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Multidisciplinary Consideration of Potential Pathophysiologic Mechanisms of Paradoxical Erythema with Topical Brimonidine Therapy

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ABSTRACT

Rosacea is a chronic inflammatory disease with transient and non-transient redness as key characteristics. Brimonidine is a selective α_2 -adrenergic receptor (AR) agonist approved for persistent facial erythema of rosacea based on significant efficacy and good safety data. The majority of patients treated with brimonidine report a benefit; however, there have been sporadic reports of worsening erythema after the initial response. A group of dermatologists,

receptor physiology, and neuroimmunology scientists met to explore potential mechanisms contributing to side effects as well as differences in efficacy. We propose the following could contribute to erythema after application: (1) local inflammation and perivascular inflammatory cells with abnormally functioning ARs may lead to vasodilatation; (2) abnormal saturation and cells expressing different AR subtypes with varying ligand affinity; (3) barrier dysfunction and increased skin concentrations of brimonidine with increased actions at endothelial and presynaptic receptors, resulting in increased vasodilatation; and (4) genetic predisposition

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and receptor polymorphism(s) leading to different smooth muscle responses. Approximately 80% of patients treated with brimonidine experience a significant improvement without erythema worsening as an adverse event. Attention to optimizing skin barrier function, setting patient expectations, and strategies to minimize potential problems may possibly reduce further the number of patients who experience side effects.

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Keywords: Adrenergic receptors; Brimonidine; Dermatology; Erythema; Rosacea; Vasoconstriction; Worsening of erythema

INTRODUCTION

Transient and non-transient erythema are key characteristics of rosacea. Up to 85% of individuals with rosacea suffer from facial redness [1]; managing this redness poses a challenge for patients and clinicians alike [2]. Rosacea-related erythema can have short or long durations, and may take many forms, including persistent underlying redness, transient erythema (flushing) that is triggered by stimuli, or redness associated with individual inflammatory lesions or telangiectasias [2–4].

Relatively little is understood about the mechanisms that cause of redness, but both vascular and inflammatory events are involved [5–9]. Neurogenic inflammation may have a role; in this case, dysregulated neurovascular communication may lead to sustained vasodilation induced by various trigger factors (e.g., spicy food, exercise, heat, etc.) and thereby prolong flushing (\pm stinging/burning). Neurologic factors also can influence vascular responses, and both sensory and autonomic

nerves interact with immune cells in the process of flushing. Non-transient erythema of rosacea could represent a form of neurogenic inflammation, with immune mediators released by endothelial cells, keratinocytes, and immune cells resulting in chronic inflammation. Or, pathogens may activate innate immune receptors, such as toll-like receptor-2 (TLR-2) and upregulate antimicrobial peptides, such as cathelicidin LL37. LL37 can induce inflammation and vascular responses, and stimulate the release of cytokines and other mediators that secondarily activate neurovascular changes [10, 11].

Topical brimonidine gel 0.33% is approved to treat rosacea-associated redness [12, 13]. This agent selectively binds α_2 -adrenergic receptors (ARs) on vascular smooth muscle resulting in local transient vasoconstriction following topical application. Approximately 80% of patients treated with brimonidine report redness relief [14]. As the effects of brimonidine wear off (typically 10–12 h after application), erythema is expected to slowly return to baseline. In post-marketing experience, there were some reports of a transient worsening erythema rather than a return to baseline levels manifesting as [15–17]:

- Paradoxical erythema—redness appearing within 6 h after the application of brimonidine (can be worse than baseline).
- Exaggerated recurrence of erythema—redness greater than baseline that occurs as therapy wears off (10–12 h post-application).
- Allergic contact dermatitis—redness (usually accompanied by other signs, such as eczema and pruritus) occurring several months after the initiation of therapy.

Side effects were not reported in publications of the pivotal clinical trials as “paradoxical erythema;” however, Holmes et al. [18] conducted an analysis of adverse events and

stated 3.6% of subjects reported erythema and 1.8% flushing during the phase 3 study; in the long-term study, 9.1% of subjects had flushing and 6.5% had erythema. Tanghetti et al. [15] estimated that 10–20% of patients are at risk for worsening of redness. Jackson et al. [19] state “in our clinics, approximately 4–15% of patients have complained of worsening erythema or flushing,” adding that while this led to discontinuation of drug for some, many patients were able to successfully continue treatment, because “worsening of erythema was only temporary and not a daily issue.” Furthermore, they noted that erythema typically occurred during the initiation of therapy and subsided with regular use [19]. In response to a case report published in 2016, Tanghetti agreed, noting “Once the paradoxical erythema subsided, some patients

were able to resume therapy without recurrence of this problem” [55].

We discuss physiologic mechanisms that may contribute to worsening erythema (Fig. 1). In our opinion, the most likely candidates are:

- *Local inflammation* with perivascular inflammatory cells bearing *increased* or *modified* brimonidine-responsive ARs, leading to increased drug effect to release mediators and produce sustained vasodilatation (Fig. 1).
- *High concentration* of brimonidine in the skin (e.g., due to skin barrier dysfunction). Brimonidine may penetrate in higher concentrations to endothelium and nerve terminals to cause vasodilatation (Figs. 1, 2).
- *Abnormal saturation effects* and inhibited release of norepinephrine (NE) from sympathetic nerve terminals due to the

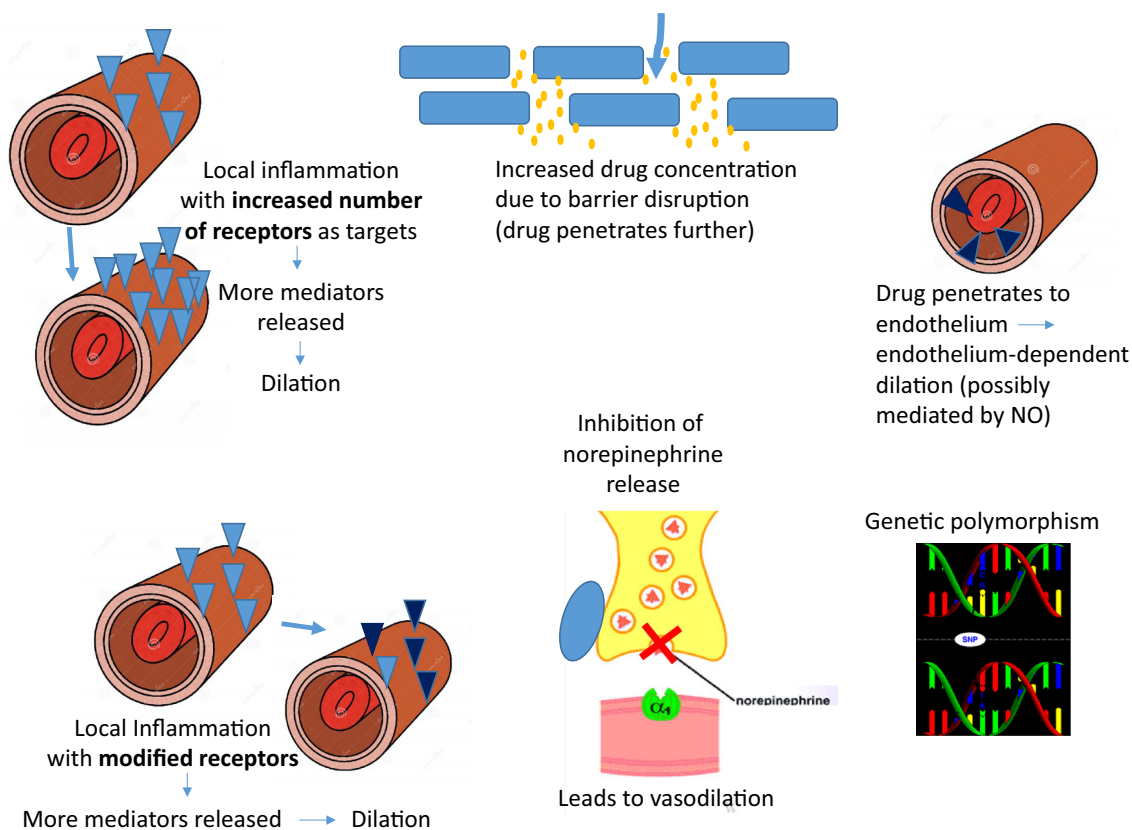


Fig. 1 Rosacea. Schematic representation of possible mechanisms that contribute to the exacerbation of erythema during brimonidine therapy. *NO* nitric oxide

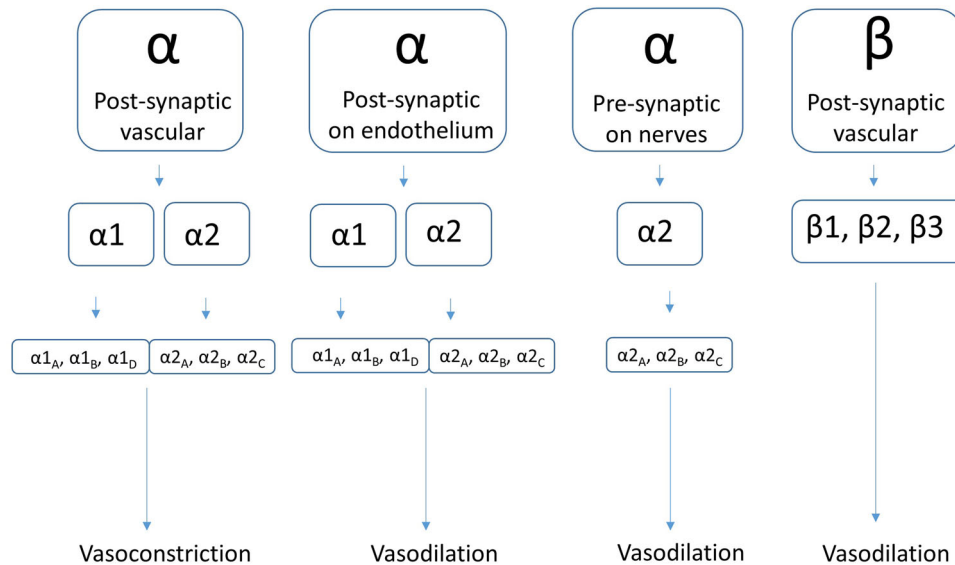


Fig. 2 Rosacea. Possible sites of adrenergic receptors in the control of vascular tone: (1) post-synaptic α -ARs on vascular smooth muscle, (2) post-synaptic α -ARs on

vascular endothelium, (3) pre-synaptic α_2 -ARs on nerve terminals, and (4) post-synaptic β -ARs on vascular smooth muscles

action of brimonidine on α_2 -ARs, with a net effect of reduced NE availability.

- *Genetic polymorphism(s)* for genes increase the affinity of brimonidine to the receptor, resulting in increased smooth muscle responses and sustained vasodilation.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

BRIEF REVIEW OF ADRENERGIC RECEPTOR FUNCTIONS

Overview

Review of receptor physiology is helpful to understand what may be affecting the action of brimonidine. G protein-coupled receptors (GPCRs), including ARs, interact with catecholamines, particularly NE and

epinephrine. ARs are found throughout the body, including in the vascular smooth muscle, vascular endothelium, on presynaptic nerve terminals, and on a subset of immune cells. There are a number of subtypes based on physiologic function, pharmacology, structure, and signal transduction (Fig. 2) [20]. The function of α -ARs in the skin is primarily to regulate blood flow through vasoconstriction following catecholamine binding to receptors on vascular smooth muscle, where the mobilization of calcium stores results in muscle cell contraction. Detailed molecular mechanisms of ARs are described elsewhere [21].

Factors that Affect Receptor Function

α_2 Receptors

α -ARs are divided into α_1 and α_2 subtypes. The relative contribution of α_1 and α_2 subtypes in subcutaneous vessels can vary with location, receptor density, local NE concentration, and temperature [20, 22, 23]. The density of arterial

α_2 -ARs increases from proximal to distal location [20], and α_2 -ARs are thought to dominate in small vessels (<200 microns) [24].

Expression of α -ARs on non-smooth muscle cells can also mediate receptor function. Within the vasculature, α_2 -ARs on endothelial cells relax blood vessels by release of nitric oxide (NO) [25], an effect opposite that of ARs on vascular smooth muscle. Presynaptic nerve terminals likewise express α_2 -ARs and induce vasorelaxation by inhibiting release of NE and, subsequently, adrenergic neurotransmission via a negative feedback function [26].

α 1 Receptors

Sensory nerve fibers have also been shown to express α_1 -ARs, which generate axon-reflex vasodilation peripheral to the area of vasoconstriction [27]. The more recently described α_{1D} -AR may be the most important receptor in terms of sympathetic nervous control of arteries, as it predominates at the sympathetic neuroeffector junction [28].

Receptor Expression on Immune Cells

Finally, several immune cell subsets present in the skin express α_1 - and α_2 -ARs. α_1 -ARs are expressed on cells with known pro-inflammatory activities, whereas α_2 -ARs appear to mediate anti-inflammatory effects [29, 30].

ADRENERGIC RECEPTORS: SPECULATIONS ABOUT ROLE IN ROSACEA AND WITH BRIMONIDINE THERAPY

Rosacea is a disease of chronic, cyclic inflammation, and vasodilation. α -ARs in skin of selected rosacea patients may exhibit an altered physiological response to brimonidine

that may be dependent or independent of the disease or the agonist. Possible factors that may contribute to episodes of worsening erythema are discussed below.

Impact of Concentration and/or Chronic Agonism

In rosacea patients, epidermal barrier function is disturbed and stratum corneum hydration is reduced [31, 32]. This may lead to higher drug concentrations in skin and possibly also altered drug clearance. Differences in application techniques can affect the distribution of brimonidine and local drug concentrations.

Local brimonidine concentrations may influence worsening erythema by: (1) the saturation of α_2 -receptors on vascular smooth muscle, resulting in the binding of additional cell types or AR subtypes and/or (2) the chronic agonism of α -ARs, resulting in the downregulation and desensitization of receptors.

Brimonidine is a selective α_{2A} -AR agonist, but it exhibits a reduced affinity for α_{2C} - and α_{1A} -ARs as well [24]. Binding to the more recently characterized α_{1D} subtype was not tested, but may also occur when brimonidine is present at high concentrations. The effect of brimonidine on other receptors or cell types might be concentration dependent, and a spillover effect after saturation of the α_{2A} -AR on vascular smooth muscle could occur.

Increased local concentrations ('spillover effect') may allow brimonidine to act on at least one endothelial receptor (α_{2A} -AR and other subtypes), thereby promoting NO-mediated vasodilation. Brimonidine may also act on presynaptic ARs of nerve terminals leading to reduced vasoconstriction (α_{2A} - and α_{2C} -mediated). Both effects could promote

local vasodilation (α_2 -mediated) and worsen erythema.

α_{2A} -ARs expressed on presynaptic nerves modulate an intense, acute release of NE that is evoked by high-frequency neuronal stimulation occurring with stress responses. In contrast, α_{2C} -ARs on presynaptic nerve terminals regulate the basal, long-term release of NE due to low-frequency stimulation. Thus, these receptors tightly regulate neurotransmitter release from adrenergic nerves under basal and stressful conditions through their inhibitory presynaptic feedback loop.

Taken together, differences in sympathetic nerve firing rates, and thus local NE concentrations, could impact brimonidine efficacy by competing for α_2 -AR binding.

Neuronal activation could also lead to release of other neuromediators that induce vasodilation. For example, axon-reflex vasodilation mediated by α_1 -ARs is partially mediated by prostaglandins (which have been shown to be increased in rosacea skin) and the overall activity has been suggested to contribute to local vascular disturbances in acute or chronic inflammation. Furthermore, α_1 -ARs have been found in subpopulations of neurons in rat skin, which are immunoreactive to the TRPV1 (transient receptor potential cation channel subfamily V member 1) ion channel and the neuromediator calcitonin gene-related peptide (CGRP; glucagon-related peptide), both of which are involved in vasodilation and neurogenic inflammation in human rosacea skin [6, 33, 34].

Enhanced concentration of brimonidine may also result in the activation of α_1 -ARs present on immune cells, such as macrophages and mast cells, both of which are present at increased densities in rosacea-affected skin. Known effects include an increased release of vasodilatory mediators, such as prostaglandin E_2 , histamine, tryptase, and neuropeptides,

which could in turn result in worsened erythema [35].

The ‘spillover’ effect may explain paradoxical-worsening erythema following the application of brimonidine, where an initial reduction in erythema is observable prior to the saturation of vascular α_2 -ARs. This may be followed by enhanced binding to other receptor subtypes on different cell types that override local vasoconstriction by vasodilatory and/or inflammatory mechanisms within a few hours of application.

Alternatively, chronic α_2 -AR agonism may downregulate or desensitize vasoconstrictive α_2 -ARs, leading to reflexive vasodilation via vasodilatory α -ARs. This hypothesis is supported by the fact that similar feedback loops have been demonstrated with other α adrenergic agonists, e.g., rhinitis medicamentosa induced by nasally administered oxymetazoline and xylometazoline [36]. However, the adaptation of receptors with chronic ophthalmic use has not been reported, and minimal to no tachyphylaxis has been reported with chronic topical use [12].

To minimize the potential for complications related to concentration and skin barrier function, we agree with the recommendations by Tanghetti et al. [15] to set realistic patient expectations by providing clear education, to teach patients to apply the medication in a very thin layer initially, and to make the first trial of medication on a day when the patient is able to observe the effect in privacy.

Impact of Inflammation

Rosacea is characterized by abnormal inflammatory responses to regular environmental stimuli (e.g., ultraviolet light and microbes) mediated by abnormally

increased neuromediators [37, 38], proteases, cytokines, vitamin D, and TLR-2 signaling [8, 9, 33, 39]. TLR-2 signaling can recruit a variety of inflammatory mediators, many of which are regulated by the transcription factor NF- κ B, such as interleukin-6 (IL-6) or tumor necrosis factor- α (TNF- α) [6, 9, 40].

An NF- κ B binding site in the promoter region of G protein receptor kinase (GRKs) could be involved in shifting GPCR signaling [41]. These kinases are well known to regulate GPCR cell function, including receptor internalization and desensitization, thereby leading to reduced receptor numbers (by downregulation) as well as alternate signaling via recruitment of β -arrestin [42]. Moreover, shifts in AR signaling have been linked to the induction of inflammation by increasing NF- κ B levels [43–51]. This could be a possible mechanism for the adverse rebound effect observed in some patients using brimonidine.

Mast cells may contribute to the inflammatory loop in rosacea as well. Mast cell-deficient mice do not display rosacea-like inflammation [52, 53], and α adrenergic blockade increases acetylcholine release as well as subsequent pituitary adenylate cyclase-activating polypeptide (PACAP) release and protease-activated receptor 2 (PAR2) activation, contributing to inflammation and vasodilation. The stimulation of neuropeptide release by innate immune receptors, such as TLR2 and PAR2, may be critically involved in inflammatory vasodilation, as observed in all three skin subtypes of rosacea [6, 7].

COX-2 and prostaglandin production, both of which are elevated in rosacea, may increase α -receptor-mediated NO, thereby contributing to vasodilation and edema via a prostanoid-dependent pathway. Furthermore, the effects of brimonidine treatment may be different in the early versus late inflammation,

as immune and vascular responses can shift with prolonged stimuli, thereby changing the repertoire and density of ARs and GPCRs.

Skin deposits of nitrogen (NO_2 and NO_3) are converted to NO and promote vasodilation independent of the endothelium in the presence of ultraviolet A irradiation, a common trigger in rosacea.

An inflammatory milieu and heightened neuronal activity are present in rosacea [7, 9], and it is possible that worsening erythema could represent an exaggerated compensatory neuroinflammatory mechanism of the vasculature aside from what is suggested here, such as release of neuropeptides and systemic adrenergic or other vasoactive peptides.

Best results may be obtained when rosacea-associated inflammation is managed using the traditional rosacea treatments in conjunction with brimonidine therapy. Using brimonidine to reduce the overall erythema can unmask redness from inflammatory lesions, which is unpalatable for patients. It may also be useful to educate patients about overall facial erythema, telangiectasias, and perilesional erythema [15].

Impact of Genetic Polymorphisms

Genetic polymorphism in ARs is common and may cause lack of or reduced functional receptor subtypes on vascular smooth muscle in some individuals. Polymorphisms in the receptors may produce differential binding, altered binding sensitivity, or receptor distribution. The impact of polymorphism on ARs is evidenced by the drug response to albuterol (salbutamol) in asthma, where it has been demonstrated that responses to receptor-blocking drugs can change [54].

Polymorphic differences in avidity or altered kinetics among α_{2A} -ARs expressed on different

tissues may also explain the worsening erythema phenomenon, particularly with regard to exaggerated recurrence as drug effect wanes. If the avidity of brimonidine for the α_2 -AR on presynaptic nerve terminals is greater than that on vascular smooth muscle, the vasoconstrictive effect on vessels may wear off as expected, but negative feedback inhibition on nerve terminals may remain for a longer period, with transiently sustained erythema.

This potential mechanism also underscores the prudence of advising patients to make the first trial of medication on the weekend or a day when the patient can be comfortable even in the unlikely event that worsening erythema occurs [15].

SUMMARY AND CONCLUSIONS

Brimonidine has proven strong vasoconstrictive effects on α_2 -ARs of vessels and—to a lesser extent—on α_1 -ARs [24]. In rosacea, ARs on other tissues—such as endothelium, presynaptic adrenergic nerve terminals, and immune cells—may also promote vasodilation. Skin reactivity to adrenergic agonists may be influenced by a complex system of activation and inhibition, systemic factors, such as epinephrine/NE levels, local tissue factors (including NO), receptor up- and downregulations, desensitization, inflammation, and exterior (e.g., temperature, ultraviolet light, microbes, and proteases) or endogenous factors (increase of local body temperature via exercising, pH changes, microbiota). In turn, worsening erythema events may occur with brimonidine use for reasons that are entirely patient dependent and can be allergic (very rarely) or non-allergic (more often) on nature.

The worsening phenomenon that occurs in some patients as the effects of brimonidine

agonism wane may be explained by receptor desensitization and internalization, negative feedback loops, or activation of other compensatory mediators that lead to vasodilation. Skin barrier dysfunction can increase local concentrations of brimonidine and can be effectively treated with moisturizers prior to brimonidine therapy. In addition, the paradoxical-worsening phenomenon occurring within hours of brimonidine application may be explained by high concentrations of brimonidine within skin that leads to the saturation of receptors and ‘spillover’ effect to other α -AR subtypes with unwanted effects (vasodilation).

Brimonidine effects are predominantly beneficial. We hypothesize that certain individual characteristics may potentially override the vasoconstrictive effect transiently (e.g., barrier dysfunction) or permanently (e.g., receptor polymorphisms). Future studies are important to define those subgroups that may be most likely to benefit from brimonidine, since it is the first efficacious topical treatment against a frequent—and often challenging to treat—symptom in rosacea. It is crucial for clinicians to educate patients who should be taught to start with a very thin layer of medication and to use other strategies that can optimize brimonidine therapy [15].

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criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given the final approval for the version to be published.

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Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

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REFERENCES

- Gupta AK, et al. *J Eur Acad Dermatol Venereol.* 2005;19:273–5.
- Del Rosso JQ, Gallo RL, Tanghetti E, Webster G, Thiboutot D. An evaluation of potential correlations between pathophysiologic mechanisms, clinical manifestations, and management of rosacea. *Cutis Cutan Med Pract.* 2013;91(3 Suppl):1–8.
- Del Rosso JQ. Advances in understanding and managing rosacea: part 1: connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. *J Clin Aesth Dermatol.* 2012;5(3):16–25.
- Del Rosso JQ. Advances in understanding and managing rosacea: part 2: the central role, evaluation, and medical management of diffuse and persistent facial erythema of rosacea. *J Clin Aesth Dermatol.* 2012;5(3):26–36.
- Del Rosso JQ, Gallo RL, Kircik L, Thiboutot D, Baldwin HE, Cohen D. Why is rosacea considered to be an inflammatory disorder? The primary role, clinical relevance, and therapeutic correlations of abnormal innate immune response in rosacea-prone skin. *J Drugs Dermatol JDD.* 2012;11(6):694–700.
- Steinhoff M, Schaubert J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. *J Am Acad Dermatol.* 2013;69(6 Suppl 1):S15–26.
- Steinhoff M, Buddenkotte J, Aubert J, Sulk M, Novak P, Schwab VD, et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc Soc Investig Dermatol Inc Eur Soc Dermatol Res.* 2011;15(1):2–11.
- Schwab VD, Sulk M, Seeliger S, Nowak P, Aubert J, Mess C, et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc Soc Investig Dermatol Inc Eur Soc Dermatol Res.* 2011;15(1):53–62.
- Buhl T, Sulk M, Nowak P, Buddenkotte J, McDonald I, Aubert J, et al. Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways. *J Invest Dermatol.* 2015;135(9):2198–208.
- Yamasaki K, Di Nardo A, Bardan A, Murakami M, Ohtake T, Coda A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13(8):975–80.
- Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity. *J Investig Dermatol Symp Proc Soc Investig Dermatol Inc Eur Soc Dermatol Res.* 2011;15(1):12–5.
- Moore A, Kempers S, Murakawa G, Weiss J, Tauscher A, Swinyer L, et al. Long-term safety and efficacy of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of a 1-year open-label study. *J Drugs Dermatol JDD.* 2014;13(1):56–61.

13. Fowler J Jr, Jackson M, Moore A, Jarratt M, Jones T, Meadows K, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol JDD*. 2013;12(6):650–6.
14. Layton AM, Schaller M, Homey B, Hofmann MA, Bewley AP, Lehmann P, et al. Brimonidine gel 0.33% rapidly improves patient-reported outcomes by controlling facial erythema of rosacea: a randomized, double-blind, vehicle-controlled study. *J Eur Acad Dermat Venereol JEADV*. 2015;29(12):2405–10.
15. Tanghetti EA, Jackson JM, Belasco KT, Friedrichs A, Hougier F, Johnson SM, et al. Optimizing the use of topical brimonidine in rosacea management: panel recommendations. *J Drugs Dermatol JDD*. 2015;14(1):33–40.
16. Ilkovitch D, Pomerantz RG. Brimonidine effective but may lead to significant rebound erythema. *J Am Acad Dermatol*. 2014;70(5):e109–10.
17. Routt ET, Levitt JO. Rebound erythema and burning sensation from a new topical brimonidine tartrate gel 0.33%. *J Am Acad Dermatol*. 2014;70(2):e37–8.
18. Holmes AD, Waite KA, Chen MC, Palaniswamy K, Wisner TH, Draelos ZD, et al. Dermatological adverse events associated with topical brimonidine gel 0.33% in subjects with erythema of rosacea: a retrospective review of clinical studies. *J Clin Aesth Dermatol*. 2015;8(8):29–35.
19. 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;8:529–38.
20. Guimaraes S, Moura D. Vascular adrenoceptors: an update. *Pharmacol Rev*. 2001;53(2):319–56.
21. Minneman KP, Han C, Abel PW. Comparison of alpha 1-adrenergic receptor subtypes distinguished by chlorethylclonidine and WB 4101. *Mol Pharmacol*. 1988;33(5):509–14.
22. Bailey SR, Eid AH, Mitra S, Flavahan S, Flavahan NA. Rho kinase mediates cold-induced constriction of cutaneous arteries: role of alpha2C-adrenoceptor translocation. *Circ Res*. 2004;94(10):1367–74.
23. Borbujo J, Garcia-Villalon AL, Valle J, Gomez B, Diequez G. Postjunctional alpha-1 and alpha-2 adrenoceptors in human skin arteries. An in vitro study. *J Pharmacol Exp Ther*. 1989;249(1):284–7.
24. Piwnica D, Rosignoli C, de Menonville ST, Alvarez T, Schuppli Nollet M, Roye O, et al. Vasoconstriction and anti-inflammatory properties of the selective alpha-adrenergic receptor agonist brimonidine. *J Dermatol Sci*. 2014;75(1):49–54.
25. Matsuda H, Kuon E, Holtz J, Busse R. Endothelium-mediated dilations contribute to the polarity of the arterial wall in vasomotion induced by alpha 2-adrenergic agonists. *J Cardiovasc Pharmacol*. 1985;7(4):680–8.
26. Starke K. Presynaptic alpha-autoreceptors. *Rev Physiol Biochem Pharmacol*. 1987;107:73–146.
27. Drummond PD. Inflammation contributes to axon reflex vasodilatation evoked by iontophoresis of an alpha-1 adrenoceptor agonist. *Auton Neurosci*. 2011;159(1–2):90–7.
28. Docherty JR. Vasopressor nerve responses in the pithed rat, previously identified as alpha2-adrenoceptor mediated, may be alpha1D-adrenoceptor mediated. *Eur J Pharmacol*. 2011;658(2–3):182–6.
29. Grisanti LA, Perez DM, Porter JE. Modulation of immune cell function by alpha(1)-adrenergic receptor activation. *Curr Top Membr*. 2011;67:113–38.
30. Averbeck B, Reeh PW, Michaelis M. Modulation of CGRP and PGE2 release from isolated rat skin by alpha-adrenoceptors and kappa-opioid-receptors. *Neuroreport*. 2001;12(10):2097–100.
31. Lonne-Rahm SB, Fischer T, Berg M. Stinging and rosacea. *Acta Dermatovenereol*. 1999;79(6):460–1.
32. Dirschka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br J Dermatol*. 2004;150(6):1136–41.
33. Helfrich YR, Maier LE, Cui Y, Fisher GJ, Chubb H, Fligel S, et al. Clinical, histologic, and molecular analysis of differences between erythematotelangiectatic rosacea and telangiectatic photoaging. *JAMA Dermatol*. 2015;151(8):825–36.
34. Sulk M, Seeliger S, Aubert J, Schwab VD, Cevikbas F, Rivier M, et al. Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. *J Invest Dermatol*. 2012;132(4):1253–62.
35. Steinhoff M, Vergnolle N, Young SH, Tognetto M, Amadesi S, Ennes HS, et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med*. 2000;6(2):151–8.
36. Gilsbach R, Hein L. Are the pharmacology and physiology of alpha(2) adrenoceptors determined

- by alpha(2)-heteroreceptors and autoreceptors respectively? *Br J Pharmacol.* 2012;165(1):90–102.
37. Schaubert J. Antimicrobial peptides, Vitamin D(3) and more. How rosacea may develop. *Hautarzt.* 2011;62(11):815–9.
38. Schaubert J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol.* 2009;124(3 Suppl 2):R13–8.
39. Yamasaki K, Kanada K, Macleod DT, Borkowski AW, Morizane S, Nakatsuji T, et al. TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Invest Dermatol.* 2011;131(3):688–97.
40. Li Q, Verma IM. NF-kappaB regulation in the immune system. *Nat Rev Immunol.* 2002;2(10):725–34.
41. Lorton D, Bellinger DL. Molecular mechanisms underlying beta-adrenergic receptor-mediated cross-talk between sympathetic neurons and immune cells. *Int J Mol Sci.* 2015;16(3):5635–65.
42. Steinhoff MS, von Mentzer B, Geppetti P, Pothoulakis C, Bunnett NW. Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol Rev.* 2014;94(1):265–301.
43. Galandrin S, Bouvier M. Distinct signaling profiles of beta1 and beta2 adrenergic receptor ligands toward adenylyl cyclase and mitogen-activated protein kinase reveals the pluridimensionality of efficacy. *Mol Pharmacol.* 2006;70(5):1575–84.
44. Luttrell LM, Gesty-Palmer D. Beyond desensitization: physiological relevance of arrestin-dependent signaling. *Pharmacol Rev.* 2010;62(2):305–30.
45. Ghanouni P, Gryczynski Z, Steenhuis JJ, Lee TW, Farrens DL, Lakowicz JR, et al. Functionally different agonists induce distinct conformations in the G protein coupling domain of the beta 2 adrenergic receptor. *J Biol Chem.* 2001;276(27):24433–6.
46. Reiner S, Ambrosio M, Hoffmann C, Lohse MJ. Differential signaling of the endogenous agonists at the beta2-adrenergic receptor. *J Biol Chem.* 2010;285(46):36188–98.
47. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. *Nat Rev Drug Discov.* 2013;12(3):205–16.
48. Small KM, Schwarb MR, Glinka C, Theiss CT, Brown KM, Seman CA, et al. Alpha2A- and alpha2C-adrenergic receptors form homo- and heterodimers: the heterodimeric state impairs agonist-promoted GRK phosphorylation and beta-arrestin recruitment. *Biochemistry.* 2006;45(15):4760–7.
49. Violin JD, Lefkowitz RJ. Beta-arrestin-biased ligands at seven-transmembrane receptors. *Trends Pharmacol Sci.* 2007;28(8):416–22.
50. Whalen EJ, Rajagopal S, Lefkowitz RJ. Therapeutic potential of beta-arrestin- and G protein-biased agonists. *Trends Mol Med.* 2011;17(3):126–39.
51. Wisler JW, Xiao K, Thomsen AR, Lefkowitz RJ. Recent developments in biased agonism. *Curr Opin Cell Biol.* 2014;27:18–24.
52. Di Nardo A, Vitiello A, Gallo RL. Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. *J Immunol.* 2003;170(5):2274–8.
53. Moormann C, Artuc M, Pohl E, Varga G, Buddenkotte J, Vergnolle N, et al. Functional characterization and expression analysis of the proteinase-activated receptor-2 in human cutaneous mast cells. *J Invest Dermatol.* 2006;126(4):746–55.
54. Shahane G, Parsania C, Sengupta D, Joshi M. Molecular insights into the dynamics of pharmacogenetically important N-terminal variants of the human beta2-adrenergic receptor. *PLoS Comput Biol.* 2014;10(12):e1004006.
55. Practice Update. Available from: <http://www.practiceupdate.com/content/paradoxical-erythema-reaction-to-long-term-brimonidine-gel-for-facial-erythema-of-rosacea/41069/65/4/1#collapse1>. Accessed August 1, 2016.