Acute stimulatory effect of tumor necrosis factor on the basolateral 50 pS K channels in the thick ascending limb of the rat kidney

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Received December 18, 2017; Accepted August 13, 2018

DOI: 10.3892/mmr.2018.9475

Abstract. The aim of the present study was to investigate the acute effect and mechanism of tumor necrosis factor (TNF) on basolateral 50 pS K channels in the thick ascending limb (TAL) of the rat kidney. The TAL tubules were isolated from the rat kidney, and the activity of the 50 pS K channels was recorded using the patch-clamp technique. The results indicated that the application of TNF (10 nM) significantly activated the 50 pS K channels and the TNF effect was concentration-dependent. Inhibition of protein kinase A, phospholipase A_2 and protein tyrosine kinase using pathway inhibitors (H89, AACOCF3 and Herbimycin A, respectively) did not abolish the stimulatory effect of TNF, indicating that none of these pathways mediated the TNF effect. By contrast, the phenylarsine oxide inhibitor against protein tyrosine phosphatase (PTP) decreased the activity of the 50 pS K channels and blocked the stimulatory effect of TNF on these channels. Furthermore, western blot analysis demonstrated that the application of TNF (10 nM) in the TAL increased the phosphorylation of PTP, an indication of PTP activity stimulation. Thus, it was concluded that the acute application of TNF may stimulate the basolateral 50 pS K channel in the TAL and the stimulatory effect of TNF may be mediated by the PTP-dependent pathway.

Introduction

Approximately 20-25% of filtered Na and Cl load is reabsorbed by the thick ascending limb (TAL) of the kidney, and thus it serves a key role in regulating urine concentration (1,2). Transepithelial Na and Cl transport occurs via a two-step process: Na and Cl enter the cells through type II Na-K-Cl cotransporters (NKCC2) in the apical membrane and then leave the cells via the basolateral membrane through Na pumps and Cl channels (3). During this process, the activity of NKCC2 can be regulated by apical and basolateral K channels. Indirectly affected by basolateral K channels through the generation of the cell membrane potential and driving Cl diffusion, NKCC2 activity is maintained by apical K channels through K recycling (4,5). Gu *et al* (6) demonstrated that several types of K channels are present in the basolateral membrane of TAL, with the 50 pS K channel being the primary type, which is regulated by many factors (7). However, the regulatory mechanism remains unclear.

Tumor necrosis factor (TNF) is produced by various epithelial cells, including those of the TAL, and is one of the main inflammatory cytokines with a great variety of actions in regulating inflammatory, immune and stress responses, as well as host defense, and cellular apoptosis and necrosis (8-10). Wei *et al* (11) demonstrated that TNF stimulates the apical 70 pS K channels and regulates NKCC2 activity by activating protein tyrosine phosphatase (PTP) in the TAL. As aforementioned, apical and basolateral K channels can regulate NKCC2 activity, thus, it may also be possible that TNF modulates NKCC2 activity by affecting basolateral K channel activity. Therefore, the present study aimed to determine the acute effect of TNF on basolateral 50 pS K channels and explore the regulatory mechanism of TNF.

Materials and methods

Reagents. TNF, H89, herbimycin A, arachidonyl trifluoromethyl ketone (AACOCF3), phenylarsine oxide (PAO), polylysine and collagenase were purchased from Sigma-Aldrich; Merck KGaA (Darmstadt, Germany). Antibodies against phospho (p)-PTP, PTP and actin were obtained from Affinity Biotechnology (Exeter, UK).

TNF treatment. Following patching and recording the 50 pS potassium channel current for 2-3 min, TNF (10 nM) was

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Key words: tumor necrosis factor, basolateral K channel, thick ascending limb, protein tyrosine phosphatase

added to the bath and the 50 pS potassium channel current recorded for 3-5 min.

Inhibitor treatment. After recording 50 pS potassium channel current for 2~3 min, the inhibitor (5 μM H89/5 μM herbimycin A/5 μM AACOCF3/1 μM PAO) was added to the bath. Following recording for 3-5 min, then the TNF was added to observe the change of 50 pS potassium channel current.

Preparation of the TALs. Male and female pathogen-free Sprague-Dawley rats (n=80; male:female 1:1; 4-5 weeks old: weight, 50-60 g; Animal Facility of The Second Affiliated Hospital of Harbin Medical University, Harbin, China) were housed at 20-25˚C, 50-65% relative humidity and a 12-h light/dark cycle with free access to normal rat chow and tap water. Rats were sacrificed by cervical dislocation and the kidneys were removed immediately. The kidney was cut into 1-mm thick slices with a blade, and then incubated at 37˚C in a HEPES buffer solution containing 10 mM HEPES, 140 mM NaCl, 5 mM KCl, 1.5 mM $MgCl_2$ and 1.8 mM $CaCl_2$ (pH 7.4) with collagenase type 1A (1 mg/ml) for 40-60 min. The collagenase-treated TALs were isolated under a dissecting microscope and placed on a 5x5 mm cover glass coated with polylysine. The cover glass with TALs was transferred to a chamber filled with HEPES buffer solution and mounted on an inverted microscope (Leica Microsystems GmbH, Wetzlar, Germany). The present study was approved by the Medical Ethics Committee of Jiamusi University (Heilongjiang, China).

Patch-clamp technique. The patch-clamp electrodes were pulled with a P-97 electrode-puller, and filled with a pipette solution containing 10 mM HEPES, 140 mM KCl and 1.8 mM $MgCl_2$ (pH 7.4). The channel currents recorded by an Axon 700B patch-clamp amplifier, were low-pass filtered at 0.5 kHz and digitized with an Axon interface (Digidata 1400A). Data were analyzed using the pClamp 10.0 software system (Axon Instruments; Molecular Devices, LLC, Sunnyvale, CA, USA). The channel activity was expressed as a product of channel open probability (P_o) and channel number (N), and calculated as follows from data samples of 90-sec duration in the steady state: $NP_o=\sum (1t_1+2t_2+...it_i)$, where t_i is the fractional open time spent at each of the observed current levels.

Western blot analysis. Total protein was extracted from the TAL tissues using RIPA lysis buffer (Beyotime Institute of Biotechnology, Haimen, China). Once protein concentrations were determined using the BCA method, 40 μl of protein extract was mixed with 10 μl of 5X SDS-PAGE loading buffer and boiled for 5 min. Following separation by electrophoresis at 50 μg protein/lane on a 10% SDS-PAGE gel, 50 μg of medullary TAL protein was transferred onto a nitrocellulose membrane. The membranes were then placed in blocking solution containing 5% nonfat dry milk in Tris-buffered saline-0.05% Tween (TBS-T) and blocked for 1 h at room temperature. The membranes were incubated with the rabbit anti-rat primary antibody (1:1,000; AF3412; Affinity Biosciences, Cincinnati, OH, USA) and β-actin (1:5,000; AF7018; Affinity Biosciences) for 12 h at 4˚C. Subsequently, the membranes were washed four times with TBS-T and incubated with goat anti-rabbit secondary antibody (1:5,000; ZB-2301; OriGene Technologies, Inc., Beijing, China) for 1 h at room temperature. Finally, the membranes were washed again with TBS-T four times and the protein bands were detected with enhanced chemiluminescence (Pierce; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The protein bands were scanned and quantified to analyze the protein expression using ImageJ software (version 1.45s; National Institutes of Health, Bethesda, MD, USA).

Statistical analysis. All data are presented as the mean ± standard error of the mean. The Student's t-test was used to determine the differences between two groups and analysis of variance followed by Student-Newman-Keuls post hoc test were used to determine the differences among multiple groups. SPSS software version 19.0 (IBM Corp., Armonk, NY, USA) was used and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Effect of TNF on 50 pS K channel activity. Previous studies have demonstrated that many factors regulate basolateral 50 pS K channels; for example, adenosine stimulating and calcium inhibiting the K channel (6,12,13). The aim of the present study was to investigate the regulation of TNF on 50 pS K channels. The addition of 10 nM TNF to the bath increased the channel activity (NP_o) from 0.28±0.07 to 0.55±0.12 in a cell-attached patch (n=5; $P<0.01$; Fig. 1). The stimulatory effect of TNF on 50 pS K channel activity was concentration-dependent. The dose-response curve presented in Fig. 2 demonstrated that 50 pS K channel activity increased with rising concentrations of TNF from 1 to 20 nM (n=5; $P<0.05$).

Role of protein kinase A (PKA) in the stimulatory effect of TNF. Once the stimulatory effect of TNF on the basolateral 50 pS K channels had been demonstrated, the present study investigated the mechanism underlying the stimulatory effect of TNF. Previous studies have reported that the activity of 50 pS K channels is increased by stimulating PKA or inhibiting phospholipase A_2 (PLA_2) (6,12). Therefore, the role of PKA in the stimulatory effect of TNF on 50 pS K channels was determined. Notably, no significant differences were observed in regard to the channel activity nor the stimulatory effect of TNF on the channel following the inhibition of PKA with H89, an inhibitor of PKA (Fig. 3). The results summarized in Fig. 4 revealed that H89 did not alter the channel activity (NP_o 0.29±0.08 to 0.3±0.09), but did significantly increase channel activity following the application of TNF (0.62±0.13; n=5; $P<0.01$). This suggested that the PKA-dependent pathway did not mediate the stimulatory effect of TNF on the 50 pS K channel.

Role of PLA_2 in the stimulatory effect of TNF. Next, the present study determined the role of AACOCF3 (5 μM), an inhibitor of PLA_2, in the stimulatory effect of TNF on the 50 pS K channels (Fig. 5). The results of the present study were in agreement with those of previous reports (12,13), as AACOCF3 significantly stimulated 50 pS K channel activity and increased the NP_o from 0.38±0.09 to 0.71±0.21 (n=5; $P<0.01$). As shown in Fig. 4, the addition of TNF increased the NP_o from 0.71±0.21

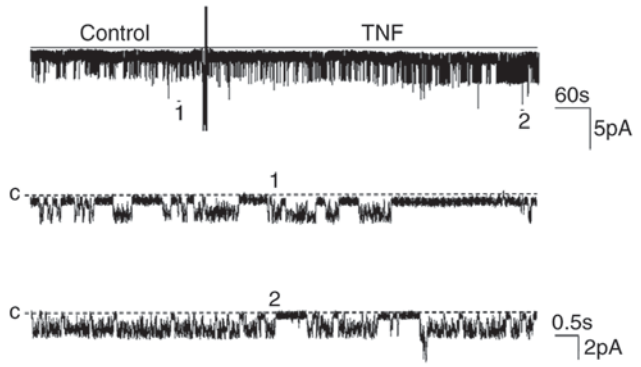

Figure 1. Effect of TNF (10 nM) on 50 pS K channel activity. The experiment was recorded by a cell-attached patch clamp. The top trace represents the experimental time course. The other traces with numbers represent the fast time resolution (trace 1 without TNF, trace 2 with TNF). The holding potential was 0 mV, and the channel closed current is indicated by 'C'. TNF, tumor necrosis factor.

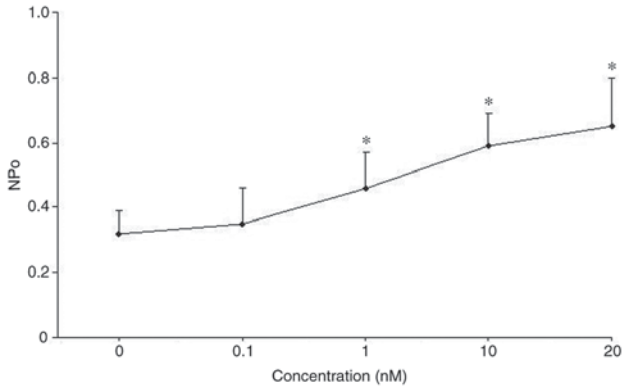

Figure 2. Dose-response curve of tumor necrosis factor on the 50 pS K channels. *P<0.05 vs. control group (0 nM). *NPo*, channel activity.

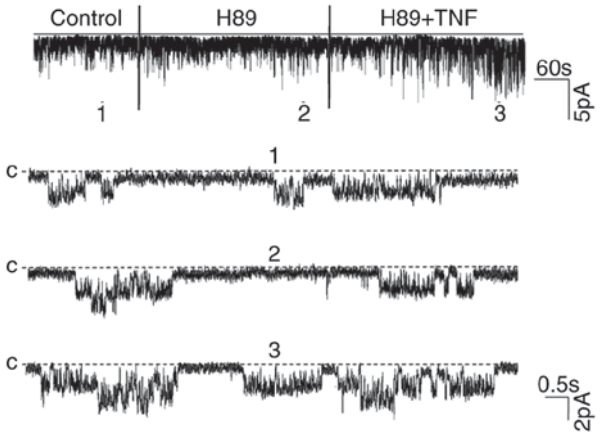

Figure 3. Effect of TNF (10 nM) on 50 pS K channel activity in the presence of H89 (5 μM). The top trace represents the experimental time course. The other traces with numbers represent the fast time resolution (1-3; enlargements of top trace). The holding potential was 0 mV, and the channel closed current is indicated by 'C'. TNF, tumor necrosis factor; H89, protein kinase A inhibitor.

to 1.25±0.26 (n=5; P<0.01) following the inhibition of PLA_2 with AACOCF3, indicating that the effect of TNF on the K channel was not mediated by the PLA_2-dependent pathway.

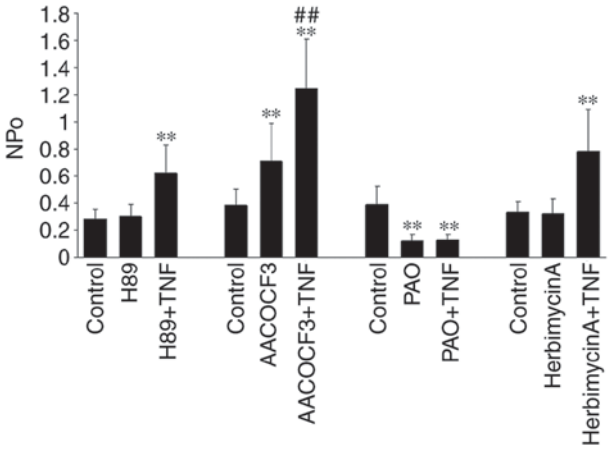

Figure 4. Effect of TNF on the 50 pS K channel *NPo* in the presence of H89 (5 μM), AACOCF3 (5 μM), PAO (1 μM) and Herbimycin A (5 μM). Experiments were performed in cell-attached patches. **P<0.01 vs. control group; ##P<0.01 vs. AACOCF3 group. TNF, tumor necrosis factor; *NPo*, channel activity; H89, a protein kinase A inhibitor; AACOCF3, arachidonyl trifluoromethyl ketone (phospholipase A_2 inhibitor); PAO, phenylarsine oxide (a protein tyrosine phosphatase inhibitor); Herbimycin A, a protein tyrosine kinase inhibitor.

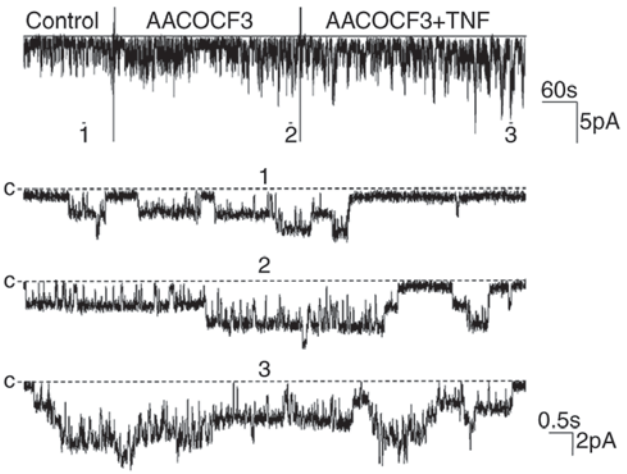

Figure 5. Effect of TNF (10 nM) on 50 pS K channel activity in the presence of AACOCF3 (5 μM). The top trace represents the experimental time course. The other traces with numbers represent the fast time resolution (1-3; enlargements of top trace). The holding potential was 0 mV, and the channel closed current is indicated by 'C'. TNF, tumor necrosis factor; AACOCF3, arachidonyl trifluoromethyl ketone (phospholipase A_2 inhibitor).

Role of PTP in the stimulatory effect of TNF. It has been reported previously that PTP can be increased by stimulating TNF receptors (14). Thus, it is necessary to explore the role of PTP in mediating the stimulatory effect of TNF on 50 pS K channels. The effect of TNF on channel activity was examined in the presence of PAO (1 μM), an inhibitor of PTP. The results indicated that PAO markedly decreased channel activity and eliminated the stimulatory effect of TNF (Fig. 6). The statistical results in Fig. 4 revealed that the NP_o of the 50 pS K channel was decreased following PAO treatment from 0.39±0.13 to 0.12±0.05 (n=5; P<0.01) and the application of TNF did not increase the NP_o of the channel (0.13±0.04; n=5; P>0.05), suggesting that the stimulatory effect of TNF may be derived from PTP stimulation. In order

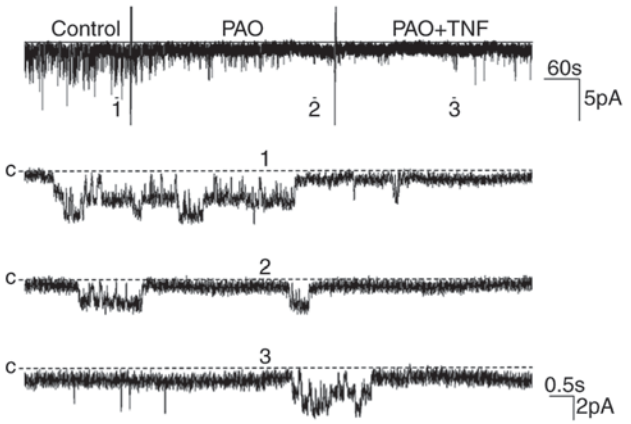

Figure 6. Effect of TNF (10 nM) on 50 pS K channel activity in the presence of PAO (1 μM). The top trace represents the experimental time course. The other traces with numbers represent the fast time resolution (1-3; enlargements of top trace). The holding potential was 0 mV, and the channel closed current is indicated by 'C'. TNF, tumor necrosis factor; PAO, phenylarsine oxide (a protein tyrosine phosphatase inhibitor).

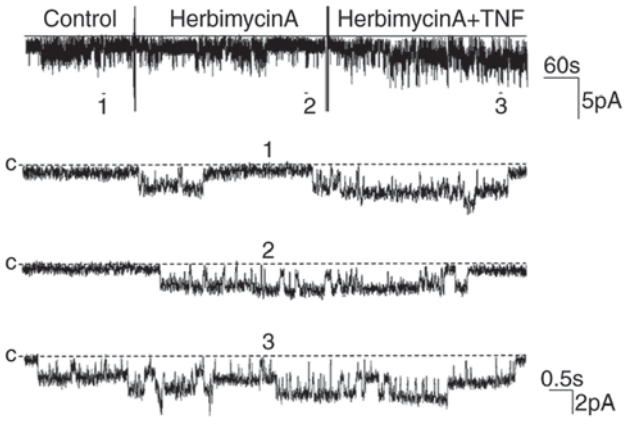

Figure 8. Effect of TNF (10 nM) on 50 pS K channel activity in the presence of Herbimycin A (5 μM). The top trace represents the experimental time course. The other traces with numbers represent the fast time resolution (1-3; enlargements of top trace). The holding potential was 0 mV, and the channel closed current is indicated by 'C'. TNF, tumor necrosis factor; Herbimycin A, a protein tyrosine kinase inhibitor.

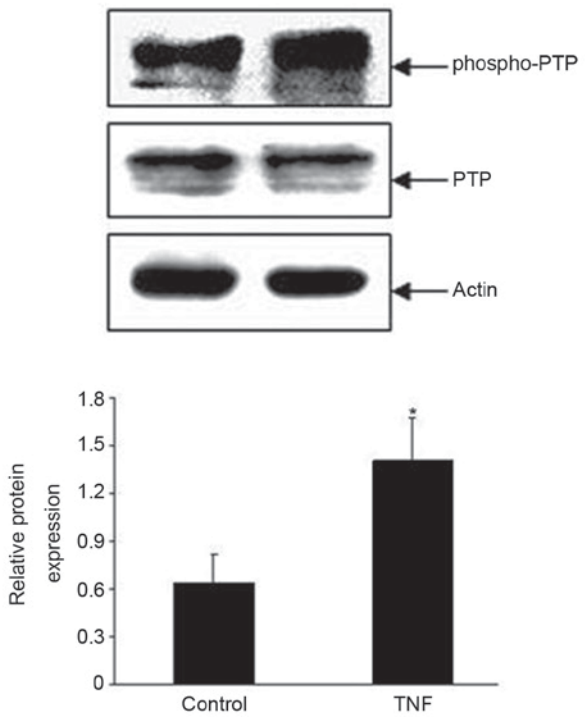

Figure 7. Effect of TNF on the phosphorylation of PTP at tyrosine residue 580 in the TAL. TALs were treated with 10 nM TNF for 5 min and the phosphorylation levels of PTP were determined by western blot analysis. This is a representative figure from 3 repeated experiments (n=3; *P<0.01). TNF, tumor necrosis factor; PTP, protein tyrosine phosphatase; TAL, thick ascending limb.

to further confirm the effect of PTP, a primary antibody directed against phosphorylated PTP at tyrosine residue 580 (p-PTP) was used to examine whether the application of TNF (10 nM) for 5 min in the TAL affected the phosphorylation level of PTP. Fig. 7 presents a representative western blot image revealing that TNF treatment significantly increased the phosphorylation level of PTP at tyrosine residue 580 by 55±10% (n=3; P<0.01). These results indicated that PTP activity stimulation may have increased the TNF-induced stimulatory effect on 50 pS K channels.

Role of protein tyrosine kinase (PTK) in the stimulatory effect of TNF. The aforementioned results suggested that the stimulatory effect of TNF on the 50 pS K channels may have resulted from stimulation of PTP and then enhancement of tyrosine dephosphorylation. However, PTP tyrosine phosphorylation is determined by PTK as well as PTP (15). Therefore, the present study further investigated whether the PTK pathway mediated the stimulatory effect of TNF on the 50 pS K channel. Firstly, the changes in channel activity following treatment with Herbimycin A (5 μM), an inhibitor of PTK, were observed (Fig. 8). Then, the role of PTK in the stimulatory effect of TNF on the channel was also determined. The statistical results revealed that Herbimycin A did not significantly alter the channel activity nor the stimulatory effect of TNF. The NP_o value was 0.33±0.08 prior to the addition of Herbimycin A, and 0.32±0.10 following treatment (n=5; P>0.05; Fig. 4). Furthermore, the addition of TNF significantly increased the channel activity (NP_o, 0.78±0.20; n=5; P<0.01; Fig. 4). These results indicated that the stimulatory effect of TNF was not mediated by the PTK-dependent pathway. The histogram of statistical results is shown in Fig. 4.

Discussion

In the present study, an important observation was demonstrated: The acute application of TNF stimulated the basolateral 50 pS K channel in the TAL through a PTP-dependent pathway. This was supported by two lines of evidence: i) The stimulatory effect of TNF on the channel was absent in the presence of the PTP inhibitor; and ii) the phosphorylation level of PTP at Tyr580 in the TAL was enhanced following TNF treatment. Therefore, it was hypothesized that TNF may activate PTP and enhance tyrosine dephosphorylation, thereby increasing basolateral 50 pS K channel activity in the TAL.

Usually, TNF production is low or absent prior to cellular stimulation; however, it increases significantly when exposed

to inflammation, infection and injury. Thus, it is possible that TNF may be associated with the occurrence of inflammation, cell differentiation and cell death (16). It has been reported that TNF regulates several pathophysiological events associated with renal inflammatory diseases (17,18), for instance, it contributes to lipopolysaccharide-induced glomerular endothelial injury (19). In addition, recent studies have suggested that TNF can be produced by physiologically relevant stimulations. It has been demonstrated that stimulation of the Ca^{2+}-sensing receptor (CaR) and hypertonic NaCl intake may increase TNF generation in TAL cells, and thereby regulate NaCl transport (20-23).

Wang *et al* (20) demonstrated that stimulation of the CaR increases TNF production via TAL cell incubation with high Ca^{2+} for >3 h. Furthermore, TNF increases cyclooxygenase (COX)-2 expression and prostaglandin E2 (PGE_2) production in TAL cells following CaR stimulation. It has been reported previously that inhibition of COX-2 in the TAL blocks TNF-mediated inhibition of Rubidium-86 (^{86}Rb) uptake, an *in vitro* indicator of natriuresis (20). In addition, PGE_2 has been demonstrated to inhibit the apical K channel (24) and basolateral K channel in the TAL (25), decreasing NaCl reabsorption in that segment. Therefore, TNF production induced by CaR stimulation may be a renal mechanism for regulating water and salt excretion.

Hao *et al* (23) demonstrated that hypertonic NaCl intake for 3 days increases renal TNF production via a pathway involving NKCC2 in the TAL. Furthermore, it has been revealed that the protein expression and activity of NKCC2 increases in TNF-deficient mice (26), indicating that TNF inhibits NKCC2 as part of a negative feedback regulator. Thus, TNF may inhibit NaCl reabsorption in the TAL as an endogenous inhibitor of NKCC2, subsequently leading to polyuria and natriuresis (27,28).

The present study demonstrated that acute application of TNF increased the activity of the basolateral 50 pS K channel. As the basolateral K channels determine the driving force for Cl diffusion across the basolateral membrane, a TNF-induced increase in channel activity should be associated with an increase in NaCl transport in the TAL. This conclusion is inconsistent with the inhibitory effect of TNF on NaCl transport in the TAL. Such a discrepancy may partly be accounted for by the temporal factor. TNF reduced ^{86}Rb uptake and NKCC expression following h or days, whereas stimulation of channel activity by TNF occurred in a few min. The effects of TNF on channel activity may be time-dependent and biphasic: The acute effect of TNF is to stimulate, whereas the chronic effect of TNF is to inhibit NaCl transport in the TAL. This phenomenon is similar to the delayed suppressive and acute stimulatory effect of interferon-γ on 40 pS K^+ channel activity in cultured human proximal tubule cells (29,30). In addition, the results of the present study are consistent with the report by Wei *et al* (11), which demonstrated that TNF stimulated apical 70 pS K^+ channel activity, consequently increasing NaCl transport in the TAL.

The significance of TNF in modulating renal tubular K^+ channels in the TAL is not well understood. However, many reports have demonstrated that changes in the activity of K^+ channels are involved in cell injury. For instance, Nietsch *et al* (31) reported that exposure to TNF for 3-5 min increased the opening times of K^+ channels and blockers of K^+ channels attenuated the progression to cell death by TNF at 4 h following TNF exposure in a rat liver cell line. Their observation indicates that channel opening is an early event in the TNF-mediated pathway leading to liver cell death (31). In addition, many studies have revealed that the occurrence of certain diseases, including diabetic nephropathy, is associated with an increase in TNF expression (32,33). Therefore, further studies should focus on exploring whether activation of the basolateral K channels induced by TNF is an early event of cell injury in the TAL.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Chinese National Nature Science Foundation (grant no. 31400994), National Undergraduate Innovation Project (grant no. 201610222030) and North Medicine and Functional Food Characteristic Construction Project.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ZY, GL and ZX performed the experiments. MX and ZT acquired and analyzed data. MM and LY analyzed data and drafted the manuscript. SY and WQ designed the project and revised the manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Jiamusi University (Heilongjiang, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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