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Invited review

The vanilloid receptor and hypertension[1]

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Key words

TRP family; afferent neurons; capsaicin; calcitonin gene-related peptide; substance P; vanilloid receptor; renin-angiotensin-aldosterone system; endothelin, sympathetic nervous system; salt-sensitive hypertension

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Abstract

Mammalian transient receptor potential (TRP) channels consist of six related protein sub-families that are involved in a variety of pathophysiological function, and disease development. The TRPV1 channel, a member of the TRPV sub-family, is identified by expression cloning using the "hot" pepper-derived vanilloid compound capsaicin as a ligand. Therefore, TRPV1 is also referred as the vanilloid receptor (VR1) or the capsaicin receptor. VR1 is mainly expressed in a subpopulation of primary afferent neurons that project to cardiovascular and renal tissues. These capsaicin-sensitive primary afferent neurons are not only involved in the perception of somatic and visceral pain, but also have a "sensory-effector" function. Regarding the latter, these neurons release stored neuropeptides through a calcium-dependent mechanism via the binding of capsaicin to VR1. The most studied sensory neuropeptides are calcitonin gene-related peptide (CGRP) and substance P (SP), which are potent vasodilators and natriuretic/diuretic factors. Recent evidence using the model of neonatal degeneration of capsaicin-sensitive sensory nerves revealed novel mechanisms that underlie increased salt sensitivity and several experimental models of hypertension. These mechanisms include insufficient suppression of plasma renin activity and plasma aldosterone levels subsequent to salt loading, enhancement of sympathoexcitatory response in the face of a salt challenge, activation of the endothelin-1 receptor, and impaired natriuretic response to salt loading in capsaicin-pretreated rats. These data indicate that sensory nerves counterbalance the prohypertensive effects of several neurohormonal systems to maintain normal blood pressure when challenged with salt loading. The therapeutic utilities of vanilloid compounds, endogenous agonists, and sensory neuropeptides are also discussed.

Introduction

Mammalian transient receptor potential (TRP) channels consist of six related protein sub-families known as TRPV, TRPC, TRPM, TRPP, TRPML, and TRPA[1]. These channels are widely distributed and involved in sensing local stimuli ranging from changes in hemodynamics to pH and osmolarity. The TRPV1 channel, a member of the TRPV sub-family, was identified by expression cloning using the "hot" pepper-derived vanilloid compound capsaicin as a ligand. TRPV1 is therefore referred as the vanilloid receptor (VR1) or the capsaicin receptor. Capsaicin as well as other closely related vanilloid substances are principal constituents in the hot chilli peppers and responsible for the pungency of these spices[2].

Over the last several centuries, knowledge about the physiological actions of capsaicin has grown and capsaicin has become a powerful tool, as will be described, for studying mechanisms underlying hypertension. Ever since its isolation in the mid-nineteenth century, capsaicin has been documented to act on sensory fibers with neuroselectivity[3,4]. Nelson elucidated the structure of capsaicin, reporting it as 8-methyl-vannillyl-6-noneamide, an acylamide derivative of homovanillic acid[5]. The compound consists of three functional moieties: vannilyl, acylamide, and alkyl[2]. Jancso later showed that capsaicin-sensitive nerve endings could be

stimulated as well as destroyed by a sufficiently high dose of capsaicin[6]. The neurotoxicity effect of capsaicin is of paramount importance, for reasons that will become clear, to neurobiologists using capsaicin sensitive-sensory nerve degeneration to study blood pressure regulation. The review that follows outlines the advances that have been made since Jancso's publications, with regard to mechanisms of capsaicin's action, cardiovascular effects of select neuropeptides released by a subset of capsaicin-sensitive primary afferent neurons (CSPAN) innervating cardiovascular and renal tissues, and pathophysiologic mechanisms of hypertension elucidated by capsaicin sensitive sensory-nerve degeneration. Capsaicin pharmacology and the nature of capsaicin-sensitive sensory nerves are discussed in greater detail in a number of other excellent scholarly reviews[7–9]. This review is restricted to a discussion of the effects of capsaicin on the cardiovascular system. Other authors have reviewed the effects of capsaicin on the somatosensory, respiratory, thermoregulatory, and gastrointestinal systems[10–14].

VR1 positive sensory neurons

VR1-positive sensory neurons refer to a subset of primary afferent neurons that express the VR1 receptors which can be activated by capsaicin. The pharmacological property of sensitivity to capsaicin distinguishes these afferent neurons, mostly having unmyelinated (C fibers) or thinly myelinated axons (Aδ fibers), from other afferent neurons[15].

Maggi[15] has described the functional anatomy of the VR1-positive primary afferent neuron by identifying four sites from which neurotransmitter release may occur: (i) central terminals of the afferent neuron in contact with second-order neurons in the CNS; (ii) terminals distributed in the prevertebral ganglia; (iii) peripheral terminals distinct from the terminal at which the sensory stimulus is applied; and (iv) the same peripheral terminal at which the sensory stimulus is applied. Neurotransmitter release at sites (i) and (ii) accounts for the sensory function of CSPAN and is central to perception of somatic and visceral pain. In contrast, and as implied by neuropeptide release from peripheral terminals (iii) and (iv), CSPAN nerve endings not only serve as sensory receptors, but also as effector sites from which neurotransmitters are released. Thus, neurotransmitter release from sites (iii) and (iv) accounts for the "sensory-efferent" function of CSPAN, with release from site (iv) not even requiring neuronal conduction[15]. Accordingly, Maggi and Meli[11] have termed release from site (iv) the "sensory receptor potential-coupled efferent response." Local sensory stimuli that may induce neurotransmitter release are varied and include nerve growth factor[16], vascular wall tension[17], the sympathetic nervous system[18], bradykinin[19], and endothelin[20].

Efferent function of VR1-positive sensory neurons

VR1-positive sensory neurons have a dual function: sensory perception and sensory efferent function. Binding of capsaicin and capsaicin agonists to VR-1 leads to neuropeptide release from a subpopulation of neuropeptide-containing primary afferent neurons[15]. Binding to this receptor opens a receptor-operated permeable cation channel[21–25] that ultimately results in the influx of sodium and calcium ions. Sodium influx is sufficient for afferent impulse conduction. In sharp contrast, calcium influx, and thus extracellular calcium, is prerequisite for neuropeptide release. Without extracellular calcium, sensory neuropeptides are no longer released from sensory nerve endings when these endings are depolarized[15].

Given that the neuroselectivity of capsaicin is a reflection of the selective expression of the VR1 on a subpopulation of primary afferent neurons, a closer look at the VR1 is warranted. Initial evidence supporting a capsaicin-binding site on a subset of primary afferent neurons came from observations that capsaicin analogues are able to exert similar functional changes[26,27]. Additional support came from experimentation with resiniferatoxin, a phorbol ester derivative that has been shown to exhibit structural similarity [28,29] and densensitizing and excitatory properties homologous to those exhibited by capsaicin, albeit at 1000-fold lower doses[28–30]. Definitive support for the presence of a chemical moiety capable of binding to capsaicin and related agonists came with the development of capsazepine, experimentally shown to act as a competitive antagonist of vanilloid binding and activity[31]. The VR-1 has been reviewed in greater detail in an authoritative review by Caterina and Julius[32].

Concerning the nature of transmitters released from VR1-positive sensory neurons, Maggi and Meli[15] have reported that at least the following 12 different types of transmitters are present in capsaicin-sensitive sensory neurons: substance P (SP), neurokinin A, neuropeptide K, eledoisin-like peptide, somatostatin, vasoactive intestinal polypeptide, cholecystokinin-octapeptide, calcitonin gene-related peptide (CGRP), galanin, corticotrophin-releasing factor, arginin vasopressin, bombesin-like peptides. These authors also report that multiple neuropeptides can be simultaneously released from VR1-positive sensory nerve endings. However,

different neuropeptides may be preferentially released as a function of stimulus intensity[33].

It has been shown that plasma concentrations of CGRP rise transiently after administration of capsaicin in adult rats[3,4]. Given that capsaicin exerts its action through release of neuropeptides, acute administration of capsaicin produces functional changes related to the activity of the released neuropeptides[35]. In contrast, and of significance to elucidating mechanisms underlying hypertension, capsaicin administered systemically at a dose of 50 mg/kg of body weight to neonatal rats or mice leads to an irreversible loss of more than 80% of small-diameter sensory neuron cell bodies[36–41]. These observations indicate that high doses of capsaicin lead to neurotoxic effects including substantial depletion of stores of neuropeptides within VR-1 positive sensory neuron.

Innervation of cardiovascular tissue by VR1-positive sensory nerves

VR1-positive sensory nerves are found around blood vessels in virtually all vascular beds. CGRP, often co-localized with SP, is found in nerve endings of a subset of these sensory nerves[42–46]. Synthesis of these neuropeptides occurs in the dorsal root ganglia which contain cell bodies of the capsaicin-sensitive sensory nerves. CGRP, co-localized with SP, is also found in a subpopulation of VR1-positive sensory nerves innervating the hearts of rats, guinea pigs, and humans, though in a much lower density than around blood vessels[43].

CGRP is a potent vasodilator that also has positive chronotropic and ionotropic effects[43]. The coronary vasculature is a particularly susceptible target of the vasodilatory action of CGRP[47,48]. Of significance to understanding the pathogenesis of hypertension, systemic administration of CGRP decreases blood pressure in normotensive animals, normotensive humans, and spontaneously hypertensive rats[43,44]. This decrease is produced via peripheral arterial dilation mediated through nitric oxide-dependent and nitric oxide-independent mechanisms[43]. The fact that bolus injection of $CGRP_{8-37}$, a CGRP receptor antagonist, produces dose-dependent increases in mean arterial pressure in deoxycorticosterone-salt hypertensive rats indicates that CGRP-induced vasodilation may play a compensatory role in this model[49].

VR1-positive sensory nerves and established models of hypertension

At least two hypertensive models have been used for defining the role of VR1-positive sensory nerves. One is the one-kidney wrap (1K-WRAP) hypertensive model and the other the deoxycorticosterone (DOCA)-salt hypertensive model. Intrathecal administration of capsaicin to adult rats was used to deplete SP and CGRP within central processes of afferent renal nerves (ARN) within selective laminae of the dorsal horn for determining whether SP and/or CGRP localized in ARN play a role in the development of 1K-WRAP hypertension or DOCA-salt hypertension[50]. Capsaicin treatment enhanced the development of 1K-WRAP hypertension, considering that systolic blood pressure was greater in 1K-WRAP rats pretreated with capsaicin compared with vehicle-treated 1K-WRAP rats[50]. However, capsaicin pretreatment had no effect on systolic blood pressure in DOCA-salt rats, suggesting that the depletion of sensory neurotransmitters from ARN by capsaicin does not exacerbate DOCA-salt hypertension. Indeed, these authors concluded that "ARN did not play a major role in the development of DOCA-salt hypertension."[50]

Manzini and Bacciarelli[51] performed a similar study in which the effect of neonatal degeneration of VR1-positive sensory nerves on the development of DOCA-salt hypertension was investigated. As expected by the degeneration of sensory neurons in capsaicin-pretreated animals, substance P-like immunoreactivity was virtually undetectable in capsaicin-pretreated animals and blood pressure was much less responsive to acute administration to capsaicin as compared to control animals. DOCA-salt induced-hypertension was of quicker onset and of greater magnitude in the animals pretreated with capsaicin. Hypertensive rats pretreated with capsaicin also had a greater incidence of cardiac necrosis. These authors, in contrast to Burg *et al*, concluded that capsaicin-sensitive sensory fibers may underlie antihypertensive mechanisms and play a protective role in preventing the development of DOCA-salt hypertension[51].

VR1-positive sensory nerves and increased salt sensitivity

Though studies by Burg *et al*[50] and Manzini and Bacciarelli[51] have shown that VR1-positive sensory nerves are implicated in blood pressure regulation, these investigations have not shown whether impairment of the sensory nervous system is sufficient to produce hypertension. We showed for the first time in 1998 that neonatal degeneration of VR1-sensitive sensory nerves rendered an adult rat salt-sensitive[52]. We administered 50 mg/kg capsaicin or vehicle subcutaneously to newborn Wistar rats on the first and second days of life, and a high or normal sodium diet was given

immediately following the weaning period. We found that neonatal treatment with capsaicin led to elevation of blood pressure in rats fed a high sodium diet, but not in those fed a normal sodium diet. High salt intake increased urine volume and sodium excretion in both vehicle and capsaicin treated rats. However, these parameters were significantly lower in capsaicin treated rats fed a high-salt diet compared to vehicle treated rats fed a high-salt diet. These results suggest that capsaicin neonatal treatment might impair renal function when rats are loaded with salt.

Role of the renin-angiotensin-aldosterone system (RAAS) To define the molecular mechanisms underlying sensory nerve function involved in the pathogenesis of salt-sensitive hypertension, we[53] subsequently explored the role of the RAAS in the aforementioned salt-sensitive hypertensive model induced by sensory denervation. Capsaicin plus high-salt-treated rats were given losartan (a type I angiotensin II receptor blocker), prazosin (a selective α_1-adeno-receptor blocker), or hydralazine (a nonspecific vasodilator). Both tail-cuff systolic blood pressure and mean arterial blood pressure were higher in capsaicin-treated rats fed a high-salt diet and capsaicin treated rats fed a high-salt diet plus prazosin when compared to capsaicin treated-rats fed a high-salt diet plus losartan or hydralazine, the vehicle-treated rats fed a high-salt diet, or capsaicin-treated rats fed a normal salt diet. These results suggest that losartan and hydralazine, but not prazosin, are able to prevent the development of salt-induced hypertension in capsaicin-pretreated animals. Of significance to understanding the pathophysiology of salt-sensitive hypertension, these results revealed that there was an interaction between the sensory nervous system and the RAAS in a manner that prevents the development of salt-induced hypertension in sensory-intact rats. This study also confirmed that capsaicin might impair the natriuretic response to a high salt intake, as rats pretreated with capsaicin and fed a high-salt diet have decreased urinary volume and sodium excretion. Interestingly, losartan and hydralazine did not protect against the impaired natriuretic response, even though these agents did prevent the development of hypertension in salt-loaded capsaicin pretreated rats. These results indicate that intact sensory innervation is essential for the normal natriuretic response to sodium loading and that the antihypertensive effects of losartan and hydralazine may be mediated by mechanisms for example, vasodilatory mechanism, other than those that protect against the impairment of urinary sodium and water excretion in this model.

To further investigate the roles of the type 1 (AT1) and 2 (AT2) angiotensin II (AII) receptors in the development of salt-induced hypertension in capsaicin-pretreated rats, we[54] treated capsaicin-pretreated rats fed a high-salt diet with candesartan (a selective blocker of the AT1 receptor), PD 123319 (a selective blocker of the AT2 receptor), or a combination of these two drugs. Development of hypertension in capsaicin treated rats fed a high-salt diet was prevented or attenuated by candesartan and PD 123319, respectively, indicating that both of these antagonists were protective and effective in lowering increased blood pressure induced by a salt challenge in capsaicin-pretreated animals. The antihypertensive effect of PD 123319 is unexpected and the underlying mechanisms remain to be defined. Plasma renin activity (PRA) was suppressed by high salt intake in both vehicle- or capsaicin-treated rats, but it was significantly less suppressed in the latter than in the former. This observation suggests that PRA may be insufficiently suppressed in capsaicin-pretreated animals, likely contributing to hypertension in these animals.

We next studied aldosterone and its interaction with the sensory nervous system in the induction of salt-sensitive hypertension, in light of the aforementioned finding that PRA is insufficiently suppressed in neonatally capsaicin-pretreated rats challenged with a salt load[54,55]. Both vehicle- and capsaicin-treated rats fed a high-salt diet was given spironolactone, an aldosterone receptor antagonist for 3 weeks. We found that chronic spironolactone treatment appeared to restore renal functional impairment and prevented the development of hypertension in neonatally capsaicin-pretreated rats fed a high-salt diet[55]. This is in contrast to our previous report with losartan and hydralazine, which have been shown to attenuate elevated blood pressure in capsaicin pretreated rats challenged with a salt load, but not able to improve renal functional impairment[53]. These results indicate that the antihypertensive effect of spironolactone in this model is mediated by improving renal function, consistent with the role of aldosterone receptors in the kidney that cause sodium and water retention.

Albeit markedly suppressed by salt loading, plasma aldosterone levels (PAL) and PRA were significantly higher in capsaicin-pretreated rats challenged with salt load than sensory-nerve-intact rats fed the same high-salt diet[55]. This suggests PRA and PAL are insufficiently suppressed in sensory-denervated rats, contributing to increased salt sensitivity and renal functional impairment in these animals. Insufficiently suppressed PAL in response to salt loading can be attributed to one or both of the following: (i) increased circulating and/or tissue AII levels; and/or (ii) upregulation of the AII type I receptor in the zona glomerulosa of the adrenal gland, a receptor to which binding of AII increases aldosterone synthesis and secretion. We[55] found that the

AT1 receptor content in the adrenal gland was not altered in any of the experimental groups, strongly suggesting that insufficiently suppressed PAL is a reflection of insufficiently suppressed circulating and/or tissue AII levels.

In contrast to above mentioned studies that define the role of the RAAS in the development of hypertension in capsaicin treated rats fed a high-salt diet, we studied the role of sensory nerves in attenuating the development of hypertension induced by AII infusion[56]. AII or vehicle-infused rats were pretreated with capsaicin or vehicle. Mean arterial pressure was higher in rats infused with AII, and it was higher in AII-infused rats pretreated with capsaicin compared to rats infused with AII alone. Northern blot analysis revealed that AII-infused rats had an increase in the level of CGRP mRNA in the dorsal root ganglia, suggesting that subpressor infusion of AII either stimulates the synthesis of CGRP mRNA or retards its degradation. Taken together, these data suggest that neuropeptides released by sensory nerves attenuate elevated blood pressure induced by AII infusion and that the increase in CGRP synthesis appears to be a compensatory response to diminish increased blood pressure induced by AII infusion. Furthermore, 24-h urinary and sodium excretions were lower in AII-infused rats pretreated with capsaicin than they were in rats infused with AII alone. These results are consistent with the finding that degeneration of VR1 positive sensory nerves impairs the natriuretic response to a salt load[52–55].

Role of the sympathetic nervous system Defining the interaction between the sympathetic and sensory nervous systems, we found that sympathectomy produced by administration of guanethidine subcutaneously prevented the development of salt-sensitive hypertension induced by sensory nerve degeneration[57]. This finding suggests that: (i) enhanced sympathoexcitatory response occurs in capsaicin-pretreated rats fed a high-salt diet, which may contribute to increased salt sensitivity in these animals; and (ii) there is a balance between antihypertensive effects of sensory nerves and prohypertensive effects of the sympathetic nervous system in a normal rat. This balance is disrupted following capsaicin-pretreatment and consequential sensory nerve degeneration, such that the animal is salt-sensitive. Sympathectomy may also result in less renin release by withdrawing the stimulation of the α_1-adrenergic receptors.

These findings appear to be in contrast to our previous results in which prazosin is not able to prevent the development of salt-induced hypertension in capsaicin-pretreated animals[53]. To reconcile this finding about prazosin with the antihypertensive effect of sympathectomy, one should keep in mind the following considerations: (i) the dose of prazosin may not have been high enough to decrease blood pressure in neonatally capsaicin-pretreated rats challenged with a salt load, even though the same dose resulted in reduction in blood pressure in spontaneously hypertensive rats[58]; (ii) alpha-1 adrenoreceptors are necessary for preventing salt-induced hypertension, an idea supported by findings by Osborn *et al*[59] who have shown that blockade of the α_1-adrenoreceptor with prazosin renders the rat salt-sensitive and leads to the development of salt-sensitive hypertension; and (iii) the sympathetic nervous system may contribute to the development of salt-induced hypertension in neonatally capsaicin-pretreated rats via a non-α_1-adrenoreceptor mechanism.

Role of the endothelin system We investigated the role of endothelin-1 (ET-1) and its receptors in sensory-dependent salt-sensitive hypertension, in light of the finding that AII is a stimulus for ET-1 production[60–63]. We found that plasma ET-1 levels and blood pressure were elevated in sensory-denervated rats fed a high-salt diet. Moreover, development of salt-sensitive hypertension in these rats can be prevented by blockade of the ET_A receptor, just as it can be prevented with losartan[53] and candesartan[54], hydralazine[53], sympathectomy[57], and spironolactone[55]. Unlike chronic treatment with spironolactone[55], however, blockade of the ET_A receptor is not able to alleviate renal functional impairment in capsaicin-pretreated rats fed a high-sodium diet.

Furthermore, elevated plasma ET-1 levels may reflect one or both of the following: (i) decreased internalization by ET_B receptors, which have been shown to act as clearance receptors for ET-1[64–65]; or (ii) increased production. Because we observed that plasma ET-1 levels in sensory denervated rats that were salt loaded were unaffected by blockade of the ET_B clearance receptor[60], it is clear that elevated plasma ET-1 levels are indeed the result of increased production, consistent with the possibility of increased synthesis and release of ET-1 secondary to insufficiently suppressed PRA in these capsaicin-pretreated animals[54,55].

VR1-positive sensory nerves and pulmonary hypertension

The role of neuropeptides released by sensory nerves in hypoxic pulmonary hypertension have been studied[66,67]. Tjen-A-Looi revealed that rats pretreated with capsaicin and subsequently placed in hypobaric hypoxia (10% O_2, 16 d) had increased pulmonary artery pressure and right ventricular hypertrophy compared to sensory-nerve-intact rats subjected to the same hypoxia[66]. These investigators concluded that depleted stores of CGRP secondary to capsaicin

administration exacerbated hypoxic pulmonary hypertension. Interestingly, these authors reported that depletion of SP did not exacerbate pulmonary artery pressure and right ventricular hypertrophy. Regarding the latter observation, it follows that endogenous CGRP may indeed modulate pulmonary vascular tone and counterbalance hypoxic pulmonary vasoconstriction, reducing elevated pulmonary artery pressure and right ventricular hypertrophy in pulmonary hypertension.

In contrast to the protective effect of CGRP on pulmonary artery pressure observed by Tjen-A-Looi[66], Zhou and Lai[67] found that SP was implicated in pulmonary hypertension. Zhou and Lai induced ventilatory dysfunction and pulmonary hypertension in Sprague-Dawley rats by administering monocrotaline (MCT). SP levels were elevated 1–2 weeks after the administration of MCT. Compared to rats given MCT alone, rats given MCT plus capsaicin showed attenuated increases in pulmonary arterial pressure and the weight ratio of right ventricle/(left ventricle+septum). These data suggest that MCT produces pneumotoxicity that may be mediated or at least accompanied by elevated SP levels. Because capsaicin treatment depletes this neuropeptide, capsaicin attenuates MCT-induced pneumotoxicity[67].

Clinical and therapeutic implications

Given that excitation of VR1-positive sensory nerves is followed by a refractory state, capsaicin has being found to have therapeutic potential in the treatment of neuropathic pain[68]. But, and as has been suggested within this review, capsaicin has implications beyond the treatment of pain as an agent capable of acting on the cardiovascular system. The observation that capsaicin (an agonist of the VR1) is able to produce a hypotensive effect in SHR is an indication that activation of the VR1 may be an efficacious means of preventing the development of hypertension – a prospect with far-reaching therapeutic implications[69].

Of growing interest is the compelling evidence that vanilloid receptors on sensory nerves may mediate the vasodilator action of anandamide[70–74], which was originally isolated from the brain as an endogenous cannabinoid receptor ligand[75]. Indeed, our recent data indicate that administration of methanandamide caused a greater hypotensive effect in SHR rats as compared with control animals, suggesting that anandamide may serve as an endogenous compound able to stimulate VR1 and consequently produce a decrease in blood pressure[69]. It follows that changes in circulating or tissue anandamide levels under particular pathophysiological conditions may alter VR1 function and thereby regulate blood pressure. The search for endogenous VR1 activators and inhibitors is certainly motivated by the implications that such vanilloid therapy may treat hypertension.

In addition to vanilloid therapy, there are broad implications for the clinical application of neuropeptides stored in the endings of VR1-positive sensory nerves. In particular, the clinical utility of CGRP receptor agonists in the treatment of cardiovascular disorders is discussed below and in greater detail in a review by Feuerstein *et al*[76].

Considering its potent vasodilatory action, CGRP has been evaluated in the treatment of subarachnoid hemorrhage and shown to relax severely constricted vessels in animal models of this disorder[77]. However, the European CGRP in Subarachnoid Hemorrhage Study Group[78] was not able to produce definitive evidence supporting the use of this neuropeptide in the treatment of subarachnoid hemorrhage. Their study was complicated by almost two-thirds of patients in the treatment group not being able to complete the course of the trial because of frequent episodes of CGRP-induced hypotension. Perhaps this adverse systemic side effect could be minimized by intrathecal administration of CGRP.

Other studies have shown that CGRP has potential beneficial hemodynamic effects in congestive heart failure[79–80]. Shekhar *et al* observed that CGRP infusion over 8 h increased cardiac output by 72% while reducing right atrial and pulmonary wedge pressure[80]. Unfortunately, these favorable hemodynamic responses returned to pre-infusion levels once CGRP delivery was withdrawn. The need for continuous infusion of CGRP thus diminishes its clinical utility in the treatment of congestive heart failure.

Similarly, CGRP has been evaluated in the treatment of coronary heart disease. Indeed, it has been shown to improve exercise tolerance in patients with chronic stable angina[81]. But, specificity for CGRP or related agonists for the coronary vasculature has not been demonstrated and CGRP infusion for the treatment of coronary heart disease would thus be expected to produce systemic side effects, as it does in the treatment of heart failure.

As another example of the possible clinical utility of CGRP, it has been demonstrated that patients with Raynaud's disease are deficient in cutaneous CGRP-containing nerve fibers[82]. However, CGRP has not been shown to be useful in the treatment of this peripheral vascular disease.

Conclusion remarks

It is estimated that 50 million individuals in the United

States suffer from hypertension. The detrimental consequences of this disease involve myocardial infarction, congestive heart failure, stroke, and renal failure. Despite intensive research in this field, the molecular basis underlying human essential hypertension is largely unknown and pharmacologic prevention of end organ damage induced by hypertension is a challenge. Defining how sensory nerves sense changes in the environment, alter their afferent and efferent activities, and cross-talk with other systems to modulate cardiovascular and renal function and blood pressure may provide valuable new insight into the interactions that lead to hypertension and increased salt sensitivity. Such insight may unveil novel pharmacologic approaches to tackle hypertension and end organ damage. The study of abnormalities in VR1 expression, VR1-induced release of sensory neurotrans-mitters, and post-signaling pathways may also have significant impact in our understanding of the pathogenesis of hypertension and have far-reaching clinical and therapeutic implications.

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