The TRPM8 channel as a potential therapeutic target for bladder hypersensitive disorders

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Abstract

In the lower urinary tract, transient receptor potential (TRP) channels are primarily involved in physiological function, especially in cellular sensors responding to chemical and physical stimuli. Among TRP channels, TRP melastatin 8 (TRPM8) channels, responding to cold temperature and/or chemical agents, such as menthol or icilin, are mainly expressed in the nerve endings of the primary afferent neurons and in the cell bodies of dorsal root ganglia innervating the urinary bladder (via Aδ- and C-fibers); this suggests that TRPM8 channels primarily contribute to bladder sensory (afferent) function. Storage symptoms of overactive bladder, benign prostatic hyperplasia, and interstitial cystitis are commonly related to sensory function (bladder hypersensitivity); thus, TRPM8 channels may also contribute to the pathophysiology of bladder hypersensitivity. Indeed, it has been reported in a pharmacological investigation using rodents that TRPM8 channels contribute to the pathophysiological bladder afferent hypersensitivity of mechanosensitive C-fibers. Similar findings have also been reported in humans. Therefore, a TRPM8 antagonist would be a promising therapeutic target for bladder hypersensitive disorders, including urinary urgency or nociceptive pain. In this review article, the functional role of the TRPM8 channel in the lower urinary tract and the potential of its antagonist for the treatment of bladder disorders was described.

Key words: TRPM cation channels, afferent, urinary bladder diseases

─── Pharmacotherapy of Lower Urinary Tract Symptoms (LUTS) ───

LUTS are divided into three groups; storage, voiding, and post micturition symptoms (1). Among these symptoms, most influential factor on quality of life has been suggested storage symptom (2). Overactive bladder (OAB), benign prostatic hyperplasia (BPH), and interstitial cystitis/bladder pain syndrome (IC/BPS) are representative diseases resulting in storage symptoms. A large number of drugs (e.g., anti-cholinergics and

β3-adrenoceptor agonists for OAB, α1-adrenoceptor antagonists and phosphodiesterase-5 inhibitor for BPH) have been approved and used as the pharmacotherapy for such diseases. The modes and sites of action of these drugs have been proven on efferent functions such as an inhibitory effect of smooth muscle contraction or a facilitation of smooth muscle relaxation. However, a definite number of patients have resistance to such approved pharmacotherapy, thus, a new drug having a novel target and mechanism is still required. Regarding new treatment targets or mechanisms for storage symptoms, the contribution of afferent sensory transduction has been significantly promising, as the clinical implications play a significant role in the urgency of OAB.

The Introduction of Transient Receptor Potential (TRP) Cation Channels

Mammalian TRP channels can be divided into six subfamilies using sequence homology: Canonical (TRPCs), Vanilloid (TRPVs), Melastatin (TRPMs), Mucolipins (TRPMLs), Polycystins (TRPPs), and Ankyrin (TRPA), which are all membrane proteins involved in the cellular sensory response to chemical and physical stimulus and in many precise cellular functions (3). They are diversely and widely expressed on various organs and modulate ion entry such as Na^+ and Ca^{2+} flux. They also mediate various neural signaling processes implicated in sensations, such as temperature, pressure, pH, smell, taste, vision, and pain perception (3–5). Considering their diverse physiological function, TRP channel-related interruptions at the origin of diverse acquired and inherited diseases, as well as modulators of TRP channels may be developed as novel treatment options for various diseases (6–8).

Several TRP channels have been studied (basic and clinical research) with regard to LUTS. Unfortunately, no pharmacological treatment option with TRP channel modulators has been launched in the market. However, targeting TRP channels remains promising in the pathophysiology of LUTS. Here, the authors state a perspective on how drugs that target TRP channels (especially TRPM8 channel) may become valuable options for the current pharmacological treatment of LUTS, especially those accompanied with storage dysfunction, such as urinary urgency and bladder nociceptive pain.

TRP Channels Expressed on the Lower Urinary Tract (LUT) and Their Physiological Function

In the LUT, several TRP channel subfamilies are expressed (Table 1). Based on their expression pattern, these TRP channels have been proposed as promising novel therapeutic targets for LUTS, especially bladder storage dysfunction related to OAB, BPH or bladder outlet obstruction (BOO), and IC/BPS. The most famous and historical TRP channels focused on LUTS were TRPV1. In 1990, a blockade (desensitization) by capsaicin, a TRPV1 agonist, on the spinal reflex was shown in acute spinal cats several weeks after spinal cord transection, which indicates that a long latency spinal reflex could be activated by C-fiber bladder afferents (9). Taking such an animal study, either capsaicin or resiniferatoxin (a TRPV1 agonist) have been applied to treat detrusor overactivity in patients with spinal cord injury (10–12). Additionally, it has been reported that the TRPV1 channel is involved in bladder overactivity through the activation of sensory afferent nerve, but it is not associated with normal voiding function in rats where the selective TRPV1 antagonist suppressed the capsaicin induced increase in nerve discharge and intravesical pressure and also increased the intercontraction interval and voided volume in bladder overactivity (13). Unfortunately, such drugs have not yet been launched for the treatment of neurogenic OAB. As a relevant channel of TRPV1, an involvement of the TRPA1 channel on the

Table 1. Characteristics of TRP channels expressed on lower urinary tract

TRP channels	Temperature sensitivity	Activators	Expressions	References
TRPV1	43 °C<	pH (<5.9), Capsaicin, Resiniferatoxin, Anandamide	Urothelium, Interstitial cells, Sensory neuron	(9–12, 71–73)
TRPV2	52 °C<	Osmolarity, Mechanical stretch, Probenecid	Urothelium, Sensory neuron	(62, 74)
TRPV4	24–32 °C	Osmolarity, Mechanical stretch, GSK1016790A, 4α-PDD	Urothelium	(17, 18, 21, 75–77)
TRPC1	–	Tonantzitlolone	Urothelium	(78)
TRPC4	–	Tonantzitlolone	Urothelium	(78)
TRPM2	36–47 °C	H_2O_2, ADP ribose	Urothelium	(79)
TRPM7			Urothelium (Intercellular junction)	(80)
TRPM8	<22–28 °C	Icilin, Menthol, Eucalyptol	Prostate, Urothelium, Sensory neuron	(26, 49–52, 61, 81)
TRPA1	<17 °C*	Allyl isothiocyanate, Cinnamaldehyde	Urothelium, Sensory neuron	(61, 82)

*Temperature sensitivity of TRPA1 channel has not proven in human.

LUT function has also been reported. Andrade et al. firstly suggested that the TRPA1 channel could contribute to bladder disorders, wherein TRPA1 channel-related sensory afferent dysfunction has been involved in some pathophysiological activities (14). As it comprises such previous findings, a previous pharmacological investigation has reported that the TRPA1 channel contributes to activate mechanosensitive afferent nerves of both Aδ- and C-fibers in the rat bladder (15). For pain relief, TRPA1 antagonists have been tested for alleviation of pain in preliminary trials (16), which may also be able to apply to bladder nociceptive pain. Recently, in contrast, it has been reported that stimulation of TRPV4 channels may be a target for the treatment of detrusor underactivity (17, 18), characterized by an absent or low-pressure, and/or poorly-sustained detrusor contraction combined with low urinary flow (19). In a genetic study, TRPV4 mutations can cause a degenerative disorder of the peripheral nerves, often leading to urinary urgency with or without incontinence (20). It was previously revealed that TRPV4 activation in the bladder facilitates the micturition reflex by activating mechanosensitive, capsaicin-insensitive C-fiber afferent activities of the rat bladder (21). Therefore, the TRPV4 channel may be a target for the treatment of bladder disorders including underactive bladder and detrusor underactivity.

TRPM8 channels respond to temperature changes ranging from innocuous to noxious cold, and chemical agents, such as icilin and menthol (22, 23). TRPM8 channels are expressed in urothelial cells (human and rodents), sensory nerve fibers (Aδ- and C-fibers) within the urothelium and suburothelium of the bladder (human and rodents), and primary sensory neurons (cell body in the L6 dorsal root ganglion) (rodents) (24–27). Therefore, the TRPM8 channel may be a potential target for the treatment of LUTS, especially for that of bladder sensory disorders.

——— LUTS Implied with Bladder Sensory (Afferent) Dysfunction ———

Urinary urgency, the primary symptom of OAB, is defined as the complaint of a sudden compelling desire to pass urine that is difficult to defer (1, 28); alternatively, this symptom is bladder sensory (afferent) hypersensitivity. The development of urinary urgency has been suggested to be associated with detrusor overactivity during the storage phase in patients with BPH or BOO (29–32). Moreover, IC/BPS is a condition with chronic pelvic pain, pressure, or discomfort related to the urinary bladder accompanied by other urinary symptoms

(33). These bladder sensory hypersensitivities, including urinary urgency and nociceptive pain, have been suggested to be regulated by the urothelium, which actively participates in sensory functions, expressing various receptors for neurotransmitters (34).

The pelvic and hypogastric nerves convey sensations of bladder fullness to the spinal cord (35). Bladder pelvic afferent nerves are composed of Aδ-fibers and C-fibers. Aδ-fibres are primarily located within the detrusor smooth muscle layer, whereas C-fibres are more widespread and can be found not only in the detrusor smooth muscle but also in the lamina propria and often directly adjacent to the urothelium (34, 36–38). It has been demonstrated that Aδ-fibers affect normal mechanosensitive response; however, C-fibers appear to be mechanoinsensitive and responding to abnormal (i.e., noxious and inflammatory) stimuli as "silent" fibers, as it is shown that they may not participate in normal micturition, a mechanosensitive response, in cats (39, 40). In contrast, a previous report have indicated that some C-fibers may be volume receptors (mechanosensitive receptors) in rats and may not respond to bladder contraction (41). Instead, it was reported that C-fibers respond to normal bladder distension, a mechanosensitive response, as Aδ-fibers; therefore, it is difficult to distinguish between Aδ-fibers and C-fibers without conducting velocity measurements (42). Thus, C-fibers seemingly participate in normal mechanosensory response in the rat bladder and may also fulfill a potentially different role in bladder sensory function in response to abnormal stimuli as "silent" fibers.

Physiological and Pathophysiological Contribution of TRPM8 Channels in LUT

Cold stimulation (<22–28 °C) and chemical stimulation (menthol, icilin) activate TRPM8 channels (Table 1). TRPM8 channels are expressed on nerve fibers, which are different noxious primary sensory fibers expressing TRPV1 and TRPA1 channels and urothelial cells (22, 43). Previous animal studies indicated that TRPM8-knockout mice lack temperature discrimination, noxious cold temperature sensation, injury-evoked hypersensitivity to cold after nerve injury, and/or inflammation (43, 44). In contrast, several animal models of neuropathic pain showed that the expression of TRPM8 channel is upregulated on primary sensory fibers, and sensitivity to cold stimulation is increased in these fibers (45, 46), e.g., TRPM8 channels are involved in oxaliplatin-induced neuropathy (47, 48). Therefore, TRPM8 channels may provide abnormal cold sensitivity under pathological conditions, leading to neuropathic pain, such as cold allodynia.

It was previously revealed that TRPM8 channels might contribute to activating the bladder afferent pathways during bladder filling in normal rats. This effect was at least partly mediated via mechanosensitive C-fibers (49). Additionally, it was recently demonstrated that TRPM8 channels affect chemical (acetic acid or prostaglandin E_2)-induced pathological activation of mechanosensitive bladder C-fibers in rats (50–52). Moreover, the possible contribution of TRPM8 channels has also been proposed in each pathophysiological condition, such as OAB (52, 53) and BOO in rats (54, 55), and IC/BPS in humans (27, 56).

TRPM8 Channel Related to OAB

Recently, it was reported that novel TRPM8 antagonists (KPR-2579 and KPR-5714) exhibited an inhibitory effect on bladder overactivity induced by intravesical acetic acid instillation without affecting body temperature in rats (50–52). Additionally, KPR-5714 can also inhibit bladder overactivity caused by cold exposure and cerebral infarction (52). Regarding cold exposure-induced bladder overactivity, the main action site is the TRPM8 channel on the skin rather than the bladder (57–59). In contrast, pharmacological investigations have

certainly indicated physiological and pathophysiological roles of the TRPM8 channel in the urinary bladder (49). Our previous studies suggest that TRPM8 channels contribute to activating bladder afferent pathways through mechanosensitive C-fibers (49–52), and this specific mechanism of the TRPM8 channel on sensory bladder function may possibly contribute to the storage symptoms, such as urinary urgency in OAB. Additionally, it was recently revealed that the combined administration of KPR-5714 and mirabegron (a β_3-adrenoceptor agonist) or tolterodine tartrate (an anticholinergic agent) indicated the additive effects on bladder overactivity caused by cold exposure and cerebral infarction in rats, suggesting that the combination therapy using an TRPM8 antagonist with a β_3-adrenoceptor agonist or anticholinergic agent can be the potential treatment option for obtaining an additive effect compared with the monotherapy for OAB (53).

TRPM8 Channel Related to BOO

BPH often occurs in older men and causes LUTS (60). BPH is one of the main factors resulting in BOO. In animal studies, it has been reported that the expression of TRPM8-positive neuronal cells was increased in the urinary bladder (urothelium) and dorsal root ganglia in BOO rats (54, 55). These previous studies also showed that intravesical instillation of menthol, a TRPM8 agonist, in BOO rats shortens the intercontraction interval, indirectly indicating the activation of bladder sensory hyperactivity. Alternatively, Du et al. reported that no significant change in the TRPM8 channel expression was observed after BOO or BPH in humans, whereas TRPA1 channel expression significantly increased (61); it seems that there is a discrepancy between species.

TRPM8 Channel Related to IC/BPS

Mukerji et al. firstly reported increased TRPM8 channels in nerve fibers of overactive and painful bladders and its relationship with clinical symptoms (27). Additionally, Homma et al. reported that the expression of TRPM8 channels increased in the patient with hunner type IC, characterized by a specific lesion (hunner lesion) and inflammation-related symptoms, including increased urinary frequency and bladder sensation (62). More recently, Wu et al. reported using immunostainings that the number of neurons and sensory nerves display a significant upward trend in the bladder tissue of patients with IC/BPS and that the expression levels of TRPM8 channels on neurons and sensory nerves also significantly increase in patients with IC/BPS (63). Thus, TRPM8 channels may be involved in the abnormal sensory response related to nociceptive pain of the bladder, and TRPM8 antagonist would be a promising therapeutic target for hypersensitive bladder disorders, including pain.

Potential Therapeutic Drugs of TRPM8 Antagonist Related to Urinary Bladder Disorders

Several newly developed TRPM8 antagonists have high selectivity against the TRPM8 channel, at least more than 100-fold selectivity over other ion channels, such as TRPA1, TRPV1, TRPM2, Nav, and Cav (52, 64–66). In contrast, TRPM8 channels have thermal sensitivity; thus, it is possible that drugs acting on the TRPM8 channel can influence body temperature. Hypothermic effects of TRPM8 antagonists have been demonstrated in rodents (49, 67), which may be an unfavorable effect for clinical development. However, it was recently reported that such hypothermic effects could be negligible, at least in some of the TRPM8 antagonists (50–52). Therefore, such TRPM8 antagonists may provide a promising drug for the treatment of bladder sensory disorders (i.e., urinary urgency and bladder pain) without affecting body temperature.

Regretfully, so far, TRPM8 antagonists have unsuccessfully reached the market in various disease areas. A potent and selective TRPM8 antagonist (PF-05105679) reached a phase one clinical trial, but trial volunteers complained of non-tolerated adverse effects (hot sensation in the face, hands, and arms). Thus, it stopped further progress into advanced clinical trials (68). Similarly, in other clinical trials on healthy subjects and patients with migraines using a TRPM8 antagonist (AMG333), adverse effects (feeling hot, paresthesia, dysesthesia, and dysgeusia) were observed, and the study was discontinued (69).

Perspectives

In the last 30 years, the constant research on TRP channels, including the TRPM8 channel, has revealed their participation in numerous physiological processes and various pathological conditions (70). However, forthcoming treatment using TRPM8 modulators needs more coordinated investigations and will remain exciting targets for the treatment of LUTS. Further studies regarding more detailed pathophysiological contribution of the TRPM8 channel in hypersensitive bladder disorders are required for accelerating innovative drug discovery.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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