knapp PA, Muntener M, Schurch B (2004) Oral nitric oxide donors: a new pharmacological approach to detrusor-sphincter dyssynergia in spinal cord injured patients? Eur Urol 45(4):516–520. 2004/03/26 edn. doi:10.1016/j.eururo.2003.11.006. S030228380300575X [pii]

Rosow CE, Gomery P, Chen TY, Stefanovich P, Stambler N, Israel R (2007) Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. Clin Pharmacol Ther 82(1):48–53. doi:10.1038/sj.clpt.6100164

Shannon HE, Bymaster FP, Calligaro DO, Greenwood B, Mitch CH, Sawyer BD, Ward JS, Wong DT, Olesen PH, Sheardown MJ, Swedberg MD, Suzdak PD, Sauerberg P (1994) Xanomeline: a novel muscarinic receptor agonist with functional selectivity for M1 receptors. J Pharmacol Exp Ther 269(1):271–281

Slonimsky JD, Yang B, Hinterneder JM, Nokes EB, Birren SJ (2003) BDNF and CNTF regulate cholinergic properties of sympathetic neurons through independent mechanisms. Mol Cell Neurosci 23(4):648–660. 2003/08/23 edn

Smith PP, Chalmers DJ, Feinn RS (2014a) Does defective volume sensation contribute to detrusor underactivity? Neurourol Urodyn. doi:10.1002/nau.22653 epub.

Smith PP, DeAngelis A, Kuchel GA (2012) Detrusor expulsive strength is preserved, but responsiveness to bladder filling and urinary sensitivity is diminished in the aging mouse. Am J Physiol Regul Integr Comp Physiol 302(5):R577–586. doi:10.1152/ajpregu.00508.2011

Smith PP, Tyagi P, Kuchel GA, Pore S, Chermansky C, Chancellor M, Yoshimura N, Levanovich P (2014b) Advanced therapeutic directions to treat the underactive bladder. Int Urol Nephrol 46(Suppl 1):S35–44 doi:10.1007/s11255-014-0809-8

Somogyi GT, de Groat WC (1999) Function, signal transduction mechanisms and plasticity of presynaptic muscarinic receptors in the urinary bladder. Life Sci 64(6–7):411–418

Song QX, Chermansky CJ, Birder LA, Li L, Damaser MS (2014) Brain-derived neurotrophic factor in urinary continence and incontinence. Nat Rev Urol 11(10):579–588. doi:10.1038/nrurol.2014.244

Streng T, Axelsson HE, Hedlund P, Andersson DA, Jordt SE, Bevan S, Andersson KE, Hogestatt ED, Zygmunt PM (2008) Distribution and function of the hydrogen sulfide-sensitive TRPA1 ion channel in rat urinary bladder. Eur Urol 53(2):391–399. doi:10.1016/j.eururo.2007.10.024

Streng T, Christoph T, Andersson KE (2004) Urodynamic effects of the K+ channel (KCNQ) opener retigabine in freely moving, conscious rats. J Urol 172(5 Pt 1):2054–2058

Tadic SD, Tannenbaum C, Resnick NM, Griffiths D (2013) Brain responses to bladder filling in older women without urgency incontinence. Neurourol Urodyn 32(5):435–440. doi:10.1002/nau.22320

Takahisa N, Yoshida S, Hakozaki A, Orimoto N, Sasaki E, Hayashi Y (2013) Therapeutic effect of Tac-302, a novel neurite outgrowth enhancer, on voiding dysfunction in rats with STZ-induced diabetes J Urol 189(4):e49

Takeda M, Araki I, Mochizuki T, Nakagomi H, Kobayashi H, Sawada N, Zakohji H (2010) The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: pathophysiology of voiding dysfunction and pharmacological therapy. J Pharmacol Sci 112(2):121–127

Thorneloe KS, Nelson MT (2003) Properties and molecular basis of the mouse urinary bladder voltage-gated K+ current. J Physiol 549(Pt 1):65–74. doi:10.1113/jphysiol.2003.039859

Torrens M, Morrison JFB (1987) The physiology of the lower urinary tract. Springer, London

Turner WH, Brading AF (1997) Smooth muscle of the bladder in the normal and the diseased state: pathophysiology, diagnosis and treatment. Pharmacol Ther 75(2):77–110

Tyagi P, Smith PP, Kuchel GA, de Groat WC, Birder LA, Chermansky CJ, Adam RM, Tse V, Chancellor MB, Yoshimura N (2014) Pathophysiology and animal modeling of underactive bladder. Int Urol Nephrol 46(Suppl 1) S11–S21. doi:10.1007/s11255-014-0808-9

Uchiyama T, Sakakibara R, Yoshiyama M, Yamamoto T, Ito T, Liu Z, Yamaguchi C, Awa Y, Yano HM, Yanagisawa M, Yamanishi T, Hattori T, Kuwabara S (2009) Biphasic effect of apomorphine, an anti-parkinsonian drug, on bladder function in rats. Neuroscience 162(4):1333–1338. doi:10.1016/j.neuroscience.2009.06.001

Walczak JS, Price TJ, Cervero F (2009) Cannabinoid CB1 receptors are expressed in the mouse urinary bladder and their activation modulates afferent bladder activity. Neuroscience 159(3):1154–1163. doi:10.1016/j.neuroscience.2009.01.050

Wang HJ, Tyagi P, Chuang YC, Yoshimura N, Huang CC, Chancellor MB (2015) Pharmacologic and molecular characterization of underactive bladder induced by lumbar canal stenosis. Urology 85(6):1284–90. doi:10.1016/j.urology.2015.01.017

Witsell DL, Stinnett S, Chambers MS (2012) Effectiveness of cevimeline to improve oral health in patients with postradiation xerostomia. Head Neck 34(8):1136–1142. doi:10.1002/hed.21894

Wu ZZ, Li DP, Chen SR, Pan HL (2009) Aminopyridines potentiate synaptic and neuromuscular transmission by targeting the voltage-activated calcium channel beta subunit. J Biol Chem 284(52):36453–36461. doi:10.1074/jbc.M109.075523

Xue L, Li Y, Han X, Yao L, Yuan J, Qin W, Liu F, Wang H (2012) Investigation of hyperpolarization-activated cyclic nucleotide-gated channels in interstitial cells of Cajal of human bladder. Urology 80(1):e213–228. doi:10.1016/j.urology.2012.04.005

Yamanishi T, Yasuda K, Kamai T, Tsujii T, Sakakibara R, Uchiyama T, Yoshida K (2004) Combination of a cholinergic drug and an alpha-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with underactive detrusor. Int J Urol 11(2):88–96

Yang Z, Dolber PC, Fraser MO (2010) Differential vulnerabilities of urethral afferents in diabetes and discovery of a novel urethra-to-urethra reflex. Am J Physiol Renal Physiol 298(1):F118–124. doi:10.1152/ajprenal.00281.2009

Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A (2004) Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology 63(3 Suppl 1):17–23. doi:10.1016/j.urology.2003.11.003

Yoshizawaa T, Hayashi Y, Yoshida A, Ito Y, Yamada S, Takahashia S (2012) Therapeutic effects of the cyclohexenone derivative Tac-302 on the bladder dysfunction in Streptozotocin (Stz)-induced diabetic rats. J Urol 187(4):e43.

Zeng J, Pan C, Jiang C, Lindstrom S (2012) Cause of residual urine in bladder outlet obstruction: an experimental study in the rat. J Urol 188(3):1027–1032. doi:10.1016/j.juro.2012.04.101

Zhao Z, Yang J, Thurmond P, Azadzoi K (2015) Prolonged ischemia mediates overactive bladder transition to underactive bladder. J Urol 193(4):e76.