The TRPM2 channel: A thermo-sensitive metabolic sensor

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ABSTRACT
Living organisms continually experience changes in ambient temperature. To detect such temperature changes for adaptive behavioral responses, we evolved the ability to sense temperature. Thermosensitive transient receptor potential (TRP) channels, so-called thermo-TRPs, are involved in many physiologic functions in diverse organisms and constitute important temperature sensors. One of the important roles of thermo-TRPs is detecting ambient temperature in sensory neurons. Importantly, the functional expression of thermo-TRPs is observed not only in sensory neurons but also in tissues and cells that are not exposed to drastic temperature changes, indicating that thermo-TRPs are involved in many physiologic functions within the body's normal temperature range. Among such thermo-TRPs, this review focuses on one thermo-sensitive metabolic sensor in particular, TRPM2, and summarizes recent progress to clarify the regulatory mechanisms and physiologic functions of TRPM2 at body temperature under various metabolic states.

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thought to function within the body’s normal temperature range. Several reports have shown that temperature thresholds for these thermo-TRPs can be regulated by endogenous factors. Nicotinic acid (vitamin B3) strongly decreases temperature thresholds for TRPV3 activation and increases that of TRPV4. Temperature thresholds for TRPM2 activation are regulated by redox signals, findings that we will examine in detail in the later part of this review. The activity of these thermo-TRPs at body temperature can be changed in vivo, although further study is necessary to clarify the detailed mechanisms.

A body temperature sensor, TRPM2

TRPM2 is broadly expressed in various tissues such as the brain, pancreas, spleen, kidney and a wide range of immunocytes, including lymphocytes, neutrophils, and monocytes/macrophages. TRPM2 plays important roles in \(Ca^{2+}\) signaling in these tissues and cells. The TRPM2 channel is temperature-sensitive and is also activated by intracellular endogenous ligands and reactive oxygen species. Although these effective stimuli can independently activate the TRPM2 channel, more importantly, they have synergistic effects on TRPM2. TRPM2 is a non-selective cation channel having a characteristic C-terminal Nudix domain that is homologous to the NUDT9 adenosine diphosphoribose (ADPR) pyrophosphatase, an enzyme that converts ADPR to adenosine monophosphate and ribose 5-phosphate. However, the Nudix domain in TRPM2 lacks enzymatic activity and ADPR binding to the domain is sufficient for channel gating. Endogenous TRPM2 agonists include ADPR, cyclic ADPR (cADPR) and pyridine dinucleotides including \(\beta\)-nicotinamide adenine dinucleotide (NAD), nicotinic acid adenine dinucleotide (NAAD) and NAADP. However, a recent report found that pyridine dinucleotides are not involved in TRPM2 activation.

Endogenous activators of TRPM2

The most potent intracellular endogenous ligand is ADPR, which is generated by multiple pathways. One possible source is the nucleus where serial enzymatic reactions by poly-ADPR polymerase (PARP) and poly-ADPR glycohydrolase (PARG) produce ADPR. PARP is activated by DNA damage upon oxidative stress and attaches a poly-ADPR chain to institute DNA repair. PARG hydrolyzes poly-ADPR chains to generate free ADPR. Mitochondria represent another source of ADPR. Cellular stress allows NAD\(^+\) to leak out from the mitochondrial matrix and NAD glycohydrolase, which is localized in the mitochondrial outer membrane, converts NAD to ADPR. ADP-ribosyl cyclases, such as ecto-enzyme CD38, are also involved in ADPR production. CD38 catalyzes cADPR formation from NAD\(^+\) and hydrolyzes cADPR to generate ADPR. However, it remains unclear how ADPR, generated extracellularly by CD38, enters the cell. Adenosine monophosphate (AMP) inhibits ADPR action on TRPM2. cADPR formed by ADP-ribosyl cyclase activity also affects the TRPM2 channel together with its effect on ryanodine receptors to release \(Ca^{2+}\) from intracellular \(Ca^{2+}\) stores. cADPR augments the effect of ADPR, strongly suggesting synergistic interaction between ADPR and cADPR for TRPM2 activation.

TRPM2 is also activated by redox signals and its activation is involved in cell death induced by oxidative stress. Hydrogen peroxide (H\(_2\)O\(_2\)), an important molecule participating in redox signaling in vivo, potentially causes TRPM2 activation. Reactive oxygen species (ROS) have been considered deleterious by-products. However, they are generated by enzymatic reactions in response to many physiologic stimuli initiated by glucose, insulin, growth factors, hormones and cytokines, thereby acting as signaling molecules to regulate many protein functions. The activation mechanism of TRPM2 by H\(_2\)O\(_2\) has been explored and the involvement of several pathways has been suggested. Indirect action mediated by ADPR production through the PARP/PARG pathway from the nucleus or from mitochondria and direct action independent of ADPR have been proposed. Moreover, TRPM2 activation is completely dependent on intracellular \(Ca^{2+}\) or \(Ca^{2+}\) entering the cytosol through the activated channel pore. Even at a high concentration (500 \(\mu\)M), ADPR fails to activate TRPM2 in the
absence of [Ca$^{2+}$]$i$. Elevation of [Ca$^{2+}$]$i$ or reduction of Ca$^{2+}$-chelating strength of intracellular solution shifts the concentration-response curve of ADPR for TRPM2 activation to the left.

**Temperature sensitivity of TRPM2**

The most characteristic feature of TRPM2 is its temperature sensitivity. We previously reported heat-evoked TRPM2 activation can be observed in intact TRPM2 heterologously expressed in HEK293T cells over a temperature range of 33°C to 34°C. However, the amplitude of heat-evoked current without any endogenous agonists was very small compared with that recorded in the presence of agonists, which was confirmed in our recent study. Because small currents suggest partial activation of the channels, we hypothesized that high temperature stimulation could cause robust channel activation even in the absence of endogenous ligands. High temperature stimulation is hard to achieve in patch-clamp recordings due to technical limitation. Therefore, we analyzed the temperature thresholds for TRPM2 activation using [Ca$^{2+}$]$i$, measurement, using a large number of cells to enhance reliability. As a result, surprisingly, very high temperature stimulation exceeding the physiologic temperature range led to activation of naive TRPM2 channels and the calculated temperature threshold was about 47°C (Fig. 2A). The result suggests that TRPM2 activity is negligible at body temperature in the absence of any factor changing temperature thresholds, such as redox signals described below.

Intracellular endogenous ligands and ROS can independently activate the TRPM2 channel as mentioned above, and, most importantly, they act on TRPM2 synergistically especially for temperature sensitivity. The heat-evoked response of TRPM2 is dramatically enhanced by low concentrations of intracellular ADPR, which fails to activate TRPM2 by itself. Intracellular cADPR treatment also potentiates TRPM2 activation by heat although the effectiveness of cADPR at room temperature is very low. Our recent work has clearly shown that redox signals and temperature act synergistically. H$_2$O$_2$-induced activation of TRPM2 is enhanced by temperature elevation. We previously reported that TRPM2 activity at body temperature is dramatically enhanced by H$_2$O$_2$ and clarified the underlying mechanism of H$_2$O$_2$ action. Although the temperature threshold for naive TRPM2 is around 47°C, H$_2$O$_2$-treatment lowers the temperature thresholds for TRPM2 activation to physiologic temperature (Fig. 2A). H$_2$O$_2$-induced changes in temperature thresholds for TRPM2 activation explain the phenomenon termed “sensitization,” that is, the temperature sensitivity of TRPM2 is enhanced by H$_2$O$_2$. Heat (40°C)-evoked responses of TRPM2 were dramatically enhanced by H$_2$O$_2$-treatment when TRPM2 was heterologously expressed, and such H$_2$O$_2$-induced enhancement was observed in peritoneal macrophages and pancreatic β-cells of wild-type (Wt) mice, but not in TRPM2 knockout (TRPM2KO) cells.

H$_2$O$_2$-induced sensitization of TRPM2 to temperature was recapitulated during inside-out single channel recording, where intracellular organelles, including the nucleus and mitochondria, do not exist (Fig. 2B). In contrast, TRPM2 sensitization in intact cells was significantly affected by PJ-34, a PARP inhibitor. These data suggested that direct action by H$_2$O$_2$ and PARP-dependent ADPR production could synergistically enhance the temperature sensitivity of TRPM2 (Fig. 2C). Inconsistency of the results obtained in inside-out single-channel recordings and whole-cell recordings could be partly explained by intracellular factors such as AMP (an ADPR metabolite that acts as an endogenous inhibitor of TRPM2) that is absent in the inside-out single channel recordings. TRPM2 sensitization by H$_2$O$_2$ showed that TRPM2 became active in vivo when the temperature thresholds were decreased down to the body temperature range by redox signals. In other words, TRPM2 activity at body temperature is regulated by cellular redox signaling. Taken together, the temperature threshold for TRPM2 activation in vivo is under the control of cellular/systemic metabolic states, including intracellular concentrations of ADPR/cADPR, [Ca$^{2+}$]$i$, and redox signaling.

Systematic studies of dose-response relations are necessary to clarify the effects of these endogenous factors on temperature thresholds for TRPM2 activation (Fig. 2C). As noted above, TRPM2 is broadly expressed in the brain, liver, spleen, pancreatic β-cells and immunocytes, where the temperature is maintained over a narrow core body temperature range. Therefore, TRPM2 activity at body temperature is thought to exert physiologic/pathological roles in such organs and cells. Involvement of TRPM2 in oxidative
stress-induced cell death has been intensely investigated\textsuperscript{23} although its relation to body temperature remains unknown.

**Physiological functions of TRPM2 at body temperature**

TRPM2 is widely expressed in immunocytes\textsuperscript{11,29-34} and its participation in immunity and inflammation has been characterized in a wide range of *in vivo* infection models and *in vitro* experiments.\textsuperscript{25} In terms of TRPM2 function at body temperature, we have proposed that TRPM2 is involved in fever-enhanced phagocytic activity of mouse peritoneal macrophages.\textsuperscript{11} Consistent with the results shown above that H\textsubscript{2}O\textsubscript{2} lowers the temperature threshold for TRPM2 activation, TRPM2 activity in the presence of a redox signal increases in a slight temperature elevation from normal body temperature (36.9°C) to febrile temperature (38.2°C). In addition, temperature elevation (37°C to 38.5°C) augmented the phagocytic activity of Wt macrophages challenged with zymosan, a TLR2 agonist that evokes NADPH oxidase activation and ROS production in phagosomes. TRPM2KO cells failed to show such temperature-dependent augmentation, indicating that TRPM2 activity at body temperature contributes to fever-enhanced phagocytic activity in macrophages. Consistent with those results, several reports have shown that TRPM2-deficiency dampens bacterial clearance in both *in vivo* and *in vitro* experiments.\textsuperscript{25}

![Figure 2](image-url)

**Figure 2.** Mechanisms of activation and modulation of TRPM2 channels. (A) H\textsubscript{2}O\textsubscript{2}-treatment lowered the temperature threshold for TRPM2 activation. The temperature-fura2 ratio relationship is plotted for H\textsubscript{2}O\textsubscript{2}-untreated and H\textsubscript{2}O\textsubscript{2}-treated (100 \textmu M, 3 min) HEK293T cells expressing mouse TRPM2. The lower column shows average temperature thresholds for each group (Mean ± SEM). (B) H\textsubscript{2}O\textsubscript{2}-enhanced heat-evoked TRPM2 single-channel openings in inside-out single-channel recordings. (a, b) Magnified traces at the time points indicated in the upper column. (C) TRPM2 integrates body temperature and intracellular endogenous ligands of TRPM2, reflecting signal input to the cell. Redox signal lowers temperature threshold for TRPM2 activation by direct and ADPR-mediated indirect actions.
TRPM2 is reportedly involved in $[\text{Ca}^{2+}]_{i}$ increases, evoking insulin secretion induced by glucose stimulation. This occurs in cooperation with the primary pathway of ATP-sensitive K$^+$ (K$_{\text{ATP}}$) channel closure and L-type voltage-gated Ca$^{2+}$ channel activation. Insulin is secreted from pancreatic islets for hypoglycaemic effects to control blood glucose levels. Downregulation or knockout of TRPM2 dampens glucose-stimulated insulin secretion. Corresponding to the result in in vitro experiments, TRPM2KO mice show attenuated insulin secretion and higher blood glucose levels in glucose tolerance tests. Because pancreatic islets are constantly at body temperature, it is reasonable that TRPM2 function is affected by body temperature changes. ROS are endogenously generated in pancreatic $\beta$-cells in response to extracellular signals such as insulin, cytokines, hormones and blood glucose elevation. Physiological oscillation of redox signals is thought to act as a signaling molecule, although unregulated ROS production causes cell death and aggravates chronic inflammation. Consistent with the notion of ROS-dependent insulin secretion, glucose-stimulated insulin secretion was attenuated by N-acetyl cysteine (NAC), an antioxidant, in Wt islets, but not in TRPM2KO islets. In addition, the NAC-sensitive fraction of insulin secretion in Wt islets was increased with temperature elevation at 33°C, 37°C and 40°C. The NAC-sensitive fraction of insulin secretion was reduced in TRPM2KO islets, suggesting that ROS and temperature-dependent upregulation of insulin secretion occurs via TRPM2 activity. Moreover, TRPM2 is reportedly involved in hormone-regulated insulin secretion. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) enhance glucose-stimulated insulin secretion from pancreatic islets. The effects of incretin are TRPM2-dependent. TRPM2 may also participate in insulin resistance in peripheral tissues because TRPM2 activation aggravates inflammation. These data suggest TRPM2 activity at body temperature could regulate physiologic functions of tissues mentioned before to affect systemic blood glucose metabolism.

The heat-evoked response of TRPM2 regulates oxytocin release from the hypothalamus in a CD38-dependent manner. Oxytocin is a peptide hormone released in response to stress condition and exerts anti-anxiety and anti-stress effects. Oxytocin release is known to be increased by fever. Extracellular application of cADPR to isolated hypothalami increased oxytocin release at febrile temperatures (38.5°C), but not at lower temperatures (35°C). The response was abolished when CD38 was downregulated in the hypothalamus. Psychological stress or intraperitoneal LPS injection increased oxytocin release in normal mice in vivo. In contrast, mice showed attenuated oxytocin release when CD38 was downregulated, even though stress or LPS-induced body temperature elevation was comparable regardless of CD38 function. Moreover, social stress upregulated TRPM2 expression in the hypothalamus and there was increased oxytocin release from the hypothalamus evoked by cADPR application. These data suggest that TRPM2 activity in temperature ranges associated with fever is involved in oxytocin release in response to stress conditions.

TRPM2 roles in body temperature regulation

Recently, 2 independent groups reported TRPM2s contribution to body temperature regulation. Song et al. revealed that TRPM2 is expressed in warmth-sensitive neurons (WSNs) in the preoptic area (POA) of the hypothalamus and behaves as a heat sensor. In a portion (16.3%) of cultured Wt POA neurons, high temperature stimulation (45°C) evoked a $[\text{Ca}^{2+}]_{i}$-increase that was inhibited by 2-aminoethoxydiphenyl borate (2-APB), a non-selective TRPM2 inhibitor. The response completely disappeared in TRPM2KO cells. Moreover, a mild heat (40°C)-evoked response in Wt POA neurons has a characteristic feature of TRPM2, sensitization by H$_2$O$_2$-treatment. POA is the thermoregulatory center and WSNs in the POA are likely monitoring changes in brain temperature to drive autonomic and behavioral thermoregulation. Neural activities of WSNs are increased by elevation of brain temperature, promoting heat loss. In contrast, a drop in brain temperature inhibited the neural activity to keep body temperature in a proper range. Fever developed by preoptic injection of prostaglandin E2 is lower in Wt mice than TRPM2KO. In addition, specific activation of TRPM2-expressing POA neurons caused a dramatic decrease in core body temperature accompanied by inhibition of locomotor activity and tail
vasodilation, suggesting the promotion of heat loss. By contrast, neural inhibition drove hyperthermia. These data suggest that TRPM2 in WSNs of the POA works as a temperature sensor to regulate neural activity to maintain body temperature (Fig. 3).

TRPM2 in somatosensory and autonomic neurons appears to mediate warmth sensing, thereby regulating body temperature. Tan et al. discovered novel heat-sensitive portions of peripheral neurons whose temperature sensitivity is not attributed to already-known thermo-TRPs expressed in sensory neurons, TRPV1 and TRPM3. Responses evoked by high temperature stimulation (47°C) were observed in 46% of DRG neurons and 58% of superior cervical ganglion neurons prepared from Wt mice, and the ratios were decreased in TRPM2KO cells to 17% and 12%, respectively. As observed in WSNs of POA neurons, heat-evoked responses in peripheral neurons were sensitized by H2O2-treatment, confirming the characteristics of TRPM2. The temperature sensitivity of sensory neurons in the skin is responsible for detecting ambient temperature, mediating autonomic/behavioral thermoregulation. A thermal preference test showed that TRPM2KO mice preferred warmer temperature in the innocuous temperature range (23~38°C) as compared with Wt, suggesting the roles of TRPM2 as a warmth sensor in skin to mediate behavioral thermoregulation (Fig. 3).

Perspective and expectation

TRPM2 is sensitive to body temperature as well as endogenous metabolites ADPR/cADPR, intracellular Ca2+ and redox states, all of which represent signal inputs to the cells. Therefore, TRPM2 could integrate the information and modulate physiologic functions in response to systemic metabolic states. Understanding the machinery of TRPM2-mediated regulation of physiologic functions could provide novel strategies to control pathological situations where metabolic states are involved.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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