Preventive Effect of SA13353 [1-[2-(1-Adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea], a Novel Transient Receptor Potential Vanilloid 1 Agonist, on Ischemia/Reperfusion-Induced Renal Injury in Rats

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ABSTRACT

Tumor necrosis factor (TNF)-α plays a crucial role in the pathogenesis of ischemia/reperfusion-induced renal injury. We demonstrated recently that the preischemic treatment with resiniferatoxin, a transient receptor potential vanilloid 1 (TRPV1) agonist, attenuates renal TNF-α mRNA expression and improves ischemia/reperfusion-induced renal injury. In addition, we found that SA13353 [1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea], a novel orally active TRPV1 agonist, inhibits TNF-α production through the activation of capsaicin-sensitive afferent neurons and reduces the severity of symptoms in established rat collagen-induced arthritis. In the present study, we investigated the preventive effects of SA13353 on ischemia/reperfusion-induced renal injury in rats. Ischemic acute kidney injury (AKI) was induced by occlusion of the left renal artery and vein for 45 min followed by reperfusion, 2 weeks later, a computerized nephrectomy. Renal function and proteinuria in AKI rats rapidly decreased at 24 h after reperfusion. Treatment with SA13353 (3, 10, and 30 mg/kg p.o.) 30 min before ischemia/reperfusion attenuated the ischemia/reperfusion-induced renal dysfunction. Histopathological examination of the kidney of AKI rats revealed severe renal damage, which were significantly suppressed by the SA13353 treatment. In renal tissues exposed to ischemia/reperfusion, neutrophil infiltration, superoxide production, TNF-α mRNA expression, and cytokine-induced neutrophil chemoattractant-1 mRNA expression were augmented, but these alterations were attenuated by the treatment with SA13353. On the other hand, ischemia/reperfusion enhanced renal interleukin-10 mRNA expression and its plasma concentration were further augmented by SA13353 treatment. These results demonstrate that the novel TRPV1 agonist SA13353 prevents the ischemia/reperfusion-induced AKI. This renoprotective effects seem to be closely related to the inhibition of inflammatory response via TRPV1 activation.

Renal ischemia, followed by reperfusion, is one of the most common causes of acute kidney injury (AKI) and places a significant burden on the health care system. AKI is caused by ischemic and nephrotoxic insults acting alone or in combination. It is associated with increased morbidity, prolonged hospitalizations, and increased mortality (Kelly and Molitoris, 2000). The renal tubules are susceptible to hypoxic injury because of a number of factors, but they are also capable of rapid regeneration and functional recovery. The molecular mechanisms underlying ischemia/reperfusion-induced renal injury are not fully understood, but it has been reported that several causal factors [e.g., tumor necrosis factor (TNF)-α mRNA expression, ATP depletion, enhancement of reactive oxygen species production, phospholipase activation, neutrophil infiltration, vasoactive peptides, etc.] are contributive to the pathogenesis of this renal damage (Edelstein et al., 2000).

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Abbreviations: AKI, acute kidney injury; TNF-α, tumor necrosis factor; IL, interleukin; TRPV1, transient receptor potential vanilloid type 1; SA13353, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea; CINC, cytokine-induced neutrophil chemoattractant; BUN, blood urea nitrogen; Pcr, plasma creatinine concentration; FE_{Na^+}, fractional excretion of sodium; PCR, polymerase chain reaction; Rps18, ribosomal protein S18; CGRP, calcitonin gene-related peptide; LPS, lipopolysaccharide.
Among them, TNF-α is released during renal ischemia/reperfusion and plays an important role in the ensuing neutrophil-mediated kidney injury (Donnahoo et al., 1999). TNF-α up-regulates neutrophil adhesion molecules, in particular intercellular adhesion molecule-1, after renal ischemia/reperfusion, and this molecule then plays an important role in tissue neutrophil influx. Accumulating evidence indicates that renal TNF-α is an autocrine contributor to renal dysfunction induced by the ischemia/reperfusion (Ramesh and Reeves, 2004). On the other hand, the anti-inflammatory cytokine interleukin (IL)-10, which is a potent inhibitor of fever generation and early phase inflammation, has many effects such as inhibition of cytokines, chemokines, and neutrophil activation (de Vries, 1995). In addition, IL-10 has been shown recently to improve ischemic and cisplatin-induced AKI by inhibiting the maladaptive activation of genes that cause leukocyte activation and adhesion (Deng et al., 2001).

Transient receptor potential vanilloid 1 (TRPV1), formerly termed vanilloid receptor 1, is a nonselective cation channel that can be activated by noxious heat, protons, and vanilloids, such as capsaicin (Caterina et al., 1997), and is a range of putative endogenous mediators (Van Der Stelt and Di Marzo, 2004). TRPV1 was known originally to be a receptor with nociceptive primary afferent fibers, but subsequent observations revealed that it is broadly expressed in the epidermis, and visceral cells (Nagy et al., 2004). It is controversial that TRPV1 agonists act as a savatox of inflammation or inhibitors of it. Keeble et al. (2005) and Szabo et al. (2005) have demonstrated that TRPV1 plays a potential role in acute and chronic inflammation in the knee joint. In contrast, Kissin et al. (2005) have shown that capsaicin, a potent capsaicin analog, enhances knee joint inflammation. Small doses of capsaicin are known to reduce systemic inflammatory responses in septic rats (Kurbis et al., 2004). Moreover, it has been demonstrated that lipopolysaccharide-induced systemic inflammation and airway inflammation are augmented in the TRPV1-knockout mice, thereby suggesting the protective role of TRPV1-mediated action against the onset and severity of endotoxemia and endotoxin-induced airway inflammation (Christ et al., 2004; Helyes et al., 2007). A recent study demonstrated the recovery process of ischemia/reperfusion-induced cardiac dysfunction was impaired in TRPV1 knockout mice (Wang and Wang, 2005). TRPV1 expression is seen in a high percentage of primary afferent neurons that project to cardiovascular and visceral tissues (Wang, 2005). It has been demonstrated most recently that TRPV1 protein is highly present in the renal pelvis and exclusively expresses in renal papillar tissue and primary renal afferent fibres in a response to mechanostimulation (Feng et al., 2005). Moreover, the TRPV1 protein is abundantly located in renal medulla, although its functional roles are unknown (Feng et al., 2008). The renal medulla contains nephron segments that are most susceptible to ischemic injury (Brady et al., 2000). We have obtained evidence recently that the TRPV1 agonists capsaicin and resiniferatoxin attenuate renal TNF-α mRNA expression, increase renal IL-10 mRNA expression, and improve ischemia/reperfusion-induced renal injury in rats (Ueda et al., 2008). SA13353 was originally identified by us as a potent and orally active inhibitor of TNF-α production, and this effect was due to the activation of capsaicin-sensitive afferent neurons mediated via TRPV1 in vivo (Murai et al., 2008). In the present study, we investigated the effects of treatment with the TRPV1 agonist, SA13353, on the ischemic AKI in rats and evaluated the possible involvement of TNF-α, IL-10, and cytokine-induced neutrophil chemoattractant (CINC)-1 in the SA13353-induced actions.
weeks before the study (at 8 weeks of age), the right kidney was removed through a small flank incision under pentobarbital anesthesia (50 mg/kg i.p.). After a 2-week recovery period, uninephrectomized rats were divided into sham-operated control, vehicle-treated ischemic AKI, and drug-treated ischemic AKI groups. These all animals abstained from food for 12 h before the ischemia. To induce ischemic AKI, the rats were anesthetized with pentobarbital (50 mg/kg i.p.), and the left kidney was exposed through a small flank incision. The left renal artery and vein were occluded with a non-traumatic clamp for 45 min. At the end of the ischemic period, the clamp was removed for blood reperfusion. SA13353 (3, 10, and 30 mg/kg) and its vehicle (1% methylcellulose) were given orally 30 min before the start of reperfusion for evaluation of superoxide (O$_2^-$) production, neutrophil infiltration, mRNA expressions, and plasma concentrations of IL-10 and CINC-1.

The kidneys were excised and examined using a light microscope. In separate experiments, animals were sacrificed at various time points after the start of reperfusion for evaluation of superoxide (O$_2^-$) production, neutrophil infiltration, mRNA expressions, and plasma concentrations of IL-10 and CINC-1.

Histopathological changes were analyzed for tubular necrosis and neutrophil infiltration, respectively. Urine and plasma concentrations of IL-10 and CINC-1 were determined at 2 and 4 h after the reperfusion, based on our previous study (Ueda et al., 2008).

Renal Functional Parameters. Blood urea nitrogen (BUN) and plasma creatinine concentration (Pcr) were determined using a commercial assay kit, the BUN-test-Wako (Wako Pure Chemicals, Osaka, Japan), respectively. Urine and plasma sodium concentrations were determined using a flame photometer (205D; Hitachi, Fukushima, Japan). The fractional excretion of sodium (FE$_{\text{Na}}$; percentage) was calculated from the following formula: FE$_{\text{Na}}$ = (U$_{\text{Na}}$/P$_{\text{Na}}$) × (V/$N_a$), where U$_{\text{Na}}$ is the urinary excretion of sodium and P$_{\text{Na}}$ is the plasma sodium concentration.

Histological Analysis. Exposed left kidneys were processed for light microscopic observation according to standard procedures. The kidneys were frozen in liquid nitrogen and cut into 4-μm-thick sections, which were then dehydrated, embedded in paraffin, and stained with hematoxylin and eosin. Histological changes were evaluated by two independent pathologists. For quantitative analysis, 50 randomly selected high-power fields (×400) of the outer zone of medulla were counted using a light microscope.

Neutrophil Infiltration. Neutrophil infiltration was evaluated using naphthol AS-D chloroacetate esterase staining (91C; Sigma-Aldrich, St. Louis, MO) (Ueda et al., 2008) by counting the number of neutrophils present in the outer zone of the medulla of the kidneys. Neutrophils were counted in 50 randomly selected high-power fields (×400) of the outer zone of medulla. Data were expressed as neutrophils per millimeter squared of tissue.

Measurement of Renal O$_2^-$ Production. Renal O$_2^-$ production was measured using a lucigenin-enhanced chemiluminescence assay, as described previously (Nakajima et al., 2006). The whole kidney was removed from rats and cut into strips (2-mm pieces). Immediately afterward, renal tissue segments were placed in test tubes containing modified Krebs-HEPES buffer (pH 7.4, 99.01 mM NaCl, 4.69 mM KCl, 1.187 mM CaCl$_2$, 1.20 mM MgSO$_4$, 1.03 mM KH$_2$PO$_4$, 25 mM Na-HEPES, and 14.53 mM glucose) and allowed to equilibrate in the dark for 15 min at 37°C before measurements. After the equilibration, lucigenin (10 μM) was added to the tube, and then the luminescence was measured using a luminometer (Sirius-2; Berthold Technologies, Bad Wildbad, Germany) with a relative light unit integrated every 15 s for 18 min. The renal O$_2^-$ production was expressed as relative light units per minute per milligram dry tissue weight.

Total RNA was extracted from the left kidney, and reverse transcription was performed using commercially available kit (Nippon Gene, Tokyo, Japan) following the manufacturer’s instructions. Total RNA was reverse transcribed using a commercially available kit Takara Bio, Otsu, Japan. Ten microliters of reverse transcription was incubated at 37°C for 2 h. The PCR primer was synthesized from normal protein S18 forward, 5′-AAGGCTTAGCACATTGCAGCAAT-3′; Rps18 reverse, 5′-TTGCTGATTCTTTCCT-3′; TNF-α forward, 5′-ACTCTCAGAAGCCGGGCT-3′; TNF-α reverse, 5′-CCACACCTTTCTTCTTCTGG-3′; IL-10 forward, 5′-CAAGGGCTTGGAACACAGATTTCTGCGGA-3′; and IL-10 reverse, 5′-AGCTGCTTGTCTTGATTTAATGCTGCTGAA-3′; and CINC-1 reverse, 5′-AGGCCATTGGCCTGACATT-3′. All primers were purchased from Takara Bio. The PCR reactions were carried out in an ABI Prism 7000 (Applied Biosystems, Foster City, CA). Reverse transcription-PCR amplifications were performed in a volume of 50 μl. Each reaction mixture contained 2 μl of cDNA, 25 μl of iPAT Green PCR master mix (QIAGEN GmbH, Hilden, Germany), and 0.5 μM each primer. Each reverse transcription-PCR run started with a denaturation step at 95°C for 15 min to activate the Taq polymerase. The PCR reactions were done for 45 cycles. Each cycle consisted of: denaturation at 94°C for 15 s, annealing of primers for 1 min at 55°C and elongation for 1 min at 72°C. The mRNA copy numbers were calculated from the cycle threshold value using the ABI Prism 7000 Sequence Detection System (Applied Biosystems). Results of mRNA copy numbers were normalized against Rps18 mRNA.

Measurements of IL-10 and CINC-1 Protein. Plasma concentrations of IL-10 and CINC-1 were measured using the Bio-Plex Suspension System (Bio-Rad, Hercules, CA).

Statistical Analysis. Values are expressed as the mean ± S.E.M. Relevant data were processed by InStat (GraphPad Software Inc., San Diego, CA). For statistical analysis, we used one-way analysis of variance followed by Dunnett’s tests for multiple comparisons. Histological data were analyzed using the Mann-Whitney test. For all comparisons, differences were considered significant at P < 0.05.

Results

Screenings for the Target Molecules of SA13353. Although SA13353 was inactive (<50% inhibition at 1 μM) to most of the tested targets, the compound showed a binding affinity for the rat vanilloid receptor, a candidate target molecule. An IC$_{50}$ value of SA13353 for rat vanilloid receptor was 191 ± 28 nM (mean of three independent experiments).

Taking into account the $K_i$ value for the radioligand (0.046 nM), the $K_i$ value for SA13353 was 35.8 ± 5.2 nM. Capsaicin, the reference for the TRPV1 agonist (Caterina et al., 1997), showed a binding affinity for this receptor, with an IC$_{50}$ value of 3140 nM. For further details, please see the online Supplemental Table 1.
Pharmacokinetics and Excretion Route of SA13353. Plasma concentration of SA13353 peaked at 0.5 to 1 h after oral administration and thereafter decreased gradually (Fig. 1A). The mean $C_{\text{max}}$ and $T_{\text{max}}$ values of SA13353 after oral administration at a dose of 30 mg/kg was 476 ± 135 nM and 0.63 ± 0.13 h, respectively, and mean area under the plasma concentration-time curve from 0 to 24 h calculated by the linear trapezoidal rule was 3970 ± 860 nM/h. After oral doses of [14C]SA13353 (3 mg/kg) to male rats, 85.09 ± 1.90 and 8.96 ± 1.50% of the radioactivity dose were excreted in the feces and urine, respectively, during the 7-day sample collection period, indicating that SA13353 was predominantly excreted into feces (Fig. 1B). The recovery of radioactivity in feces, urine, expired air traps, and cage washings was 95.44 ± 1.76% of dose during this period. Therefore, we considered that the urinary excretion route is minor, and there is no effect of uninephrectomy on pharmacokinetics of SA13353. In addition, there were not more potent active metabolites than SA13353, and plasma concentrations of metabolites were not higher than that of SA13353 (data not shown). Taking into account the results of the binding and enzyme assays, SA13353 seems to be a near-pure TRPV1 agonist in this study.

Renal Function after the Ischemia/Reperfusion and Effects of SA13353. The renal function of rats subjected to 45-min ischemia showed a marked deterioration when measured 24 h after the reperfusion (Fig. 2). Compared with sham-operated rats, vehicle-treated AKI rats showed significant increase in BUN (173.33 ± 95.44 mg/dl), $P_{\text{cr}}$ (4.28 ± 0.63 mg/dl), $\text{FEN}_a$ (3.40 ± 0.41 mg/dl), $\text{FE}_{\text{Na}}$ (15.99 ± 3.84 versus 0.79 ± 0.46%). The administration of SA13353 (3, 10, and 30 mg/kg) 30 min before ischemia produced a dose-dependent protective effect against the ischemia/reperfusion-induced renal dysfunction. When a higher dose of SA13353 (30 mg/kg) was given, renal function changes induced by ischemia/reperfusion were markedly improved (BUN, 74.50 ± 10.91 mg/dl; $P_{\text{cr}}$, 1.92 ± 0.29 mg/dl; $\text{FEN}_a$, 3.40 ± 0.41 mg/dl; $\text{FE}_{\text{Na}}$, 15.99 ± 3.84 versus 0.79 ± 0.46%). The administration of SA13353 (3, 10, and 30 mg/kg) 30 min before ischemia produced a dose-dependent protective effect against the ischemia/reperfusion-induced renal dysfunction. When a higher dose of SA13353 (30 mg/kg) was given, renal function changes induced by ischemia/reperfusion were markedly improved (BUN, 74.50 ± 10.91 mg/dl; $P_{\text{cr}}$, 1.92 ± 0.29 mg/dl; $\text{FEN}_a$, 3.40 ± 0.41 mg/dl; $\text{FE}_{\text{Na}}$, 15.99 ± 3.84 versus 0.79 ± 0.46%).

Histological Renal Damage after the Ischemia/Reperfusion and Effects of SA13353. Histopathological examinations revealed severe lesions in the kidney of vehicle-treated rats (24 h after the ischemia/reperfusion). These changes were characterized by tubular necrosis in the outer zone outer stripe of the medulla (Figs. 3C and 4A; score, 4.00 ± 0.00) and medullary congestion and hemorrhage in the outer zone inner stripe of the medulla (Figs. 3E and 4B).

Neutrophil Infiltration in the Kidney after the Ischemia/Reperfusion and Effects of SA13353. Neutrophils were observed in the kidney of vehicle-treated AKI rats 6 h after the reperfusion (Fig. 3A) and the number of infiltration neutrophils in the vehicle-treated AKI rats was significantly increased compared with the sham-operated rats (Fig. 5, A and D). On the other hand, the neutrophil infiltration was markedly suppressed in the renal tissues of AKI rats treated with SA13353 (30 mg/kg) (Fig. 5, C and D).

Renal O2 Production after the Ischemia/Reperfusion and Effects of SA13353. Experiments were conducted with SA13353 oral O2 production in AKI rats. As shown in Fig. 5E, the increased level of renal O2 production at 6 h after the ischemia/reperfusion was markedly suppressed by the treatment with SA13353 (30 mg/kg).

Preventive Effects of SA13353 on Renal Injury. Preventive Effects of SA13353 on Renal Injury.

**Discussion**

Postischemic AKI is a frequent clinical syndrome with a high morbidity and mortality (Kelly and Molitoris, 2000). Reperfusion of previously ischemic renal tissue initiates a series of complex cellular events that results in injury and the eventual death of renal cells because of a combination of...
Grades of score: 0, no change; 1, mild; 2, moderate; 3, severe; and 4, very severe.

Acetylcysteine, have been considered to be useful for the prevention and management of AKI (Venkataramani and Kellum, 2003), and much remains to be elucidated with regard to which interventions are beneficial to clinical outcomes. TRPV1 has also been suggested to play a role in ischemia-reperfusion via a variety of vascular beds (Engel, 1995). The activation of TRPV1 leads to release of several neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), and somatostatin (Buck and Burks, 1986). CGRP is strongly coexpressed in many TRPV1-expressing nerve fibers in the kidney, including sensory fibers in the renal nerve, the dural vasculature (Dux et al., 2003), and is suggested to confer a beneficial counterbalance to the development of hypertension (Márquez et al., 2006).

We have already demonstrated that TRPV1 agonists capsaicin and resiniferatoxin prevent ischemia/reperfusion-induced renal injury in rats (Oda et al., 2008). Because the oral toxicity of capsaicin is relatively high (oral LD₅₀ values of nearly 100–200 mg/kg in mice or rats) (Saito and Yamamoto, 1996), we tried to find a safer TRPV1 agonist than capsaicin, ultimately selecting SA13353 (Murai et al., 2008) from numerous compounds available (oral LD₅₀ values of 2000 mg/kg in rats). In the present study, we found that the treatment with SA13353 prevented the ischemia/reperfusion-induced renal dysfunction in rats. We have demonstrated most recently that SA13353 significantly inhibits lipopolysaccharide (LPS)-induced TNF-α production in a dose-dependent manner in rats (Murai et al., 2008). SA13353 inhibited a binding affinity for the rat vanilloid receptor and increased neuropeptide release from the rat dorsal root ganglion neurons. However, the neuropeptide release by SA13353 was blocked by pretreatment with the TRPV1 antagonist capsazepine. Although SA13353 inhibited LPS-induced TNF-α production in vivo, its effect was not observed in sensory denervation rat and TRPV1 knockout mice. These results suggest that SA13353 inhibits TNF-α production through activation of capsaicin-sensitive afferent neurons mediated via TRPV1 in vivo.

To investigate the possible mechanisms underlying renoprotective effects of SA13353 against the ischemia/reperfusion-induced renal injury, we first evaluated the effects of SA13353 on neutrophil infiltration, which is one of the major causes for renal injury after ischemia/reperfusion. Neutrophil is implicated as a mediator of tissue-destructive events in reperfusion injury (Weiss, 1989). The plasma membrane of the triggered neutrophil is the site of an unusual enzyme, termed the NADPH oxidase, which underlies the cell’s ability to generate a family of reactive oxidation chemicals. The
superoxide radical and its metabolites play an important role in the pathogenesis of tissue injury (Hirota et al., 1990). SA13353 extremely attenuated neutrophil infiltration and $O_2^-$ production, which may be derived mainly from the infiltrating neutrophil after ischemia/reperfusion.

Next, we investigated the possible inhibitory mechanisms of SA13353 on neutrophil infiltration observed in the renal tissue exposed to ischemia/reperfusion. Expressions of adhesion molecules including intercellular adhesion molecule-1 on endothelial cells are important for neutrophil infiltration. For expression of adhesion molecules, some cytokines, including TNF-$\alpha$, have a critical role (Springer, 1990). CINC-1, a major factor in acute inflammation, is responsible for the activation of neutrophils and for neutrophil chemotaxis to sites of injury (Watanabe et al., 1992). On the other hand, the anti-inflammatory cytokine IL-10 has been shown recently to inhibit ischemic and cisplatin-induced AKI (Deng et al., 2001). Therefore, we investigated the effects of SA13353 on TNF-$\alpha$, CINC-1, and IL-10 mRNA expression in the postischemic kidneys. We noted that the preischemic treatment with SA13353 attenuated the ischemia/reperfusion-induced augmentation of TNF-$\alpha$ and CINC-1 mRNA expression level. On the other hand, SA13353 further enhanced the increases in IL-10 mRNA and its serum protein levels elicited by the ischemia/reperfusion. Previous studies have demonstrated that neuropeptides such as CGRP (Feng et al., 1997; Gomes et al., 2005; Harzenetter et al., 2007) and somatostatin (Landa et
al., 1995) inhibited the LPS-induced TNF-α production in vivo and in vitro. We also found recently that the administration of SA13353 evoked the release of CGRP and somatostatin (Dai et al., 2008). Taken together, we suggest that the activation of capsaicin-sensitiveafferent neurons by SA13353 might result in the following release of neuropeptides that may play a role in the inflammatory reactions after ischemia/reperfusion.

In separate experiments, we confirm that the preventive effects of SA13353 on ischemia/reperfusion-induced renal injury are mediated by TRPV1, as we attempted to utilize the TRPV1 antagonist capsazepine. However, because capsaicine itself afforded the ischemia/reperfusion-induced renal injury, we could not evaluate its antagonizing activity on TRPV1 agonist-induced renoprotective effects (unpublished observations). Capsazepine not only a TRPV1 antagonist but also inhibits voltage-activated calcium channels and nACH receptors (Docherty et al., 1997; Docherty et al., 2004), thereby suggesting that capsazepine might not be appropriate for antagonizing study in the ischemia/reperfusion-induced renal injury model. Another TRPV1 antagonist, iodo-resiniferatoxin, is also reported to be inadequate as the TRPV1 antagonizing study in vivo (Seabrook et al., 2002). In a preliminary experiment, we noted that iodo-resiniferatoxin inhibited LPS-induced TNF-α production in vivo. Thus, further studies using TRPV1 antagonists with other pharmacological properties or TRPV1 knockout animals are required to elucidate the TRPV1-mediated renoprotective effect and its precise mechanisms.

In the present study, SA13353 was administered before the start of 45-min ischemia. However, because AKI cannot be predicted in many clinical cases, it is important to evaluate whether TRPV1 agonists can reverse the ischemia/reperfusion-induced renal dysfunction or at least enhance the recovery process when given after the reperfusion. Therefore, we examined the effect of the posts ischemic treatment (at 30 min after the start of reperfusion) with SA13353 (30 mg/kg p.o.), but the agent produced no significant renoprotective effect (unpublished observations). SA13353 administered after the reperfusion may be too late to overcome severe renal injury, although these cases are uncommon. Further studies using a mild disease model or higher doses of SA13353 are required to clarify whether SA13353 treatment after the reperfusion exerts a renoprotective effect.

In conclusion, the preischemic treatment with SA13353 prevents ischemia/reperfusion-induced renal injury, probably via TRPV1-mediated mechanisms, which are closely related to the inhibition of inflammatory responses. Taken together with the previous study using capsaicin and resiniferatoxin in a rat model (2008), renoprotective effects by TRPV1 agonists might be useful to preserve renal function in patients with AKI after cardiac and vascular surgery.

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References


