The role of TRPV1 in improving VSMC function and attenuating hypertension

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Transient receptor potential vanilloid type 1 (TRPV1) channel, a ligand-gated cation channel of the TRP subfamily, can be activated by multiple stimuli, including capsaicin. Currently, cumulative studies have demonstrated an interesting link between TRPV1 and cardiovascular diseases, including hypertension. Additionally, the protective effect of TRPV1 against hypertension and its related disorders has been proved to be partly involved with the improved action of vascular smooth muscle cells (VSMCs). This review focuses on the current knowledge of TRPV1 in improving VSMC function and attenuating hypertension.

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1. Introduction

Hypertension is the one of most common cardiovascular diseases in humans and is a major independent risk factor leading to devastating cardio-cerebrovascular events such as myocardial infarction, stroke, heart failure, and sudden cardiac death. Despite extensive research in this field, the mechanisms involved in essential hypertension are largely undefined. The main changes observed in the resistance vessels of hypertensive subjects include cell hyperplasia and reorganization, which increase the ratio of vascular wall thickness to lumen and enhance the vascular sensitivity response to vasoconstrictors (Deng and Li, 2005). Thus, this vascular remodeling increases the vascular resistance and induces the development and maintenance of hypertension. Evidence indicates that the nervous system, renin-angiotensin aldosterone system, endothelial function, oxidative stress and other biochemical agents regulate cardiovascular and renal function and modify blood pressure under pathophysiological conditions (Wang and Wang, 2007).
Transient receptor potential (TRP) proteins constitute a vast non-voltage-gated cation channel superfamily that contributes to cardiovascular functions (Inoue et al., 2006). The transient receptor potential vanilloid type 1 (TRPV1) channel, a ligand-gated cation channel of the TRP subfamily, can be activated by multiple stimuli, including the “hot” pepper-derived vanilloid compound, capsaicin (Caterina et al., 2000). Accumulating studies support that TRPV1 is an important regulator of hypertension by activating the release of neuropeptides and initiating the phosphorylation of downstream second messengers (Hollis and Wang, 2013). Vascular smooth muscle cells (VSMCs) are highly specialized cells contributing to the formation of blood vessel walls and maintenance of vascular tension. Additionally, VSMC phenotypic plasticity plays a critical role in arterial remodeling commonly observed in hypertension. Many distinct members of the TRP superfamily have been detected in VSMCs. The emergence of TRPV1 channel as an important factor in hypertension has prompted research into the molecular mechanism of VSMC-dependent pathways in blood pressure regulation. Therefore, this review presents the current knowledge of TRPV1 in VSMC function and hypertension.

2. TRPV1

The capsaicin receptor is a non-selective calcium influx channel which was isolated and cloned from sensory neurons in 1997 (Caterina et al., 1997). This 95 KD protein is composed of 838 amino acids with two intracellular terminals and six transmembrane segments (TM1–6) including a pore-forming loop between TM5 and TM6 (Fig. 1). Due to its vanilloid acid structure in the ligand, this receptor is named transient receptor potential (TRP) vanilloid receptor subtype 1 (TRPV1), or vanilloid receptor subtype 1 (VR1) for short. On the basis of amino acid homology, the TRP family includes seven main subfamilies: TRPA (transient receptor potential ankyrin), TRPC (transient receptor potential canonical), TRPM (transient receptor potential melastatin), TRPP (transient receptor potential polycystin), TRPN (transient receptor potential NOMPC, referred to as no mechanoreceptor potential C), and TRPV (transient receptor potential vanilloid), among which TRPV has not been found in the mammalian genome (Pedersen et al., 2005). Most of these channels are multi-modally activated or modulated in response to various stimuli, and demonstrated to be involved in the regulation of the cardiovascular system (Inoue et al., 2006).

TRPV1 receptors are primarily expressed on two types of sensory nerves with small unmyelinated C-fibers or medium sized Aδ-fibers (Caterina et al., 1997; Ma, 2002). TRPV1 is a signal detector of polymodal nociceptors and can be activated by a variety of stimuli, including noxious chemicals, mechanical force and heat. The minimum threshold for heat-evoked responses at pH 7.4 is approxi- mate 43 °C, while a high concentration of protons (i.e. a low pH) has an analogous effect at normal physiological temperatures (~37 °C) (Tominaga et al., 1998).

In addition to capsaicin, TRPV1 can also be activated by anandamide, and endogenous arachidonic acid derivative which has similar structure with capsaicin (Pacher et al., 2005a). The endocannabnergic system, including anandamide, produces hypoten- sive effect in cardiovascular system through activating cannabinoid (CB) and TRPV1 receptors (Pacher et al., 2005b). Reportedly, anandamide prevents the salt-induced elevation of blood pressure, at least in partly via activation of TRPV1 receptors (Wang et al., 2005).
oxidized low density lipoprotein (oxLDL)-treated VSMCs, and ultimately slows down the process of atherosclerosis (Li et al., 2014). Accumulating evidence suggests that TRPV1 receptors can also constitute a protective mechanism against gastrointestinal injury and renal damage (Peng and Li, 2010; Wang et al., 2008a; Wang and Wang, 2011).

Although the protective effect of TRPV1 on hypertension and its related disorders has been well established, the precise cytological mechanisms are still poorly understood. Hypertension is accompanied by vascular remodeling and increased vascular resistance, which are attributed partly to hypertrophy and/or hyperplasia of the VSMCs (Intengan and Schiffrin, 2001). In addition, intimal hyperplasia can also be resulted from increased VSMC number, mainly due to VSMC migration from the underlying media during hypertension. It is acceptable that the protective effects of TRPV1 in hypertension work in concert with the ameliorated action of the VSMCs.

4. Neurotransmitters and VSMC

The cardiovascular system is widely innervated by capsaicin-sensitive sensory nerves, which play important roles in regulating peripheral vascular tone through the release of vasoactive neurotransmitters, including vasoconstrictors and vasodilators. Capsaicin-sensitive sensory nerves regulate blood pressure mainly through TRPV1 receptor activation and the following release of vasodilator neuropeptide, CGRP (Deng and Li, 2005; Wimalawansa, 1996). There is evidence that CGRP released from perivascular nerves may inhibit the proliferation of VSMCs, thus impede the formation of atheromatosus lesions and vascular stenosis (Li et al., 1997). Nitric oxide (NO) can induce the potentiation of anti-proliferative effects of CGRP in VSMCs via enhanced accumulation of cyclic adenosine monophosphate (cAMP) (Wang et al., 1999). In addition, cAMP/PKA pathway appears to mediate the inhibitory effect of CGRP on proliferation of cultured aortic and pulmonary artery smooth muscle cell (Chattergoon et al., 2004). During vascular injury, such as wire-induced injury, endogenous CGRP can largely suppress oxidative stress, VSMC proliferation and migration which are extremely significant in CGRP deficient mice (Yang et al., 2013). Recent research also suggests that CGRP-modified mesenchymal stem cells inhibit VSMC phenotypic modulation and proliferation (Shi et al., 2013). Apoptosis is another key factor responsible for VSMC turnover in neointimal formation. Contradictory evidence exists regarding the effect of CGRP on apoptosis. It has been proved that CGRP can protect VSMCs from oxidative stress induced apoptosis via activation of mitogen-activated protein kinases (MAP kinases) (Schaeffer et al., 2003). On the contrary, evidence also indicates that CGRP inhibits balloon injury-induced neointimal formation and promotes VSMC apoptosis (Wang et al., 2004). The effect of CGRP on VSMC apoptosis seems complicated and varies depending on different injuries and periods. Furthermore, activated CGRP receptors can promote the dissociation of endothelin-1 (ET-1) from ETα receptors, resulting in the termination of the persistent vasoconstrictive effect of ET-1 and the inhibition of hypertension and proliferation of VSMCs (Bouallegue et al., 2013; Meens et al., 2010).

In peripheral nervous system, CGRP and SP are often concomitant and provide vasodilatory effects in many vascular beds (Katki et al., 2001; Wimalawansa, 1996). It has been shown that SP can stimulate the production of adrenomedullin in VSMC, which induces vasorelaxation, urinary sodium excretion and blood pressure reduction as an autocrine or paracrine factor (Hirata et al., 1995; Sugo et al., 1995).

Furthermore, CGRP-independent and SP-independent phosphorylation of TRPV1 may interact with Akt, Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), AMP-activated protein kinase (AMPK), eNOS, and following nitric oxide production to induce vasodilation and angiogenesis (Hollis and Wang, 2013). Therefore, a lot of evidence indicates that capsaicin-sensitive sensory nerves and their neurotransmitters are intimately associated with the pathogenesis of hypertension (Fig. 1).

5. Ca²⁺ and VSMC

Calcium ion (Ca²⁺) is known as the ubiquitous intracellular messenger that regulates a wide repertoire of cellular functions. Intracellular calcium concentration ([Ca²⁺]) mediates the alterations in both cell morphology and gene expression, which were simultaneously required in cell migration and proliferation (Houe et al., 2008). Calcium influx from the extracellular space depends on various cytomembranous calcium channels, including superfamily of TRP channels (Guibert et al., 2011). It has been reported that TRPV1 promotes chronic hypoxia-induced enhancement of [Ca²⁺], and proliferation of human pulmonary arterial smooth muscle cells (PASMC) (Wang et al., 2008b). Furthermore, TRPV1 activation has been proved to stimulate the migration of rat PASMC (Martin et al., 2012). As results of SMC proliferation and migration, pulmonary artery contractility increases and pulmonary hypertension occurs.

Despite its numerous physiological functions in SMCs, the involvement of TRPV1 in migration or proliferation of SMCs in resistance vessels or the aorta are still largely unknown. One likely reason is that components of these vessels differ regionally. Different types of VSMC may present different reactivity to [Ca²⁺]. Moreover, VSMCs express a large repertoire of ion channels that have important roles in cellular electrical and contractile responses via mediating calcium transport into and out of cell. The role of TRPV1 in the synergy and competition among the calcium ion channels is definitely worth exploring. Furthermore, maintaining [Ca²⁺], may be a protective mechanism in preventing VSMCs apoptosis in pathological cases.

6. Inflammation and VSMC

Numerous inflammatory cytokines and chemokines are involved in the immunological reaction and vascular remodeling during hypertension. Anti-inflammation therefore may act as a positive role on alleviating hypertensive development. In recent years, several studies have reported on the potential benefits of TRPV1 in the abatement of inflammatory response. Wei et al. found that the serum levels of interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), monocyte chemotactrant protein 1 (MCP-1) and macrophage inflammatory protein 2 (MIP-2) were higher in ApoE⁻/⁻ TRPV1⁻/⁻ than in ApoE⁻/⁻ mice (Wei et al., 2013). Likewise, TRPV1 gene deletion aggravates inflammation via upregulating plasma cytokines and chemokines in mice after myocardial infarction (Huang et al., 2009). In adipose tissue and liver, activation of TRPV1 by dietary capsaicin can lower inflammatory mediator release and macrophage infiltration (Kang et al., 2010). Moreover, activation of TRPV1 can inhibit cytokine-induced human dendritic cell differentiation, and proinflammatory cytokine secretion (Toh et al., 2009). A recent research has shown that deletion of TRPV1 exacerbated renal injury during salt-sensitive hypertension via enhancing inflammatory responses (Wang et al., 2015). Therefore, activation of TRPV1 may contribute to reducing inflammation, and then improving relevant organ lesions during hypertension.

VSMC is capable of producing many proinflammatory mediators which result in the initiation and propagation of the inflammatory response, and they in turn alter VSMC phenotype and function in vascular disease (Raines and Ferri, 2005). AMPK has been proved to
inhibit VSMC proliferation and migration, and vascular remodeling (Stone et al., 2013). In addition, AMPK signaling pathway can be activated by TRPV1-induced significant elevation in cytosolic Ca2+ (Li et al., 2014). It has reported that oxLDL could induce VSMC-derived foam cell formation, phenotypic modulation and proinflammatory molecule expression, while activation of TRPV1 was demonstrated to provide an ameliorative effect on oxLDL-treated VSMCs (Kiyani et al., 2014; Li et al., 2014). TRPV1-induced anti-inflammation on VSMCs is acceptant theoretically, although it is far from clear what specific mechanisms are involved. Inhibition of the inflammatory response is widely accepted as a promising target for attenuation of VSMC phenotypic modulation and intimal hyperplasia formation (Zhang et al., 2010, 2011). Reportedly, the decrease of intima-media thickness of intracranial arteries, reversion of cerebrovascular hypertrophy and improvement of endothelium-dependent relaxation were found in SHRsp treated with dietary capsaicin compared with untreated SHRsps (Xu et al., 2011). Therefore, activation of TRPV1 may also play a positive role in the VSMC-associated vascular remodeling (Fig. 1).

7. Conclusions

The hypotensive effect produced by capsaicin indicates that activation of TRPV1 may be an effective means to prevent the development of hypertension. Evidence that TRPV1 improves VSMC function via neurotransmitter secretion, calcium ion influx and inflammation reduction, has advanced our knowledge of TRPV1 role in cardiovascular diseases. Further details regarding TRPV1 expression, TRPV1-induced release of sensory neurotransmitters and anti-inflammation, and post-signaling pathway function may provide valuable understanding of the pathogenesis of hypertension and related organ damage. Therefore, TRPV1 may be a promising therapeutic target in hypertension and hypertension-related cardiovascular diseases.

Conflict of interest

The authors do not declare any conflict of interest relevant to this manuscript.

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