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Individuals are faced with varying aspects of health problems that have an impact on their quality of life. Suffering a nonfatal heart attack certainly changes one’s appreciation of life, which may result in a vigilant awareness of blood pressure, a change in diet, an initiation of an exercise program, a reduction in smoking along with other adjustments of daily life. The severity of a health condition may be manifested in subtle ways, yet have a major impact on quality of life. For many of us, we do not realize the simplicity of normal urinary bladder function. However, overactive bladder syndrome (OAB, also referred to as overactive detrusor function) is a condition that has symptoms of urgency for urination (micturition) with or without urge incontinence, high frequency of urination, and nocturia (waking at night to urinate) (1). OAB has a significant cost to the individual and the healthcare system. Indeed, in 2008, an estimated ~11% of the world population was affected by OAB and it was estimated to grow to 20% by 2018 (6). In 2008 alone, it was estimated that the collective direct cost burden for Canada, Germany, UK, Italy, Sweden, and Spain was £3.9 billion, which did not include nursing home costs (7). Other costs of OAB escalate the personal and economic impact when one factors in absenteeism from work and decreased productivity while at work (7). It is obvious that the cost burden of OAB to the quality of life of the individual, the healthcare system, and the workforce is substantial.

Generally, our understanding of the reason why OAB is manifested is unknown. The detrusor smooth muscle (DSM) of the wall of the urinary bladder is key to the function of the bladder (1). The cells of the DSM relax during the process of filling and storing urine in the bladder for long periods of time without leakage. Additionally, for urination to occur, the DSM cells must synchronously contract in concert with coordinated function of the internal and external sphincters of the urethra. This integrative function is controlled by neural and hormonal signals (1). In OAB, there can be involuntary contractions of DSM cells during the storage time of urine that results in leakage. There are strategies to reduce the complications of OAB that include lifestyle changes (reduced fluid intake), acupuncture (2), and pharmacological therapy (8). For example, if one could pharmacologically target a specific protein channel involved in membrane potential function of DSM cells with a drug that results in relaxation of the DSM; this would be of great benefit.

In this issue of the American Journal Physiology-Cell Physiology, Petkov and colleagues (5) provide a very exciting study in which they report a novel regulatory mechanism in the human urinary bladder in which the transient receptor potential melastatin 4 channel (TRPM4) is instrumental in human DSM excitability and contractility. The implications from their results suggest that TRPM4 may be a novel therapeutic target for ameliorating symptoms of OAB.

TRPM4 is a Ca$^{2+}$-activated nonselective cation channel that depolarizes the cell membrane through Na$^+$ entry and subsequent activation of L-type Ca$^{2+}$ channels (Fig. 1) in heterologous expression systems (3). Additionally, inhibition of TRPM4 of cerebral artery smooth muscle cells resulted in hyperpolarizing cell membrane potential and relaxation of smooth muscle cells (4). This combination of characteristics of TRPM4 led to this study by Petkov and colleagues (5).

The Petkov lab has previously reported a role of TRPM4 in the function of the DSM of the guinea pig bladder (9). However, in the paper highlighted here, Petkov and coworkers (5) have gone to the next research echelon by examining the role of TRPM4 in human DSM tissues (from patients without OAB symptoms) and isolated DSM cells. Their results can be summarized as follows. First, initial experiments were focused on identifying TRPM4 within the human bladder. Therefore, they used RT-PCR and identified mRNA transcript of TRPM4 within whole human bladder. Further, with isolated DSM cells, they performed single-cell RT-PCR experiments and unequivocally identified, for the first time, TRPM4 transcript within human bladder. Second, the authors executed Western blot, immunohistochemistry with confocal microscopy and immunocytochemistry with TRPM4 channel-specific antibody experiments to identify TRPM4 protein (~134 kDa) within human DSM, and identified that TRPM4 and α-smooth muscle VDCC and the HDSMC relaxes. At present, it is not well understood whether TRPV4 plays a role in contraction of HDSMCs.

Fig. 1. Shown is diagram of a human detrusor smooth muscle cell (HDSMC) that comprises the muscular wall of the urinary bladder. A potential physiological role of the TRPM4 (and TRPV4?) channels is to produce either a contraction or relaxation of the HDSMC. For contraction, when intracellular Ca$^{2+}$ activates TRPM4, this results in the entry of Na$^+$ into HDSMCs. The resulting depolarization of HDSMCs activates voltage-dependent Ca$^{2+}$ channels (VDCC), which in turn leads to contraction of HDSMCs. The use of a TRPM4 antagonist such as 9-phenanthrol inhibits TRPM4, and thus, the cells become hyperpolarized and there is not a stimulatory downstream effect of VDCC and the HDSMC relax. At present, it is not well understood whether TRPV4 plays a role in contraction of HDSMCs.
Actin were colocalized spatially within the same cell, and that TRPM4 channel protein was expressed in DSM single cells via an α-smooth muscle actin marker. Third, Petkov and colleagues used 9-phenanthrol (30 μM), a specific inhibitor of TRPM4 (4), to investigate the function of TRPM4 in the excitability of isolated DSM cells. Using perforated patch-clamp experiments, the authors reported that 9-phenanthrol decreased the transient inward cationic current activity of TRPM4 channels by over 50%, providing direct evidence that TRPM4 modulates excitability of DSM cells. Fourth, to further characterize TRPM4 channels of DSM cells, Petkov and coworkers defined the current-voltage relationship of the cationic current via TRPM4 and demonstrated that 9-phenanthrol inhibited outward current by over 40%. Fifth, since TRPM4 altered whole cell currents of DSM cells, the authors proceeded to determine the role of TRPM4 on the membrane potential, with current-clamp experiments of isolated DSM cells. They reported that application of 9-phenanthrol hyperpolarized the cell membrane of DSM cells by 24 mV (membrane potential more negative). Thus, they provide the first evidence that TRPM4 regulated the resting membrane potential of human DSM cells. Sixth, the authors shifted to in vitro experiments and examined the effect of TRPM4 in the spontaneous and phasic contractile responses of human DSM isolated strips. Inhibition of TRPM4 channels, with 9-phenanthrol, significantly reduced the spontaneous and phasic contraction amplitude, muscle force integral, contraction duration, contraction frequency and muscle tone of the DSM. These data clearly demonstrated that TRPM4 is a key modulator of human DSM under physiological conditions. Seventh, since initiation of bladder emptying contractions is dependent on parasympathetic activation of muscarinic receptors and the release of acetylcholine, Petkov and coworkers performed functional experiments to examine the role of TRPM4 channels when muscarinic receptors were activated. They used carbachol, a muscarinic receptor agonist, and 9-phenanthrol to assess the role of TRPM4 in this process with their human DSM-isolated strip preparation. In fact, during carbachol stimulation, 9-phenanthrol significantly decreased the amplitude of the carbachol-stimulated contraction, the contraction duration, contraction frequency, and the muscle tone of the DSM. These data are very exciting evidence that TRPM4 can modulate DSM function during the physiological process of urination. Finally, Petkov and colleagues tested the role of TRPM4 channels in nerve-evoked contractions, which simulate normal urinary function. Using their human DSM-isolated strip preparation, they demonstrated a 9-phenanthrol concentration-dependent inhibition of nerve-evoked contraction amplitude and force of the DSM. Overall, Petkov and colleagues have provided novel results on the role of TRPM4 in modulation of the human DSM. These data certainly provide substantial evidence that TRPM4 plays a major role in DSM function, and this channel is a very likely candidate as a therapeutic target for OAB.

The study by Petkov and colleagues has identified and confirmed a novel channel protein candidate that may be a wide-ranging potential target for the treatment of OAB. However, that statement is easy to write but much more difficult to put into action and practice. All scientific studies have caveats and this study is no exception. First, we still must understand the basic physiology and pathophysiology of the DSM of patients with OAB. Is the expression of TRPM4 any different for patients suffering with OAB? The answer to this question still eludes scientists. Regrettably, the authors were unable to obtain a sufficient quantity of human DSM samples from OAB patients for comparable experiments conducted in their study. Second, other possible channels might be involved in the proper function of the human DSM. Is TRPV4 expressed in human detrusor muscle (Fig. 1)? Thorneloe et al. (10) have reported TRPV (vanilloid)4 in the mouse urinary bladder DSM and have demonstrated that, in isolated mouse DSM, GSK1016790A, a selective and potent TRPV4 activator, increased DSM contractions and that administration of GSK1016790A results in bladder overactivity in wild-type, but not TRPV4-knockout, mice. Now, since TRPV4 has been shown to be a regulator of bladder contractility (10), this channel may also be a therapeutic target for bladder dysfunction. Therefore, it is very important to determine whether TRPV4 is present within human DSM. If so, this is extremely exciting as there may be two potential channels that might be therapeutically targeted (separately or in concert) to ameliorate the symptoms of OAB (Fig. 1). Lastly, the authors used 9-phenanthrol at 30 μM to examine the function of TRPM4 in the DSM; such a concentration would never be used in the clinical setting. However, the structure of 9-phenanthrol would be a logical parent structure for medicinal chemists to develop a more potent inhibitor of TRPM4 with negligible side effects. Undoubtedly, this is a possibility that will take considerable monetary input through many years of basic research and clinical trials to bring to fruition.

In summary, it must be very thrilling for patients with OAB to increase hope for potential treatments of OAB as novel protein channels are identified within the DSM. However, as the population ages and the life expectancy increases due to better health care, the propensity of the cases of OAB will increase at an alarmingly high rate. Therefore, in the future, there will be a need for multiple types of therapeutic approaches including both traditional (e.g., pharmacotherapy) and nontraditional (e.g., acupuncture) to manage the growing numbers of OAB patients and the potential health problems of OAB.

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