Review

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Potential Role of TRPM8 in Cold-Induced Hypertension and Its Clinical Implications

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Seasonal variation in blood pressure that is higher in winter and lower in summer has been attributed to several factors that include changes in the activity of autonomic nervous system, vasopressin and expression of endothelial nitric oxide synthase (eNOS). Transient receptor potential melastatin 8 (TRPM8), a non-selective Ca^{2+}-permeable cationic channel, serves as a molecular transducer to sense cold by the somatosensory system. TRPM8 is sensitive to protein kinase C (PKC) and phosphatidyl inositol-4,5-biphosphate [PI(4,5)P_2] suggesting that TRPM8 is stimulated by phospholipase C (PLC)-coupled receptors. Activated PLC inhibits TRPM8 by reducing cellular PI(4,5)P_2 levels and by activating PKC via diacyl glycerol. Bradykinin and prostaglandin E2 (PGE2), which are pro-inflammatory molecules, reduce the responses to cold, suggesting that phospholipase A2 (PLA2), which releases polyunsaturated fatty acids (PUFAs), the precursors of various eicosanoids, from the cell membrane lipid pool can modulate the function of TRPM8. TRPM8 functions as a nociceptor and modulates immune response. These and other studies indicate that cold-induced activation of transient receptor potential melastatin 8 (TRPM8) plays a role in the pathobiology of hypertension, preeclampsia and in the regulation of inflammation and immunity.

Keywords: cold; TRPM8; phospholipase A2; polyunsaturated fatty acids; hypertension; eicosanoids

Introduction

Seasonal changes in blood pressure (higher in winter and lower in summer) can be attributed to the effect of environmental temperature on blood vessels. Exposure to cold temperature causes blood vessels to become temporarily narrow and hence, more pressure is needed to force blood through narrowed veins and arteries. In addition, several risk factors including but not limited to temperature, physical activity, air pollution, ultraviolet radiation, serum levels of cholesterol, catecholamines, and vasopressin can produce changes in blood pressure. A 1 degree C decrease in living room temperature rises of 1.3 mmHg in systolic blood pressure (SBP) and 0.6 mmHg in diastolic blood pressure (DBP) [1]. A 1 degree C decrease in the outdoor temperature rises 0.43 mmHg in SBP and 0.29 mmHg in DBP in healthy elderly [2]. Cold temperatures activate sympathetic nervous system and increase the secretion of catecholamines, which results in an increase in the heart rate and peripheral vascular resistance [3]. Alterations in the expression of endothelial nitric oxide synthase (eNOS) are yet another mechanism involved in the relationship between temperature and vascular diameter [4,5]. It is likely that cold temperature impairs eNOS expression while elevated core or environmental temperature increases eNOS. In addition, cold exposure activates the pro-inflammatory transcription factor nuclear factor κB (NF-κB) [6]. These results emphasize the influence of environmental temperatures on the vascular endothelial biology.

Vasopressin, norepinephrine, epinephrine, angiotensin-II, aldosterone, catecholamines and endothelin-1 are also known to have a role in seasonal variation in blood pressure. Cold temperatures increase mean plasma norepinephrine, urinary excretion of catecholamines and sodium [7]. Some studies reported an increase in plasma aldosterone from summer to winter. This is in addition to an increase in plasma norepinephrine, epinephrine, and plasma renin activity. Of all the hormones studied, norepinephrine seems to be the more consistently associated with elevation in blood pressure in response to cold [8].

Seasonal Variation in Endothelial Dysfunction

Endothelial dysfunction resulting in reduced nitric oxide (NO) bioavailability and oxidative stress can occur due to seasonal variations in temperature that can alter arterial diameter [9–12]. Oxidative stress reduces the function of renal dopamine receptors that results in sodium retention and increase in blood pressure [13].

It was shown that Intermittent cold-stress stimulation produces maternal hypertension, renal and placental lesions, with adverse events in their offspring [14]. This led to the suggestion that events seen in pregnant mice are somewhat like features of pre-eclampsia. This implies that cold-stress induced hypertension could be employed to investigate pathobiology of pregnancy-induced hypertension. Cold-induced hypertension produced an increase in plasma angiotensin-II levels in the pregnant mice and their kidneys showed lesions suggestive of glomerulonephritis and placental lesions that resulted in intra-uterine growth retardation (IUGR).

Cold thermosphere neurons express a wide variety of ion channels. The nonselective Ca^{2+}-permeable cationic channel transient receptor potential melastatin 8 (TRPM8) is the main molecular transducer responsible for sensing cold in the somatosensory system. TRPM8, a calcium-permeable cation channel, is activated by cold, cooling compounds and voltage. TRPM8 detects cold temperatures in the somatosensory system. Hence, in the current review, the role of TRPM8 in cold-induced hypertension, preeclampsia and in the regulation of inflammation and immunity are discussed.

TRPM8 is the Cold-Thermoreceptor

TRPM8 is activated by membrane depolarization, cold, menthol, and inflammatory agents. For its action, TRPM8 needs phosphatidy linositol-4,5-biphosphate [$PI(4,5)P_2$] [15]. TRPM8 is expressed in trigeminal and dorsal root ganglion neurons, and in the geniculate ganglia. TRPM8 is present in several tissues including but not limited to prostate, genitourinary tract, lung, liver, vascular smooth muscle, bladder, sperm, and odontoblasts, and in some tumors. TRPM8 co-localizes with peripherin and intermediate filaments NF200. In a subset of somatosensory neurons, TRPM8 is co-expressed with nociceptor markers, such as transient receptor potential vanilloid subfamily member 1 (TRPV1) channels, calcitonin gene-related peptide (CGRP), and substance P. It has been shown that lack of functional expression of TRPM8 ion channels compromises cold sensitivity.

Activation of TRPM8 is dependent on extracellular Ca^{2+}, and $PI(4,5)P_2$. Ca^{2+} influx through TRPM8 activates Ca^{2+}-dependent phospholipase C that results in a reduction of $PI(4,5)P_2$ levels and channel desensitization. TRPM8 desensitization may also due to activation of Ca^{2+}-dependent protein kinase C (PKC), which causes dephosphorylation of TRPM8 via protein phosphatase 1 that leads to downregulation of the channel. These results imply that the sensitivity of TRPM8 to various stimuli is regulated by PKC and $PI(4,5)P_2$ suggesting that TRPM8 stimulation is dependent on phospholipase C (PLC)-coupled receptors. Thus, activation of PLC inhibits TRPM8 channel by reducing cellular $PI(4,5)P_2$ levels and by a diacyl glycerol-induced activation of PKC.

Pro-inflammatory bradykinin and prostaglandin E2 (PGE2) reduce the response to cold. Phospholipase A2 (PLA2) modulation of RPM8 function can be attributed to its ability to induce the release of polyunsaturated fatty acids (PUFAs) and formation of lysophospholipids that in turn modulate the channel TRPM8 function in diametrically opposite directions. Sensory neurons expressed G_i-coupled α2A-adrenoreceptor (α2A-AR) when stimulated reduce the TRPM8 channel activity as a result of phosphorylation that is dependent on PKA. TRPM8 and trkA are coexpressed wherein trkA is the high-affinity tyrosine kinase receptor for nerve growth factor (NGF). NGF upregulates the TRPM8 channel function in cultured dorsal root ganglion DRG neurons. These results emphasize the fact that several regulatory mechanisms operate to fine tune the function of TRPM8 channel. In this context the involvement of PGE2 and PUFAs in the regulation of TRPM8 channel is of particular interest since PGE2 has pro-inflammatory, pyrexia-inducing, and immunomodulatory actions.

In addition to TRPM8, there is a role for other channels in sensing cold. Trigeminal or dorsal root ganglions when exposed to cold results not only the opening of TRPM8 channels, but also alter the activity of K^+ channels of the two-pore domain family, TWIK—related K+ channel 1 (TREK1) and/or TRAAK by decreasing their activity, which enables animals to perceive the sensations of cold and warm temperatures [16,17]. Hyperpolarization-activated and cyclic nucleotide-gated channel 1 (HCN1) is another channel that provides a hyperpolarization-activated and cyclic nucleotide-modulated current in cold-sensitive neurons [18–20]. In addition, cold inactivates sodium channels to prevent the generation of action potentials. Despite these evidences and advances in understanding the function of various ion channels, together with TRPM8, it is not yet clear as to how they orchestrated animals and humans to perceive the phenomenon of cold transduction.

TRPM8, TRPV Channels, Nociceptor Function and Immunosurveillance

TRPM8 channels serve as thermostat molecules in the cutaneous nerve endings and induce nerve impulses to convey the messages to the brain to activate the target neurons meant for “cold in the skin” and initiate heat-seeking behaviors [21,22]. With the fall in skin temperature below a set-point, the nerve endings generate thermostat molecules that alter the nerve impulses such that the impulses are conveyed to the brain to activate the target neurons [23]. Studies with menthol- and capsaicin-responsive dorsal root ganglion neurons in culture, revealed that up to 50% of TRPM8-expressing neurons also express TRPV1, suggesting that these neurons are polymodal nociceptors [24,25]. Thus, TRPM8 can function as a nociceptor.

Immune response can be modified by activating TRPM8 ion channel. Pronounced changes in immune

parameters for the spleen cells and immunoglobulin levels have been reported following activation of TRPM8. Skin is rich in temperature-sensitive TRP ion channels including TRPM8, implying that cooling modulates immune response. TRPM8 activation induces T cell activation and differentiation into effector cells and suggests that TRPM8 is utilized to mount an effective immune response [26]. TRPM8 activation can induce renin-angiotensin-aldosterone system (RAAS)-mediated hypertension and immunosuppression. This TRPM8-induced immunosuppression is like immunosuppressive treatments of intravenous immunoglobulin (IVIg) against various inflammatory diseases. Treatment with antihypertensive drugs aliskiren and losartan can ameliorate cold-induced immunosuppression, indicating the involvement of the RAAS and hypertension [27]. These results are in contrast with the results [5] that intermittent cold-stress stimulation induces maternal hypertension, renal and placental lesions, body weight and placenta reduction in their offspring and lower plasma angiotensin-II levels. It is likely that animals exposed to cold-stress stimulation have an increased NO production that can suppress angiotensin-II production. Previously, we showed that NO suppresses angiotensin converting enzyme (ACE) activity to restore blood pressure to normal [28]. Hence, it will be interesting to study the plasma NO levels in those who had cold-stressed hypertension during pregnancy to know whether NO deficiency accounts for hypertension. Since aliskiren and losartan reversed high plasma Ig levels and ameliorated cold-induced immunosuppression [27], it will be interesting to know whether aliskiren and losartan can ameliorate cold-induced immunosuppression.

Malignant hypertension produces striking “onion skin” changes in the renal arteriole that is associated with infiltration of mononuclear inflammatory cells. Several studies have shown that inflammatory events participate in the pathobiology of hypertension as evidenced by the observation that many anti-inflammatory and/or immunoregulatory drugs (especially nonsteroidal anti-inflammatory drugs and cyclosporine) can induce the development of hypertension. Adaptive immune response, and in particular, lymphocytes, seem to have a role in the pathobiology of hypertension and vascular diseases [29]. This is supported by the observation that inflammation and immune activation are involved in the pathobiology of endothelial dysfunction, hypertension, and pre-eclampsia [29–31]. Preeclampsia is characterized by hypertension, fluid retention, peripheral edema and headache and in some instances convulsions and is responsible for IUGR of the fetus. In preeclampsia, placental abnormalities could be due to endothelial dysfunction and abnormalities in the plasma levels of NO, vascular endothelial growth factor (VEGF), placental growth factor (PlGF), soluble fms-like tyrosine kinase [sFlt1, also known as soluble vascular endothelial growth factor receptor 1 (sVEGFR1)] [30]. The IUGR manifestations reported [5] in addition to the presence of hypertension in the cold stress stimulated mice with pregnancy is reminiscent of some of the features of preeclampsia. Hence, it is likely that some of the abnormalities reported in preeclampsia such as NO, VEGF, PlGF, sFlt1 may also be present in this model.

Enzymes cyclo-oxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are the major pro-inflammatory pathways that have a significant role in many diseases including endothelial dysfunction, insulin resistance, hypertension, type 2 diabetes mellitus, coronary heart disease, obesity, and preeclampsia [30]. It is noteworthy that iNOS binds to COX-2 and S-nitrosylates it to enhance COX-2 catalytic activity. This implies that a synergistic molecular interaction exists between these two inflammatory systems [32] that lend further support to the perceived role of COX-2-NOS system in the pathobiology of hypertension, preeclampsia, and other diseases [30]. This is further supported by the observation that endothelial dysfunction is common in the coronary microcirculation of those with hypercholesterolemia and salt-sensitive hypertension seen in Dahl/Rapp rats that can be corrected by L-arginine, the precursor of NO [33,34]. In view of these observations it is a promising approach to consider correcting the COX-2-NOS abnormalities in the prevention and management of hypertension, coronary heart disease, and preeclampsia.

The fact that TRPM8+ mucosal fibers express CGRP in human and mouse colon [35] and TRPM8 neurons have nociceptor function is interesting. CGRP directly increases exhaustion of cytotoxic $CD8^{+}$T cells and leads to an increase in tumor growth, whereas reducing the release of CGRP from tumor innervating nociceptors could enhance anti-tumor immunity [36] adding yet another layer of evidence to the role of TRPM8 in the regulation of immune response and their putative role in several diseases including but not limited to hypertension and cold response.

Bioactive Lipids in Cold-Induced Brown Adipose Tissue Beneficial Actions

Exposure to cold resolves obesity-induced inflammation and improves insulin sensitivity and glucose tolerance in diet-induced obese mice by browning of the adipose tissue that is in part, due to the secretion of maresin 2, a potent anti-inflammatory molecule derived from docosahexaenoic acid (DHA). Many human studies showed that exposure to mildly cold temperatures (50 to 55 °F) is sufficient to activate brown adipose tissue and improve insulin sensitivity [37–39]. Brown adipose tissue dysfunction occurs with aging and obesity and has been related to chronic unresolved inflammation. In animal studies, lipoxins and protectins were significantly lower in aged and diet-induced obese mice compared to control young mice. The most significantly reduced bioactive lipids were lipoxin B4 (LXB4, derived from arachidonic acid), maresin 2 (MaR2), protectin

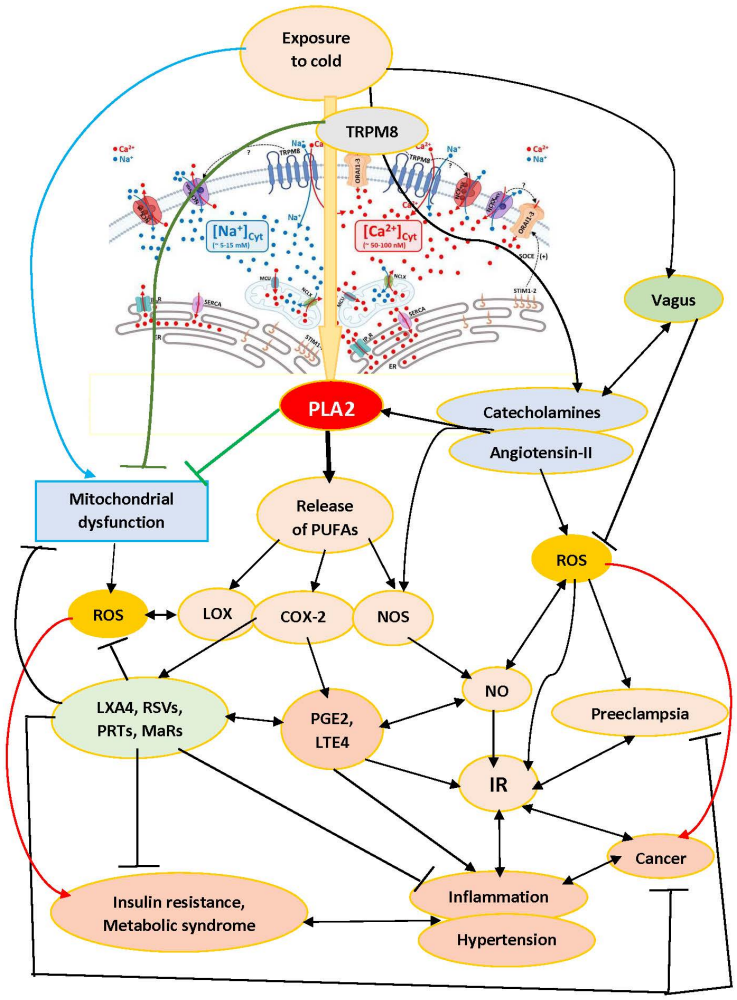

Fig. 1. Scheme showing potential relationship among various downstream events that can occur on exposure to cold and activation of TRPM8 channel. For details see text. TRPM8, Transient receptor potential melastatin 8; PLA2, phospholipase A2; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; LOX, lipoxygenase; COX-2, cyclo-oxygenase-2; NOS, nitric oxide synthase; NO, nitric oxide; LXA4, lipoxin A4; RSVs, resolvins; PRTs, protectins; MaRs, maresins; PGE2, prostaglandin E2; IR = immune response; LTE4 = Leukotriene E4.

DX (PDX, derived from DHA) and resolvin D 6 (RvD6, derived from DHA6). It is noteworthy that despite feeding with DHA, the animals were not able to counteract the impaired cold exposure response in brown adipose tissue of obese-aged mice suggesting a defect in the production of these useful bioactive lipids. These results imply that a defect in the production of lipoxins, resolvins, protectins and maresins may underlie the impaired response of adipose tissue to cold [40]. It is not known whether these bioactive lipids have any influence on the expression and actions of TRPM8 and TRPV channels and their nociceptive function. Previously, we reported that lipoxin A4 (LXA4), resolvins, and PDX can prevent chemical-induced type 1 and type 2 diabetes mellitus in experimental animals, improve insulin resistance and suppress inflammation [41–44]. These results [37–44] suggest that depending on the degree of cold temperatures to which the body is exposed there could be both beneficial and harmful effects.

Conclusions and Potential Therapeutic Implications

On exposure to cold, TRPM8 is activated, which activates, in turn, phospholipase A2 (PLA2). It (PLA2) induces the release of various PUFAs from the cell membrane lipid pool. Exposure to cold can also influence the autonomic nervous system. Catecholamines and angiotensin-II, which are released in increased amounts because of exposure to cold, activate PLA2 and induce the release of PUFAs. Activation of the sympathetic nervous system in response to cold results in vagal activation that has a negative influence on sympathetic activation. Catecholamines and angiotensin-II have pro-inflammatory action and produce vasoconstriction that causes an increase in blood pressure. In contrast, vagal activation and release of acetylcholine have a dampening action on inflammation and reduce blood pressure. Thus, maintaining a balance between sympathetic and parasympathetic arms of the autonomic nervous system is essential to maintain normal homeostasis and regulate blood pressure. PLA2 induced release of PUFAs {such as arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)} form the precursors to various pro- and anti-inflammatory eicosanoids. AA, EPA, and DHA are acted upon by cyclo-oxygenase (COX) and lipoxygenase (LOX) enzymes to form various eicosanoids. AA is the precursor of prostaglandin E2 (PGE2), a pro-inflammatory, vasodilator and platelet aggregator molecule. AA is also the precursor of lipoxin A4 (LXA4), a vasodilator, anti-inflammatory and platelet anti-aggregator molecule. Under some very specific conditions, PGE2 enhances the production of LXA4 and thus, triggers the initiation of inflammation resolution process. Thus, the balance between PGE2 and LXA4, both derived from AA, is necessary for maintaining homeostasis and regulating inflammation. EPA is the precursor of prostaglandins (PGs) of 3 series and leukotrienes (LTs) that are pro-inflammatory in nature but less potent compared to those derived from AA. EPA is also the precursor of resolvins (RSVs) of E series that are anti-inflammatory in nature. DHA does not give rise to any PGs or LTs but is the precursor of potent anti-inflammatory molecules resolvins of D series, protectins (PRTs) and maresins (MaRs). Thus, outcome of activation of PLA2 by TRPM8, angiotensin-II and catecholamines depends on the type of PUFAs released and the balance between pro- and anti-inflammatory metabolites formed from them. PUFAs, LXA4, RSVs, PRTs, MaRs induce the formation of NO and suppress or enhance reactive oxygen species (ROS) generation depending on the local conditions. There is evidence to suggest that PUFAs, eicosanoids, catecholamines, acetylcholine and NO interact among themselves to regulate inflammation vascular tone, blood pressure and immune response [45]. Cold exposure causes mitochondrial dysfunction that is abrogated by TRPM8 activation, PUFAS and some of their metabolites. All these molecules may also participate in oncogenesis and its regulation (Fig. 1) [46]. Microsoft Office-2016 (Microsoft, Redmond, WAS, USA) were the software used in the preparation of Fig. 1.

In view of the preceding discussion, it is imperative that more detailed studies are needed to investigate the role of cold-induced hypertension and its potential benefits in metabolism and the role of TRPM8 in inflammation and immunity and its potential relationship to bioactive lipids and their role in various diseases. This is supported by the observation that TRPM8 activation antagonizes angiotensin II induced mitochondrial respiratory dysfunction and suppresses inappropriate ROS generation by preserving pyruvate dehydrogenase activity. Furthermore, long-term noxious cold stimulation and angiotensin-induced vasoconstriction and increase in blood pressure were inhibited by TRPM8 stimulation by dietary menthol by attenuating excessive mitochondrial reactive oxygen species generation [47]. These results suggest that TRPM8 stimulation preserves mitochondrial function. In this context, it is noteworthy that PUFAs (which are released by the activation of TRPM8 by virtue of its action on PLA2) and their (PUFAs) anti-inflammatory metabolites suppress mitochondrial dysfunction [48–51]. Based on the evidence presented here, it is evident that TRPM8 could be a potential target in the prevention and management of hypertension, preeclampsia, and metabolic syndrome.

Availability of Data and Materials

All the data is provided in the review.

Author Contributions

UND is the sole contributor. UND conceptualized, drafted and revised the content of the review. The final manuscript was read by the author and approved for publication. The author accepts responsibility for every aspect of it.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest. The author is the founder of UND Life Sciences.

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