TRPM8, A Calcium Permeable Non-selective Cation Channel

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ABSTRACT

TRPM8 is known as a cold-sensing channel, which is permeable to calcium and monovalent cations. It was originally identified in prostate cancer cells. The physiological and pathological functions of TRPM8 in prostate cells remain unclear, however, it has been suggested the channel may serve as a diagnostic and prognostic marker in prostate cancer. This mini-review highlights our current understanding of TRPM8.

INTRODUCTION

The transient receptor potential (TRP) family of non-selective cation channels plays critical roles in homeostasis and pathology (Pedersen et al., 2005; Patapoutian et al., 2003; Voets and Nilius, 2003). The TRP channels are divided into three major subfamilies: TRPV, TRPC and TRPM (Patapoutian et al., 2003; Pedersen et al., 2005). The TRPM subfamily has eight members, TRPM1 – TRPM8; they are structurally similar to the putative tumour suppressor melastatin which was identified in melanoma cells (Tsavaler et al., 2001). The TRPM8 channel, also known as the Cold and Menthol Receptor, CMR1, is highly sensitive to low temperature (McKemy et al., 2002). The thermosensitive channel gene, trp-p8, was originally identified and cloned by screening a prostate-specific subtracted cDNA library (Tsavaler et al., 2001). This gene has a 47% similarity to human melastatin protein and thus renamed as TRPM8 as a part of the TRP melastatin (TRPM) family. TRPM8 have been found

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in various tissues including the sensory ganglia (Peier et al., 2002; Tsuzuki et al., 2004), and the prostate (Tsavaler et al., 2001), and upregulated in androgen-dependent prostate cancer cells (Henshall et al., 2003; Zhang and Barritt, 2006). Although its physiological role of the channel in prostate remains not very clear, this thermosensitive channel regulates the calcium level to support the survival of various prostate cancer cells (Zhang and Barritt, 2004). Thus, TRPM8 has been considered as a potential pharmaceutical targets or diagnostic biomarker for cancer. This minireview will brief the current understanding of the molecular structures, biophysiocal and pharmacological properties, thermosensitivity, functional roles in prostate cancel cells and therapeutic potentials of TRPM8 channels.

MOLECULAR STRUCTURE

The TRPM8 subunit consists of 1104 amino acids (Tsavaler et al., 2001). There is currently no crystal structure of TRPM8 available. The topological arrangement of TRPM8 is based on that of the voltage-gated potassium channel. A functional TRPM8 channel is considered as a tetramer comprised of four identical subunits, each containing six putative transmembrane spanning domains with a cytoplasmic amino- and carboxyl termini (Tsavaler et al., 2001; Latorre et al., 2007). The ion pore region of the channel is predicted between the transmembrane helices five (S5) and six (S6) (Montell et al., 2002; Perraud et al., 2003; Voets and Nilius, 2003). The N-terminus contains 4 regions that are homologous amongst all members of the TRPM subfamily. Voltage sensitivity resides in the S1-S4 domains (Zhang and Barritt, 2006; Voets et al., 2007a; Kuhn et al., 2010). The selectivity filter is located between and the S5 and S6 segments (Montell et al., 2002; Voets and Nilius, 2003; Voets et al., 2007a), and D920 and Q914 residues are important for ion permeability (Latorre et al., 2007).

The C-terminus of 120 amino acids forms a coiled-coil structure that is responsible for the proper assembly of the tetrameric channel (Fleig and Penner, 2004; Tsuruda et al., 2006). The C-terminus consists of a highly conserved TRP box which is essential for channel activation (Rohacs et al., 2005). Channel opening is weakly sensitive to voltage and regulated by PI(4, 5)P2. The S4-S5 linker domains interact with the C-terminal domain of S6, resulting in opening of the channel (Voets et al., 2007a).

BIOPHYSICAL AND PHARMACOLOGICAL PROPERTIES

TRPM8 ion permeability

Similar to most TRP channels, TRPM8 is a non-selective cation channel. It is permeable to sodium (Na^+), potassium (K^+), cesium (Cs^+) and calcium (Ca^{2+}); leads to an elevation of the intracellular Ca^{2+} level (McKemy et al., 2002; Peier et al., 2002). The Ca^{2+} serves as signalling element in cold-sensing. The permeability ratio between Ca^{2+} and Na^+ (P_{Ca}/P_{Na}) however, varies between 0.97 (Peier et al., 2002) and 3.2 (McKemy et al., 2002). The permeability of the channel to monovalent ions is in order of Cs > K > Na (Peier et al., 2002).

Activation

TRPM8 can be activated by temperatures below 28 degrees, membrane depolarization, and menthol and methol-like ligands. The channel is most well known for its sensitivity to cold. At physiological membrane potentials, TRPM8 elicits a significant inward current at temperatures below 25°C (McKemy et al., 2002). TRPM8 activation by cooling corresponds to a shifting of the voltage-dependent activation curve (Voets et al., 2004). The voltage-dependency of the channels is weak.

The voltage-sensitivity of the channels is resided in the transmembrane segments 1-4. Typically as a non-selective cation channel, TRPM channels exhibit a linear ohmic I-V relation (Voets et al., 2004). In the presence of menthol, The current-voltage curve shows strong outward reactivation with a reversal potential of ~0mV (McKemy et al., 2002; Hui et al., 2005). In the absence of other stimuli, the I-V curve shifted to more depolarizing potentials (Nilius et al., 2005). We have previously showed that application of methanol to TRPM8 channels induces two conductances (γ_S) and (γ_L) to divalent (calcium, barium) and monovalents (sodium, potassium), respectively (Hui et al., 2005). The outward rectifying conductance of the channel is reduced in calcium, due likely to the channel deactivation. Single channel recording showed that the open probability (Po) increases with depolarization (Hui et al., 2005). Based on these observations, it is hypothesized a gating model in which the closed and open states are differentially modulated by temperature and voltage.

There are a number of models describing TRPM8 activation. The simplest two-state model is proposed based on its cold-sensing behaviour (Voets et al., 2007b). This model adequately explains the additive nature of thermal and chemical stimuli. However, single channel recordings of TRPM8 show bursting open property, indicating a multi-state model. The brief bursts of activity can be explained by rapid alternations between open and closed states. The inter-burst durations of activity are likely due to the transition of the channel to a second closed state with a much longer time constant. In an allosteric coupling model of TRPM8 gating (Brauchi et al., 2004), the open and closed states are accordant with on/off transitions of the temperature and voltage sensors. The allosterical modeling indicates the temperature dependent step is independent of voltage (Latorre et al., 2007), which is supported by the findings that the C-terminus modulates the temperature sensitivity without affecting voltage dependence (Latorre et al., 2007). A recent study showed that voltage is only a partial activator but is neither essential nor sufficient for TRPM8 gating (Matta and Ahern, 2007).

The mechanisms of TRPM8 channel activation are rather complicate, and may require interplay between substrate binding, cold temperatures and depolarization.

Menthol and other agonists

Research for pharmacological agents sensitive to TRPM8 has been extremely active since 2002 following discovery of the channel. A number of natural and synthetic compounds have been identified as agonists or antagonists of TRPM8. The most common agonists are menthol and icilin. Menthol is a natural cooling agent found in mint leaves and often used in throat lozenges. The effects of menthol and cold on TRPM8 are additive; both shift the voltage dependent activation curve towards physiological conditions (Voets et al., 2004). Site-directed mutagenesis showed that Y745 and R842 are critical for menthol binding (Voets et al., 2007b; Malkia et al., 2009), suggesting that menthol may bind to the hydrophobic cleft located between the S2 and S4 domains. Mutation of Y1005 and L1009 in the TRP domain at the C-terminus reduces menthol potency, suggesting these two sites are important for menthol action (Voets et al., 2007b). Voltage and temperature sensors reside on different structural domains; further investigation is required to understand whether methanol acts directly on the voltage sensor (Malkia et al., 2007).

Icilin, a synthetic cooling agent, is ~200 times more potent than menthol (McKemy et al., 2002). The effect of icilin requires calcium (Chuang et al., 2004). Although the molecular mechanism of icilin effect is not well understood, it has been reported that N799, D802 and G805 in the S3 domain is required for icilin effect. Mutation of these sites does not affect menthol sensitivity, suggesting no structural overlap between menthol and icilin binding sites, hence the mechanisms of activation between menthol and icilin on the channel are independent (Chuang et al., 2004; Kuhn et al., 2009).

Carboxamides (WS-12, CPS-369, CPS-113), carboxylic acid estr (WS-30) and phosphine oxide (WS-148) are also agonists of TRPM8 (Bodding et al., 2007). WS-12 has high potency and may act on the same activation site as icilin (Bodding et al., 2007). Another group of the channel agonists is the natural odorant, including linalool, geraniol and hydroxycitronellal (Behrendt et al., 2004; Harteneck, 2005). These compounds are currently used in aroma therapy against headaches.

Antagonists

TRPM8 antagonists include capsazepine, N-(4-tertbutyl-phenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1 (2H)-carboxamide (BCTC) and a thio-derivative of BCTC (Behrendt et al., 2004; Harteneck, 2005). Capsazepine is a competitive inhibitor of menthol. BCTC is structurally close to icilin (Behrendt et al., 2004). These antagonists decrease temperature sensitivity of the channel by shifting voltage dependence (Malkia et al., 2007). Limited information is available regarding the mechanisms of the TRPM8 inhibitors.

TRPM8 CHANNEL REGULATION

TRPM8 can be activated by PI(4,5)P2 in the absence of other stimuli (Rohacs et al., 2005). The PI(4,5)P2 effect is mediated by direct interaction with the positive change cluster on the C-terminus TRP domain the S4-S5 loop (Rohacs and Nilius, 2007). In addition, PI(4,5) P2 can recover TRPM8 inactivation induced by the phospholipid phosphatases (Liu and Qin, 2005).

Calcium plays a regulatory role in both activation and inactivation of TRPM8. Increase in cytoplasmic calcium

(Ca^{2+}) is required for icilin mediated activation of the channel (Chuang et al., 2004). Calcium also activates phospholipase-C (PLC) which hydrolyzes PI(4, 5)P2, leading to desensitization of the channel (Zhang and Barritt, 2006; Kuhn et al., 2007). These evicences further support the notion that TRPM8 activation is regulated by intracellular Ca^{2+} level, however, less is known about the calcium sensitivity of the channel regulation. Such information is critical for drug development.

CLINICAL SIGNIFICANCES

TRPM8 is expressed in a wide variety of tissues including the liver, vascular smooth muscle, dorsal root ganglion, trigeminal ganglion, taste papillae, thymus, breast, ileum, testis, prostate, seminiferous tubules, scrotal skin, and bladder (Peier et al., 2002; Stein et al., 2004; Tsuzuki et al., 2004; Zhang et al., 2004; Voets et al., 2007a; Takashima et al., 2010). TRPM8 are expressed in a number of cancerous tissue cell lines; relatively high expression in LNCaP cells, as compared to DU145 and PC-3 cells. The TRPM8 expression level is strongly enhanced by androgen (Zhang et al., 2004).

Thermosensation and analgesic effect

Consistent with its role in thermosensation, TRPM8 is found in pain and temperature sensing neurons (Stein et al., 2004; Zhang et al., 2004; Voets et al., 2007a). Activation of TRPM8 by methanol has been shown to treat many pain related diseases including: irritable bowel disease, nerve damage, migraine headaches, and postherpetic neuralgia (Weil et al., 2005). Thus, TRPM8 is a therapeutic target for developing analgesic drugs. Studies reveal that opening of the TRPM8 channel is mediated by interaction of S4-S5 domain with C-terminal part of S-6 which induces opening of the pore. Mutations of the S4-S5 alter the gating properties of the channel and ultimately lead to decreased thermal sensitivity (Voets et al., 2007a). Low temperature induces Na^{+} or Ca^{2+} influx through TRPM8 channels and results in membrane depolarization and a subsequent cold sensation (McKemy et al., 2002). Mild cold induced activation of TRPM8 results in analgesia in chronic pain states (Proudfoot et al., 2006). The functional role of TRPM8 as a cold sensor is confirmed in TRPM8 knockout mice in vivo. Mice lacking TRPM8 have significant longer latency to avoid cold stimuli in comparison to the wild type mice (Chung and Caterina, 2007). TRPM8 is critical for detection of temperature changes and for triggering behavioural response to pain; suggesting therapeutic potential of TRPM8 blocker in pain (Chung and Caterina, 2007).

Cancer therapy

TRPM8 has significant implication in cancer therapy. An increased levels of trp8 mRNA has been found in prostate cancer cells (Tsavaler et al., 2001), and various types of cancer cells including melanoma, colorectal carcinoma and breast carcinoma (Zhang and Barritt, 2006). TRPM8 may function as an oncogene and promote carcinogenesis by disrupting calcium homeostasis leading to apoptosis resistance and uncontrollable cell division. TRPM8 contains a binding site for p53, a known tumour suppressor gene, suggesting its potential involvement in mediating cell growth and cell cycle.

TRPM8 is upregulated in a number of cancerous cells including melanoma, colorectal cancer, breast cancer, lung cancer, and of course prostate cancer cells (Stein et al., 2004; Zhang and Barritt, 2006; Bodding, 2007; Voets et al., 2007a). Although the physiological role of TRPM8 in these tissues remains inconcludisve, it has been suggested that TRPM8 can have a temperature-sensing role in the bladder to control the cooling reflex, which is the detrusor contraction and voiding in patients with supraspinal lesions (Stein et al., 2004; Zhang and Barritt, 2006). The prostate is located near the bladder, but it is not clear whether TRPM8 could also have a similar cool sensing role in the prostate. The expression of TRPM8 is closely correlated with the prostate cancer phenotype. TRPM8 expression in prostate cancer is primarily regulated by androgens (Henshall et al., 2003; Zhang and Barritt, 2004), and prostate-specific antigen (PSA) (Gkika et al., 2010). Understanding the regulatory mechanisms underlying TRPM8 expression can provide insight into its roles in prostate cancer.

TRPM8 is mainly expressed in the apical secretory epithelial cells (Bidaux et al., 2005). Since secretion is calcium-dependent, the Ca^{2+} conductance of TRPM8 indicates that the channel may regulate secretion (Bidaux et al., 2005). Active TRPM8 channels are essential for survival of the LNCaP line of prostate cancer cells (Zhang and Barritt, 2004). Decrease in TRPM8 expression using TRPM8 targeted siRNA or TRPM8 inhibition by a blocker capsazepine induces apoptosis and reduces cell viability. Due to that TRPM8 agonist, menthol, also reduces prostate cancer

cell viability (Zhang and Barritt, 2004), it has been hypothesized that TRPM8 channels may play necessary roles in Ca^{2+} and Na^{2+} homeostasis in prostate cancer cells. These findings lead to new therapeutic strategies of manipulating TRPM8 functions to alter calcium induced secretion of the cancer cells. Development of selective and potent TRPM8 agonists and antagonists holds therapeutic significance for prostate cancer therapy and prevention.

Another important aspect of TRPM8 is its potential to serve as a prognostic prostate cancer marker (Zhang and Barritt, 2006; Bai et al., 2010). Measurements of TRPM8 mRNA level (Zhang and Barritt, 2004) and subcellular localization (Bidaux et al., 2007) can be used to track the progress of prostate cancer.

CONCLUSION

TRPM8 has shown promising therapeutic potential in pain and cancer. Although it is still in its infancy, our knowledge of the channel is rapidly growing since its discovery in 2002. Further study is required to enhance our understanding of the biophysical and pharmacological properties, the molecular and structural determinants of the channel properties, and the regulatory mechanisms underlying tissue-specific expression of the channel. With the availability of the advanced technologies in molecular pharmacology and genetic analysis, we anticipate new preventive, diagnostic, and therapeutic approaches of manipulating functional TRPM8 channel in prostate cancer in the near future.

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