peripheral T-cell lymphoma. Int J Dermatol 2017;56:617-622.
6. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol 2013;31:1970-1976.
7. Gupta V, Seshadri D, Khaitan BK, Nath D, Mridha AR. Peripheral T-cell lymphoma, not otherwise specified presenting with multiple tender cutaneous nodules and plaques. Indian J Dermatol Venereol Leprol 2015;81:313-315.
8. Friedman BJ, McHargue CA, Nauss MD. Peripheral T-cell lymphoma, not otherwise specified with prominent cutaneous involvement. Indian J Dermatol Venereol Leprol 2015;81:535-537.

https://doi.org/10.5021/ad.2020.32.4.342

Novel Anti-Inflammatory Effects of Brimonidine on *Propionibacterium acnes*-Induced Inflammatory Reaction

So-Ra Choi[1,2], Jin Gwi Yoo[1,2], Soo Jung Kim[2], Chong Won Choi[2], Young Lee[1,2], ChangDeok Kim[1,2], Young-Joon Seo[1,2], Jeung-Hoon Lee[1,2], Myung Im[2], Kyung Duck Park[3]

Departments of [1]Medical Science and [2]Dermatology, School of Medicine, Chungnam National University, Daejeon, [3]Department of Dermatology, School of Medicine, Kyungpook National University, Daegu, Korea

Dear Editor:

Brimonidine is a highly specific $\alpha 2$ adrenergic receptor (AR-$\alpha 2$) agonist with vasoconstrictive activity and has been approved as the treatment of open-angle glaucoma for almost 20 years[1]. Brimonidine has also been approved for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older[2-4]. We clinically experienced that topical brimonidine tartrate treatment of patients with acne and rosacea resulted in alleviation of flushing as well as improvement of acne. Since it is well recognized that inflammatory reaction induced by *Propionibacterium acnes* is critically important in the pathogenesis of acne[5], we speculate that brimonidine has an anti-inflammatory effect in addition to its genuine vasoconstrictive effect.

To verify this idea, we first examined whether AR-$\alpha 2$ was expressed in both the monocytes (THP-1 cells) and keratinocytes. Reverse transcription polymerase chain reaction (RT-PCR) showed that AR-$\alpha 2$ was clearly expressed in both the monocytes and keratinocytes (Fig. 1A), suggesting that brimonidine can directly affect the cells involved in acne-related inflammatory reaction.

We investigated the effects of brimonidine on *P. acnes*-induced inflammatory cytokine secretion in monocytes that are importantly involved in acne pathogenesis. THP-1 cells were pre-treated with brimonidine (30 μM) or dexamethasone (5 μM) for 1 hour, then *P. acnes* (1×10^7 colony-forming unit/ml) were added into the cultures. After 24 hours incubation, culture medium was collected and then cytokines were measured by enzyme-linked immunosorbent assay. Although it's potential effect was not as dramatic as dexamethasone (positive control), brimonidine significantly inhibited *P. acnes*-induced secretion of interleukin (IL)-1β and IL-6 (Fig. 1B). Next, we checked the effects of brimonidine on *P. acnes*-induced messenger RNA

Received June 3, 2019, Revised August 22, 2019, Accepted for publication September 18, 2019

Corresponding author: Kyung Duck Park, Department of Dermatology, School of Medicine, Kyungpook National University, 130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea. Tel: 82-53-200-5838, Fax: 82-53-426-0770, E-mail: gdpk1217@knu.ac.kr
ORCID: https://orcid.org/0000-0002-6067-7262

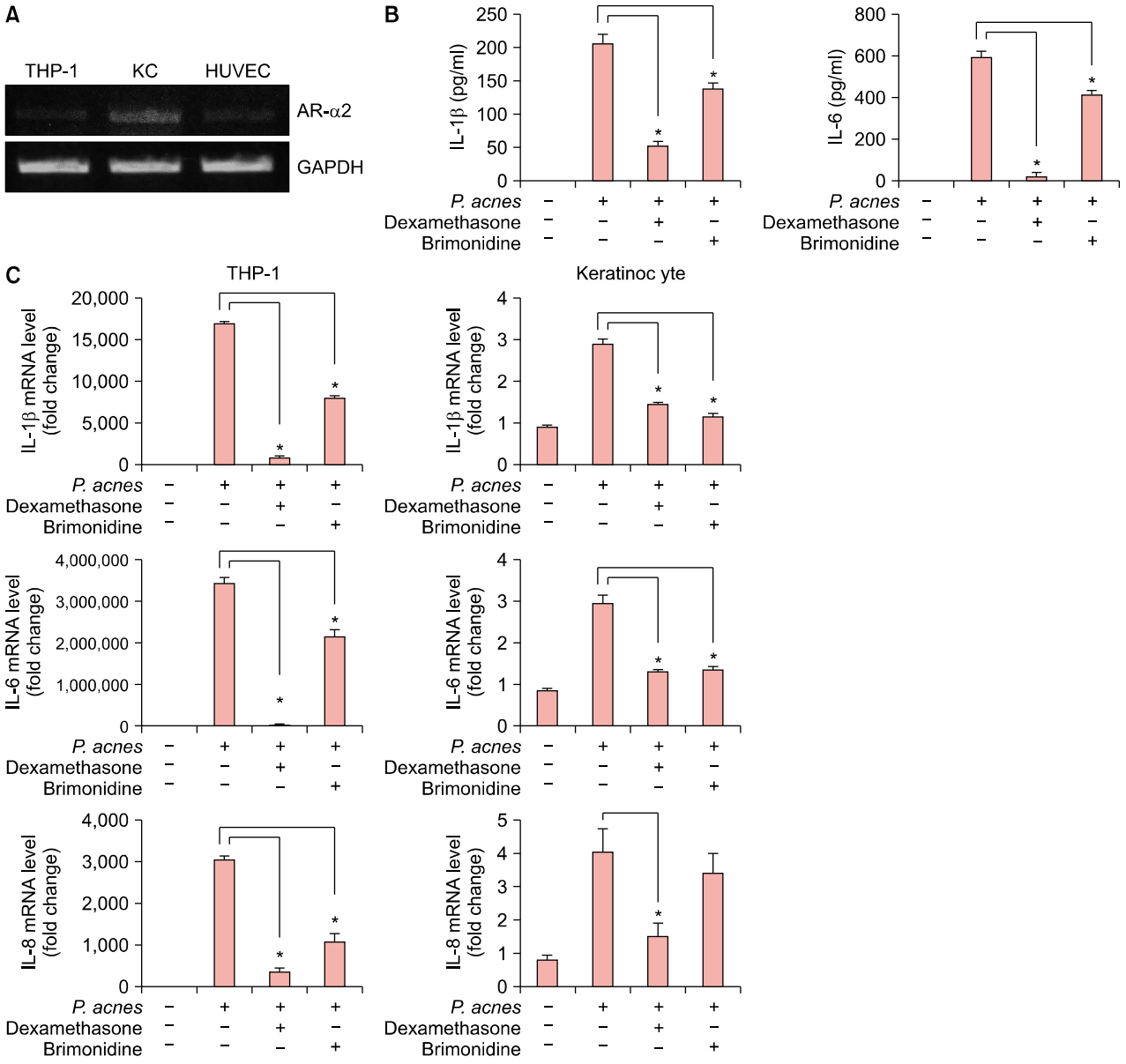

Fig. 1. Expression of α2 adrenergic receptor (AR-α2) in both monocyte and keratinocyte and effects of brimonidine on these cells. Reverse transcription polymerase chain reaction showed that AR-α2 was expressed in THP-1 cells and keratinocytes (A). THP-1 cells and keratinocytes were pre-treated with brimonidine (30 μM) or dexamethasone (5 μM) for 1 hour, then *Propionibacterium acnes* was added into the cultures. After 24 hours incubation, cytokines (B) and messenger RNA (mRNA) (C) were measured. Results were expressed as mean±standard deviation. Data were evaluated statistically using a one-way analysis of variance (ANOVA) and $*p<0.01$ was regarded as statistically significant. KC: keratinocyte, HUVEC: human umbilical vein endothelial cell, GAPDH: glyceraldehyde 3-phosphate dehydrogenase; IL: interleukin.

level of pro-inflammatory cytokines. Brimonidine markedly suppressed *P. acnes*-induced cytokine expression, including IL-1β, IL-6, and IL-8 in THP-1 cells. Similarly, *P. acnes*-induced IL-1β and IL-6 were significantly inhibited by brimonidine in keratinocytes. However, *P. acnes*-induced IL-8 was not affected obviously in keratinocytes (Fig. 1C). These results suggest that brimonidine has an inhibitory effect on *P. acnes*-induced inflammatory reaction, in addition to its original vasoconstrictive activity.

Brimonidine is an AR-α2 agonist, which is now used as a topical treatment for rosacea. Recently, Piwnica et al.[6] showed that brimonidine had a potent vasoconstrictive property using *ex vivo* human skin model. They also demonstrated that brimonidine had an anti-inflammatory effect using arachidonic acid- and/or 12-*O*-Tetradecanoylphorbol-13-acetate-induced mouse ear edema model[6]. In other study,

topical treatment of brimonidine resulted in reduction of ultraviolet B-induced erythema in mouse ear[7]. It was thought that anti-inflammatory effect of brimonidine was resulted from vasoconstriction.

In this study, we demonstrated that brimonidine alleviated *P. acnes*-induced pro-inflammatory cytokine secretion in monocytes and keratinocytes. These findings were consistent with the anti-inflammatory property of brimonidine identified by Piwnica et al[6]. However, based on our data in which brimonidine directly affected monocytes and keratinocytes rather than vascular cells and/or synapse, it can be hypothesized that brimonidine has dual action mechanism depending on target cells. Interestingly, it has been known that AR-α2 agonist inhibits the activity of adenylate cyclase thereby decreasing cyclic adenosine monophosphate (cAMP)[8]. And, it has been also demonstrated that cAMP promotes nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity via protein kinase A activation[9]. Therefore, there is a possibility that brimonidine decreases cAMP, thereby affecting NF-κB signaling negatively in the immune cells and keratinocytes. Since the activation of NF-κB signaling is pivotal to the pathogenesis of inflammatory skin diseases such as acne, it is easily assumed that if brimonidine inhibits NF-κB signaling then acne lesion getting better. Elucidation of precise action mechanism of brimonidine on inflammatory reaction will be an interesting further study.

In summary, we demonstrate that brimonidine has additional anti-inflammatory property besides its vasoconstrictive potential, suggesting that brimonidine is beneficial in the treatment of patients with acne and rosacea via dual action mechanisms.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

So-Ra Choi, https://orcid.org/0000-0001-5081-0886
Jin Gwi Yoo, https://orcid.org/0000-0002-3764-8594
Soo Jung Kim, https://orcid.org/0000-0002-5140-1432
Chong Won Choi, https://orcid.org/0000-0001-9994-8819
Young Lee, https://orcid.org/0000-0001-9205-1785
ChangDeok Kim, https://orcid.org/0000-0001-9341-6491
Young-Joon Seo, https://orcid.org/0000-0002-4955-590X
Jeung-Hoon Lee, https://orcid.org/0000-0002-4869-940X
Myung Im, https://orcid.org/0000-0003-2019-6488
Kyung Duck Park, https://orcid.org/0000-0002-6067-7262

REFERENCES

1. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine Study Group. Am J Ophthalmol 1999;127:20-26.
2. Fowler J, Jarratt M, Moore A, Meadows K, Pollack A, Steinhoff M, et al. Once-daily topical brimonidine tartrate gel 0•5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. Br J Dermatol 2012;166:633-641.
3. Steinhoff M, Schmelz M, Schauber J. Facial erythema of rosacea- aetiology, different pathophysiologies and treatment options. Acta Derm Venereol 2016;96:579-586.
4. Jackson JM, Knuckles M, Minni JP, Johnson SM, Belasco KT. The role of brimonidine tartrate gel in the treatment of rosacea. Clin Cosmet Investig Dermatol 2015;8:529-538.
5. Liu PF, Hsieh YD, Lin YC, Two A, Shu CW, Huang CM. Propionibacterium acnes in the pathogenesis and immunotherapy of acne vulgaris. Curr Drug Metab 2015;16:245-254.
6. Piwnica D, Rosignoli C, de Ménonville ST, Alvarez T, Schuppli Nollet M, Roye O, et al. Vasoconstriction and anti-inflammatory properties of the selective α-adrenergic receptor agonist brimonidine. J Dermatol Sci 2014;75:49-54.
7. Hsia E, Tian M, Gil D. Reduction in ultraviolet B light-induced erythema by oxymetazoline and brimonidine is mediated by different α-adrenoceptors. Exp Dermatol 2018;27:763-768.
8. Dong CJ, Guo Y, Ye Y, Hare WA. Presynaptic inhibition by α2 receptor/adenylate cyclase/PDE4 complex at retinal rod bipolar synapse. J Neurosci 2014;34:9432-9440.
9. Gerlo S, Kooijman R, Beck IM, Kolmus K, Spooren A, Haegeman G. Cyclic AMP: a selective modulator of NF-κB action. Cell Mol Life Sci 2011;68:3823-3841.