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The Effect of Capsaicin on Neuroinflammatory Mediators of Rosacea

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Background: Rosacea is a chronic inflammatory skin disease with a pathophysiological mechanism that remains unclear. Recently, dysregulation of the sensory nerve system has been implicated in the development of this condition.
Objective: This study aimed to investigate the effect of capsaicin on neuroinflammatory mediators in rosacea. In addition, this study aimed to evaluate the attenuating effects of capsazepine, a transient receptor potential vanilloid type 1 (TRPV1) antagonist.
Methods: We obtained skin tissue from both rosacea patients and normal individuals for an *in vivo* study. In addition, normal human epidermal keratinocytes (NHEKs) were cultured, and treated with capsaicin and capsazepine for an *in vitro* study. Quantitative changes in neuroinflammatory mediators were evaluated by semi-quantitative reverse transcription-polymerase chain reaction (PCR), real-time PCR, enzyme-linked immunosorbent assay, and immunofluorescence staining.
Results: The data showed the increase of TRPV1, TRPV4, cathelicidin (LL37) and tumor necrosis factor-α (TNF-α) in skin tissue by real-time PCR. In addition, the data showed that cathelicidin (LL37), kallikrein-5 (KLK-5), TNF-α, vascular endothelial growth factor (VEGF), interleukin (IL)-1α, IL-1β, IL-8, and protease-activated receptor 2 (PAR2) increased in capsaicin-treated NHEKs. Capsazepine attenuated the expression of TRPV1 and other mediators, except for IL-8, in capsaicin-treated NHEKs.
Conclusion: We confirmed that TRPV1, TRPV4, cathelicidin (LL37) and TNF-α are increased in rosacea skin, and that capsaicin is associated with increase of neuroinflammatory mediators such as LL37, KLK-5, TNF-α, VEGF, IL-1α, IL-1β, IL-8, and PAR2. Modulators or inhibitors of neuroinflammatory mediators including TRPV1 could be potential therapeutic option in the treatment of patients with rosacea.

Keywords: Capsaicin, Rosacea

INTRODUCTION

Rosacea is a common chronic inflammatory skin disease that almost exclusively affects the facial area[1]. The manifestations of rosacea include erythema, flushing, telangiectasia, papules, pustules, and phymatous change[1]. The pathogenesis of rosacea has not been fully described, but several factors, such as genetic factors, immune dysregulation, neurovascular dysregulation, and various environmental aspects, are known to play a role[2]. Recent findings suggest that genetic and environmental components are triggers of rosacea and initiate and aggravate the condition by dysregulation of both innate and adaptive immune system responses[3]. These trigger factors induce the release of inflammatory mediators from variable cells in the skin such as keratinocytes, endothelial cells, mast cells, macrophages, T helper (Th) type 1, and Th-17 cells[1,2].

It is known that, in rosacea patients, transient receptor potential vanilloid type 1 (TRPV1) is upregulated, leading to abnormal flushing[1]. TRPV1 is a nonselective channel that integrates noxious chemical and physical stimuli in visceral

sensation[4]. Capsaicin is an agonist of the TRPV1 receptor[4]. However, it is still not clear whether TRPV1 is associated with other inflammatory mediators when it is stimulated with capsaicin or attenuated with capsazepine, a TRPV1 antagonist.

In this study, we aimed to confirm the upregulation of neuroinflammatory mediators in rosacea skin and investigate the effect of capsaicin on neuroinflammatory factors such as cathelicidin (LL37), kallikrein-5 (KLK-5), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), interleukin (IL)-1α, IL-1β, IL-8, and protease-activated receptor 2 (PAR2). Moreover, capsazepine reduced TRPV1 activation; therefore, this study further solidified the potential of capsaicin-TRPV1 antagonist (capsazepine) as a therapeutic option for rosacea.

MATERIALS AND METHODS

Human tissue samples

Human skin samples were obtained from the face of patients with erythematotelangiectatic rosacea after obtaining informed consent according to the guidelines of the local ethics committee of our hospital and the Declaration of Helsinki Principles (IRB no. CNUH-2019-353). After injection of local anesthesia, 3-mm punch biopsies were taken from the erythematous lesioned skin of individuals with rosacea (n=6) and skin of normal healthy volunteers (n=6) with informed consent for all procedures. In the case of the normal control group, after explaining the purpose and process of this study, we collected extra tissue generated during skin graft or flap surgery on the face for other skin diseases. In addition, we confirmed and used only skin tissue not including other skin diseases.

Immunofluorescence staining

Each three skin tissue samples obtained from rosacea patients and normal individuals through punch biopsies were immediately frozen in liquid nitrogen. Fresh frozen tissues were embedded in Tissue-Tek O.C.T. Compound (Sakura Finetechnical Co., Tokyo, Japan) in cryomolds with liquid nitrogen. Cryosections (6 μm) were prepared using a Leica CM1850 cryostat (Leica Biosystems, Nussloch, Germany) and mounted on slides (Fisherbrand, Pittsburgh, PA, USA). The sections were air-dried for 30 min, washed with phosphate-buffered saline (PBS; Lonza, Walkersville, MD, USA), and incubated with goat polyclonal anti-VR1 (TRPV1) antibody (Santa Cruz Biotechnology, Santa Cruz, CA USA) and rabbit polyclonal anti-LL37 antibody (Abcam, Cambridge, MA, USA). Alexa Fluor 594–conjugated chicken anti-goat immunoglobulin G (IgG) (Molecular Probes/Invitrogen, Carlsbad, CA, USA) and Alexa Fluor 488–conjugated goat anti-rabbit IgG (Molecular Probes/Invitrogen), respectively, were used as secondary antibodies. Sections were mounted in DAPI (Vector Laboratories, Burlingame, CA, USA). Images were visualized using confocal microscopy with a laser scanning microscope (LSM 800 with Airyscan; Carl Zeiss, Jena, Germany) and analyzed using the ZEN 2 browser imaging software (ZEN 2.6 [blue edition]; Carl Zeiss).

Cell culture and stimulation of normal human epidermal keratinocytes

We purchased normal human epidermal keratinocytes (NHEKs) from EpiLife (Cascade Biologics, Portland, OR, USA). Cells were cultured in basal keratinocyte growth medium (EpiLife), supplemented with human keratinocyte growth supplement (HKGS) and antibiotics (100 U/ml penicillin and 100 mg/ml streptomycin) in a 5% CO_2 incubator. Passages 2~9 were used for all experiments. NHEKs (1×10^4 cells/well) were seeded into 96 well plates. After application of capsaicin and capsazepine (Sigma-Aldrich, St. Louis, MO, USA) at various concentrations, cell viability was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma-Aldrich) assay according to the manufacturer's instructions. NHEKs at 70% confluence were stimulated with capsaicin (Sigma-Aldrich). The expression of TRPV1, LL37, KLK-5, TNF-α, VEGF, IL-1α, IL-1β, IL-8, and PAR2 was evaluated at times ranging from 0 to 12 h and at various concentrations of capsaicin (0.1, 1, 5, 10, and 20 μM). Regulation of these mediators induced by capsaicin (20 μM) was also evaluated after the application of a specific TRPV1 antagonist, capsazepine (Sigma-Aldrich) at various concentrations (1, 5, 10, and 20 μM). Capsazepine was added 30 min before capsaicin stimulation and incubated for the indicated times.

Semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR) and real-time PCR

Total mRNA was isolated using a RNeasy Mini Kit (Qiagen, Valencia, CA, USA). Subsequently, cDNA was reverse transcribed from 500 ng of total RNA using the Omniscript RT

kit (Qiagen) and subjected to semi-quantitative RT-PCR with the HiPi PCR PreMix (ELPIS, Daejeon, Korea). PCR reactions were performed using the following primers: human TRPV1, human TRPV2, human TRPV3, human TRPV4, human LL37, human KLK-5, human TNF-α, human VEGF, human IL-8, human IL-1α, human IL-1β, human PAR2, and human glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Table 1). Expression levels were normalized to the endogenous GAPDH levels. For experiments to measure mRNA levels, semi-quantitative RT-PCR and quantitative real-time PCRs were performed with the same primer sets for target genes. Real-time PCR was performed in triplicate with the HOT FIREPol EvaGreen® qPCR Mix Plus (Solis BioDyne, Tartu, Estonia) using a Thermal Cycler Dice RealTime System (Takara Bio Inc., Shiga, Japan). The thermal cycling conditions were as follows: 95℃ for 5 min, followed by 50 cycles of 95℃ for 10 s, 55℃~62℃ for 20 s, and 72℃ for 30 s. The relative abundance of a given transcript was estimated using the $2^{-\Delta\Delta Ct}$ method following normalization to endogenous GAPDH.

Enzyme-linked immunosorbent assay

Commercial enzyme-linked immunosorbent assay (ELISA) kits were used according to the manufacturer's protocols to quantify the immune molecules: human TRPV1 (Mybiosource, San Diego, CA, USA), human LL37 (Hycultbiotech, Uden, Netherlands), human VEGF (R&D Systems, Inc., Minneapolis, MN, USA), and human TNF-α (R&D Systems, Inc.).

Immunocytofluorescence staining

Cells were fixed in 4% paraformaldehyde and blocked with 5% goat serum. They were then incubated with rabbit polyclonal anti-VR1 (TRPV1) antibody (Abcam), rabbit polyclonal anti-

Table 1. Primer sense and anti-sense sequences, semi-quantitative RT-PCR/real-time PCR conditions

Gene	Sense and anti-sense sequence	Conditions (℃)	Size (bp)	Cycle
TRPV1	5′-TTCTTGTTCGGGTTTTCCAC-3′ 5′-TCTCCTGTGCGATCTTGTTG-3′	58	322	33
TRPV2	5′-GGAGGAAGACAGGACCCTTGACA-3′ 5′-TTCCCTTTCGGTAGTTGAGGTTGA-3′	62	265	32
TRPV3	5′-TCCTCACCTTTGTTCTCCTCCT-3′ 5′-CGCAAACACAGTCGGAAATCAT-3′	60	211	33
TRPV4	5′-TGGCTTCTCGCATACCGT-3′ 5′- GGCTCTGGCGTTGGCTTA-3′	60	413	32
LL37	5′-TCGGATGCTAACCTCTACCG-3′ 5′-GGGTACAAGATTCCGCAAAA-3′	59	348	35
KLK-5	5′-CCACTACTCCCTGTCACCAG-3′ 5′-GTAATCTCCCCAGGACACGA-3′	60	435	28
TNF-α	5′-AGCCCATGTTGTAGCAAACC-3′ 5′-TAGATGGGCTCATACCAGGG-3′	58	317	32
VEGF	5′-ATGAACTTTCTGCTGTCTTGGGT-3′ 5′-TGGCCTTGGTGAGGTTTGATCC-3′	60	350	28
IL-8	5′-TCTGCAGCTCTGTGTGAAGG-3′ 5′-TGAATTCTCAGCCCTCTTCAA-3′	60	232	30
IL-1α	5′-GGTAGTAGCAACCAACGGGA-3′ 5′-CTTCATCTTGGGCAGTCACA-3′	60	398	28
IL-1β	5′-TCCAGCTGTAGAGTGGGCTT-3′ 5′-GCTGAGGAAGATGCTGGTTC-3′	60	396	30
PAR2	5′-TGAAGATTGCCTATCACATAC-3′ 5′-GGCTCTTAATCAGAAAATAATGCA-3′	55	561	30
GAPDH	5′-GTCTTCACCACCATGGAGAAGGC-3′ 5′-CGGAAGGCCATGCCAGTGAGCTT-3′	60	400	28

PCR: polymerase chain reaction, TRPV: transient receptor potential vanilloid, KLK: kallikrein, TNF: tumor necrosis factor, VEGF: vascular endothelial growth factor, PAR2: protease-activated receptor 2, GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

LL37 antibody (Abcam), guinea pig polyclonal anti-substance P (Novusbio Biological, Littleton, CO, USA), and rabbit polyclonal anti-KLK-5 antibody (Abcam). Alexa Fluor 594-conjugated chicken anti-rabbit IgG, Alexa Fluor 488-conjugated goat anti-rabbit IgG, and Alexa Fluor 594-conjugated goat anti-guinea pig IgG (all from Molecular Probes/Invitrogen), were used as secondary antibodies. Sections were mounted in DAPI (Vector Laboratories) and visualised on a confocal microscope and a laser scanning microscope (LSM 800 with Airyscan; Carl Zeiss). Image analysis was performed using the ZEN 2 browser imaging software (ZEN 2.6 [blue edition]; Carl Zeiss).

Statistical analysis

All values are expressed as the mean±standard deviation. For statistical analyses, the independent t-test or one-way analysis of variance (ANOVA) with a post hoc Tukey HSD test were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), when multiple comparisons were made. Statistical significance was set at $p<0.05$.

RESULTS

NHEKs survival

Cell viability was evaluated after the cells were exposed to various doses of capsaicin and capsazepine (0, 0.098, 0.195, 0.391, 0.781, 1.563, 3.125, 6.25, 12.5, 25, 50, and 100 μM). Cell viability was not influenced by any dose of capsaicin or capsazepine (Supplementary Fig. 1).

Increased expression of neuroinflammatory mediators in rosacea skin compared with normal skin

Immunofluorescence staining revealed that both TRPV1 and cathelicidin (LL37) were more strongly expressed in almost the similar area in the entire epidermis of rosacea patients compared to those of normal skin (Fig. 1). Moreover, we performed real-time PCR on skin tissue samples obtained from patients with rosacea and normal individuals. Real-time PCR revealed markedly increased mRNA levels of TRPV1, TRPV4, LL37, and TNF-α in rosacea skin compared with that in normal skin (Fig. 2).

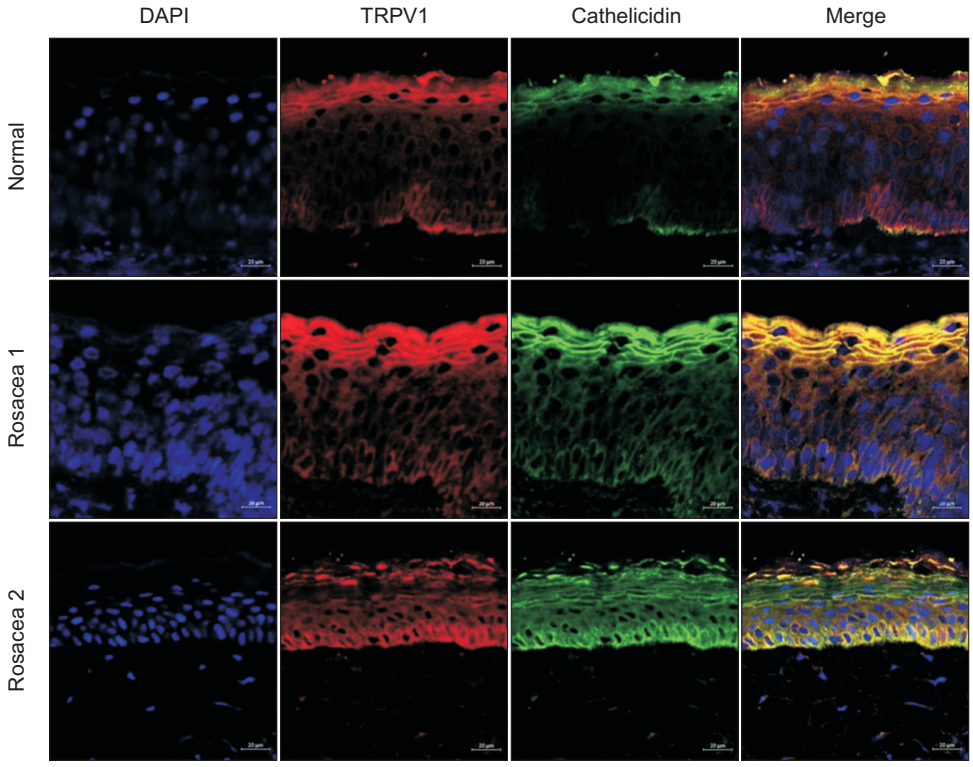

Fig. 1. Immunofluorescence staining: increased transient receptor potential vanilloid type 1 (TRPV1) and cathelicidin (LL37) expression in the epidermis of two patients with rosacea compared to normal skin. Expression of TRPV1 and cathelicidin (LL37) visualized by immunofluorescence staining *in vivo*. Nuclei were stained with DAPI (blue). Red indicates TRPV1; Green indicates cathelicidin (LL37); immunofluorescence, 40×. Scale bars, 20 μm.

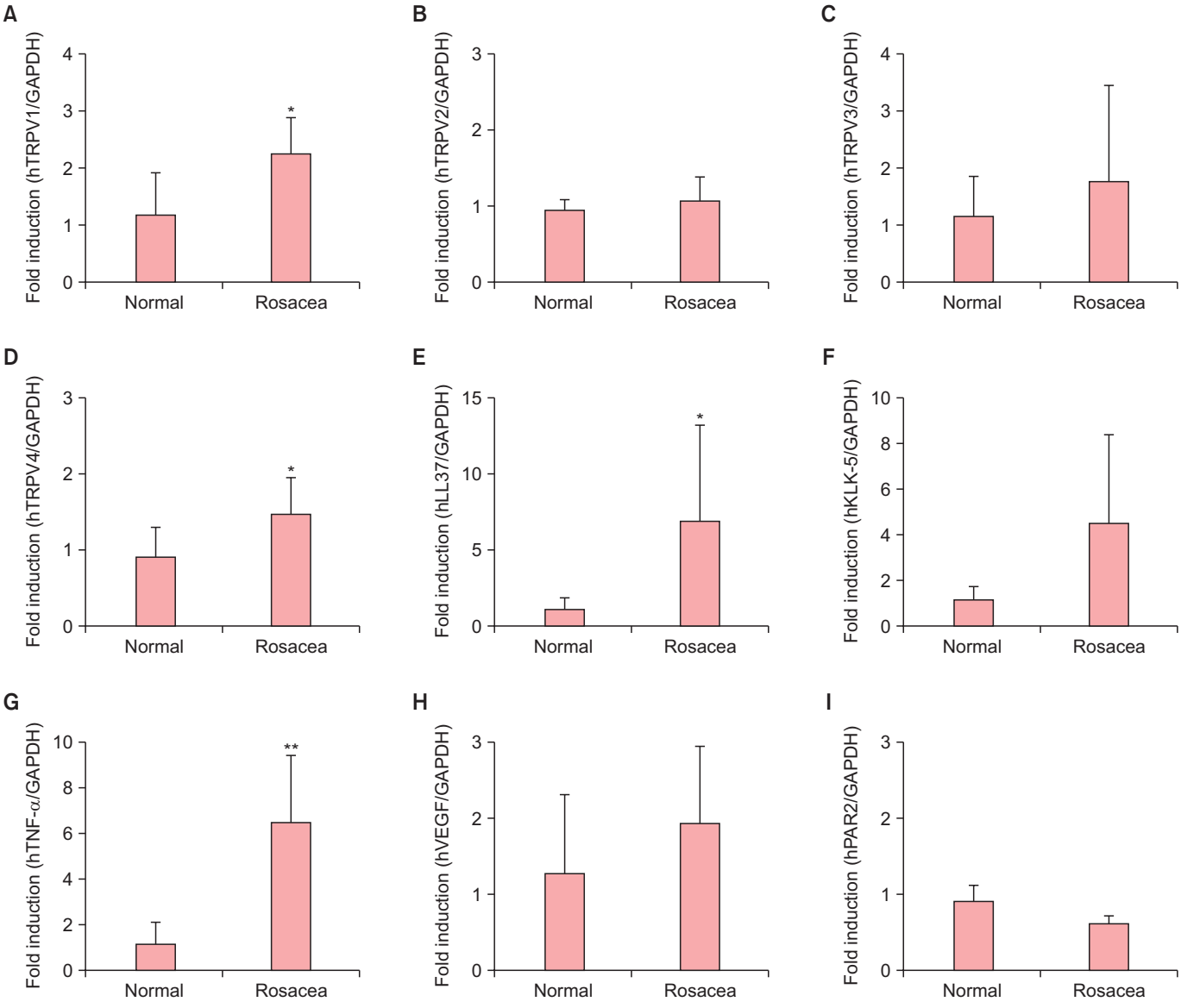

Fig. 2. Comparison of mRNA levels of neuroinflammatory mediators in skin tissue specimens *in vivo*. Columns represent the relative densities of each factor in rosacea skin (n=6) and normal skin (n=6). mRNA levels of (A) hTRPV1, (D) hTRPV4, (E) hLL37, and (G) hTNF-α increased significantly in the rosacea skin compared to normal skin on real-time PCR. In contrast, (B) hTRPV2, (C) hTRPV3, (F) hKLK-5, (H) hVEGF, and (I) hPAR2 showed no significant increase on real-time PCR. TRPV: transient receptor potential vanilloid, TNF-α: tumor necrosis factor-α, KLK-5: kallikrein-5, VEGF: vascular endothelial growth factor, PAR2: protease-activated receptor 2, PCR: polymerase chain reaction, GAPDH: glyceraldehyde 3-phosphate dehydrogenase. Statistically significant (*$p<0.05$; **$p<0.01$).

Capsaicin induced the increase of neuroinflammatory mediators in NHEKs

We performed semi-quantitative RT-PCR and ELISA to evaluate the association between capsaicin and neuroinflammatory mediators. Semi-quantified mRNA levels of TRPV1 (≥1 μM, $p=0.001$), LL37 (≥1 μM, $p=0.01$), KLK-5 (≥5 μM, $p=0.01$), TNF-α (≥1 μM, $p=0.01$), VEGF (≥5 μM, $p=0.003$), IL-1α (≥0.1 μM, $p=0.04$), IL-1β (≥5 μM, $p=0.01$), IL-8 (≥10 μM, $p=0.04$), PAR2 (≥10 μM, $p=0.01$) significantly increased 6 h after capsaicin treatment (Fig. 3). The mRNA levels increased to the maximum with capsaicin at 20 μM for all factors. ELISA results showed that capsaicin significantly increased the protein levels of human TRPV1 (≥5 μM, $p<0.001$), LL37 (≥5 μM, $p=0.04$), VEGF (≥5 μM, $p<0.001$), and TNF-α (≥5 μM, $p=0.006$) (Fig. 4A). In addition, immunocytofluorescence staining showed that the expressions of TRPV1, LL37, sub-

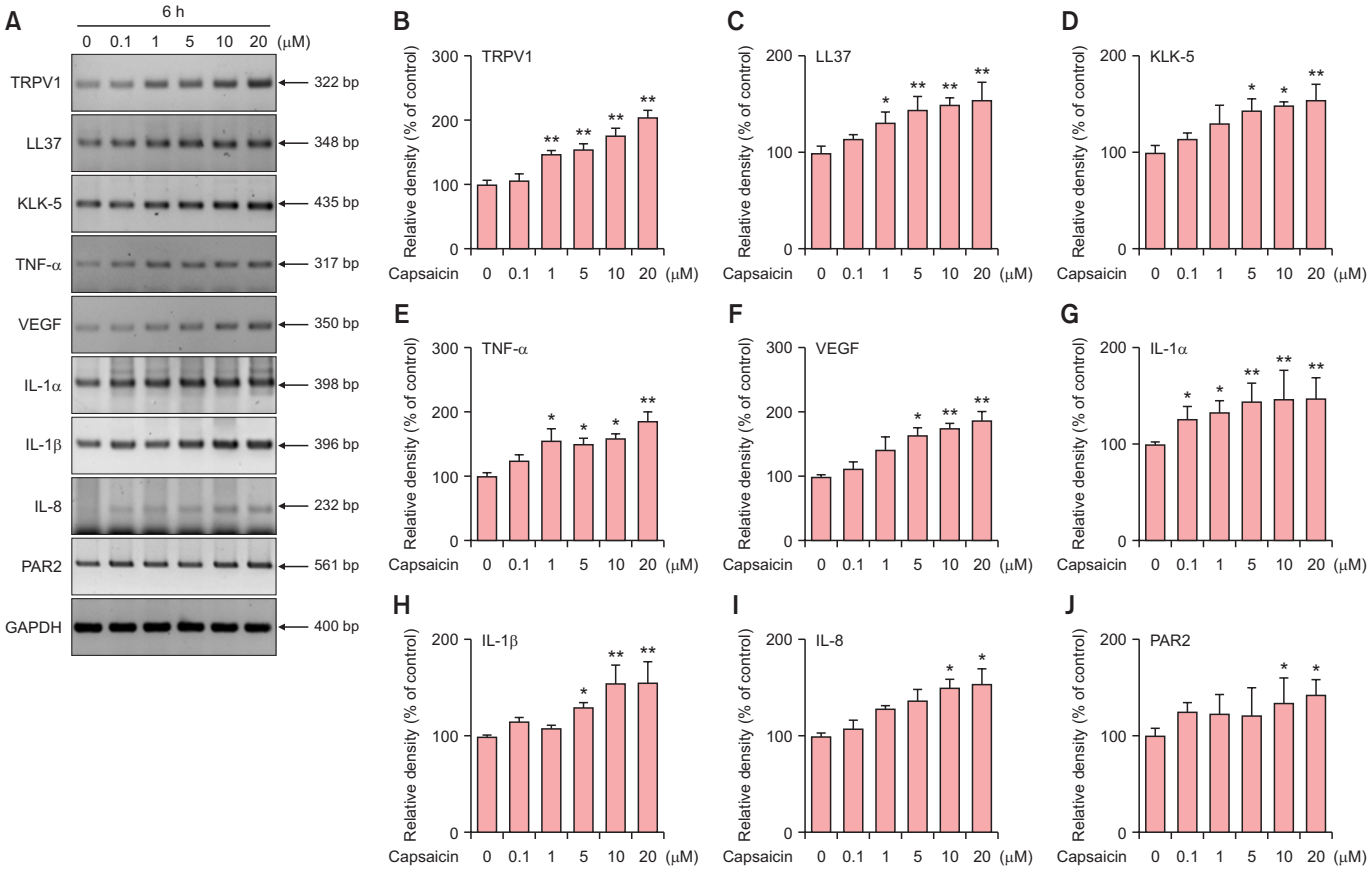

Fig. 3. (A) mRNA levels of TRPV1, LL37, KLK-5, TNF-α, VEGF, IL-1α, IL-1β, IL-8, and PAR2 in NHEKs *in vitro*. Columns represent relative densities of each factor in NHEKs after 6 h from capsaicin stimulation. mRNA levels of (B) TRPV1, (C) LL37, (D) KLK-5, (E) TNF-α, (F) VEGF, (G) IL-1α, (H) IL-1β, (I) IL-8, and (J) PAR2 increased in capsaicin-stimulated NHEKs on semi-quantitative RT-PCR. TRPV1: transient receptor potential vanilloid type 1, KLK-5: kallikrein-5, TNF-α: tumor necrosis factor-α, VEGF: vascular endothelial growth factor, IL: interleukin, PAR2: protease-activated receptor 2, NHEKs: normal human epidermal keratinocytes, RT-PCR: reverse transcription-polymerase chain reaction, GAPDH: glyceraldehyde 3-phosphate dehydrogenase. Statistically significant (*$p<0.05$; **$p<0.01$).

stance P, and KLK-5 significantly increased when stimulated by capsaicin (Supplementary Fig. 2).

Capsazepine attenuates neuroinflammatory mediators in capsaicin-stimulated NHEKs

Despite the upregulation by capsaicin, semi-quantified mRNA levels of TPRV1 (≥1 μM, $p=0.02$), LL37 (≥20 μM, $p<0.001$), KLK-5 (≥5 μM, $p=0.003$), TNF-α (≥1 μM, $p=0.02$), VEGF (≥1 μM, $p=0.004$), IL-1α (≥1 μM, $p=0.01$), IL-1β (≥1 μM, $p<0.001$), and PAR2 (≥1 μM, $p=0.02$) decreased with capsazepine (Fig. 5). As shown by ELISA, capsazepine significantly decreased the protein levels of human TRPV1 (≥1 μM, $p=0.04$), LL37 (≥5 μM, $p=0.009$), VEGF (≥1 μM, $p=0.008$), and TNF-α (≥5 μM, $p<0.001$) in capsaicin-stimulated NHEKs (Fig. 4B). Immunocytofluorescence staining showed that the expression of TPRV1, LL37, substance P, and KLK-5 in the capsaicin-stimulated condition decreased with capsazepine, similar to that in the control group (Supplementary Fig. 2).

DISCUSSION

The pathophysiology of rosacea includes genetic factors, dysregulation of the innate and adaptive immune system, vascular and neuronal dysfunction, and microorganisms[5,6]. The trigger factors of rosacea, such as heat, stress, ultraviolet light, and spicy food, dysregulate the neurovascular and immune systems by activating transient receptor potential vanilloids (TRPVs) and other neuroinflammatory mediators in the skin of patients with rosacea[7-9].

TRPV1 is expressed on neuronal or non-neuronal cells

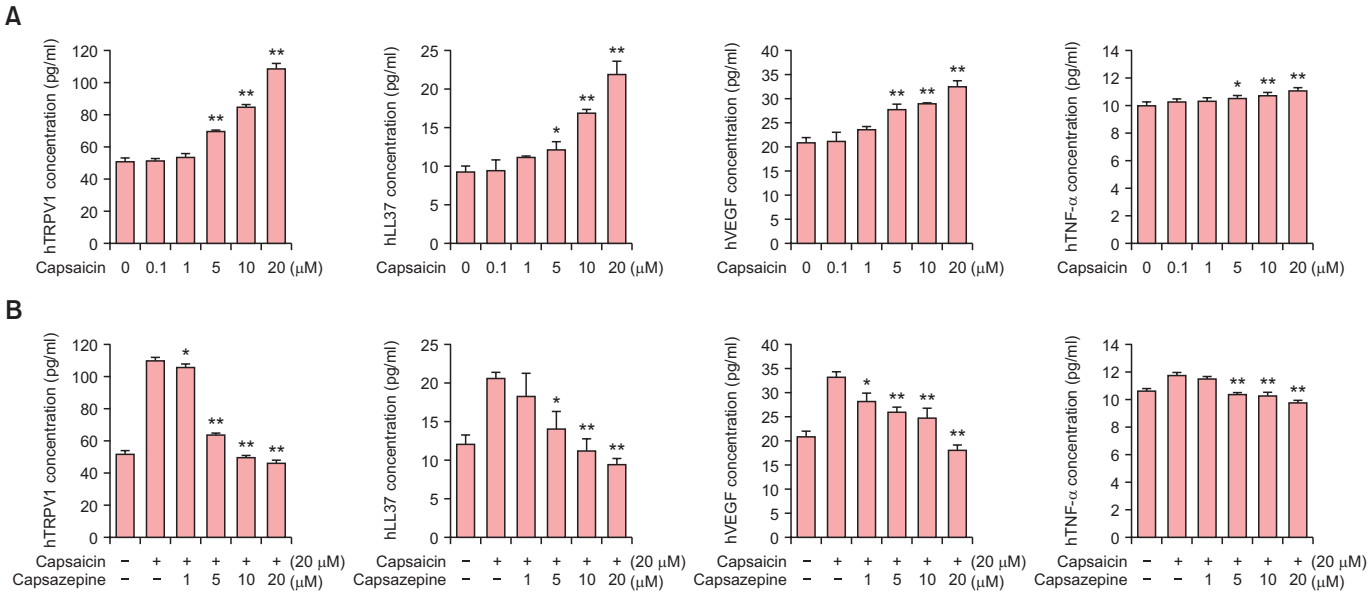

Fig. 4. (A) Protein levels of hTRPV1, hLL37, hVEGF, and hTNF-α increased with capsaicin and (B) decreased with capsazepine in 20 μM capsaicin-stimulated condition on ELISA. hTRPV1: human transient receptor potential vanilloid type 1, hLL37: human LL37, hVEGF: human vascular endothelial growth factor, hTNF-α: human tumor necrosis factor-α, ELISA: enzyme-linked immunosorbent assay. Statistically significant (*$p<0.05$; **$p<0.01$).

(e.g., keratinocytes) and play an important role in nociception and neurogenic inflammation[10-12]. Therefore, TRPV1 is closely associated with manifestations of rosacea[12]. Capsaicin, the pungent ingredient of the hot chili pepper, is known to act as an agonist of TRPV1[13]. TRPV1 expression was shown to be increased in all rosacea subtypes in previous studies[12]. In addition, it is known that activation of TRPV1 causes the release of the mediators of neurogenic inflammation and pain related to rosacea such as substance P, VEGF, and calcitonin gene-related peptide[14]. VEGF has been reported to enhance angiogenesis and lymphangiogenesis in rosacea skin, which is also associated with neurovascular dysfunction[15,16]. Moreover, excessive production of LL37 and KLK-5 has also been reported to play a role in the rosacea pathophysiology[11,17]. Rosacea patients have an increased baseline on expression of KLK-5 and LL37, resulting in vasodilatation and leukocyte chemotaxis[11,14,17,18]. This study found that both TRPV1 and LL37 were expressed more strongly in almost the same area in the entire epidermis of the rosacea patients compared to that in normal skin. These results suggest that there is a close relationship between LL37 and TRPV1.

During neurogenic inflammation, PAR2 is activated by rosacea-associated microorganism-derived proteases, resulting in the induction of the release of pro-inflammatory agents such as TNF-α, IL-1 and finally enhanced expression of LL37[3,18]. Likewise, these mediators are upregulated in rosacea patients, resulting in neurogenic dysregulation associated with rosacea symptoms such as persistent erythema and inflammation[11,18]. There have been few reports on how these factors, including TRPV1, are related to the pathogenesis of rosacea. *In vitro* data showed that TRPV1 activation induced by capsaicin is closely related to the expression of LL37, KLK-5, TNF-α, VEGF, IL-1α, IL-1β, IL-8, and PAR2 which are the main components in the pathophysiology of rosacea. Therefore, we confirmed that neuroinflammatory mediators increased after processing with capsaicin, but this is not known whether TRPV1 is directly activated or indirectly activated by capsaicin. In addition, recently, TRPV1-independent actions of capsaicin have been reported in several studies[19]. TRPV1 knock-out experiment is thought to be necessary, but it was not implemented in this study. We think that it is the limitation of this study and further studies are necessary to confirm these predictable effects.

In conclusion, this study demonstrated that TRPV1, LL37, and other neuroinflammatory mediators increase simultaneously when stimulated with capsaicin in the epidermal keratinocytes. Currently, there are many treatment options for rosacea patients, such as oral medication (e.g., beta-blockers,

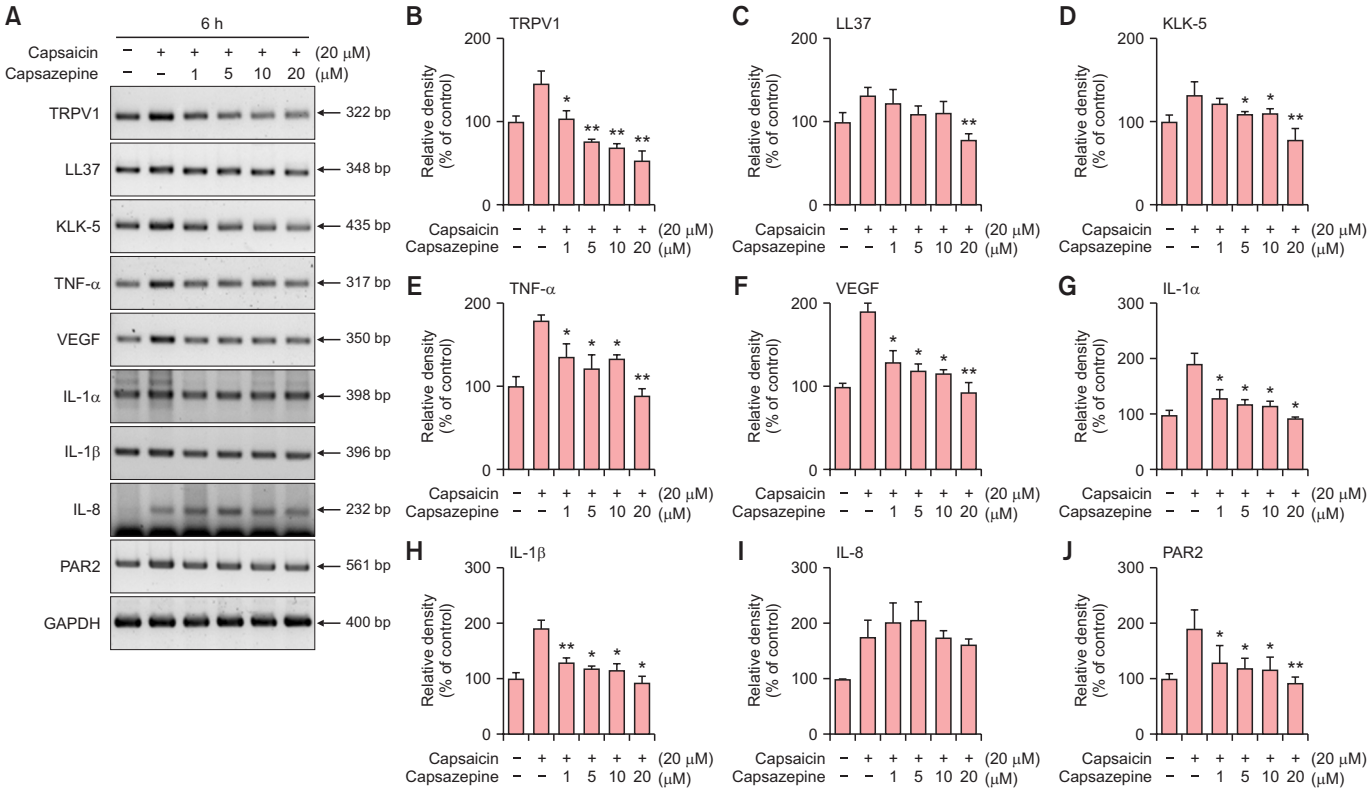

Fig. 5. (A) Capsazepine decreased the mRNA levels of TRPV1, LL37, KLK-5, TNF-α, VEGF, IL-1α, IL-1β, IL-8, and PAR2 in NHEKs *in vitro*. Columns represent relative densities of each factor in capsaicin-stimulated NHEKs after capsazepine treatment. mRNA levels of (B) TRPV1, (C) LL37, (D) KLK-5, (E) TNF-α, (F) VEGF, (G) IL-1α, (H) IL-1β, and (J) PAR2 decreased when treated with capsazepine in capsaicin-stimulated NHEKs on semi-quantitative RT-PCR. In contrast, (I) IL-8 showed no significant decrease on semi-quantitative RT-PCR. TRPV1: transient receptor potential vanilloid type 1, KLK-5: kallikrein-5, TNF-α: tumor necrosis factor-α, VEGF: vascular endothelial growth factor, IL: interleukin, PAR2: protease-activated receptor 2, NHEKs: normal human epidermal keratinocytes, RT-PCR: reverse transcription-polymerase chain reaction, GAPDH: glyceraldehyde 3-phosphate dehydrogenase. Statistically significant (*$p<0.05$; **$p<0.01$).

α2-adrenergic agonists, and tetracycline), topical agents (e.g., brimonidine, ivermectin, and metronidazole), and light or laser therapy[7,20]. In this study, capsazepine, a TRPV1 antagonist, attenuated the expression of TRPV1 stimulated by capsaicin and of also other neurogenic mediators associated with rosacea. Therefore, we anticipate that capsaicin and TRPV1 antagonist could play a role in rosacea management. However, there are few *in vivo* experiments and clinical trials which conducted on whether capsazepine, a TRPV1 antagonist, can improve subjective and objective symptoms in rosacea patients. Therefore, further studies and clinical trials about this suggestion will be required to confirm the effect of TRPV1 on rosacea treatment.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad.21.223-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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