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Transient Receptor Potential Channel Signaling in Hypertension: Mechanisms, Translation, and Therapeutic Targeting

Hipertansiyonda Geçici Reseptör Potansiyel Kanal Sinyal İletimi: Mekanizmalar, Translasyon ve Terapötik Hedefler

ABSTRACT

Arterial hypertension (HT) is a major risk factor in the pathogenesis of cardiovascular diseases and has a high prevalence. The pathogenesis of primary HT, which accounts for the majority of HT cases, has not been fully elucidated; therefore, effective treatment targets remain an important area of research. Transient receptor potential (TRP) channels represent a distinct class of cation channels that play a pivotal role in signal transduction by altering membrane potential or intracellular Ca^{2+} concentration. Based on sequence similarity, TRP channels are classified into six subfamilies: TRP canonical (TRPC), TRP melastatin (TRPM), TRP vanilloid (TRPV), TRP mucolipin (TRPML), TRP ankyrin (TRPA), and TRP polycystin (TRPP). These channels exhibit broad expression across diverse tissues and cell types and play critical roles in numerous pathophysiological processes through the regulation of ion concentrations (Ca^{2+}, Mg^{2+}, Na^{+}, and K^{+}) and the modulation of intracellular signal transduction pathways. Research involving human subjects, as well as experimental models, highlights the essential role of TRP channels in maintaining vascular homeostasis and regulating blood pressure. TRP channels, particularly TRPCs, have gained increasing attention for their role in resistant HT, a condition in which blood pressure remains uncontrolled despite the use of multiple antihypertensive drugs. Additionally, these channels have been identified as central mediators of inflammation and oxidative stress, processes that are pivotal in the pathogenesis of cardiovascular disorders, including HT. This review summarizes current evidence on TRPC, TRPV, and TRPM channels in HT, highlighting emerging translational findings and potential therapeutic implications.

Keywords: Blood pressure, hypertension, nitric oxide, transient receptor potential channels, vascular smooth muscle

ÖZET

Arteriyel hipertansiyon (HT), kardiyovasküler hastalıkların patogenezinde önemli bir risk faktörüdür ve yüksek prevalansa sahiptir. Hipertansiyon vakalarının çoğunu oluşturan primer HT'nin patogenezi tam olarak aydınlatılamamıştır; bu nedenle, etkili tedavi hedefleri hala önemli bir araştırma alanıdır. Geçici reseptör potansiyel (TRP) kanalları, membran potansiyelini veya hücre içi Ca^{2+} konsantrasyonunu değiştirerek sinyal iletiminde kritik bir rol oynayan belirgin bir katyon kanal sınıfını temsil eder. Dizi benzerliğine dayalı olarak, TRP kanalları altı alt aileye ayrılır: TRP kanonik (TRPC), TRP melastatin (TRPM), TRP vanilloid (TRPV), TRP mukolipin (TRPML), TRP ankirin (TRPA) ve TRP polikistitin (TRPP). Bu kanallar, çeşitli dokularda ve hücre tiplerinde yaygın bir şekilde ifade edilir ve iyon konsantrasyonlarını (Ca^{2+}, Mg^{2+}, Na^{+} ve K^{+}) düzenleyerek ve hücre içi sinyal iletim yollarını modüle ederek birçok patofizyolojik süreçte kritik roller oynar. İnsan denekleri ile yapılan araştırmalar ve deneysel modeller, TRP kanallarının vasküler homeostazın korunmasında ve kan basıncının düzenlenmesinde önemli bir rol oynadığını vurgulamaktadır. TRP kanalları, özellikle TRPC'ler, kan basıncının birden fazla antihipertansif ilaç kullanılmasına rağmen kontrol altına alınamadığı dirençli HT'deki rolleri nedeniyle giderek daha fazla ilgi görmektedir. Ayrıca, bu kanallar, HT dahil kardiyovasküler bozuklukların patogenezinde önemli bir rol oynayan inflamasyon ve oksidatif stresin merkezi aracısı olarak tanımlanmıştır. Bu derleme, HT'deki TRPC, TRPV ve TRPM kanalları ile ilgili mevcut kanıtları özetlemekte, ortaya çıkan çeviri bulguları ve potansiyel terapötik çıkarımları vurgulamaktadır.

Anahtar Kelimeler: Kan basıncı, hipertansiyon, nitrik oksit, geçici reseptör potansiyel kanalları, vasküler düz kas

REVIEW
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Hypertension (HT) is a clinical condition characterized by chronically elevated blood pressure in the systemic arteries and is considered a critical risk factor for cardiovascular and cerebrovascular diseases.[1] Approximately 1.4 billion adults worldwide (aged 30–79 years) have arterial HT, and more than 73% of these patients do not have controlled blood pressure.[2] Chronic high blood pressure increases morbidity and mortality because it leads to serious complications, such as left ventricular hypertrophy, congestive heart failure, stroke, myocardial infarction, and chronic kidney disease; furthermore, it imposes a significant burden on healthcare systems and the global economy.[3]

The development of HT can be influenced by anatomic, genetic, endocrine, humoral, hemodynamic, environmental, and neural factors.[1] Although primary HT accounts for the majority of cases, treatment failure is a significant challenge because its pathogenesis has not yet been fully elucidated. Understanding the pathogenesis of primary HT is essential for identifying novel therapeutic targets. Numerous studies have underscored the role of ion channels in the pathogenesis of vascular disorders.[4] Ion channels frequently studied in HT include voltage-dependent Ca^{2+} channels, Ca^{2+}-activated K^+ (KCa) channels, voltage-sensitive K^+ channels, and transient receptor potential (TRP) channels.[4,5]

Transient receptor potential channels are cation channels that contribute significantly to signal transduction by modulating membrane potential or intracellular Ca^{2+} concentration. In humans, a total of 28 TRP channels have been characterized and classified into six distinct families according to sequence similarity: TRP canonical (TRPC), TRP melastatin (TRPM), TRP vanilloid (TRPV), TRP ankyrin (TRPA), TRP mucolipin (TRPML), and TRP polycystin (TRPP).[5] These channels are broadly distributed across human tissues, including the brain, kidneys, heart, and lungs.[6]

Transient receptor potential channels are integral to a wide array of physiological and pathological processes, including cell biology, migration, proliferation, carcinogenesis, immunological responses, tissue homeostasis, sensory transduction, and electrolyte homeostasis. These processes occur in response to a variety of extracellular and intracellular stimuli, including alterations in temperature, changes in pH or osmolarity, depletion of intracellular Ca^{2+} stores, and exposure to volatile chemicals and cytokines.[5-7]

Transient receptor potential channels are expressed in various tissues, such as the brain, kidney, heart, lung, and vascular tissue.[6] In vascular tissue, TRP channels are expressed in endothelial cells, vascular smooth muscle (VSM) cells, perivascular sensory neurons, and perivascular adipose tissue, where they play important roles in regulating cell proliferation, angiogenesis, permeability, and vascular tone.[5] Studies investigating the involvement of TRP channels in blood pressure regulation have indicated that alterations in their expression and function may contribute to vascular dysfunction and HT.[5,7] This review examines the roles of TRPC, TRPV, and TRPM channels in HT.

Hypertension and Transient Receptor Potential Channels

Hypertension is defined by a sustained elevation in vascular tone. The predominant pathological manifestation of this condition is vascular remodeling, characterized by increased medial thickness resulting from hyperplastic and/or hypertrophic changes in VSM cells.[5] Hypertensive vasculopathy can be explained by alterations in cytosolic Ca^{2+} handling and increased intracellular Ca^{2+} concentration, impaired nitric oxide (NO) bioavailability in endothelial cells, and the release of vasoactive agonists that influence Ca^{2+} signaling in VSM cells.[8] Some isoforms, such as TRPC3 and TRPC5, play a role in HT pathogenesis by contributing to vascular remodeling and vasoconstriction through their effects on intracellular Ca^{2+} concentration and VSM cell proliferation.[5] These isoforms are associated with abnormal Ca^{2+} utilization and vascular dysfunction related to HT and other cardiovascular diseases.[9,10] In contrast, some TRP isoforms, such as TRPV1 and TRPV4, exert protective effects against HT by contributing to endothelium-mediated vasodilation (Figure 1). Decreased expression and dysfunction of these channels have been observed in HT.[11,12]

Transient Receptor Potential Canonical Channels

In vascular tissue, TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7 are expressed in VSM and endothelial cells. These channels play important roles in receptor-operated Ca^{2+} entry, store-operated Ca^{2+} entry, angiogenesis, regulation of vascular permeability, and vascular tone.[5,6]

TRPC1, a member of the TRP channel family, is primarily localized in VSM and endothelial cells and is involved in VSM contraction, proliferation, migration, and endothelium-mediated vasodilation.[6] Recent studies have demonstrated that VSM-specific TRPC1 deletion significantly mitigates angiotensin II–induced HT and cardiovascular remodeling.[13] Furthermore, endothelial TRPC1 deficiency has been shown to promote aortic hypercontractility and exacerbate hypertensive responses.[14]

The TRPC3 channel is expressed in VSM cells in various vascular beds (such as the coronary, pulmonary, renal, and cerebral arteries) as well as in the aorta. It contributes to the regulation of vascular tone though activation of G-protein-coupled receptors, including angiotensin II (Ang II) and endothelin-1 receptors.[6] The expression of TRPC3 is elevated in monocytes from spontaneously hypertensive rats (SHRs) and in patients with primary HT, and this increase correlates with elevated levels of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1 (IL-1).[10-15] This finding suggests that TRPC3-mediated calcium influx in monocytes may activate specific intracellular signaling cascades (e.g., nuclear factor of activated T cells [NFAT] and mitogen-activated protein

ABBREVIATIONS

Ang II	Angiotensin II
EnaCs	Epithelial sodium channels
HT	Hypertension
IL	Interleukin
KCa	Calcium-activated potassium channel
NO	Nitric oxide
SHR	Spontaneously hypertensive rat
TRP	Transient receptor potential
TRPA	Transient receptor ankyrin
TRPC	Transient receptor canonical
TRPM	Transient receptor melastatin
TRPML	Transient receptor mucolipin
TRPP	Transient receptor polycystin
TRPV	Transient receptor vanilloid
VSM	Vascular smooth muscle

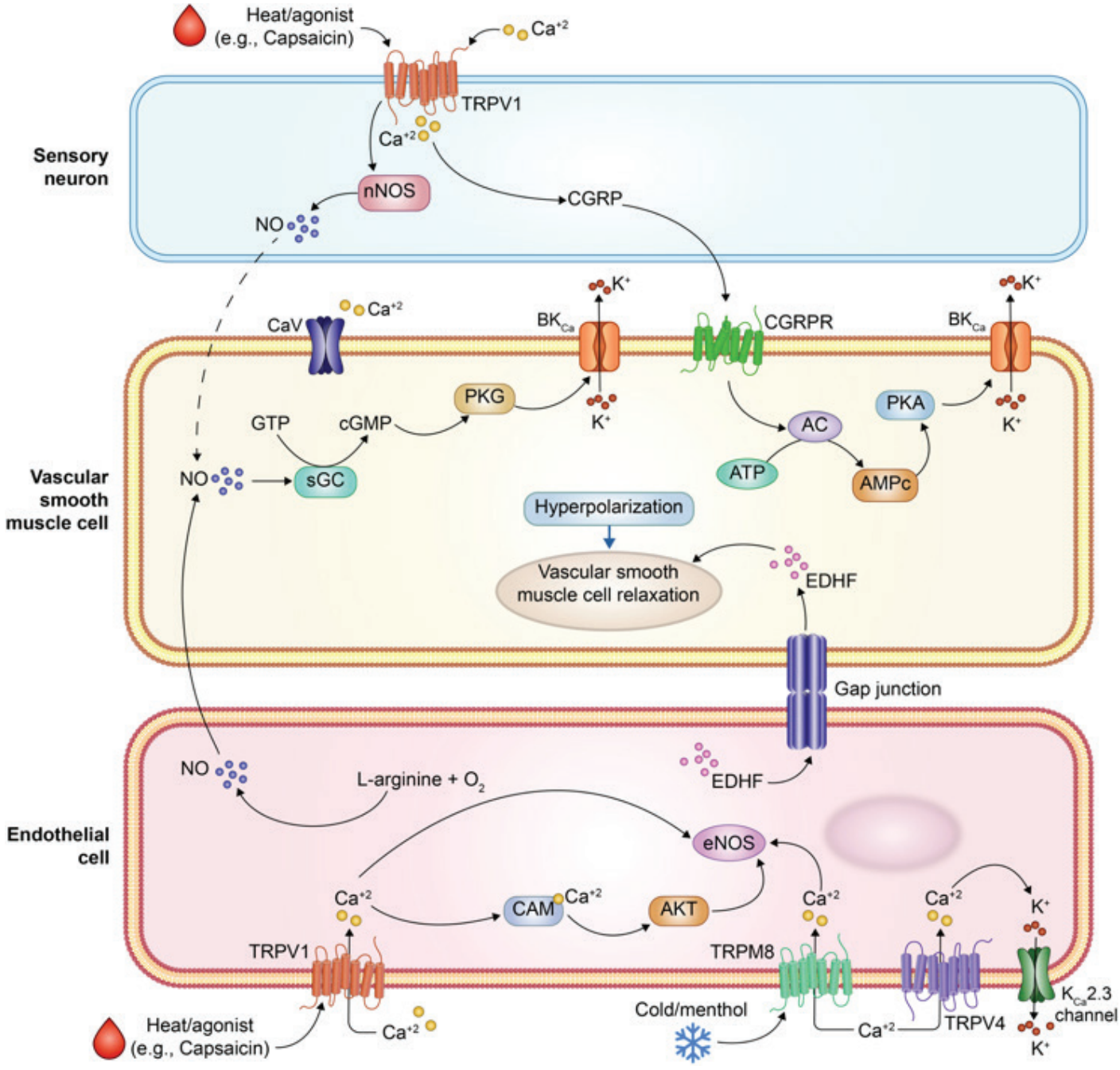


Figure 1. Signal transduction mechanisms of transient receptor potential vanilloid 1 (TRPV1), transient receptor potential vanilloid 4 (TRPV4), and transient receptor potential melastatin 8 (TRPM8) channels in vascular tissue.

AC, Adenylate cyclase; AKT, Protein kinase B; ATP, Adenosine triphosphate; BKCa, Large-conductance Ca^{2+}-activated K^+ channel; CaM, Calmodulin; cAMP, Cyclic adenosine monophosphate; Cav, Voltage-activated Ca^{2+} channel; CGRP, Calcitonin gene-related peptide; CGRPR, Calcitonin gene-related peptide receptor; cGMP, Cyclic guanosine monophosphate; EDHF, Endothelium-derived hyperpolarization factor; eNOS, Endothelial nitric oxide synthase; GTP, Guanosine triphosphate; KCa2.3, Small-conductance Ca^{2+}-activated K^+ channel 2.3; nNOS, Neuronal nitric oxide synthase; PKA, Protein kinase A; PKG, Protein kinase G; sGC, Soluble guanylate cyclase (Adapted from reference 7).

kinase [MAPK] pathways) that drive the transcription and release of these cytokines, thereby contributing to vascular inflammation and the pathogenesis of HT. In monocytes from patients with primary HT, the expression of TRPC3 and TRPC5 is increased, while store-operated Ca^{2+} entry facilitated by these channels, as well as cation influx triggered by 1-oleoyl-2-acetyl-sn-glycerol, are also enhanced. Consequently, enhanced activation of monocytes via TRPC channels may contribute to the pathogenesis of HT.[9] In a separate study, increased monocyte migration in patients with HT was correlated with elevated TRPC3 expression.[16] Additionally, a positive correlation between high salt intake, systolic blood pressure, and TRPC3 expression has been identified in patients with HT.[17]

The TRPC6 channel is permeable to cations, including Ca^{2+}, Na^{+}, and Mg^{2+}, and plays a significant role in both physiological and pathophysiological processes in vascular tissue.[6] Research using animal and cell culture models has demonstrated that TRPC6 channel plays a significant role in essential vascular processes, such as VSM responses to changes in arterial blood pressure, known as the Bayliss effect, and endothelium-mediated vasodilation.[18] TRPC1 and TRPC6 channels together contribute to increases in medial thickness, medial area, lumen diameter, collagen accumulation, and medial VSM hyperplasia, which are indicators of arterial remodeling associated with aging and elevated systolic blood pressure.[19] Additionally, heteromultimeric structures of TRPC3 and TRPC6 are altered in HT, thereby enhancing depolarization of VSM cells.[20] Elucidating the specific roles of TRPC3 and TRPC6 in the pathogenesis of HT presents significant challenges, as these channels are integral components of complex and compensatory networks involving multiple TRP subtypes and ion channels.[6]

Transient Receptor Potential Vanilloid Channels

TRPV1, TRPV2, TRPV3, and TRPV4 channels are expressed in vascular tissue and mediate functions such as mechanosensitive Ca^{2+} entry, vasoconstriction, vasodilation, angiogenesis, and permeability.[5,6]

Research examining the association between the TRPV1 channel, which is integral to the regulation of vascular tone and arterial blood pressure, and HT has demonstrated that deletion of the TRPV1 gene in rats results in increased blood pressure, enhanced salt sensitivity, exacerbation of salt-induced HT, and elevated renal inflammatory responses and kidney damage.[21,22] In salt-induced HT models, TRPV1 gene expression is reduced in the mesenteric arteries of rats.[22] Reduced TRPV1 mRNA expression has also been detected in aortic tissue from patients with HT.[12]

Studies examining the relationship between TRPV1 gene polymorphisms and HT have shown that these polymorphisms correlate with elevated systolic and diastolic blood pressure in a Mexican population. Similarly, in a population in Iran, these polymorphisms have been associated with increased salt consumption and a higher risk of HT.[23,24] Moreover, TRPV1 gene polymorphisms have been linked to salt sensitivity, salt intake, and the risk of HT.[25]

Furthermore, the TRPV1 channel plays a crucial role in regulating salt-induced HT in mice, functioning in conjunction with epithelial sodium channels (ENaCs), which are essential for renal sodium reabsorption and systemic blood pressure regulation.[26] Prolonged activation of TRPV1 by capsaicin may inhibit ENaC activity and exert a protective effect against salt-induced HT by reducing ENaC-mediated Na^{+} reabsorption.[7] In Dahl salt-sensitive rats fed a high-salt diet, increased susceptibility to HT has been attributed, in part, to reduced involvement of the TRPV1 pathway.[7]

The TRPV4 channel is involved in processes such as vasodilation and vasoconstriction, vascular permeability, vascular remodeling, and vascular injury.[6] Studies examining the relationship between TRPV4 expression alterations and dysfunction in the pathogenesis of HT has shown that both the expression and function of TRPV4 are reduced in the mesenteric artery tissue of SHRs and in the cerebral parenchymal arterioles of mice with Ang II-induced HT.[27,28] Additionally, TRPV4 mRNA expression is decreased in the aortic tissue of patients with HT.[12] Conversely, some studies have reported increased TRPV4 expression and function in the mesenteric arteries of rats with salt-induced HT. However, in the aortic tissue of mice with salt-induced HT, TRPV4 expression remains unchanged, whereas TRPV4-mediated vasoconstriction is enhanced.[29]

Studies investigating the role of TRPV4 channel in obesity-related HT have reported increased TRPV4 expression in VSM cells of the mesenteric arteries in obese mice. These findings suggest that TRPV4 channels in VSM cells may contribute to the development of vasoconstriction and HT, whereas endothelial TRPV4 dysfunction may also play a role in obesity-induced HT.[30,31]

The TRPV4 channel physically and functionally interacts with KCa2.3 (Figure 1).[32] This interaction is crucial for the response mediated by the endothelium-derived hyperpolarizing factor, which significantly contributes to vasodilation, blood flow, and the regulation of blood pressure in resistance arteries. Decreased expression of the TRPV4 channel and reduced TRPV4–KCa2.3 interaction in endothelial cells may lead to endothelial dysfunction and HT.[32,33] Additionally, when the endothelial TRPV4 channel is activated, Ca^{2+} influx induces Ca^{2+}-mediated activation of endothelial NO synthase and subsequent NO production.[33] Consequently, the TRPV4 channel may serve as a potential therapeutic target in the management of HT.[7]

Transient Receptor Potential Melastatins

TRPM2, TRPM4, TRPM6, TRPM7, and TRPM8 channels are expressed in vascular tissue and play integral roles in the regulation of vascular tone, endothelial permeability, and angiogenesis.[6]

TRPM channels, especially TRPM6, TRPM7, and TRPM8, have significant roles in HT, and alterations in TRPM channel activity have been associated with multiple forms of HT.[34] In the VSM cells of the mesenteric arteries of SHRs, TRPM7 expression and intracellular Mg^{2+} concentration are reduced.[35] Disrupted Mg^{2+} regulation, linked to altered TRPM7 activity, may contribute to inflammatory responses, cellular proliferation, and vascular remodeling associated with HT.[36]

TRPM8 is a polymodal, Ca^{2+}-permeable, nonselective cation channel primarily recognized as the physiological sensor for environmental cold. Furthermore, activation of TRPM8 influences vascular function and blood pressure regulation.[7] A genome-wide association study conducted in China identified a significant correlation between TRPM8 polymorphisms and susceptibility to HT development.[37] In a study using a renovascular HT model, the TRPM8 expression level in the aortic tissues of hypertensive rats was lower than that in the aortic tissues of rats in the control group, and exogenous Ang II administration reduced TRPM8 gene expression levels in cultured rat VSM cells.[38] In another study, TRPM8 gene expression in the hypothalamic tissue of rats with hereditary stress-induced arterial HT was lower than that in the hypothalamic tissue of normotensive rats.[39] Additionally, the TRPM8 gene expression level in the aortic tissue of patients with HT was lower than that in the ascending aortic tissue of individuals in the normotensive control group.[12]

Activation of the TRPM8 channel through the topical application of menthol has been shown to elevate proinflammatory cytokines, such as IL-6 and IL-1β, in the bloodstream of normotensive rats. However, this elevation was not detected in rats with hereditary stress-induced arterial HT, indicating a potential reduction in TRPM8 channel activity in HT.[40] Additionally, topical application of menthol has been demonstrated to induce cutaneous vasorelaxation through mechanisms involving sensory neurons, endothelium-derived relaxing factors, and NO.[41] Intravenous administration of menthol resulted in a reduction in systemic blood pressure in cats and rabbits. Furthermore, dietary intake of menthol has been associated with decreased blood pressure in mice, SHRs, and individuals with pre-HT.[42] The context-dependent outcomes of TRPM8 activation underscore the complexity of its role in HT. These variations likely stem from differences in specific vascular beds, the nature of stimuli (e.g., menthol vs. cold), the overall physiological state of the organism, and interactions with autonomic nervous system activity. Future research is needed to delineate these contextual factors and clarify whether TRPM8 activation primarily exerts protective or detrimental effects in specific hypertensive conditions.[7]

Clinical and Translational Evidence for Dietary/ Environmental TRP Channel Activation

In recent years, the cardiovascular effects mediated by TRPV1 following dietary capsaicin intake have garnered significant attention in clinical research. Several population-based studies have identified an inverse correlation between the consumption of spicy foods and the risk of HT, supporting the hypothesis that chronic dietary exposure to TRPV1 agonists may contribute to blood pressure regulation.[43,44] Nevertheless, meta-analyses of randomized controlled trials investigating capsaicin or red pepper supplementation have generally not demonstrated a significant impact on either systolic or diastolic blood pressure.[45] Consequently, although current clinical data suggest a potential role of TRPV1 activation, they do not conclusively establish that capsaicin consistently exerts an antihypertensive effect on HT. This discrepancy may arise from several factors, including differences in patient populations, the specific formulation and dosage of capsaicin, the duration of the intervention, and the potential for compensatory mechanisms within the more complex human physiological system compared to controlled animal models.

Translational human data concerning TRPM8 activation are notably supported by findings derived from menthol studies. In research involving prehypertensive individuals, administration of menthol capsules over an eight-week period resulted in a moderate reduction in blood pressure and an improvement in flow-mediated dilation.[42] Furthermore, menthol-induced cutaneous vasodilation has been directly investigated in both male and female subjects with essential HT. Although menthol has been shown to induce dose-dependent vasodilation, with the magnitude of the response comparable to that observed in normotensive individuals, the underlying mechanisms differ. Specifically, nitric oxide synthase inhibition and sensory nerve blockade were found to attenuate the menthol response in patients with HT, suggesting that TRPM8-related vasoreactivity is context dependent and influenced by associated signaling pathways.[46] A systematic review assessing interventions involving Mentha species underscores the inconsistency of their effects on blood pressure and highlights the necessity for higher-quality randomized studies.[47] Collectively, these findings suggest that, while the TRPM8/menthol axis holds translational promise for HT research, further elucidation of its clinical efficacy and underlying mechanisms is required.

Integrating Omics and Translational Evidence in TRP Channel Dysregulation in Hypertension

Recent advancements in translational and omics-based research have provided novel insights into the involvement of TRP channels in the pathophysiology of HT. Evidence indicates that the expression levels of TRPC6, TRPV1/2/4, and TRPM8 transcripts in human aortic tissues are altered in patients with HT, underscoring the potential clinical relevance of vascular TRP channels.[12] Furthermore, multi-omics analyses of human aortic arch tissue have identified Piezo-type mechanosensitive ion channel component 1 (PIEZO1), TRPV2, and TRPM4 channels as potential ion channels associated with baroreceptor function.[48] These findings suggest the need to re-evaluate TRP channels in HT research using cell-type specific and translational methodologies. Integrating omics-based data with functional vascular studies could significantly enhance the understanding of TRP channel-mediated mechanisms and facilitate the identification of patient subgroups that may benefit from targeted therapeutic interventions.

Strength of Evidence and Translational Limitations

Although evidence supporting the role of TRP channels in HT has increased significantly, findings remain heterogeneous across TRP subfamilies, vascular beds, and experimental designs. The strongest inferences regarding causality are derived from genetic and mechanistic animal studies; however, these models have limitations, including developmental adaptation, compensatory channel rearrangement, and interspecies physiological differences. For example, phenotypes observed after germline gene deletion may reflect network-level compensatory mechanisms rather than a simple "loss-of-function" effect. Indeed, in mice deficient in TRPC6, increased blood pressure and vascular contractility have been observed; this has been partly attributed to increased basal cation influx and could be reduced by suppression of TRPC3. These findings indicate functional overlap within the TRPC3/6 axis.[49] Additionally, many pharmacological studies rely on research compounds with limited selectivity or tissue penetration, making it difficult to attribute observed blood pressure phenotypes to a specific TRP isoform. These limitations underscore the need for greater caution when directly translating mechanistic findings into claims of druggability and highlight the importance of considering cell type-specific roles (e.g., endothelial cells, vascular smooth muscle cells, or sensory neurons) as well as contextual factors such as salt load, obesity, or activation of the renin–angiotensin–aldosterone system (RAAS). Future research endeavors integrating human vascular tissue data, omics technologies, and clinical phenotyping—including resistant HT—will be crucial in determining whether TRP channels can transition from mechanistic interests to viable therapeutic targets.

Therapeutic Targeting of TRP Channels in Hypertension

Research findings suggest that alterations in the expression of TRP channels may represent promising therapeutic targets in the pathogenesis and management of HT. Notably, TRPC1 and TRPC6 channels have been shown to be susceptible to pharmacological modulation, and certain existing cardiovascular medications—such as losartan and nifedipine—may influence the expression of these channels.[50,51] However, the formation of heteromultimeric structures by TRP channels and their mutual interactions complicate the targeting of a single subtype. For instance, inhibition of TRPC1 may inadvertently enhance TRPC6 activity, potentially resulting in adverse effects. Furthermore, the role of TRPC1 in vasodilation through its interaction with TRPV4 in endothelial cells suggests that nonselective inhibition strategies could negatively affect endothelial function.

TRPC3 and TRPC6 channels have been identified as critical contributors to the pathogenesis of resistant HT and myocardial fibrosis.[52] In this context, therapeutic targeting of TRPC3/6 channels may represent a dual strategy, potentially lowering blood pressure while mitigating fibrotic progression. Nevertheless, the structural similarities among TRPC channels and the scarcity of selective modulators pose significant challenges to translational advancement in this field. Therefore, the development of highly selective TRPC3/6 inhibitors, characterized by optimized bioavailability and minimized off-target effects, is essential for validating the therapeutic potential of these channels in preclinical models.

While activation of TRPV1 has demonstrated notable cardiovascular protective effects in experimental models, clinical data remain inconsistent.[43–45] Consequently, the precise role and therapeutic potential of TRPV1 in HT remain uncertain. TRPV2 and TRPV3 channels have emerged as promising targets, particularly in the context of cardiovascular complications such as cardiac hypertrophy, myocardial infarction, and heart failure; however, their roles in HT are not yet fully elucidated. Although TRPV4-mediated vasodilation can be enhanced by various pharmacological agents, the potential for this channel to exert vasoconstrictive effects under certain conditions and to produce divergent outcomes in different tissues necessitates caution when considering it as a therapeutic target.

Activation of TRPM8 is supported by translational evidence derived from menthol studies and has been associated with vasodilation and reductions in blood pressure.[42] Nevertheless, further large-scale studies are required to assess the long-term effects and clinical applicability of TRPM8 activation.

In summary, TRP channels represent promising yet complex targets for the treatment of HT. Given their cell type-specific effects, mutual interactions, and context-dependent functions, future research should prioritize more selective, tissue-specific, and mechanism-based strategies.

Conclusion

Recent advances have deepened our understanding of how TRP channels contribute to vascular function and myogenic tone and have clarified that their altered expression and activity are key factors in conditions such as HT, atherosclerosis, and cardiovascular injuries. Despite their distinct effects, the precise intracellular signaling mechanisms of TRP channels remain largely unclear because of their complex structures, isoform interactions, dual roles as ion channels and signaling regulators, and diverse cell-type specific expression patterns. Additionally, the limited specificity of pharmacological compounds and antibodies targeting TRP channels poses significant challenges in this field of research. Clarifying the precise mechanisms through which TRP channels regulate vascular function in both physiological and pathological states is essential for the development of targeted cardiovascular therapies, particularly as these channels are increasingly recognized as promising therapeutic targets. Future studies integrating clinical research, omics-based approaches, and selective pharmacological modulators will be crucial in determining whether TRP channels can serve as viable therapeutic targets in HT.

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