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Transient Receptor Potential Channels in Sensory Mechanisms of the Lower Urinary Tract

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Lower urinary tract · TRPV · TRPM · Bladder

Abstract
Background: Urine storage and excretion require a network of interactions in the urinary tract and the central nervous system, which is mediated by a reservoir of water in the bladder and the outlet to the bladder neck, urethra, and external urethral sphincter. Through communicating and coordinating each other, micturition system eventually showed a switch-like activity pattern. ***Summary:*** At cervicothoracic and lumbosacral spine, the spinal reflex pathway of the lower urinary tract (LUT) received mechanosensory input from the urothelium to regulate the bladder contraction activity, thereby controlled urination voluntarily. Impairment of above-mentioned any level could result in lower urinary tract dysfunction, placed a huge burden on patients and society. Specific expression of purinergic receptors and transient receptor potential (TRP) channels are thought to play an important role in urinary excretion in the LUT. ***Key Messages:*** This article reviewed the knowledge about the voiding reflex and described the role and function of TRP channels during voiding.

Ruiqiang Gou and Yuanyuan Liu contributed equally to the study.

Introduction

Lower urinary tract (LUT) functions by coordinating voiding through the complex central neural circuits in the brain and lumbosacral spinal cord, synchronizing the activity of the detrusor and urethral sphincter muscles [1]. Experimental animal studies have shown the maintenance of storage and regular voiding was determined by sensory information from the detrusor muscle in the bladder, mainly in pelvic nerve, encoding detrusor expansion and/or pressure, which transducted upward from the urethral sphincter (in the pudendal and pelvic cavities) [2]. Peripheral afferent signals from nerves primarily regulated sphincter dilation and/or pressure, mediated modulation of LUT state-dependent activation of corresponding reflexes, then exhibited an switch-like activity patterns that open in a complete or incomplete manner and off [3]. In this process, protective and augmented reflexes were the evidence that the complementary role of feedback from the urethral sphincter and bladder detrusor coordinated bladder-state-dependent LUT reflexes [4].

Studies also have shown that the disruption of afferent nerve signals, especially at the lumbosacral level, caused by various neurological diseases, seriously leads to lower urinary tract dysfunction (LUTD) [5]. The neurogenic

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bladder (NB) was a common clinical symptom, which means bladder and/or urethral dysfunctions were caused by different neurological disorders, such as various segments of the spinal cord injury. The main underlying pathological mechanisms of NB included detrusor atrophy or hyperactivity [6]. Neurogenic bladder palsy was a sub-group of NB, which was caused by detrusor atrophy, often manifested as urinary retention and decreased bladder compliance, followed by bladder fibrosis and ultimately kidney damage [7]. Neurogenic detrusor overactivity (NDO) is characteristic of an involuntary contraction of the detrusor muscle in response to congestion, which may result in urge incontinence with or without urge incontinence [8]. In a supra-sacral SCI, the sacral reflex arc is intact, but the control of the upper motor neurons is eliminated, resulting in increased muscle tone and excessive reflection of the detrusor and external urethral sphincters. Excessive activity of the detrusor muscle is called NDO. The damage of the lower sacral part causes the damage to the lower motor neurons and the interruption of the voiding reflex arc, which causes the detrusor and external urethral sphincters to be uncontrolled by relaxation. Taken together, different areas of the spinal cord can lead to different effects on the detrusor muscle, either overexcitability or loss of function and atrophy [9].

Common lower urinary tract symptoms (LUTS) are low bladder function and increased urination frequency, which affect the quality of life of patients in many ways and cause a heavy pathological burden [10, 11]. In addition, the frequent adverse events and irreversible renal damage during the conventional treatment of NB have also stimulated a large number of scholars to seek other therapeutic methods for LUTS. As a result, the therapy of LUTS has become a very dynamic area of research [12].

Restoration of voiding reflex activities following spinal cord injury contingent on reorganization of spinal reflex routes and changes in the properties of afferent neurons in the bladder [13]. Because the pathophysiology of LUTD has been highly controversial and problematic, it is difficult to make a diagnosis and determine applicability based solely on clinical symptoms or noninvasive methods. In addition to being under central control, the voiding reflex, which governs urination, is also modulated by mechanosensory input from urothelial neurons [14]. The urothelium can affect bladder function and sensation by releasing various neurotransmitters under external mechanical stimulation and also affect the detrusor muscle contraction [15]. Therefore, the urothelium has attracted people's attention. In addition, the existing medical means of LUTS are not feasible, highly stimulating the in-depth study of the neuronal and non-neuronal molecular mechanisms of the bladder. Urethral receptors and channels were new targets for the potentially therapeutic treatment of LUTS and could modulate voiding function or bladder perception [16]. Related studies have shown ATP is released when activating TRP channels as expressed in the LUT by stimulating, which then operates on sensory purinoceptor nerves in the subganglionic layer, transmitting sensual and/or pain perception signals to the CNS. TRP channels and the purinergic receptor in LUTs expressed in the neurological and non-neurological components can affect mechanosensory, chemosensory, and biological sensations, thereby modulating the body's voiding reflex and affecting the overall functioning of the LUT [14, 17]. The mediation of afferent nerve fibers and TRP channels in urothelial cells have emerged as important regulators affecting integral functioning of the LUT [18]. As a result, they have received a lot of focus as new pharmaceutical targets for the therapy of various forms of LUTD.

TRP Channel Expression in the Bladder

TRP channel is a multimodal cation channel superfamily, which responds to various physical, chemical, exogenous and endogenous, biological, and other stimuli in LUT, and plays the role of sensor, and also plays a variety of signal transduction functions such as regulation of various Ca^{2+}-dependent cellular events and protein kinase-induced phosphorylation [19]. Research has indicated that a variety of TRP channels TRPV2, TRPV1, TRPV4, TRPM7, TRPM8, and TRPA1 from different subfamilies have specific distribution and expression differences in the hypourethral tract; this in turn determines the function of the LUT both physiologically and pathologically. TRP was found for its function as a temperature sensor in regulating LUTD in the field of structural biology. Although the regulatory mechanism behind temperature sensitivity is unclear, it is certain that the main temperature sensors belong to the TRP cation channel family, such as the cold-sensitive channels represented by TRPM8 and heat-sensitive channel TRPV1, both of which belong to voltage-gated channels. Temperature changes regulate their polarization, and voltage changes can reflect their degree of activation leading them to become activated upon depolarization [20].

Due to its role in the bladder, TRPV1 is the most investigated [21, 22]. Observation by single-particle cryomicroscopy: the transmembrane core region of TRPV1 is a central ion conduction pathway formed by the assembly of S5-P-S6 domain tetramers, with S1–S4 voltage receptors on both sides. It is interconnected to the middle via the S4–S5 linker, so its structure is similar to the voltage-gated ion channel, can be triggered by a range of agents, receives the response to the mechanical stimulation of the bladder [23]. Other TRP channels of subfamily also have similar structure with TRPV1, but they have specific differences in subunit, so they may play different functional roles on the voiding reflex, which then transmit the signal to the brain to regulate urination and/or storage behavior [24]. Although TRP channels are complex and how interact with each other is not well understood, they are closely related to the study of mechanisms of LUT disease [25]. In this review, we reviewed the knowledge of TRP channels (TRPV1, TRPV2, TRPV4, TRPM8) in the bladder and urethra and discussed their roles in LUTD and their future potential as the molecular targets for therapy [26].

TRPV1

TRPV1 channel is known as one of the members of TRP family, and it is also referred to as a type 1 vanilloid receptor and is a highly non-selective cation channel with high Ca^{2+} penetration. The expression of TRPV1 has been found in both skin and nerve endings [27]. TRPV1 expression has been detected only in the lower layer of the urethra but not in detrusor [28]. TRPV1 is detected in the nerve fibers of both rats and humans that innervate the urethral muscle layer. After activation, TRPV1 is involved in bladder contraction and urethral sphincter relaxation for urine excretion [18].

When there is heat, low pH, and ligands in the form of capsaicin, resin toxin, and some protons, spider toxins in microenvironment, TRPV1 channel would be activated and opened [29]. By binding to the ligand, the structure of TRPV1 is rearranged, the upper gate and the lower gate of S6 are opened, which allow cations flow inside, mainly calcium ions [30, 31]. Studies have shown that a large amount of calcium ions originate from extracellular fluid in the activation pathway of phospholipase C. When the TRPV1 channel is opened, a large amount of calcium ions entering the cell, protein kinase C, were translocated to the cell membrane and bind to diacylglycerol [32]. Then, protein kinase C is allosterically activated and further phosphorylates the serine and threonine residues of proteins and enhances the transcription of various genes.

As one of the key molecular sensors of the bladder, TRPV1 could sense stimuli injury and conducting sensations in a healthy voiding reflex. TRPV1 is distributed in different regions, including neural or non-neural cells. Studies have shown that it can be found in C fibers innervating the bladder and is related to mechanosensation during bladder filling [33]. When the channel is activated, neuronal cells depolarize, transmit sensation to the center and release related neuropeptides to cause smooth muscle contraction [34]. While TRPV1 is distributed in the membrane of neural cells and urothelial cells, the controversy of the expression of TRPV1 in the urothelium still remains. According to some reports, the expression of TRPV1was observed in the urothelial cell membrane of mice and humans, while other studies did not show that TRPV1 is expressed in the urothelium of mice [35, 36].

When the channel is abnormal, afferent sensory disturbance can cause overactive bladder (OAB) [37]. Loss of TRPV1 function reduces the excitability and sensitivity of afferent nerves. Experiments have shown that after the TRPV1 gene knockout in mice, the voiding circuit is blocked, and there would be a large number of non-rhythmic bladder contractions [38]. Meanwhile, the activation of TRPV1 channels can produce burning and pain sensations and participate in the regulation of inflammation [14, 39]. In patients with cystitis, the representation of TRPV1 in urothelial ganglia and subepithelial layer is significantly increasing [40]. Neurogenic detrusor hyperactivity (NDO) is caused by the disinhibition of originally silent C fibers to form a new reflex arc, and the urothelium is involved in the afferent of transcystic sensory afferents. Thus, it could be inferred that TRPV1 distributed in the urothelium and nerve endings are related to the formation of NDO. The mechanism of action of TRPV1 is shown in Figure 1.

TRPV2

TRPV2, which is transient receptor potential cation channel subfamily V member 2, is a protein encoded by human TRPV2 gene [41, 42]. TRPV2, a representative of the TRP cation channel family, has a high permeability to Ca^{2+}. TRPV2 was discovered and described by two large groups in 1999 independently. It was identified as a proximal phase of TRPV1 in David Julius' laboratory and called the first identified heat-sensitive ion channel [41].

The structure of TRPV2 channels is similar to the potassium ion channels, the biggest family of ion

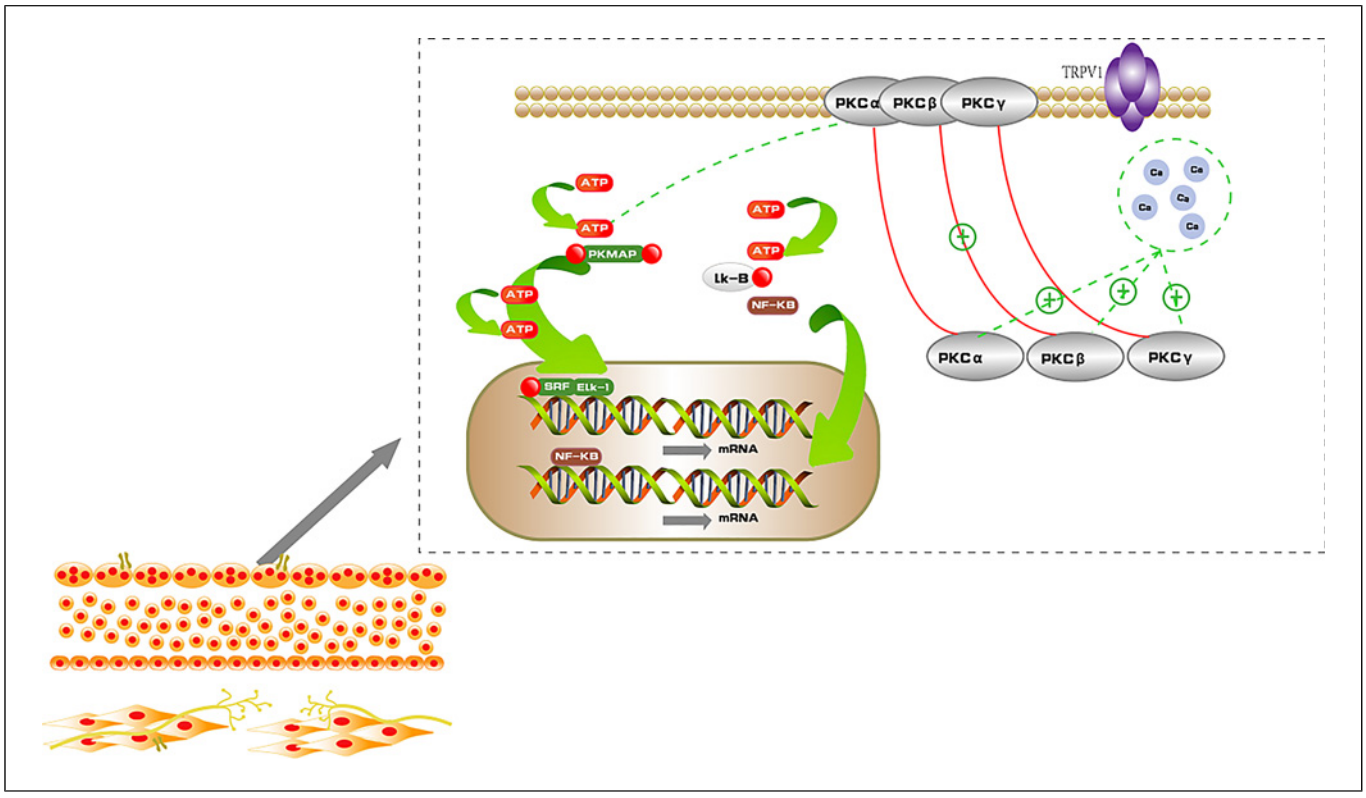

Fig. 1. Distribution and signal transduction pathway of TRPV1 in LUT. TRPV1 is distributed in different regions, including C fibers innervating the bladder and urothelial cells. When the channel is activated, a large amount of calcium ions enter the cell. Protein kinase C (PKC) translocates to the cell membrane and binds to diacylglycerol (DAG), and PKC is allosterically activated. Activated PKC plays an important function in inducing intracellular signal transduction pathways. It phosphorylates the serine and threonine residues of proteins in cells and further activates PKMAP pathway and NF-κB pathway, which increases the transcription of various genes.

channels. The channel consists of six transmembrane regions (S1–S6), and the loop between S5 and S6 forms a pore [43]. Formation of pores of circuit also defines selective filters to determine which ions enter the channel. The S1–S4 region of the protein as well as the N- and C-terminus is critical for channel selection. TRPV2 is a nonspecific cation channel, whereas calcium ions are more permeable as intracellular signaling molecules and play important roles in many different cellular processes. In the static state, the channel is turned off. It also opens the channel to allow sodium and calcium ions to enter and trigger an action potential in the activated state [44].

TRPV2 and TRPV1 shared 50% same origin. Compared with the TRPV1 channel, the TRPV2 channel could not be opened at 43°C for either capsaicin or heat stimulation. However, the TRPV2 channel could be opened at a harmful temperature of more than 52°C and activated by an agonist such as 2-marcello-2-phenyl acid and D9 four jaxon (THC). Compared with TRPV1, it showed a higher threshold of activation.

Recent research has found that TRPV2 is not only thermally activated but also can be regarded as a mechanical tension sensor and a lipid sensor [45]. TRPV2 mRNA was expressed in urinary epithelial cells or smooth muscle cells of bladder [46]. The function of this channel has also been confirmed in mouse urothelial cells [47, 48]. In the humans bladder, the immunostaining of TRPV2 was found in tiny neurofibrils, uroepithelial cells, and smooth muscle cells, but the specificity of the antibody was uncertain. Caprodossi et al. [49] showed that TRPV2 was expressed not only in uroepithelial cells of the bladder but also in DRG neuronal cells [50].

Available data indicated that TRPV2 mainly acted as an urothelial sensor of mechanical and neuroendocrine effects in LUT and as a determinant of urothelial cancer [51]. The distribution of TRPV2 channels in the LUT has important physiological and pathophysiological

significance, but its specific function and mechanism are still unclear. Liu and Wang [52] speculated that TRPV2 was associated with the development of bladder cancer, studied 5,637 cases of TRPV2 that affected bladder cancer proliferation and metastasis, and observed that TRPV2 enhanced the migration and invasion of bladder cancer [52]. However, it did not affect the proliferation of bladder cancer in vitro. Mizuno et al. [53] also found that treating mouse bladder cancer cells with TRPV2 activator could significantly reduce their proliferation rate, which suggest that TRPV2 channel is a potential therapeutic target for bladder cancer [53, 54]. In addition, Oulidi et al. [54] found that adrenaline transfer to the stromal surface through TRPV2 subsequently increases resting calcium levels, inducing migration or invasion of prostate and urothelial cancer cells.

TRPV4

TRPV4 (transient receptor potential vanilloid type4) is a registered member of TRP superfamily, which is widely presented in the whole body, including renal epithelium, auditory hair cells, hippocampal neurons, endothelial cells, bladder epithelium, etc. [55, 56]. Gevaert et al. [57] first studied that TRPV4 played an essential role on many of the physiological and pathological functions of the LUT and confirmed that TRPV4 mainly appeared in bladder substrate cells and mesangial urinary tract cells. Nilius et al. [55] found that TRPV4 channels open in response to thermal, mechanical stimuli, a low-permeability microenvironment, and acrotetraoleic acid metabolites.

Various factors bind to ion P2X receptors in the subepithelial sensory terminals to stimulate nerve conduction activity. The involvement of TRPV4 in urothelial stretch-induced release of ATP is confirmed. Using hypotonic solution, stretch or non-specific TRPV4 activators to stimulate urothelial cells or epithelial tissues of different species, the increasing intracellular Ca^{2+} and ATP release could be observed [58, 59]. TRPV4 also could be activated by external activators and endogenous ligands maintain the basic level of ATP release to maintain the cellular excitability [60, 61]. The above studies collectively supported that TRPV4 involved in urothelial sensory transduction. TRPV4 in urothelial cells appeared to sense bladder distension (among other stimuli) during urine storage. As the volume of urine increases, more ATP and other mediators are released and facilitated entry into the urination reflex pathway. TRPV4 has also been implicated in the composition of the urothelial barrier that prevents invasion of toxins and microorganisms into subepithelial tissues. The urothelial barrier in TRPV4-deficient mice is weakened, disrupting the formation of adhesion binding [62]. Thus, TRPV4 plays an influential part in controlling barrier features. Nevertheless, the mechanism by which TRPV4 activates and antagonizes the urothelial barrier remains unclear. The study on the mechanism of TRPV4 in urinary barrier may help to cure bladder infections [63, 64].

In recent years, the study of TRPV4 channel has shown that it was expressed in the LUT and one of the hot spots in urology. It was confirmed that TRPV4 was abundant not only in urothelial and detrusor muscle cells but also in afferent neurons [65]. In normal bladder function, urinary storage and excretion is controlled by a complex interaction of upper and lower nerve activity [65–67]. The TRPV4 channel of the LUT senses ATP and is one of the important sensory mediators. Thus, TRPV4 senses bladder urothelial dilatation and converts it to ATP signals in the micturition reflex tract during urine storage [67]. In their study, TRPV4 was found to be upregulated in the epithelium of the senescent and overactive urinary tract. In the study by Roberts et al. [61], they found that very low concentrations of GSH could also contract bladder smooth muscle and trigger the release of ATP from the senescent bladder mucosa after selective activation of TRPV4 using the agonist GSK, which was associated with the fact that GSK could increase Ca^{2+} levels at rest and TRVP4-induced ATP production accompanied by ROS production, a finding that points to a new target for studies of this channel mediating aging and bladder pain.

The specific mechanisms by which TRPV4 channels act as mechanosensory and nociceptive receptors in physiological or pathophysiological states have been proposed: pharmacological approaches and TRPV4 knockout mice have elucidated the contribution of TRPV4 to the function of the voiding reflex. TRPV4 knockout mice show an abnormal voiding pattern: a disturbance in voiding behavior compared to the wild type [46]. Furthermore, urinary flow dynamics results indicate that TRPV4 knockout mice have a lower frequency of voiding contractions [68, 69]. This variation does not include differences in the size and duration of micturition contractions. The use of TRPV4 agonists (commonly used TRPV4 channel activators include GSK1016790A, 4α-PDD, etc.) increases bladder overactivity, while TRPV4 antagonists lead to decreased bladder activity, and administration of ATP to the bladder causes OAB, which also confirmed the above result from the side research [70].

This makes it a promising target for treating OAB syndrome and other bladder disorders [71].

Zhao et al. [72] showed that in patients with benign prostatic hypertrophy or bladder outlet obstruction, the expression of TRPA1, TRPV4, and TRPV1 channels was high in bladder urothelium, and the regulation of these channels may offer new therapeutic approaches for the management of similar bladder diseases.

Low bladder function and increased frequency of urination are common in LUTS, cystitis, benign prostatic hyperplasia, neurological disorders, and OAB syndrome. However, in many cases, existing medical treatments are not feasible [73]. Wouter et al. showed that TRPV4 is highly manifested in urothelial epithelial cells and contributes to the perception of the normal filling state of the bladder [74, 75]. By inhibiting the expression of TRPV4 channels, bladder function can be altered in mice with cystitis. In their experiments, cyclophosphamide was used to induce inflammation in the bladders of mice. The results showed that the healthy mice with TRPV4 gene knock out had greater bladder capacity and were less likely to suffer from the cystitis stage of urinary frequency [57].

TRPV4 was also found in the endothelial cells surrounding the muscle and blood vessels but at a 20-fold lower level than in the urothelium. It was shown that the function of TRPV4 in dorsal root ganglion (DRG) neurons of control organs is associated with the tension-responsive neuroinflammatory response and material P and calcitonin gene-related peptide (CGRP) release from bladder tissue [76, 77]. In neuroinflammation, the activation of TRPV4 by neuropeptides may lead to the persistence of inflammation after injury and alterations in extracellular osmotic pressure, while TRPV4 causes visceral hypersensitivity and nociception when activated by the agonist 4αPDD [78].

Bladder function is controlled by circadian rhythms of circadian clock genes. Bladder integrity is sensed by mechanical sensors such as piezoelectric or TRPV4 in the urothelium of the mouse bladder. Piezoelectricity and TRPV4 are generated by changes in functional circadian rhythms and are controlled by clock genes [79]. When Ca^{2+} ions are in-flowed for various reasons, both may cause urinary excretion via ATP. Normally, Piezo1 and TRPV4 are active during wakefulness and inhibited during sleep, and nocturia was often induced by changes in the circadian rhythm of TRPV4 controlled by clock genes in the experiments of Ihara et al. [80] in mice.

In 2021, Kawasaki et al. [81] constructed cystitis mice model with cyclophosphamide and found that TRPV4 is directly related to bladder pain. The level of phosphorylated TRPV4 is increased in mice with chronic cystitis, which is presumed to be one of the important causes of bladder pain. In this sense, TRPV4 antagonists may be targets for the management of bladder pain in patients with cystitis. The distribution and activity factors of TRPV2 and TRPV4 in LUT are shown in Figure 2.

TRPM8

As a calcium-permeable non-selective cation channel, TRPM8 initially was cloned as a prostate-specific protein by Tsavaler et al. [82]. In addition to being in the prostate, it was detected a high expression in many tissues and organs throughout the body such as in δ and C fibers, prostate, bronchopulmonary tissue, bladder, and deep urogenital organs [83]. In humans, the TRPM8 gene mainly encodes a transmembrane protein containing 1,104 amino acid residues, which is a homotetrameric channel [84]. There are six helices that make up the transmembrane structure. The first four (S1–S4) could combine with menthol and killing to sense voltage, and the last two helices (S5–S6) build the pore module. The non-selective cation channel contains highly conserved hydrophobic regions and conserved aspartic acid residues, which is a distinctive feature of the channel [85, 86].

TRPM8 has a multimodal, unique gating mechanism similar to other TRP channels. Studies have confirmed that TRPM8 is related to the occurrence of prostate cancer because of the increasing expression. Nevertheless, whether TRPM8 expression promotes or inhibits prostate cancer growth remains controversial. Although TRPM8 did not play a decisive role in the occurrence and formation of cancer, its role as a cold/menthol-stimulated sensor in the peripheral nervous system has been paying much attention [87]. The agonists of TRPM8 are icilin, menthol, triazole-based menthol derivatives such as WS3 and WS23. Recently, rotundifolone was demonstrated more selective to activate the TRPM8 channel by Santos-Silva et al. [115]; however, chemicals such as capsazepine acting as blockers of TRPM8 can significantly attenuate these effects [83].

More studies show that it can be activated by cold and menthol involving thermal compensation [88, 89]. TRPM8 has a multimodal, unique gating mechanism similar to other TRP channels. TRPM8 will be activated by several factors, including low temperature, membrane depolarization, coolants and different osmotic pressure and pH, etc. [90, 91]. Different compounds could induce

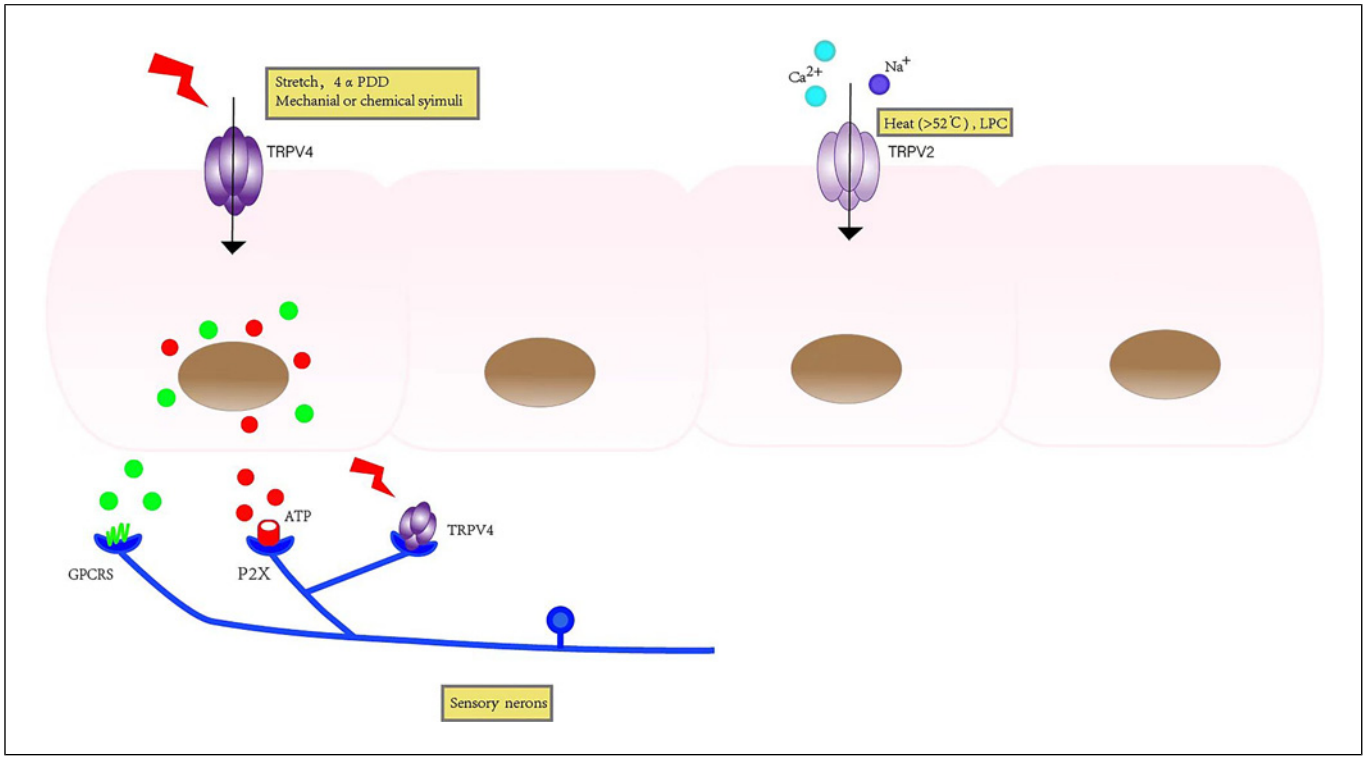

Fig. 2. Distribution and activity factors of TRPV2 and TRPV4 in LUT. TRPV2 and TRPV4 are distributed in many areas of the LUT, and both channels are activated leading to influx of ions, but the specific mechanisms differ, with TRPV2 being activated by heat and lysophosphatidylcholine (LPC) leading to influx of calcium and sodium ions. TRPV4 in the presence of stretch, chemical stimulation, and 4αPDD is activatable and ultimately stimulates cells to release ATP to activate P2X channels and downstream G protein-coupled receptors (GPCRS), eliciting downstream responses.

different activation modes of TRPM8. Experiments have shown that TRPM8 activated by icilin is dependent on intracellular Ca^{2+} levels. This is in contrast to its activation by menthol and WS-12, a menthol derivative, which was generally not significantly correlated with Ca^{2+} concentration. Among them, WS-12 can act as a specific activator of TRPM8 [91, 92].

Phosphoinositide (PIP2) will significantly affect the structure of TRPM8 channel gate with two aspects of regulatory mechanism. On the one hand, under the action of calcium-sensitive phospholipase Cβ (PLCβ), PIP2 can be catalyzed to form soluble inositol 1,4,5-triphosphate (IP3) and membrane-bound diacylglycerol. The secretion of IP3 can affect the intracellular Ca^{2+} concentration and increase the release of Ca^{2+}, thereby activating TRPM8 [88, 93]. The other is phosphoinositide-interacting TRP modulators, which are present in dorsal root ganglia, trigeminal ganglia, and enteric neurons of the peripheral nervous system. Through coordinating the action of phosphoinositide-interacting TRP modulator, TRPM8 channel became more dependent on voltage and sensitive to menthol. A possible reason for this regulatory mechanism is that increased concentration of PIP2 could lead to easier activation of TRPM8 channel. And it may be species-specific [93]. In addition to being positively regulated by PIP2, TRPM8 is also negatively regulated by PLCδ4 in neurons, the activation of which leads to reduced local concentrations of PIP2 [94]. The role of TRPM8 in LUT and its signal transduction pathways are shown in Figure 3.

TRPM3

TRPM3 is a Ca^{2+} permeable non-selective cation channel and is another pain sensing channel in the TRP family identified over several years, in addition to TRPV1 and TRPA1 [95]. It has been found to be expressed in the brain, kidney, and many tissues and cells with different functions. Apart from individual types of channels, most TRPM3 has six putative transmembrane structural domains and a region of 10 amino acid residues and four

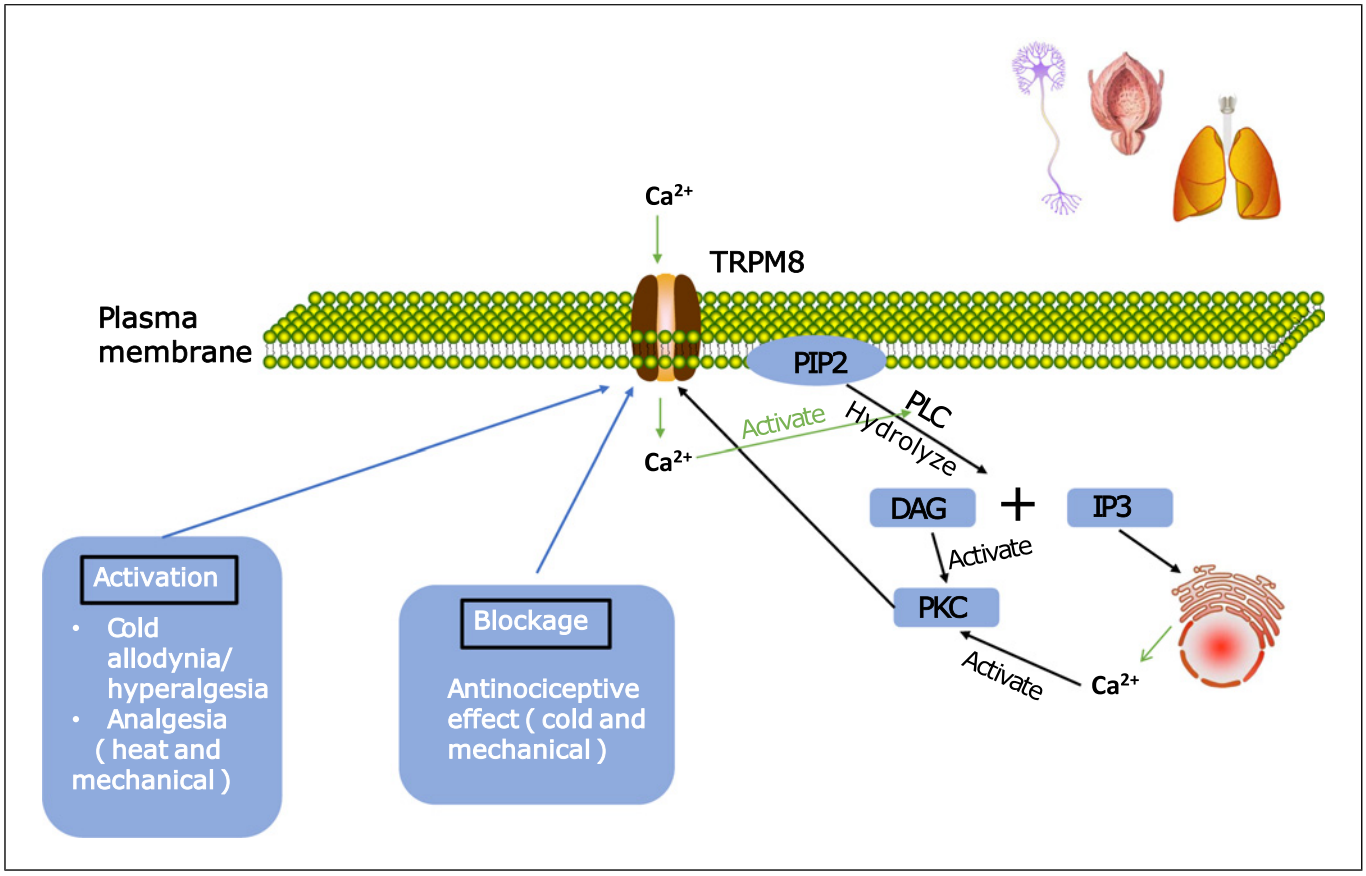

Fig. 3. Function and signal transduction pathway of TRPM8 in LUT. TRPM8 is widely distributed in the LUT, lungs, as well as the nervous system. Calcium ions can influx into the cell after the channel is activated, and phosphoinositides (PIP2) can be back hydrolyzed to soluble inositol 1,4,5-trisphosphate (IP3) and membrane-bound diacylglycerol (DAG) under the action of calcium-sensitive phospholipase (PLC) and IP3 secretion, which in turn can affect the concentration of calcium ions and thus activate the TRPM8 pathway. Channel activation is also impeded by cold or other chemical factors.

calmodulin binding sites at its amino terminus [96]. It is expressed in the DRG of the mouse bladder, can be activated by heat and the neurosteroid pregnenolone sulfate (PS), and it is often co-expressed with TRPA1 and TRPV1 in neurons to trigger the release of neuropeptides [97, 98].

Many TRP channels are known to exert effects in response to heat, and in one study it was found that PS acts as a potent agonist of TRPM3, with the same PS concentration stimulation increasing the current amplitude of the channel by more than 7-fold when the temperature increases from 15°C to 35°C [99], so that at normal human temperatures, low concentrations of PS can still cause the channel to be activated efficiently. The channel is also inhibited by other steroids, which only weakly activate TRPM3, but their action reduces the activation of the PS, and flavonoids have been found to inhibit channel activity while reducing damage to cells in mouse experiments, which greatly reduces the pain associated with activation of the channel by heat or PS agonists [100].

As TRPM3 is expressed in the DRG, it may function as an important molecular sensor in the bladder urothelium. To verify the specific function of this channel, it was found in one study that the presence or absence of TRPM3 did not affect normal bladder function, whereas a high expression of TRPM3 was detected when the bladder was inflamed and when the responsiveness of DRP neurons to TRPM3 agonists was upregulated [101]. However, it is worth noting that although a strong function of TRPM3 in innervating bladder sensory neurons has been demonstrated, whether it plays a key role in bladder filling and emptying needs to be further demonstrated, and antagonists of TRPM3 channels could be a new therapeutic target in relieving bladder pain caused by cystitis.

TRPA1

Similar to other members of the TRP channel superfamily, TRPA1 is a transient receptor-potential ion channel composed of homo or 60 heterotetramer, which was first discovered in the DRG and trigeminal ganglion, and is also expressed in pain-sensing neurons and different tissues, and is closely related to inflammation [102–104]. In a rat study, TRPA1 was found to exist in sensory nerve fibers innervating the trigone of the bladder, urothelium, subepithelial space, and muscle layer, and now it has been proved that there is an interaction between TRPA1 and TRVP1 channels, which provides a new direction and target for the study and treatment of urination reflex [102–105].

Many studies have shown that TRPA1 can be activated by a variety of receptor agonists, which covalently modify the channel upon binding to form extensive disulfide bonds between different N short cysteine residues and thus contribute to electrophilic activation, as well as to activate and increase the activity of the channel when the intracellular and intracellular calcium ion levels increase [106]. When activated, TRPA1 can activate oxidative stress by inducing the occurrence of intracellular Ca^{2+} overload, resulting in increased release of intracellular inflammatory factors, neuritis.

LUTD is a common neurological sequela, and the mechanism by which activation of TRPA1 can induce detrusor pain via C fibers has been demonstrated [107]. When TRPA1 is activated by plant-derived stimuli AI, cinnamal, and H2S, AI reduces the volume of urination while increasing the frequency of urination. H2S can induce calcium ion response and may participate in inflammatory bladder response [108]. The discovery of DO activation by TRPA1 activators in the bladder suggests that TRPA1 may play a role in sensory transduction in this organ. It is generally believed that the bladder may be innervated by two afferent nerve fibers: Type A fibers express TRPA1 receptors to promote PGE release and stimulate detrusor; B-type fibers express TRPV1, TRPA1, and TRPC receptors and release CGRP, which inhibits detrusor muscle [105]. When the expression of TRPA1 is increased in the bladder, its widespread activation leads to increased release of PGE, which leads to pain, protective reflexes, and other corresponding symptoms, and is associated with involuntary bladder contraction after spinal cord injury. If it is blocked, reduced bladder motion may occur [107–109].

Discussion

The ability of the bladder and urinary tract to sense stimuli modulates voiding activity by relying on a complex central nervous network and a small number of sensory neurons that penetrate the urothelium, whose nerve endings run along the bladder wall to the suburothelium [110]. TRP channels expressed on nerve fibers, urothelium, smooth muscle cells, and/or ICC cells, by which various parts of the urinary system communicate with each other to promote bladder sensation [28, 111, 112]. During urinary emptying, the parasympathetic nervous system mediates bladder contraction by activating bladder purinergic receptors, where afferent neuronal hypersensitivity response through purinergic receptor signaling is also involved in pathways that trigger bladder urgency. During urine storage, the contractions of the smooth muscle of the bladder are inhibited by the sympathetic nervous system, allowing the bladder to relax and distend, and convert it into ATP signaling in the voiding reflex pathway, while TRPV4 also plays an integral role in this process [113, 114]. ATP and acetylcholine is the main transmitter, which is released by the uroepithelium during mechanosensory transmission, binding to purinergic, muscarinic receptors on subepithelial sensory nerve terminals to stimulate nerve conduction activity that results in bladder filling [65].

TRPV1 was expressed in the lower layer of the urothelium and in the nerve fibers innervating the urethral muscle layer. After activation, it is involved in bladder contraction and urethral sphincter relaxation to periodically excrete urine. TRPV1 can sense the stimulation of bladder mechanical distension, bind to corresponding ligands and undergo allostery, mediate a large influx of calcium ions to initiate numerous Ca^{2+}-dependent signaling pathways, and release related neuropeptides to induce smooth muscle contraction, thereby transmitting filling signals to the central nervous system [22]. It is positively correlated with the release of inflammatory factors. Several human and animal studies have shown that abnormalities in TRPV1 are associated with the formation of NDO [115]. TRPV2 shares homology with TRPV1, but it requires a relatively higher activation threshold. Previous studies have shown that TRPV2 mRNA is expressed in animal urinary epithelial cells and bladder smooth muscle cells and may also be expressed in human bladder nerve fibers, urothelial cells, and smooth muscle cells [116]. The distribution of TRPV2 seriously affects the physiology and pathology of LUTs, being a key factor in sensing mechanical and neuroendocrine stimuli and participating in the occurrence and development of urothelial and bladder cancers [117]. TRPV4 is an important

mechanoreceptor that is specifically expressed in bladder substrate cells and intermediate uroepithelial cells and may be involved in physical (stretch, voltage difference, pain), chemical (external activators, excitability), and biological stimuli sensory pathway. Activated TRPV4 could induce increased release of Ca^{2+}, ATP, and other endogenous, exogenous mediators (P substance and procalcitonin gene-related peptide CGRP, etc.), and may target LUTD for NDO and bladder integrity, making it a therapeutic NDO and other bladder disorders a possible target for bladder pain. Based on animal experiments, we speculate that TRPV4 plays a role on the urothelial barrier, which may suggest new thoughts for therapy of urinary tract infections. TRPV2 and TRPV4 are also expressed in nerve cells and contribute to the neural reflex pathway during micturition [50]. Similar to other TRP channels, TRPM8 can be induced to activate differently by a variety of compounds by increasing local concentrations of Ca^{2+} and PIP2, among which it is highly expressed in prostate cancer and cold-related LUTs. Studies have confirmed that TRPM8 had a little effect on the occurrence of prostate cancer, but it was still controversial [118].

More human studies are needed in the future to use TRP channels to diagnose LUTD to determine whether TRP channels can serve as diagnostic biomarkers for LUTD [5]. All in all, in the response of urothelium and bladder to mechanical, chemical, or biological stimuli, any TRP channels are involved in the activity of voiding reflex, but the specific mechanism and function are not fully understood [119].

Conflict of Interest Statement

The author disclaims any conflict of interest in the publication of this paper.

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Author Contributions

Ruiqiang Gou and Yuanyuan Liu wrote the main manuscript text, Li Gou and Shengyan Mi contributed to literature retrieval and compilation, Xiaonan Li and Yichen Yang Xiaorong Cheng prepared figures, and Yibao Zhang was responsible for study design and manuscript correction.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. But if necessary, it can be obtained from Dr. Yibao (Email: zhangyb21@lzu.edu.cn), the corresponding author of this article.

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