Beneficial Effects of Capsaicin in Kidney Diseases

Subjects: Urology & Nephrology

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Capsaicin, the organic compound which attributes the spicy flavor and taste of red peppers and chili peppers, has been extensively studied for centuries as a potential natural remedy for the treatment of several illnesses. The identification of novel, effective renoprotective agents for improving the treatment of renal diseases remains a largely unmet need. Nowadays, promising evidence has been accumulated demonstrating different experimental benefits of capsaicin in some of the most important and complicated renal diseases, such as acute kidney injury (AKI) and diabetic kidney disease (DKD). Additionally, capsaicin may also play a protective role against renal fibrosis and pathological arterial calcifications, two hallmarks of progressive chronic kidney disease (CKD), and could partly antagonize the detrimental effects of nephrovascular and salt-sensitive hypertension.

Keywords: capsaicin ; kidney ; hypertension ; kidney disease

1. Acute Kidney Injury

AKI is a clinical syndrome with many causes and a multifaceted pathophysiology which is defined as an acute (within hours/days) decrease in kidney function with both structural damage and function loss of the kidneys [1]. AKI complicates around 23% of the total hospitalizations worldwide, but in the intensive care unit (ICU) setting, the incidence of this condition can be as high as 78% [2]. Patient mortality due to AKI still remains dramatically high, particularly among individuals requiring dialysis support [3]. The early identification of this condition is thus crucial to initiating adequate therapeutic measures in a timely manner, thereby preventing worse patient outcomes, including the severe clinical complications, or permanent kidney damage. Unfortunately, specific therapy for AKI is lacking in the majority of cases, and preventive measures could not be as effective as expected, particularly in critically ill subjects.

There is accruing evidence indicating that capsaicin administration may prevent AKI onset in various models of kidney damage. In particular, in an in vitro model of AKI [4], capsaicin ameliorated cytotoxicity induced by lipopolysaccharides, reducing the release of specific interleukins (i.e., IL-1β and IL-18) and reactive oxygen species (ROS). Specifically, such an effect has been attributed to the activation of the TRPV1 channel and mitochondrial uncoupling protein-2 (TRPV1/UCP2) axis, triggering a protective effect against inflammation, pyroptosis, apoptosis, and mitochondrial dysfunction.

In another model of contrast-associated AKI (CA-AKI), capsaicin significantly improved tubular damage and renal dysfunction by reducing cell apoptosis, renal malondialdehyde, and superoxide, also improving mitochondrial function and structure. Notably, these effects were all mediated by an enhanced activation of the nuclear factor-erythroid 2-related factor 2 (Nrf2) [5]. In other AKI models, capsaicin was useful in preventing cisplatin- and methotrexate-induced renal damage in rats, suggesting a protective effect against toxins and lipid peroxidation as well, which represent the causative mechanisms of renal damage in this setting [6][7][8].

Sparse evidence shows that capsaicin may also ameliorate ischemic AKI, one of the most frequently observed forms of AKI in the clinical setting. The mechanism behind this beneficial effect would likely involve TRPV1 as well as TRPV4 channels, which drive an enhanced flow of calcium–potassium in endothelial cells causing vasodilation, thereby ameliorating ischemic renal injury [9].

By the same token, the activation of TRPV1, TRPV4, TRPC6, and TRPM2 on rodent models of AKI following ischemia–reperfusion promotes renoprotection through regional vasodilation [10], an observation which might endorse these surface proteins as potential therapeutic targets for ischemic AKI. Additionally, both in vitro and in vivo studies have revealed that N-octanoyl-dopamine, an agonist of TRPV1, exerts a remarkable renoprotective effect that can ameliorate AKI outcomes [11].

In mice with ischemia/reperfusion-induced kidney damage, the stimulation of TRPV1-filled primary sensory nerves by capsaicin ameliorated AKI, although the inhibition of those channels did not affect their overall outcome [12]. Conversely, other hypotheses assume that the degeneration of sensory nerves on rodent models in vivo may aggravate such a condition [8]. TRPV1 receptors are also involved in modulating inflammation and oxidative stress following ischemic kidney injury, as demonstrated in an experimental model in which rats treated with capsaicin following a salt-induced kidney ischemia and hypertension displayed a reduction in kidney damage due to the activation of TRPV1 [13].

Salt intake increases the activity of the renal sympathetic nervous system (SNS) after renal ischemia–reperfusion [14]. Mice fed with salt and treated with capsaicin show a reduction in SNS activity, an effect which can likely be attributed to the selective activation of TRPV1 channels [15].

Beyond attenuating ischemia–reperfusion-induced renal damage, preventive capsaicin administration also reduced the expression of neutrophil infiltration, renal superoxide production, and renal tumor necrosis factors (TNFs), which are all acknowledged as key players in the pathogenesis of AKI and its progression towards chronic kidney damage [16]. Evidence on the putative renoprotective effects of capsaicin in the setting of AKI is, thus, convincing (**Table 1**). Yet, such findings remain confined to experimental models and would need to be confirmed in the clinical setting by targeted interventional trials.

Table 1. Main experimental studies testing the effects of capsaicin in different models of AKI.

Authors	Models	Results
Han et al. [4]	HK-2 cells treated with ATP and LPS	Capsaicin preincubation ameliorated LPS-induced cytotoxicity through TRPV1/UCP2 axis activation by reducing IL-1β, IL-18, and ROS release.
Ran et al. [5]	Dehydrated C57BL/6J mice treated with the contrast medium iodixanol	Preventive capsaicin administration reduced contrast-induced AKI through Nrf2 activation by decreasing superoxide, renal malondialdehyde, and apoptotic tubular cells and improving mitochondrial function.
Shimeda et al. [7]	Male Sprague–Dawley rats treated with cisplatin	Dietary capsaicin reduced cisplatin-induced renal damage by reducing lipid peroxidation.
Aldossary et al. [6]	AKI following methotrexate intoxication in rats	Capsaicin administration reduced methotrexate-induced renal damage by anti-inflammatory and antioxidant effects.
Tsagogiorgas et al. [11]	Inbred male Lewis rats treated with NOD	Treatment with the synthetic analogue of capsaicin NOD had renoprotective effects against ischemia-induced AKI through TRPV1 activation by inhibiting TNF-α mediated inflammation and through production of the vasodilator peptides CGRP and SP.
Yu et al. [13]	Male Wistar rats fed with high-salt diet	Capsaicin injection reduced renal inflammation driven by high-salt diet, oxidative stress, and fibrosis through activation of TRPV1.
Yu et al. [15]	Rats fed with high-salt diet after ischemia–reperfusion damage	Capsaicin inhibited renal sympathetic nerve activity by activating TRPV1 receptors, which prevented the appearance of salt sensitivity following renal ischemia–reperfusion damage.
Ueda et al. [16]	Uninephrectomized male Sprague–Dawley rats developing AKI following renal artery and vein occlusion	Treatment with capsaicin or its analogue resiniferatoxin reduced ischemia–reperfusion renal damage by reducing neutrophil infiltration, superoxide production, and TNF-α production and by increasing IL-10 production.

Legend: AKI: acute kidney injury; ATP: adenosine triphosphate; CGRP: calcitonin gene-related peptide; HK-2: human kidney 2; IL-1β: interleukin-1 beta; IL-10: interleukin-10; IL-18: interleukin-18; LPS: lipopolysaccharide; NOD: N-octanoyl-dopamine; Nrf2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species; SP: substance-P; TRPV1: transient receptor potential vanilloid type 1; UCP2: uncoupling protein 2; TNF-α: tumoral necrosis factor alpha.

2. Diabetic Kidney Disease

Diabetes mellitus is the leading cause of end-stage kidney disease (ESKD) worldwide, accounting for more than a half of all individuals requiring chronic dialysis treatment [17]. DKD encompasses a wide spectrum of type of renal damage due to chronic diabetes, spanning from micro-vascular alterations to selective glomerular damage with severe proteinuria and rapid progression to terminal uremia. The adoption of an optimal lifestyle, blood glucose and weight control, and the use of renoprotective agents (such as RAS inhibitors, SGLT-2 inhibitors, or mineralocorticoids) remain the mainstay combined approach to preserve renal function [18]. Yet, in a large percentage of diabetic patients, such measures are ineffective in

slowing down DKD's progression towards ESKD. The search for complementary approaches for improving renoprotection in this particular setting thus remains a timely issue.

Capsaicin has already been extensively studied as a natural method to reduce pain related to diabetic neuropathy [19], but its implications regarding DKD are still an object of intense investigation.

In particular, chronic administration of capsaicin on diabetic rats increased diuresis and the urinary excretion of the epidermal growth factor (EGF) but reduced the urinary levels of N-acetyl-b-D-glycosaminidase (NAG-L), a well-known biomarker of early kidney damage in DKD [20].

Altered intracellular calcium levels and mitochondrial dysfunction are two key features of podocyte dysfunction in DKD [21]. In diabetic mice models, oral capsaicin administration attenuated renal damage in a TRPV1-dependent manner by improving the intracellular calcium balance, by reducing the transport of calcium to the mitochondria, and by decreasing mitochondria-associated membrane formation [22]. Iron overload, which is common in diabetes, may trigger or worsen DKD [23]. In an interesting experiment, chronic capsaicin administration was tested in male Wistar rats with iron overload (IOL) and diabetes mellitus + IOL [24]. Capsaicin markedly reduced kidney iron deposits by increasing the circulating levels of hepcidin, an important regulator of iron homeostasis, but had apparently no relevant effects on biomarkers of renal damage such as albuminuria, cystatin C, and beta-2-microglobulin.

Hence, more evidence is still needed in order to better understand the true implication of capsaicin in DKD. Yet, these preliminary, interesting findings can also give a concrete hope for a possible therapeutic application of this molecule in this condition.

3. Chronic Kidney Disease

CKD is the common final route of every chronic nephropathy. In fact, regardless of the different etiologies, all chronic renal diseases converge on an irreversible histological picture, represented by renal tubulointerstitial fibrosis and renal tubular atrophy, which disrupts the cellular organization and leads progressively to renal function deterioration [25]. Despite being irreversible, the velocity of CKD progression over time is variable indeed, depending on the specific nephropathy and the additional risk factors. As for DKD, lifestyle and pharmacologic efforts to counteract CKD progression may not be fully effective in a large percentage of patients, which justifies the ample ongoing research on alternative therapeutic measures.

Experimental evidence indicates that capsaicin can reduce fibrosis accumulation on different organs [26]. In two different mouse models of renal fibrosis [27], capsaicin administration reduced fibronectin and collagen depositions in kidneys with a complex action on intracellular signals pathways, involving the inhibition of the Transforming Growth Factor-β1 small mother against decapentaplegic 2/3 signaling, which is the main promoter of profibrotic mechanisms. TRPV-1 activation by capsaicin increased intracellular calcium, upregulating various protein kinases and Silent information regulator 1, which in turn enhanced the activity of endothelial nitric oxide synthase (eNOS) with following endothelium vasodilation, finally inhibiting interstitial fibrosis [28]. These findings fit well with those reported by other studies, proving that oral capsaicin may reduce renal tubular interstitial fibrosis also by targeting the TGF-β1/epithelial–mesenchymal transition (EMT) pathway [29][30][31]. Besides renal fibrosis, pathological vascular calcification also contributes to disease progression and cardiovascular complications in CKD, representing a strong predictor of mortality in these patients [32]. Chronic Hypoxic-Inducible Factor-1 alpha (HIF-1α) accumulation is known to cause osteogenic trans-differentiation, which is one of the first steps leading to diffuse arterial calcification [33][34]. In a rat model of CKD, capsaicin could inhibit the osteogenic trans-differentiation of vessels by acting either on TRPV1 activation and HIF-1α degradation through the upregulation of Sirtuin 6 [35]; such a double, synergic mechanism to prevent vascular calcification by capsaicin would absolutely deserve additional target investigations to ascertain whether this natural compound could indeed represent a valid therapeutic option for ameliorating this serious and still irreversible complication of CKD.

4. Arterial and Renovascular Hypertension

The kidney plays a determinant role in regulating blood pressure homeostasis, and deranged hormonal or vascular kidney responses have been implicated in the pathogenesis of either essential or secondary forms of arterial hypertension. On the other hand, hypertension remains one of the major risk factors for the onset and progression of kidney diseases [36]. As briefly alluded to before, CGRP is a potent vasodilator and is the principal neurotransmitter in capsaicin-sensitive sensory nerves. Besides its vasodilatory effects, this peptide is involved in the control of arterial pressure by interacting with the renin–angiotensin–aldosterone (RAS) and the sympathetic nervous system and may modulate the proliferation of

the smooth muscle cells in the medium layer of arterial vessels [37]. As previously said, capsaicin is a potent inductor of CGRP release [38]. Accordingly, experimental administration of this substance can ameliorate hypertension in rat models, an effect which is partially mediated by an increased release of the insulin-like growth factor 1 [39]. Sodium excess is another fundamental player in the pathogenesis of hypertension [40]. Induction of TRPV4 channel activation causes hypotension in rats fed salt, suggesting that this receptor channel has a protective role against salt-induced hypertension [41]. According to this hypothesis, the preventive blockade of TRPV4 channels expressed in kidneys leads to a significant increase in the blood pressure values of salt-sensitive mice [42]. As previously mentioned, capsaicin also exerts a natriuretic role by activating TRPV1 channels, which promote the expression of epithelial sodium channels in the kidneys. Thus, long-term administration of capsaicin could be helpful for preventing the development of hypertension secondary to dietary salt overload [43].

As is well-acknowledged, renal denervation leads to a remarkable decrease in arterial pressure [44]; this is, at least in part, attributable to the disruption of overactive renal nerves expressing TRPV1. In fact, deprivation of those channels in rats in the presence of capsaicin caused a lack of sympathetic activity stimulation with a following reduction in blood pressure values and a significant increase in the glomerular filtration rate [45]. On the other hand, high salt intake after sensory denervation in rats increases blood pressure values, thus indicating that salt overload induces hypertension independently of sensory nervous activity [46]. Effectively, the blockade of TRPV1 causes an increase of blood pressure values in salt-resistant rats fed with a high salt diet, while it has no effect on salt-sensitive rats fed with a normal sodium diet; on the other hand, the stimulation of TPRV1 decreases blood pressure values more in salt-resistant animals fed with a high-salt diet than in others [47]. These results can prove that TRPV1 is activated during a chronic dietary salt overload, implying that this channel may play a central role in the pathogenesis of salt-sensitivity hypertension. Salt overload in salt-sensitive rats impairs the activity of TRPV1 in their kidneys, which suppresses the release of CGRP and substance P in the renal pelvis [48]. However, this does not happen in salt-resistant mice fed with high salt intake. Hence, bearing in mind that CGRP and substance P may act as vasodilators, these findings suggest that those two molecules, as well as capsaicin, which drives their release, could be helpful for preventing renovascular hypertension. The potential benefits of capsaicin in reno-vascular hypertension have also been highlighted in another experiment focusing on the vasodilatory effects of this molecule and its capacity of triggering the release of nitric oxide [49]. However, direct renal infusion of capsaicin increases the contralateral renal sympathetic nerve activity in a dose-dependent manner, which leads to a paradoxical increase in blood pressure through an excitatory renal reflex mediated by the paraventricular nucleus [50]. Additionally, the degeneration of TRPV1-filled nerves enhances salt-induced hypertension in rats after renal ischemia–reperfusion injury through the release of inflammatory mediators [51]. Taken all together, these findings indicate that TRPV1 channels could represent a promising target for the treatment of salt-sensitive renal hypertension, also suggesting a potential role for capsaicin as a natural remedy for ameliorating blood pressure control together with the use of common antihypertensive drugs (**Table 2**).

Table 2. Main studies testing the benefits of capsaicin administration in different models of reno-vascular hypertension.

Authors	Model	Results
Harada et al. [39]	**Spontaneously hypertensive rats and Wistar Kyoto rats**	**Capsaicin administration increased CGRP and IGF-1 plasma levels in SHR as compared to those reported in WKR.**
Gao et al. [41]	**Male Wistar rats fed with normal sodium diet and high sodium diet**	**HS diet induced TRPV4 expression in mesenteric arteries and sensory nerves with following increase in CGRP and IGF-1 levels. HS diet induced a marked increase of blood pressure when TRPV4 channel was blocked.**
Li et al. [43]	**C57BL/6 wild-type mice and TRPV1-/- mice**	**Dietary capsaicin induced natriuretic effect by inhibiting WNK1/SGK1/aENaC pathway with consequent reduction of aENaC expression at the renal level. Dietary capsaicin reduced HS diet-induced hypertension through TRPV1 activation.**
Stocker et al. [45]	**2-kidney-1-clip (2K1C) wild-type rats and 2K1C TRPV1-/- rats**	**TRPV1 channels deprivation in presence of capsaicin caused reduction in blood pressure and increase in the glomerular filtration rate due to the lack of sympathetic activity.**
Ye et al. [50]	**Spontaneously hypertensive rats and Wistar Kyoto rats**	**Renal infusion of capsaicin increased contralateral renal sympathetic nerve activation, causing an increase in blood pressure through a renal nerve reflex mediated by the paraventricular nucleus.**
Segawa et al. [49]	**2K1C rats and sham-operated rats**	**Dietary capsaicin reduced nephrovascular hypertension by promoting phosphorylation of Akt and eNOS, thus enhancing NO release.**

Legend: Akt: Ak strain transforming, also known as PKB protein chinase B; CGRP: calcitonin gene-related peptide; eNOS: endothelial nitric oxide synthase; IGF-1: insulin-like growth factor 1; HS: high sodium; SHR: spontaneously hypertensive

rats; 2K1C: 2-kidney-1-clip; NO: nitric oxide; TRPV1-/-: transient receptor potential vanilloid type 1 knock-out rats; WKR: Wistar Kyoto rats.

5. Renal Cancer

The anti-tumoral properties of capsaicin on different types of cancer cells are well-acknowledged, but definite data for recommending its daily use to synergize traditional anticancer therapy are still missing [52]. By targeting multiple signaling pathways, oncogenes, and tumor-suppressor genes, this substance may regulate the expression of different genes involved in cell survival, growth arrest, metastasis, and angiogenesis, as demonstrated in various models of cancer [53]. On top of that, capsaicin can promote changes in cell morphology and migration, probably by impacting cell-to-cell interactions, cell migration, and cell morphology; such effects would be likely driven by its interaction with the vanilloid receptors and the following regulation of calcium flow [54]. In a milestone experiment, capsaicin demonstrated a significant capacity of inhibiting migration and the invasion of renal cancer cells both in vitro and in vivo, as well as promoting cellular autophagy by activating the AMPK/mTOR pathway [55]. Such observations gave concrete support to the potential therapeutical application of this substance as an inhibitor of renal cancer invasion and peripheral metastasis. In addition, capsaicin promotes the inhibition of the PD-L1/PD-1 checkpoint, limiting the proliferation of human bladder and renal cancer cells [56]. In another model, capsaicin displayed an undisputable anticancer activity on human renal carcinoma by inducing apoptosis through the p38 and JNKs/MAPKs pathways, which are implied in the control of cell cycle progression [57]. Despite this preliminary evidence, however, the true anticancer effect of capsaicin on human renal neoplasias deserves an appropriate confirmation by focused clinical studies.

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